PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	53	(hemoglobin haemoglobin) with concentration same (stool fecal faecal) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2019/06/23 10:50 AM
L2	1	(hemoglobin haemoglobin) with concentration same (stool fecal faecal) same "ng/ml" and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2019/06/23 10:51 AM
L3	9	(hemoglobin haemoglobin) with concentration same ((stool fecal faecal) adj sample) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2019/06/23 11:18 AM
L4	260	DNA same ((stool fecal faecal) adj sample) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2019/06/23 11:35 AM
L5	2	"20080227208"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2019/06/23 01:34 PM
L6	1	"20080227208" and "10 ng/ml"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2019/06/23 01:35 PM
L7	11	(hemoglobin haemoglobin) with "5 ng/ml"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2019/06/23 01:38 PM
L8	0	NDGR4 and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/14 01:50 PM
L9	38	NDRG4 and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/14 01:50 PM
L10	6	NDRG4 same epigenetic and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/14 01:58 PM
L11	24	"2006113770"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/14 02:02 PM

L12	4	"2006113770" and NDRG4	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/14 02:11 PM
L13	6	NDRG4 same (epigenetic methylation) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/14 02:19 PM
L14	6	NDRG4 same (epigenetic methylation hypermethylation) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/14 02:19 PM
L15	0	"N-myc downstream regulated gene 4" same (epigenetic methylation hypermethylation) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/14 02:24 PM
L16	0	"N-myc downstream regulated gene 4" and (epigenetic methylation hypermethylation) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/14 02:24 PM
L17	0	"N-myc downstream regulated gene 4" and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/14 02:25 PM
L18	1	"20060019256" and uptg	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/14 02:55 PM
L19	40	(PHACTR3 FOXE1 GATA4 GPNMB TFP12 SOX17 SYNE1 LAMA MMP2 OSMR SFR2CDO1) same (epigenetic methylation hypermethylation) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/14 03:35 PM
L20	40	(PHACTR3 FOXE1 GATA4 GPNMB TFP12 SOX17 SYNE1 LAMA MMP2 OSMR SFR2CDO1) same (epigenetic methylation hypermethylation) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/15 08:07 AM
L21	3	fecal same (antibody antibodies immunoassay) same (DNA RNA polynucleotide "nucleic acid" gene) same (hyridization hybridizes hybridize) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/15 08:26 AM

L22	2	(cancer carcinoma) same (PHACTR3 NDRG4 FOXE1 GATA4 GPNMB TFP12 SOX17 SYNE1 LAMA MMP2 OSMR SFRP2 CDO1) same (hyridization hybridizes hybridize) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/15 10:40 AM
L23	1	"200483399"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/15 10:42 AM
L24	0	"200483399A2"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/01/15 10:43 AM
L25	0	"200483399A2"	(EPO)	OR	OFF	OFF	2020/01/15 11:11 AM
L26	0	"200483399"	(EPO)	OR	OFF	OFF	2020/01/15 11:11 AM
L27	40	(PHACTR3 FOXE1 GATA4 GPNMB TFP12 SOX17 SYNE1 LAMA MMP2 OSMR SFR2CDO1) same (epigenetic methylation hypermethylation) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/08/04 06:14 PM
L28	38	NDRG4 and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2020/08/04 07:10 PM
L29	15	hemoglobin with (stool fecal) with concentration and @pd<"20090203"	(USPAT)	OR	OFF	OFF	2021/06/15 10:13 AM
L30	32	(hemoglobin haemoglobin) with concentration same (stool fecal faecal) and (antibody antibodies immunoassay immunological) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/16 11:33 AM
L31	16	(hemoglobin haemoglobin) with concentration same (stool fecal faecal) same (antibody antibodies immunoassay immunological) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/16 11:33 AM
L32	1	(hemoglobin	(US-PGPUB; USPAT;	OR	ON	ON	2021/06/16

		haemoglobin) with concentration same (stool fecal faecal) same (antibody antibodies immunoassay immunological) and "ng/ml" and @pd<"20090203"	USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)				11:37 AM
L33	1048	(freeze freezing frozen) same (stool fecal faecal) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/16 12:05 PM
L34	399	(freeze freezing frozen) with (stool fecal faecal) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/16 12:05 PM
L35	236	(freeze freezing frozen) with (stool fecal faecal) with (sample fraction portion historical) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/16 12:07 PM
L36	14	(freeze freezing frozen) with (stool fecal faecal) with (fraction portion historical) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/16 12:07 PM
L37	4	(immunoassay elisa) with (stool fecal faecal) with (fresh "non-frozen") and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/16 12:31 PM
L38	1	"7832219".FMID.	(US-PGPUB; USPAT; FPRS; JPO)	OR	OFF	OFF	2021/06/16 12:32 PM
L39	4	"7832219"	(USPAT)	OR	ON	ON	2021/06/16 12:33 PM
L40	2	(freeze freezing frozen) with (stool fecal faecal) with (fraction portion historical) same buffer and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/16 01:30 PM
L41	5	(freeze freezing frozen) same (stool fecal faecal) with (fraction portion historical) same buffer and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/16 01:33 PM
L42	230	"5741650"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/06/16 01:38 PM
L43	114	"5741650"	(USPAT)	OR	ON	ON	2021/06/16 01:38 PM
L44	63	"5741650" and frozen	(USPAT)	OR	ON	ON	2021/06/16 01:40 PM

L45	65	"5741650" and (freeze freezing frozen)	(USPAT)	OR	ON	ON	2021/06/16 01:41 PM
L46	3	(feces fecal faecal faeces) with buffer with (freeze freezing frozen) and @pd<"20090203"	(USPAT)	OR	ON	ON	2021/06/16 01:51 PM
L47	0	fecal with sample same (unfrozen "not frozen") and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2022/03/17 02:40 PM
L49	85	fecal with sample same (frozen freezing) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2022/03/17 02:42 PM
L50	12	fecal with sample same (sealable sealed seal) with (vessel container) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2022/03/17 02:57 PM
L51	17	fecal with sample same (unfrozen "not frozen" freezing) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2022/03/21 03:56 PM
L52	4	"20080124714"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2022/03/21 03:58 PM
L53	6	fecal with sample same (sealable sealed seal) with (vessel container) same portion and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2022/03/21 04:18 PM
L54	179	(stool fecal faecal) with sample with portion and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2022/03/21 04:52 PM
L55	2	(stool fecal faecal) with sample with portion with (multiple duplicate) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/03/21 04:54 PM
L56	69546	((dna with (isolate extract extracted isolating)) (determine determining determins determined) with (hemoglobin haemoglobin) same (fecal faecal)) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2022/03/21 05:27 PM
L57	1	((dna with (isolate extract extracted isolating)) and (determine determining determins determined) with (hemoglobin	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2022/03/21 05:28 PM

		haemoglobin) same (fecal faecal)) and @pd<"20090203"					
L58	128	DNA same "epigenetic modification" and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2022/03/22 05:47 PM
L59	1	DNA same "epigenetic modification" and (faecal fecal) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2022/03/22 05:47 PM
L60	20	DNA same "epigenetic modification" and (faecal fecal stool) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2022/03/22 05:48 PM
L61	21	DNA same "epigenetic modification" and (faecal fecal stool feces) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2022/03/22 05:48 PM
L62	19	DNA same "epigenetic modification" and (dna "nucleic acid" chromosomal chromatin) same (faecal fecal stool feces) and @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	OFF	OFF	2022/03/22 05:49 PM
L63	0	"20050064401" and (hemoglobin haemoglobin)	(US-PGPUB)	OR	OFF	OFF	2022/03/22 06:07 PM
L64	112	immunoassay same (hemoglobin haemoglobin) and @pd<"20090203"	(US-PGPUB)	OR	OFF	OFF	2022/03/22 06:33 PM
L65	51	immunoassay with (hemoglobin haemoglobin) and @pd<"20090203"	(US-PGPUB)	OR	OFF	OFF	2022/03/22 06:33 PM
L66	2	immunoassay with (hemoglobin haemoglobin) same (stool fecal faecal) and @pd<"20090203"	(US-PGPUB)	OR	OFF	OFF	2022/03/22 06:44 PM
L67	87	sealable WITH (container vessel) AND fecal AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/06 04:19 PM
L68	14	sealable WITH (container vessel) SAME fecal AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/06 04:19 PM
L69	0	sealable WITH (container vessel) SAME (deficate	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/07 07:15 AM

		defication) AND @pd<"20090203"					
L70	0	sealable AND (container vessel) SAME (deficate defication) AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/07 07:16 AM
L71	0	(container vessel) SAME (deficate defication) AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/07 07:16 AM
L72	0	(container vessel) SAME (deficate defication) AND @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/06/07 07:16 AM
L73	12306	(container vessel) SAME (stool fecal) AND @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/06/07 07:40 AM
L74	1992	(container vessel) SAME (stool fecal) SAME (full complete entire) AND @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA,	OR	ON	ON	2022/06/07 07:41 AM

			VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L75	439	(container vessel) SAME (stool fecal) WITH (full complete entire) AND @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/06/07 07:42 AM
L76	76	(container vessel) SAME (stool fecal) WITH (full complete entire) AND (container vessel) WITH (seal sealable) AND @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/06/07 07:42 AM
L77	77	(container vessel) SAME (stool fecal "night soil") WITH (full complete entire) AND (container vessel) WITH (seal sealable) AND @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/06/07 10:15 AM
L78	1801	(container vessel) SAME (stool fecal "night soil") AND home AND @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB,	OR	ON	ON	2022/06/07 10:36 AM

			HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L79	13	(container vessel) SAME (stool fecal "night soil") SAME sealable AND home AND @pd<"20090203"	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/06/07 10:36 AM
L80	0	(deficate deficat$) SAME container AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/07 11:17 AM
L81	3	(deficate deficat$) SAME collection AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/07 11:18 AM
L82	1884	(deficate deficat$ "night soil" stool) SAME (deposit$ collect$) AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/07 11:20 AM
L83	363	(deficate deficat$ "night soil" stool) SAME (deposit$ collect$) WITH (chamber device tray container) AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/07 11:21 AM
L84	26	(deficate deficat$ "night soil" stool) SAME (deposit$ collect$) WITH (chamber device tray container) SAME home AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/07 11:21 AM
L85	171	(deficate deficat$ "night soil" stool feces faeces) SAME (directly direct) WITH (chamber device tray containe vessel) AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/07 11:53 AM

L86	2	"20070017015" AND chamber	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/07 12:02 PM
L87	2	"20070017015" AND chamber SAME (detach$ seal$)	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/07 12:04 PM
L88	0	"20070017015" AND chamber SAME (detach$ seal$) AND empt$	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/07 12:05 PM
L89	0	"20070017015" AND chamber SAME (detach$ seal$) AND empty	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/07 12:08 PM
L90	0	"20070017015" AND chamber SAME (detach$ seal$) AND empt$	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/07 12:08 PM
L91	171	(deficate deficat$ "night soil" stool feces faeces) SAME (directly direct) WITH (chamber device tray containe vessel) AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/09 01:53 PM
L92	0	(deficate deficat$) WITH container AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/09 01:54 PM
L93	0	(deficate deficat$) WITH (vessel container) AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/09 01:54 PM
L94	0	(deficate deficat$) SAME (vessel container) AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/09 01:54 PM
L95	26	fecal SAME (DNA RNA) WITH surface AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/09 04:12 PM
L96	1	fecal SAME (DNA RNA) WITH surface SAME human AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/09 04:14 PM
L97	0	fecal SAME (DNA RNA) WITH helminth SAME human AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/09 04:21 PM
L98	1	fecal SAME (DNA RNA) WITH parasite SAME human AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/09 04:22 PM
L99	15	fecal SAME (DNA RNA) WITH within SAME human AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/09 04:23 PM
L100	1	fecal SAME (DNA RNA)	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/09

		WITH parasite SAME human AND @pd<"20090203"					04:28 PM
L101	7	(feces fecal stool faecal) SAME (DNA RNA) WITH parasite SAME human AND @pd<"20090203"	(US-PGPUB; USPAT)	OR	ON	ON	2022/06/09 04:29 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Patent Owner's Ex. 2003, Page 709

DO NOT ENTER: /B.L.S./
06/09/2022

PATENT
Attorney Docket No.: **EXCTD-35239.304**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Joost Louwagie	Confirmation:	1874
Serial No.:	15/634,607	Group No.:	1634
Filed:	06/27/2017	Examiner:	Bradley L. Sisson
Entitled:	**FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD**		

AMENDMENT UNDER 37 C.F.R. §1.116 AFTER FINAL OFFICE COMMUNICATION MAILED 03/25/2022 AND REQUEST FOR AFTER-FINAL CONSIDERATION UNDER AFCP 2.0

EFS WEB FILED
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

This communication is an After Final Amendment under 37 C.F.R. §1.116(b)(2), responsive to the Final Office Communication mailed 03/25/2022, with a response due on or before 06/25/2022, and is filed with a Request for After-Final Consideration. Applicants respectfully request entry of this amendment.

The Commissioner is authorized by this paper to charge any fees during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 that may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-4302, referencing Attorney Docket No.: **EXCTD-35239.304**. This paragraph is a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

Amendments to the Claims are reflected in the Listing of Claims beginning on Page 2;

Remarks begin on Page 5.

To: DOCKETING@CASIMIRJONES.COM,Genomic_docketing@cardinal-ip.com,
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15634607	CTAV	06/14/2022	EXCTD-35239.304
	EXIN	06/14/2022	EXCTD-35239.304
	892	06/14/2022	EXCTD-35239.304
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Docket Number (Optional)
EXCTD-35239.304

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Signature /Mary Ann D. Brow/

Typed or printed name Mary Ann D. Brow

First Named Inventor	
LOUWAGIE	
Application Number	Filed
15/634,607	27-JUNE-2017
For	
FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD	
Art Unit	Examiner
1634	SISSON

Applicant hereby **appeals** to the Patent Trial and Appeal Board from the last decision of the examiner.

The fee for this Notice of Appeal is (37 CFR 41.20(b)(1)) $ 840 (previously paid)

☐ Applicant asserts small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by 50%, and the resulting fee is: $ _____

☐ Applicant certifies micro entity status. See 37 CFR 1.29. Therefore, the fee shown above is reduced by 75%, and the resulting fee is: $ _____
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I am the

☐ applicant

☑ attorney or agent of record
Registration number 42363

☐ attorney or agent acting under 37 CFR 1.34
Registration number _____

Signature /Mary Ann D. Brow/

Typed or printed name Mary Ann D. Brow

Telephone Number 608-662-1277

Date 06/27/2022

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Electronic Acknowledgement Receipt

EFS ID:	46057078
Application Number:	15634607
International Application Number:	
Confirmation Number:	1874
Title of Invention:	FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD
First Named Inventor/Applicant Name:	Joost Louwagie
Customer Number:	173254
Filer:	Mary Ann Deese Brow
Filer Authorized By:	
Attorney Docket Number:	EXCTD-35239.304
Receipt Date:	27-JUN-2022
Filing Date:	27-JUN-2017
Time Stamp:	19:26:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Pre-Appeal Brief Conference Request	2022-06_27_PABRBrief_EXCTD-003USCON2-35239_35239-304.pdf	149097 50a4f4b0c7b5f9d58fe16178e78bf2b26dc87ed9	no	5

Warnings:

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2	Pre-Appeal Brief Conference Request	2022-06-27_35239-304_PABR_form.pdf	451829 9bf7896a66edf6311fcf8a90d81b4192f115e815	no	2
Warnings:					
Information:					
3	Notice of Appeal Filed	2022-06-27_35239-304_Notice Appeal.pdf	397891 f058ec6a2b931b1f785fb038967b8658066a3773	no	2
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New Applications Under 35 U.S.C. 111

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New International Application Filed with the USPTO as a Receiving Office

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PATENT
Attorney Docket No.: **EXCTD-35239.304**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Joost Louwagie	Confirmation:	1874
Serial No.:	15/634,607	Group No.:	1634
Filed:	06/27/2017	Examiner:	Bradley L. Sisson
Entitled:	**FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD**		

APPLICANT INTERVIEW SUMMARY

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Alexandria, VA 22313-1450

A telephonic interview was conducted on June 9, 2022. Participants in the telephone call were Applicant's Representative Mary Ann D. Brow and Examiner Bradley Sisson. Claim 82 and after-final Amendment and Response filed on May 25, 2022 were discussed; no other exhibit was provided.

Applicant directed the Examiner's attention to the two different containers recited in claim 82, the sealable collection vessel in which a fecal sample is collected at home by the human subject by defecation directly into the sealable collection vessel, and the separate sealable container, used to contain a removed portion of the deposited fecal sample. Applicant further highlighted that the removed portion and the remaining portion are separately stabilized by combining with different types of buffers. Applicant pointed out that none of the cited references disclose a method comprising collection of a fecal sample at home by the human subject by defecation directly into a sealable collection vessel, or the recited method in which the freshly collected fecal specimen is portioned into a removed portion in a separate container and a remaining portion in the sealable collection vessel.

The Examiner pointed to several references not cited in the Final Office Action but communicated prior to the conference for discussion:

US 2004/0019298 A1 (Zhou et al.),

US 6,761,702 B2 (Smith),

US 2005/0075543 A1 (Calabrese),

US 2003/0086869 A 1 (Stallings et al.)

Applicant's representative noted that these references also do not disclose use a sealable collection vessel as set forth in the method of the claim, or the overall method of the claim.

The Examiner noted that the "sealable collection vessel" to receive a fecal sample by direct defecation was not described in detail. Applicant noted that patient defecation directly into a special bucket, followed by addition of a buffer and shipping to a laboratory is described on page 44, of the Experimental section of the Specification, and that the Examiner has not previously asserted any enablement or written description objection to this claim element.

No agreement regarding the patentability of the Claim 82 as amended was reached.

Dated: June 27, 2022 /Mary Ann D. Brow/

Mary Ann D. Brow
Registration No. 42,363

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Electronic Acknowledgement Receipt

EFS ID:	46057407
Application Number:	15634607
International Application Number:	
Confirmation Number:	1874
Title of Invention:	FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD
First Named Inventor/Applicant Name:	Joost Louwagie
Customer Number:	173254
Filer:	Mary Ann Deese Brow
Filer Authorized By:	
Attorney Docket Number:	EXCTD-35239.304
Receipt Date:	27-JUN-2022
Filing Date:	27-JUN-2017
Time Stamp:	20:06:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant summary of interview with examiner	2022-06-27_InterviewSummary_EXCTD-003USCON2-35239_35239-304.pdf	93889 cdfd22ff9fb3f03c9b6934bc9e22d51eeec65118	no	2

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New International Application Filed with the USPTO as a Receiving Office

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PATENT
Attorney Docket No.: **EXCTD-35239.304**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Joost Louwagie	Confirmation:	1874
Serial No.:	15/634,607	Group No.:	1634
Filed:	06/27/2017	Office:	Bradley L. Sisson
Entitled:	**FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD**		

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Appellant requests a Pre-Appeal Brief Conference for the above-identified application. This is responsive to the Final Office Communication mailed 03/25/2022 ("Office Action") and the Advisory Action mailed 06/14/2022 ("Advisory Action"), with response due by Monday, 06/27/2022, the first business day following Saturday, 06/25/2022, and is submitted along with a Notice of Appeal in compliance with 37 CFR 41.31 and the Pre-Appeal Brief Conference form PTO/SB/33.

Claims 82, 84, 87, 89-94, and 96-100 are pending in the Application, with claims 82 and 87 being independent. Claims 82, 84, 87, 96, and 97 stand rejected under pre-AIA 35 U.S.C. 103(a) as allegedly being unpatentable over Wang in view of Liang, Olek, and Kutzner, with the remaining dependent claims being rejected under §103(a) over Wang, Liang, Olek, and Kutzner, in further view of one or more of Gao, Yee, Kim, and Van Engeland.

BASIS FOR REVIEW

The combination of references fails to teach or suggest all the elements of any claim. The Office points to Appellant's alleged admissions but these do not supply missing elements. The Office has provided no other evidence or argument sufficient to supply the missing elements of these claims and therefore fails to establish obviousness of any pending claim[1].

Appellant has recognized a need for collecting fresh fecal material from a subject at home, in a manner such that the material can be tested both for blood and for alterations in the subject's DNA. The claims are directed to methods of processing a fecal sample that is freshly collected at home by the subject, by defecation directly into a sealable collection vessel. A

[1] In the Advisory Action, the Office states that the arguments set forth in the after-final Response filed 05/25/2022 ("Response") are dependent on entry of amendments to the claims, which was denied. Appellant submits that the arguments are equally applicable to the unamended claims and does not waive these arguments.

portion of the collected sample is removed to a separate container, and the removed portion and the remaining portion are separately treated with appropriate buffers to stabilize different analytes in the feces, namely blood proteins and DNA.

Appellant's claim 82 recites, *inter alia,* two different containers and two kinds of buffer:

(1) a **sealable collection vessel** in which a fecal sample is collected at home by a human subject by defecation directly into the vessel;

(2) **a separate container**;

(3) **a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample**; and

(4) **a buffer that maintains DNA integrity in a fecal sample**

The claim also recites steps for producing *specific arrangements* of these elements with different portions the freshly-collected fecal sample. Namely, after the human subject has collected a fecal sample in the sealable collection vessel, a **removed portion** is taken from the collected fecal sample and combined with buffer (3) in the separate container (2)(as numbered above), and the **remaining portion** of the fecal sample in the sealable collection vessel (1) is combined with buffer (4), as described above. Claim 84 depends from claim 82 and therefore includes the same arrangements of elements, further reciting delivering the two different containers and the contained samples and buffers to a medical diagnostics laboratory.

Similarly, claim 87 recites a pair of portions of a fecal sample in two separate containers, specifically a container containing the removed portion and a buffer, and a sealable vessel containing the stabilized remaining portion, obtained by the method of claim 82. Thus, claim 87 also comprises the same elements and arrangement of elements set forth in claim 82, as discussed above. Claim 87 further recites steps of testing the removed portion for a concentration of hemoglobin, and testing DNA extracted from the remaining portion for DNA from the human subject that has epigenic modification. Claims 89-94 and 96-100 all depend from claim 87 and therefore comprise the same elements and arrangements thereof set forth in claims 82 and 87.

The primary combination of references cited in all rejections is Wang in view of Liang, Olek, and Kutzner. (Office Action ¶¶ 14, 31, and 40). The Office points to Wang as teaching a device for collecting a portion of a fecal sample and use of a preserving fluid, but admits that Wang does not teach collecting pairs of samples (Office Action, ¶17). However, the

shortcomings of Wang are far greater. Wang fails to teach or suggest a sealable collection vessel suitable to receive a fecal sample from human subject at home by defecation directly into the vessel; collection of a sample by direct defecation by the subject into the sealable collection vessel; removal of a "removed portion" from the fecal sample collected in the sealable collection vessel; or stabilization of a "remaining portion" of the fecal sample by adding buffer to the remaining portion in the sealable collection vessel. While Wang teaches a generic "preserving reagent" to "slow degradation of the biological molecule" (Wang at ¶3), Wang discloses neither a buffer "that prevents denaturation or degradation of blood proteins found in a fecal sample" nor "a buffer that maintains DNA integrity in a fecal sample," as recited in claim 82.

The sample collection device disclosed by Wang is suited only for collecting a portion of feces using "stick 18", as illustrated in Figs. 1 and 2 of Wang, stick 18 having a "distal portion 21" having a groove to hold a small portion of a fecal sample (see, *e.g.*, Wang at ¶25).

To the extent that Wang teaches catching defecated feces directly, Wang teaches only *temporarily* catching the feces so that a sample portion can be removed using the disclosed stick device. For this purpose, Wang teaches use of a disposable paper catch web "temporarily secured to a toilet droopingly spanning the seat to catch the feces for sampling" (Office Action ¶15, referencing the Abstract of Wang; See also Wang Figs. 7-8). Wang specifies that the disposable web 61 is preferably made of a flushable paper (Wang, ¶34). Thus, the disposable web 61 of Wang is not in any way a "sealable collection vessel" that can hold a buffer. Further, Wang suggests neither preserving the remainder of the caught feces after collection of a sample portion using the disclosed sampling device, nor any manner of sending the remaining feces to a laboratory. Rather, Wang clearly points to disposing of the remaining feces, preferably by flushing it away with disposable web 61.

Regarding Appellant's claim 84, the Office admits that Wang does not teach sending pairs of samples to a lab for testing (Office Action, ¶17). Appellant points out that Wang further fails to teach delivery of a pair of containers containing the pair of samples from the same freshly-collected fecal deposit, *i.e.,* sending the separate container containing the **removed portion** of the fecal sample combined with the buffer of (3) (as numbered above), and the sealable collection vessel containing the **remaining portion** of the fecal sample and the buffer of (4), to a medical diagnostics laboratory, as recited in this claim.

The deficiencies of Wang with respect to claims 82 and 87 and the claims depending

therefrom are not remedied by combination with Liang, Olek, and/or Kutzner. Liang suffers from the same deficiencies as Wang, disclosing only collecting a small portion of feces using a "sampling wand" (Liang, ¶112). Like Wang, Liang teaches that the user collects his/her feces on a "flushable paper sheet secured across the seat of a toilet," and uses the sampling wand inserted into the feces to collect a small portion for testing. The flushable paper sheet of Liang is not a "sealable collection vessel" that can hold a buffer. Further, Liang suggests neither preserving the remainder of the feces after collection of a portion using the sampling wand, nor sending the remaining feces to a laboratory. Rather, Liang clearly points to disposing of the remaining feces, preferably by flushing it away with flushable paper sheet.

The Office points to Liang ¶112 as allegedly disclosing that "one can collect multiple samples via a "sampling wand" (Office Action, ¶18). This mischaracterizes what Liang says. Liang says the sampling wand may be inserted into the fecal sample "multiple times in order to obtain sample from different portions of the [fecal] sample. The sampling wand (member)/cap portion is then reinserted into the test apparatus. . ." (Liang, ¶112; Office Action ¶18). Thus, in the procedure of Liang highlighted by the Office, fecal material collected on the sampling wand by the multiple insertions into the feces does not produce multiple *samples*, but rather produces a *single* sample comprising the combined material collected by the multiple insertions of the wand into the feces. This combined single sample is what is inserted into the test apparatus. Nothing in Liang suggests collecting multiple samples from the same fecal specimen for separate testing.

The Office asserts it would be obvious to combine the device of Wang with the device of Liang, to "capitalize on the fecal sample being accessible on the covered toilet and collection of multiple samples that can be sent independently to the testing facility for analysis." This is the entirety of the rationale provided. However, neither reference suggests portioning a single freshly-collected fecal sample into multiple separate samples or portions, nor suggests any benefit of sending such multiple samples independently to a testing facility for analysis. This statement is no more than a conclusory assertion of a motivation without any explanation of how it could arise from the cited documents. The Office's obviousness rationale thus appears to rely on hindsight reasoning based on Appellant's disclosure.

Furthermore, Liang does not teach or suggest use of a sealable collection vessel as set forth in instant claims 82 and 87, collection of a sample by direct defecation into the sealable collection vessel; stabilization of a "remaining portion" of a fecal sample by buffer in the

sealable collection vessel, or delivery of the sealable collection vessel containing the buffer-stabilized sample together with the buffer-stabilized removed portion to a lab for testing as recited in claim 84. Thus, no matter how many of the devices of Wang and/or Liang are used to collect samples from a fecal specimen, the combination of Wang and Liang still fails to teach or suggest all the elements of claims 82 and 87, and the claims depending therefrom.

The Office points to Olek as teaching performing tests on stool samples whereby one detects DNA sequence. (Office Action, ¶22-25), and to Kutzner as disclosing detection of colorectal tumors using a combination of tests, one which looks for a component of blood, and one which is based on nucleic acid analysis, *e.g.,* PCR analysis. (Office Action, ¶14). However, Olek does not teach anything about methods of collecting or processing fecal samples, and Kutzner describes a retrospective study of mutations and blood in frozen patient samples (Kutzner, p34, col 2). Further, Kutzner specifically states that it is not obvious to the authors of the reference that combined testing of DNA markers with fecal blood detection will yield any particular result with respect to diagnostic screening. Thus, neither Olek nor Kutzner cure the deficiencies of Wang, Liang, and Olek with respect to the missing elements discussed above.

The Office points to Gao as teaching methods of detecting analytes, including hemoglobin, in a fecal sample and to Yee as teaching setting a 10 ng/ml of hemoglobin in blood as a threshold value. (Office Action, ¶¶ 34-36), and to Kim or Van Engeland[2] and teaching epigenetic markers for colorectal cancer (Office Action, ¶¶43 and 44). As set forth in the Response, none of Gao, Yee, Kim, or Van Engeland cure the deficiencies of Wang in view of Liang, Olek, and Kutzner with respect to the missing elements discussed above.

In view of the points discussed above, it is clear that the Office has erred and has failed to establish *prima facie* obviousness of claims 82, 84, 87, 89-94, and 96-100.

Respectfully submitted,

Dated: June 27, 2022

/Mary Ann D. Brow/

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Middleton, WI, 53562
608-663-2277

[2] Van Engeland does not disclose invention "by another," as required under pre-AIA 35 U.S.C. § 102(a), and therefore does not qualify as prior art to the present application.

Doc Code: AP.PRE.REQ

Document Description: Pre-Appeal Brief Conference Request

PTO/AIA/33 (03-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): EXCTD-35239.304

I hereby certify that this correspondence is being facsimile transmitted to the USPTO, transmitted via the USPTO's patent electronic filing system, or deposited with the United States Postal Service with sufficient postage in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on 06/27/2022

Signature /Mary Ann D. Brow/

Typed or printed name Mary Ann D. Brow

Application Number	Filed
15/634,607	27-June-2017

First Named Inventor: LOUWAGIE

Art Unit	Examiner
1634	SISSON

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 42363.

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

/Mary Ann D. Brow/
Signature

Mary Ann D. Brow
Typed or printed name

608-662-1277
Telephone number

06/27/2022
Date

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 1 forms are submitted.

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/634,607	06/27/2017	Joost Louwagie	EXCTD-35239.304	1874

173254 7590 08/10/2022

CASIMIR JONES, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
08/10/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DOCKETING@CASIMIRJONES.COM
Genomic_docketing@cardinal-ip.com

Notice of Panel Decision from Pre-Appeal Brief Review

Application No.	Applicant(s)		
15/634,607	Louwagie, Joost		
Examiner	**Art Unit**	**AIA (FITF) Status**	
DAVE T NGUYEN	1634	No	

This is in response to the Pre-Appeal Brief Request for Review filed 27 June 2022 .

1. ☐ **Improper Request** - The Request is improper and a conference will not be held for the following reason(s):

☐ The Notice of Appeal has not been filed concurrent with the Pre-Appeal Brief Request.
☐ The request does not include reasons why a review is appropriate.
☐ A proposed amendment is included with the Pre-Appeal Brief request.
☐ Other: _____ .

The time period for filing a response continues to run from the receipt date of the Notice of Appeal or from the mail date of the last Office communication, if no Notice of Appeal has been received.

2. ☐ **Proceed to Board of Patent Appeals and Interferences** - A Pre-Appeal Brief conference has been held. The application remains under appeal because there is at least one actual issue for appeal. Applicant is required to submit an appeal brief in accordance with 37 CFR 41.37. The time period for filing an appeal brief will be reset to be one month from mailing this decision, or the balance of the two-month time period running from the receipt of the notice of appeal, whichever is greater. Further, the time period for filing of the appeal brief is extendible under 37 CFR 1.136 based upon the mail date of this decision or the receipt date of the notice of appeal, as applicable.

☐ The panel has determined the status of the claim(s) is as follows:
Claim(s) allowed: _____ .
Claim(s) objected to: _____ .
Claim(s) rejected: _____ .
Claim(s) withdrawn from consideration: _____ .

3. ☐ **Allowable application** - A conference has been held. The rejection is withdrawn and a Notice of Allowance will be mailed. Prosecution on the merits remains closed. No further action is required by applicant at this time.

4. ☑ **Reopen Prosecution** - A conference has been held. The rejection is withdrawn and a new Office action will be mailed. No further action is required by applicant at this time.

All participants:

(1) DAVE T NGUYEN .	(3) Bradley Sisson .
(2) Ashwin Mehta .	(4) _____ .

/DAVE T NGUYEN/ Supervisory Patent Examiner, Art Unit 1634		

To: DOCKETING@CASIMIRJONES.COM,Genomic_docketing@cardinal-ip.com,
From: PAIR_eOfficeAction@uspto.gov
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Subject: Private PAIR Correspondence Notification for Customer Number 173254

Aug 10, 2022 04:58:47 AM

Dear PAIR Customer:

CASIMIR JONES, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 173254 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

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Application	Document	Mailroom Date	Attorney Docket No.
15634607	AP.PRE.DEC	08/10/2022	EXCTD-35239.304

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

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Thank you for prompt attention to this notice,

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/634,607	06/27/2017	1634	1740	EXCTD-35239.304	19	2

CONFIRMATION NO. 1874

CORRECTED FILING RECEIPT

173254
CASIMIR JONES, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

OC000000136099621

Date Mailed: 08/30/2022

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Joost Louwagie, Dornach, SWITZERLAND;

Applicant(s)

Exact Sciences Corporation, Madison, WI;

Power of Attorney: The patent practitioners associated with Customer Number 72960

Domestic Priority data as claimed by applicant

This application is a CON of 15/010,436 01/29/2016 ABN
which is a CON of 13/147,570 03/12/2012 ABN
which is a 371 of PCT/GB2010/000180 02/03/2010
which claims benefit of 61/149,581 02/03/2009

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 07/12/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/634,607**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD

Preliminary Class

435

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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NOT GRANTED

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Aug 30, 2022 03:23:11 AM

Dear PAIR Customer:

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2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562
UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
15634607	APP.FILE.REC	08/30/2022	EXCTD-35239.304

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Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

PATENT
Attorney Docket No.: **EXCTD-35239.304**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Joost Louwagie	Confirmation:	1874
Serial No.:	15/634,607	Group No.:	1634
Filed:	06/27/2017	Examiner:	Bradley L. Sisson
Entitled:	**FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD**		

PETITION UNDER 37 CFR §1.182 TO REQUEST HANDLING OF THE APPLICATION PURSUANT TO M.P.E.P. § 707.02

Madam/Sir:

Applicant files this Petition under 37 CFR §1.182 to request that the application be recognized as "special" in accordance with M.P.E.P. §707.02, and to formally request the personal attention of the Supervisory Patent Examiner to any and all further actions in this application.

Section 707.02 of the M.P.E.P. directs that the Examiner's supervisor personally checks on the pendency of an application that is up for third action or in a 5-year application, with a view to finally concluding its prosecution, and further directs that, in order to accomplish this result, the application is to be considered "special." The above-captioned application was filed on **June 6, 2017**, more than 5 years ago, and is awaiting a **sixth action**, and thus falls within the directive of §707.02.

Substantive examination of the pending claims is summarized as follows:

1. Claims were entered in a Preliminary Amendment filed 10/13/2017; with non-elected claims canceled 05/22/2019 in response to a restriction requirement.

2. 1st Non-Final Office Action was mailed 06/27/2019; Applicant responded 9/27/2019.

3. 2nd Non-Final Office Action was mailed 01/21/2020; Applicant responded 5/22/2020.

4. 1st Final Office Action was mailed 08/10/2020. Applicant appealed, filing an Appellant's Brief on 03/09/2021.

5. 3rd Non-Final Office Action was mailed 06/28/2021, withdrawing finality of prior Office Action, and citing new art. Applicant responded 11/29/2021, amending claims.

6. 2nd Final Office Action was mailed 03/25/2022, citing new art. Applicant responded with an AFCP 2.0 request with after-final amendment 05/25/2022 (amendment not entered), then a Notice of Appeal with a Pre-Appeal Brief request for review, filed 06/27/2022.

7. A Notice of Panel Decision from Pre-Appeal Review was mailed on 08/10/2022, indicating that the finality of the 2nd Final Office Action has been withdrawn and prosecution is re-opened.

8. As of the date of this Petition filing, no new Office Action has been mailed.

Applicant notes that NO amendments were made to the elected claims between their filing on 10/13/2017 and the mailing of the 3rd Non-final Office Action on 06/28/2021. Thus, the same set of elected claims was before the Examiner for four of the Office Actions listed above.

Applicant now awaits a sixth Office Action on the merits in an application that is now more than 5 years old. Accordingly, Applicant requests that the application be recognized as "special" in accordance with M.P.E.P. §707.02, and requests the personal attention of the Supervisory Patent Examiner to any and all further actions in this application, as set forth in §707.02.

Applicant submits herewith the $420 petition fee set forth in § 1.17(f). Nevertheless, if the Director finds any other fee to be due in connection with this, or any other filing, authorization is given to charge the fees to Deposit Account No. 50-4302, referencing attorney docket number **EXCTD-35239.304**.

Dated: October 4, 2022 /Mary Ann D. Brow/

Mary Ann D. Brow
Registration No. 42,363

CASIMIR JONES, S.C.
2275 Deming Way, Suite 310
Middleton, Wisconsin 53562
608.662.1277

Electronic Patent Application Fee Transmittal

Application Number:	15634607
Filing Date:	27-Jun-2017
Title of Invention:	FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD
First Named Inventor/Applicant Name:	Joost Louwagie
Filer:	Mary Ann Deese Brow
Attorney Docket Number:	EXCTD-35239.304

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
PETITION FEE- 37 CFR 1.17(F) (GROUP I)	1462	1	420	420
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**420**

Electronic Acknowledgement Receipt

EFS ID:	46751842
Application Number:	15634607
International Application Number:	
Confirmation Number:	1874
Title of Invention:	FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD
First Named Inventor/Applicant Name:	Joost Louwagie
Customer Number:	173254
Filer:	Mary Ann Deese Brow
Filer Authorized By:	
Attorney Docket Number:	EXCTD-35239.304
Receipt Date:	04-OCT-2022
Filing Date:	27-JUN-2017
Time Stamp:	15:16:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$420
RAM confirmation Number	E202204F18372972
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Petition for review by the Office of Petitions	2022-10-04_PetitionToDirector_EXCTD-003USCON2-35239_35239-304.pdf	114966 2da4ef6f807187bf3b3dc0c45e762cb7238f3237	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	38024 c6bd01b1fc6cd40a2d9b6e7cbca94f13a39fc7c6	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	152990		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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NOTICE OF ALLOWANCE AND FEE(S) DUE

173254 7590 12/02/2022

CASIMIR JONES, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

EXAMINER	
WHISENANT, ETHAN C	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/02/2022

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/634,607	06/27/2017	Joost Louwagie	EXCTD-35239.304	1874

TITLE OF INVENTION: FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	03/02/2023

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

173254 7590 12/02/2022

CASIMIR JONES, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/634,607	06/27/2017	Joost Louwagie	EXCTD-35239.304	1874

TITLE OF INVENTION: FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	03/02/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
WHISENANT, ETHAN C	1634	435-006110

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (08-18) Approved for use through 01/31/2020 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/634,607	06/27/2017	Joost Louwagie	EXCTD-35239.304	1874

173254 7590 12/02/2022

CASIMIR JONES, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

EXAMINER	
WHISENANT, ETHAN C	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/02/2022

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	**Application No.** 15/634,607	**Applicant(s)** Louwagie, Joost	
	Examiner Ethan C Whisenant	**Art Unit** 1634	**AIA (FITF) Status** No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the paper(s) filed 10 AUG 2022.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ETHAN C WHISENANT/
Primary Examiner, Art Unit 1634

Continuation of 3. The allowed claim(s) is/are: 82,84,87,89-94 and 96-100

NOTICE OF ALLOWABILITY

► **Claim(s) 82, 84, 87, 89-94 and 96-100** as amended in the paper(s) filed 10 AUG 2022 is/are pending in this application.

► The present application is being examined under the pre-AIA first to invent provisions. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

► Please note that this application has been transferred to a different examiner within Technology Center 1600, Art Unit 1634. See the closing paragraph of this action for details.

REASON(S) FOR ALLOWANCE

► **Claim(s) 82, 84, 87, 89-94 and 96-100** is/are deemed to be allowable in light of the paper(s) filed 10 AUG 2022 and the persuasive argument(s) therein. The Claims have now been renumbered as Claims 1-14 in the same order as presented by the applicant.

CONCLUSION

C. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ethan Whisenant whose telephone number is (571) 272-0754. The examiner can normally be reached Monday-Friday from 8:30 am -5:30 pm EST or any time via voice mail. If repeated attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731.

The Central Fax number for the USPTO is (571) 273-8300. Please note that the faxing of papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ETHAN C WHISENANT/
Primary Examiner, Art Unit 1634
ethan.whisenant@uspto.gov

EXAMINER SEARCH NOTES

21-22 NOV 2022 - ECW

Databases searched: All available in PE2E SEARCH
& CAplus, Medline and BIOSIS via STNext (note the search terms used below) ; and Google Scholar

Reviewed the parent(s), if any, and any search(es) performed therein : see the BIB data sheet

Reviewed, the search(es), if any, performed by prior examiners including any international examiners;
Reviewed the Search Report and Written Opinion in PCT/GB2010/000180

Search terms:

Inventor(s) e.g. Louwagie J?/au

Process$5

Feces or fecal

Sealable

Collection vessel or apparatus or device

Nuclease inhibitor?

Proteinase inhibitor?

► **See the Examiner's PE2E SEARCH notes/strategy in IFW**

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	**Art Unit**
	Ethan C Whisenant	1634

CPC								
Symbol							**Type**	**Version**
C12Q	/	1	/	6886			F	2013-01-01
G01N	/	33	/	57446			I	2013-01-01
C12Q	/	2600	/	106			A	2013-01-01
C12Q	/	2600	/	154			A	2013-01-01
C12Q	/	2600	/	158			A	2013-01-01
G01N	/	2800	/	50			A	2013-01-01
G01N	/	2800	/	52			A	2013-01-01
G01N	/	2333	/	805			A	2013-01-01

CPC Combination Sets								
Symbol							**Type**	**Set**	**Ranking**	**Version**
	/		/							

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	14	
/ETHAN C WHISENANT/ Primary Examiner, Art Unit 1634	22 November 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20221121

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	**Art Unit**
	Ethan C Whisenant	1634

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C12Q1/6886	/	1	/	6886
G01N33/574	/	33	/	574

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	14	
/ETHAN C WHISENANT/ Primary Examiner, Art Unit 1634	22 November 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20221121

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	**Art Unit**
	Ethan C Whisenant	1634

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		14		27		40		53		66		79	7	92
	2		15		28		41		54		67		80	8	93
	3		16		29		42		55		68		81	9	94
	4		17		30		43		56		69	1	82		95
	5		18		31		44		57		70		83	10	96
	6		19		32		45		58		71	2	84	11	97
	7		20		33		46		59		72		85	12	98
	8		21		34		47		60		73		86	13	99
	9		22		35		48		61		74	3	87	14	100
	10		23		36		49		62		75		88		
	11		24		37		50		63		76	4	89		
	12		25		38		51		64		77	5	90		
	13		26		39		52		65		78	6	91		

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	14	
/ETHAN C WHISENANT/ Primary Examiner, Art Unit 1634	22 November 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20221121

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	**Art Unit**
	Ethan C Whisenant	1634

CPC - Searched*		
Symbol	**Date**	**Examiner**
C12Q 16886	11/22/2022	ECW
G01N 33/574	11/22/2022	ECW

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	**Date**	**Examiner**
EAST (see transcript for databases and search terms)	06/23/2019	B. L. S.
Reviewed 15/010436 & 13/147570	06/23/2019	B. L. S.
EAST (see transcript for databases and search terms)	01/14, 15/2020	B. L. S.
STN (see transcript for databases and search terms)	01/14/2020	B. L. S.
EAST (updated)	08/04/2020	B. L. S.
EAST	06/16/2021	B. L. S.
EAST	03/22/2022	B. L. S.
PE2E Search	06/09/2022	B. L. S.
See the Examiner's Search Notes on the last pg of the NOA	11/22/2022	ECW

/ETHAN C WHISENANT/ Primary Examiner, Art Unit 1634	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	**Art Unit**
	Ethan C Whisenant	1634

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
C12Q	1/6886	11/22/2022	ECW
G01N	33/574	11/22/2022	ECW

/ETHAN C WHISENANT/ Primary Examiner, Art Unit 1634	

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	**Art Unit**
	Ethan C Whisenant	1634

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/18/2019	06/23/2019	01/15/2020	08/04/2020	06/16/2021	03/22/2022	06/09/2022	11/22/2022	
	1	-	-	-	-	-	-	-	-	
	2	-	-	-	-	-	-	-	-	
	3	-	-	-	-	-	-	-	-	
	4	-	-	-	-	-	-	-	-	
	5	-	-	-	-	-	-	-	-	
	6	-	-	-	-	-	-	-	-	
	7	-	-	-	-	-	-	-	-	
	8	-	-	-	-	-	-	-	-	
	9	-	-	-	-	-	-	-	-	
	10	-	-	-	-	-	-	-	-	
	11	-	-	-	-	-	-	-	-	
	12	-	-	-	-	-	-	-	-	
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	40	-	-	-	-	-	-	-	-	
	41	-	-	-	-	-	-	-	-	
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	**Art Unit**
	Ethan C Whisenant	1634

CLAIM		DATE								
Final	Original	03/18/2019	06/23/2019	01/15/2020	08/04/2020	06/16/2021	03/22/2022	06/09/2022	11/22/2022	
	43	-	-	-	-	-	-	-	-	
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	48	-	-	-	-	-	-	-	-	
	49	-	-	-	-	-	-	-	-	
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	80	-	-	-	-	-	-	-	-	
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1	82	÷	✓	✓	✓	✓	✓	✓	=	
	83	÷	✓	✓	✓	✓	-	-	-	
2	84	÷	✓	✓	✓	✓	✓	✓	=	
	85	÷	-	-	-	-	-	-	-	
	86	÷	-	-	-	-	-	-	-	
3	87	÷	✓	✓	✓	✓	✓	✓	=	
	88	÷	✓	✓	✓	✓	-	-	-	
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8	93	÷	✓	✓	✓	✓	✓	✓	=	
9	94	÷	✓	✓	✓	✓	✓	✓	=	

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	**Art Unit**
	Ethan C Whisenant	1634

CLAIM		DATE								
Final	Original	03/18/2019	06/23/2019	01/15/2020	08/04/2020	06/16/2021	03/22/2022	06/09/2022	11/22/2022	
	95	÷	✓	✓	✓	✓	-	✓	-	
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11	97	÷	✓	✓	✓	✓	✓	✓	=	
12	98	÷	✓	✓	✓	✓	✓	✓	=	
13	99	÷	✓	✓	✓	✓	✓	✓	=	
14	100	÷	✓	✓	✓	✓	✓	✓	=	

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L175	10223838	split OR divide	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2022/11/21 02:24 PM
L176	42026	174 AND 175	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2022/11/21 02:25 PM
L177	2933	174 SAME 175	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2022/11/21 02:25 PM
L178	14637	nuclease inhibitor	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU,	ADJ	ON	ON	2022/11/21 02:26 PM

			CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L179	0	177 SAME 178	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2022/11/21 02:26 PM
L180	8	177 AND 178	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2022/11/21 02:38 PM
L182	102661411	Process$	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN,	ADJ	ON	ON	2022/11/21 02:50 PM

			WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L183	363700	feces OR fecal sample$	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2022/11/21 02:50 PM
L184	272390	182 AND 183	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2022/11/21 02:50 PM
L185	38178	182 AND 183 AND 175	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2022/11/21 02:51 PM
L186	738	182 SAME 183 SAME 175	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB,	ADJ	ON	ON	2022/11/21 02:51 PM

			HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L187	0	182 SAME 183 SAME 175 AND 178	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2022/11/21 02:52 PM
L188	292	182 AND 183 AND 175 AND 178	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2022/11/21 02:52 PM
L189	516301	(proteinase OR protease) inhibitor	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT;	ADJ	ON	ON	2022/11/21 02:54 PM

			IBM_TDB)				
L190	195	188 AND 189	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2022/11/21 02:54 PM
L191	78984	protein marker	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2022/11/22 08:18 AM
L192	4812	183 AND 191	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2022/11/22 08:19 AM
L193	156	183 SAME 191	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV,	ADJ	ON	ON	2022/11/22 08:19 AM

			MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L194	36	183 WITH 191	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2022/11/22 08:20 AM
L195	599	Louwagie.in.	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2022/11/22 08:22 AM
L196	2	Louwagie.in. AND 193	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	ADJ	ON	ON	2022/11/22 08:22 AM
L197	52	Louwagie.in.	(US-PGPUB)	ADJ	ON	ON	2022/11/22

							08:24 AM
L198	10	Louwagie.in. AND 183	(US-PGPUB)	ADJ	ON	ON	2022/11/22 08:25 AM
L199	0	20170298448.AND 183	(US-PGPUB)	ADJ	ON	ON	2022/11/22 08:27 AM
L200	1	"20170298448." AND 183	(US-PGPUB)	ADJ	ON	ON	2022/11/22 08:27 AM
L201	1	"20170298448." AND 183 SAME 175	(US-PGPUB)	ADJ	ON	ON	2022/11/22 08:37 AM
L202	0	"20170298448." AND 183 SAME 175 AND L189 AND L178	(US-PGPUB)	ADJ	ON	ON	2022/11/22 08:39 AM
L203	0	"20170298448." AND 183 SAME 175 AND L189	(US-PGPUB)	ADJ	ON	ON	2022/11/22 08:39 AM
L204	0	"20170298448." AND 183 SAME 175 AND 178	(US-PGPUB)	ADJ	ON	ON	2022/11/22 08:40 AM
L205	1	"20170298448".pn. AND 183 SAME 175	(US-PGPUB)	ADJ	ON	ON	2022/11/22 08:51 AM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

To: DOCKETING@CASIMIRJONES.COM,Genomic_docketing@cardinal-ip.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 173254

Dec 02, 2022 03:24:28 AM

Dear PAIR Customer:

CASIMIR JONES, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 173254 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

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Application	Document	Mailroom Date	Attorney Docket No.
15634607	NOA	12/02/2022	EXCTD-35239.304

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If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/634,607	06/27/2017	Joost Louwagie	EXCTD-35239.304	1874

173254 7590 12/06/2022

CASIMIR JONES, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

EXAMINER	
WHISENANT, ETHAN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
12/06/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Genomic_docketing@cardinal-ip.com

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR/ PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
15/634,607	06/27/2017	Louwagie, Joost	EXCTD-35239.304

	EXAMINER	
CASIMIR JONES, S.C. 2275 DEMING WAY, SUITE 310 MIDDLETON, WI 53562	MARIANNE C SEIDEL	
	ART UNIT	PAPER
	1600	20221122

DATE MAILED: _____

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

This is in response to the Petition filed October 4, 2022 under 37 CFR §§ 1.182 and 37 CFR §§ 1.181, wherein applicants have requested that the application be recognized as "special" in accordance with M.P.E.P. §707.02, and to formally request the personal attention of the Supervisory Patent Examiner to any and all further actions in this application.

DECISION

This Petition is DISMISSED AS MOOT since the application has now been allowed.

Should there be any questions about this decision please contact Marianne C. Seidel by letter addressed to Director, TC 1600, at the address listed above, or by
telephone at 571-272-0584 or by facsimile sent to the general Office facsimile number, 571-273-8300.

/MC Seidel/
Marianne C. Seidel, Quality Assurance Specialist
Technology Center 1600

/MARIANNE C SEIDEL/
Quality Assurance Specialist, Art Unit 1600

To: DOCKETING@CASIMIRJONES.COM,Genomic_docketing@cardinal-ip.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 173254

Dec 07, 2022 03:26:34 AM

Dear PAIR Customer:

CASIMIR JONES, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 173254 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

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Application	Document	Mailroom Date	Attorney Docket No.
15634607	PETDEC	12/06/2022	EXCTD-35239.304

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UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

PRINTER RUSH
(PTO ASSISTANCE)

Application: 15634607	Examiner: Whisenant	GAU: 1634
From:	Location: IDC	Creation Date: 12/06/2022

Week Date: 11/28/2022

DOC CODE	DOC DATE	MISCELLANEOUS
[ ] 1449		[ ] Continuing Data
[ ] IDS		[ ] Foreign Priority
[X] CLM	05/25/2022	[ ] Document Legibility
[ ] IIFW/FWCLM		[ ] Fees
[ ] SRFW		[ ] Petition (TC)
[ ] DRW		[X] Other
[ ] OATH		
[ ] 312		
[ ] SPEC		

[RUSH] Message:

Please clarify which claim set should be entered.
Latest claim set CLM 05/25/2022 has been stampped as "DO NOT ENTER" per ANE.I 06/14/2022.

Thank you.

[XRUSH] Response:

Initials: _____

Examiner: PUBS contact - James Leija, (703) 756-1197
NOTE: This form will be included as part of the official USPTO record with the response document coded as XRUSH.
REV: AUG 16

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/634,607	06/27/2017	Joost Louwagie	EXCTD-35239.304	1874

173254 7590 12/12/2022

CASIMIR JONES, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

EXAMINER	
WHISENANT, ETHAN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
12/12/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DOCKETING@CASIMIRJONES.COM
Genomic_docketing@cardinal-ip.com

Corrected ***Notice of Allowability***	**Application No.** 15/634,607	**Applicant(s)** Louwagie, Joost	
	Examiner Ethan C Whisenant	**Art Unit** 1634	**AIA (FITF) Status** No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the e-mail of 07 DEC 2022.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ETHAN C WHISENANT/
Primary Examiner, Art Unit 1634

Continuation of 3. The allowed claim(s) is/are: 82,84,87,89-94 and 96-100

Corrected NOA

► In response to an e-mail inquiry regarding the status of the claims, the examiner is issuing this Corrected Notice of Allowability to clarify the record. The allowed Claims are : **Claims 82, 84, 87, 89-94 and 96-100** as presented in the paper(s) **filed 29 NOV 2021**. These Claims have now been renumbered as Claims 1-14 in the same order as presented by the applicant

► Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ethan Whisenant whose telephone number is (571) 272-0754. The examiner can normally be reached Monday-Friday from 8:30 am -5:30 pm EST or any time via voice mail. If repeated attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731.

The Central Fax number for the USPTO is (571) 273-8300. Please note that the faxing of papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ETHAN C WHISENANT/
Primary Examiner, Art Unit 1634
ethan.whisenant@uspto.gov

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	Art Unit
	Ethan C Whisenant	1634

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/18/2019	06/23/2019	01/15/2020	08/04/2020	06/16/2021	03/22/2022	06/09/2022	11/22/2022	12/08/2022
	1	-	-	-	-	-	-	-	-	-
	2	-	-	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-	-	-
	4	-	-	-	-	-	-	-	-	-
	5	-	-	-	-	-	-	-	-	-
	6	-	-	-	-	-	-	-	-	-
	7	-	-	-	-	-	-	-	-	-
	8	-	-	-	-	-	-	-	-	-
	9	-	-	-	-	-	-	-	-	-
	10	-	-	-	-	-	-	-	-	-
	11	-	-	-	-	-	-	-	-	-
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	14	-	-	-	-	-	-	-	-	-
	15	-	-	-	-	-	-	-	-	-
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	23	-	-	-	-	-	-	-	-	-
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	36	-	-	-	-	-	-	-	-	-
	37	-	-	-	-	-	-	-	-	-
	38	-	-	-	-	-	-	-	-	-
	39	-	-	-	-	-	-	-	-	-
	40	-	-	-	-	-	-	-	-	-
	41	-	-	-	-	-	-	-	-	-
	42	-	-	-	-	-	-	-	-	-

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	**Art Unit**
	Ethan C Whisenant	1634

CLAIM		DATE								
Final	Original	03/18/2019	06/23/2019	01/15/2020	08/04/2020	06/16/2021	03/22/2022	06/09/2022	11/22/2022	12/08/2022
	43	-	-	-	-	-	-	-	-	-
	44	-	-	-	-	-	-	-	-	-
	45	-	-	-	-	-	-	-	-	-
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	47	-	-	-	-	-	-	-	-	-
	48	-	-	-	-	-	-	-	-	-
	49	-	-	-	-	-	-	-	-	-
	50	-	-	-	-	-	-	-	-	-
	51	-	-	-	-	-	-	-	-	-
	52	-	-	-	-	-	-	-	-	-
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	60	-	-	-	-	-	-	-	-	-
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	66	-	-	-	-	-	-	-	-	-
	67	-	-	-	-	-	-	-	-	-
	68	-	-	-	-	-	-	-	-	-
	69	-	-	-	-	-	-	-	-	-
	70	-	-	-	-	-	-	-	-	-
	71	-	-	-	-	-	-	-	-	-
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	74	-	-	-	-	-	-	-	-	-
	75	-	-	-	-	-	-	-	-	-
	76	-	-	-	-	-	-	-	-	-
	77	-	-	-	-	-	-	-	-	-
	78	-	-	-	-	-	-	-	-	-
	79	-	-	-	-	-	-	-	-	-
	80	-	-	-	-	-	-	-	-	-
	81	-	-	-	-	-	-	-	-	-
1	82	÷	✓	✓	✓	✓	✓	✓	=	=
	83	÷	✓	✓	✓	✓	-	-	-	-
2	84	÷	✓	✓	✓	✓	✓	✓	=	=
	85	÷	-	-	-	-	-	-	-	-
	86	÷	-	-	-	-	-	-	-	-
3	87	÷	✓	✓	✓	✓	✓	✓	=	=
	88	÷	✓	✓	✓	✓	-	-	-	-
4	89	÷	✓	✓	✓	✓	✓	✓	=	=
5	90	÷	✓	✓	✓	✓	✓	✓	=	=
6	91	÷	✓	✓	✓	✓	✓	✓	=	=
7	92	÷	✓	✓	✓	✓	✓	✓	=	=
8	93	÷	✓	✓	✓	✓	✓	✓	=	=
9	94	÷	✓	✓	✓	✓	✓	✓	=	=

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	95	÷	✓	✓	✓	✓	-	✓	-	-
10	96	÷	✓	✓	✓	✓	✓	✓	=	=
11	97	÷	✓	✓	✓	✓	✓	✓	=	=
12	98	÷	✓	✓	✓	✓	✓	✓	=	=
13	99	÷	✓	✓	✓	✓	✓	✓	=	=
14	100	÷	✓	✓	✓	✓	✓	✓	=	=

To: DOCKETING@CASIMIRJONES.COM,Genomic_docketing@cardinal-ip.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 173254

Dec 12, 2022 03:22:03 AM

Dear PAIR Customer:

CASIMIR JONES, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562
UNITED STATES

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Patent Owner's Ex. 2003, Page 777
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	15/634,607	Filing Date	2017-06-27	Docket Number (if applicable)	EXCTD-35239.304	Art Unit	1634
First Named Inventor	JOOST LOUWAGIE			Examiner Name	WHISENANT		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☐ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 504302

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

Signature of Registered U.S. Patent Practitioner			
Signature	/Mary Ann D. Brow/	Date (YYYY-MM-DD)	2023-02-06
Name	Mary Ann D. Brow	Registration Number	42363

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C12Q 1/68

A1

(11) International Publication Number: **WO 00/50640**

(43) International Publication Date: 31 August 2000 (31.08.00)

(21) International Application Number: PCT/US00/01759

(22) International Filing Date: 24 January 2000 (24.01.00)

(30) Priority Data:
60/122,177 25 February 1999 (25.02.99) US

(71) Applicant: EXACT LABORATORIES, INC. [US/US]; 63 Great Road, Maynard, MA 01754 (US).

(72) Inventors: SHUBER, Anthony, P.; 11 Grant Street, Milford, MA 01757 (US). HUNTRESS, Frederick, A., Jr.; 396 Wilder Road, Bolton, MA 01740 (US). MOORE, James, K.; 13 Conant Drive, Stow, MA 01775 (US).

(74) Agent: MEYERS, Thomas, C.; Testa, Hurwitz & Thibeault, LLP, High Street Tower, 125 High Street, Boston, MA 02110 (US).

(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHODS FOR PRESERVING DNA INTEGRITY

(57) Abstract

Methods for extracting DNA from a biological sample that result in a higher yield of target DNA than conventional methods. More particularly, methods for extracting DNA include exposing the biological sample to inhibitors of DNA degradation.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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Methods for Preserving DNA Integrity

Cross-Reference to Related Application

The present application claims priority to and the benefit of U.S. provisional patent application serial number 60/122,177, filed February 25, 1999, the entire disclosure of which is incorporated herein by reference.

Technical Field

The invention provides methods for deoxyribonucleic acid ("DNA") extraction from a biological sample. More particularly, the invention relates to methods for high yield DNA extraction from a heterogeneous biological sample by inhibiting DNA degradation.

Background of the Invention

DNA is a relatively stable molecule that is routinely isolated from biological samples. Recently, many diseases involving instabilities (*e.g.*, mutations) in genomic DNA have been characterized. Also, many pathogens have been identified by the presence or absence of a particular DNA in a biological sample. Many diseases, such as cancer, are optimally detected early in their progression. In order for early detection to be effective, relatively low levels of DNA which are indicative of cancer must be detected against a high background of other DNA (*e.g.*, normal human DNA, bacterial DNA, etc.). This type of detection is technically difficult and typically results in low sensitivity of detection. Moreover, in certain complex specimens, including stool, what little species-specific DNA exists, is rapidly degraded, making efficient sequence-specific detection even more difficult. Thus, a need exists for methods to retain integrity of DNA in a sample, especially in samples in which the DNA to be detected is in low proportion relative to other DNA in the sample and is degraded quickly.

Summary of the Invention

The present invention provides methods for preserving the integrity of DNA in a sample. In a preferred embodiment, methods of the invention prevent enzyme-mediated DNA degradation. Preservation of DNA integrity facilitates isolation and detection of DNA.

Methods of the invention are especially useful for extracting or detecting DNA in a biological specimen, especially one that contains low levels of relevant DNA. A good example of a specimen that contains lower-levels of relevant DNA is stool. Typical human stool contains only small amounts of intact human DNA. Most of the human DNA in stool from a healthy individual is presumably from exfoliated epithelial cells, and has undergone apoptotic degradation. As the forming stool passes through the colon, colonic epithelial cells are sloughed onto the stool as part of the cellular turnover that occurs in the colon. Stool also contains sloughed cells from other luminal sources (*e.g.*, lung, stomach, esophagus, *etc.*) Sloughed cells typically have undergone or are undergoing apoptosis, leaving cellular DNA in small fragments. Enzymes, such as deoxyribonuclease ("DNase") and Micrococcal nuclease contribute to the degradation of any intact human DNA that remains. Prior art methods, while using DNase inhibitors, have failed to achieve significant yields of intact, species-specific DNA from stool. Therefore, such methods failed to consider optimization of inhibition of DNA degradation. Methods of the invention are based on the realization that optimal inhibition of DNA degrading enzyme(s) effectively preserves DNA, especially large, diagnostically-relevant DNA fragments that are present in a sample.

In one aspect, the invention comprises inhibiting nucleic acid degradation in a sample and optionally extracting a target DNA with, for example, a phenol-chloroform extraction. Preferably, the inhibition of nucleic acid degradation is sufficient to produce a critical number of

molecules of analyzable DNA. In one embodiment, methods of the invention comprise inhibiting an enzyme capable of DNA degradation in a stool sample. In a preferred embodiment, methods of the invention comprise exposing a stool sample to an ion chelator, such as a divalent ion chelator. Ion chelators, in certain embodiments inhibit DNase. Examples of preferred inhibitors include ethylenediaminetetraacetic acid ("EDTA"). Additional preferred methods of the invention comprise exposing a stool sample to a Micrococcal nuclease inhibitor, such as EGTA, also a divalent ion chelator. Inhibitors of DNA degradation may be used either alone or in combination to achieve optimal levels of DNA preservation.

Methods of the invention are practiced using any inhibitor of DNA degradation. The amount of inhibitor varies depending on the inhibitor that is used. However, an inhibitor must be used in an amount that preserves significant levels of DNA in the sample for subsequent analysis. Methods for determining sufficient levels of DNA are presented below. Such methods allow the skilled artisan to practice the invention with specificity regardless of the inhibitor used. According to preferred methods, an amount of inhibitor is used that preserves sufficient DNA in the sample for detection of a target DNA within a desired level of statistical confidence. Using methods described herein, the skilled artisan can determine an appropriate amount of any inhibitor for use in methods of the invention. The use of various specific inhibitors is exemplified below.

In another preferred embodiment, methods of the invention comprise obtaining a representative (circumfrential or cross-sectional) stool sample, exposing the sample or a portion thereof to a DNase inhibitor, and isolating DNA from the sample. One preferred DNase inhibitor is EDTA. Preferred amounts of EDTA are from about 0.042 g per gram of stool to about 0.782 g per gram of stool and especially from about 0.250 g per gram of stool to about

0.521 g per gram of stool. DNA may be extracted, for example, by a phenol-chloroform extraction. After extraction, the DNA may be analyzed by methods known in the art. For example, U.S. Patent No. 5,830,665 and U.S. Patent No. 5,670,325, which are incorporated by reference herein, disclose methods for analyzing DNA which has been extracted from a stool sample.

Methods of the invention are useful in any sample in which inhibition of DNA degradation is desired. For example, methods of the invention are especially effective in samples comprising exfoliated cells, especially exfoliated epithelial cells. The DNA contained in such samples typically degrades rapidly, making analysis of a particular DNA, especially one that exists in low proportion within the sample, difficult. For example, such samples include stool, sputum, urine, pus, and collostrum. Methods of the invention include inhibiting DNA degradation in such samples, thus preserving a sufficient amount of DNA for specific, sensitive detection. Any of the features described above, such as DNA degradation inhibitors or amounts of inhibitors that are used, can be useful in samples containing exfoliated cells.

Brief Description of the Drawings

FIG. 1 shows a flow chart describing one aspect of the invention.

FIG. 2 shows a separation gel of DNA isolated from several different homogenized stool supernatants that contained various concentrations of EDTA.

FIG. 3 shows a separation gel of DNA isolated from homogenized stool supernatant that contained various concentrations of EDTA followed by capture and amplification.

FIG. 4 shows separation gel of DNA isolated from homogenized stool supernatant that contained various concentrations EDTA followed by capture, addition of more DNA, and amplification.

FIG. 5 shows a set of curves produced by regression analysis of the data obtained using the model as described for, for example, Tables 1 and 2.

Detailed Description of the Invention

I. Introduction

The present invention provides methods for increased yield of DNA in a biological sample by preserving the integrity of DNA in the sample. Such methods are especially useful when the DNA of interest ("the target DNA") is present in the sample at a low frequency, or is rapidly degraded. More particularly, methods of the invention include, for example, inhibiting enzymes that degrade DNA.

Prior to the present invention, those skilled in the art have not been concerned with preventing DNA degradation prior to extraction from a sample. Typically, either the DNA of interest is present in samples in relatively large quantities (*e.g.*, tumor cells, blood), or methods are directed toward increasing sensitivity to low-frequency DNA, and not to preserving its integrity. However, especially in the case of low-frequency DNA in a heterogeneous sample (*e.g.*, a sample having cells and/or cellular debris from multiple cell types and/or organisms), methods for increasing sensitivity to DNA have not been entirely successful. Methods of the invention provide a new approach by preserving the integrity of DNA. Methods of the invention increase the likelihood of detecting a specific target DNA, because such methods make more intact target DNA available in the sample.

Referring to Figure 1, one generalized method of the invention involves obtaining a sample (step 2) and exposing it to a DNA degradation inhibitor (step 4). Once the sample has been exposed to the DNA degradation inhibitor, target DNA is extracted (step 6). The presence or absence of this extracted target DNA is then detected (step 8).

In heterogeneous samples, such as stool, endogenous human DNases and/or bacterial nucleases degrade DNA. Examples of nucleases include DNases, such as deoxyribonuclease I ("DNase I") and Micrococcal nuclease. DNase and Micrococcal nuclease both require a divalent cation to function optimally. For DNase, suitable ions include Mn^{+2} and Mg^{+2}. For Micrococcal nuclease, Ca^{+2} is a suitable ion. Ion chelators, and particularly divalent ion chelators, are capable of inhibiting nucleases. Ion chelators remove ions from association with the nuclease, thus inhibiting the nuclease's function. For example, EDTA or EGTA used in optimal amounts are useful ion chelators for use in the present invention.

Other compounds that inactivate, interfere with, or slow enzyme-mediated degradation of DNA are useful. For example, ligands and/or antibodies which compete for or interfere with the active site of DNA degrading enzymes, which inactivate those enzymes, and/or which block messenger systems that control DNA degrading enzymes are useful in the practice of the invention. Phenol-chloroform extraction components, at higher concentrations than those typically used during extraction, also are capable of inhibiting nucleases by separation and denaturation. For example, phenol denatures DNA degradation enzymes, and is used in methods of the invention to preserve DNA integrity. Also, proteinases which degrade and/or denature DNA degrading enzymes are useful.

Methods of the invention comprise the use of optimal amounts of DNA degradation inhibitors in order to preserve high-integrity DNA sufficient for diagnostic screening. In

heterogeneous samples, such as stool, target DNA (*e.g.*, mutated DNA or reductions in enumerated wild type DNA that are indicative of a mutation) is present in low amounts. An optimal amount of a DNA degradation inhibitor is an amount that results in a measurable improvement in the quantity of DNA available in the sample. Thus, the skilled artisan can empirically determine optimal amounts of DNA degradation inhibitors for use in methods of the invention by using inhibitor amounts necessary to preserve a diagnostically-relevant fraction of high-integrity target DNA. A method for determining diagnostically-relevant DNA amounts is presented below.

Amplification of DNA, and other stochastic processes, performed on heterogeneous samples may actually contribute to the inability to measure low-frequency DNA. For example, a typical cancer-associated (mutant) DNA in the early stages of oncogenesis represents about 1% of the DNA in a heterogeneous sample (*e.g.*, stool). If DNA in the sample is amplified at 30% PCR efficiency, any particular DNA has only a 30% chance of being amplified in any round of PCR. Thus, if a mutant DNA initially present as 1% of a sample is not amplified in the first round, the mutant DNA will represent only about 0.7% of the DNA in the sample after round 1. If no mutant is amplified in the first two rounds (0.7 x 0.7, or a 49% probability), the mutant DNA will represent only about 0.6% of the DNA in the sample going into round three of the PCR . If the post-amplification assay used to detect the mutant has a sensitivity of no more than 0.5% for the mutant, it may not be possible to reliably detect the presence of the mutant DNA. Thus, the detection method itself may actually contribute to difficulties in detecting low-frequency DNA, especially if sufficient amounts of intact DNA are not present in a sample. Thus, one means for determining an appropriate amount of inhibitor to use in methods of the invention is to determine the minimum amount of intact DNA that must be present in a sample to

avoid the stochastic effects described above, and then to use sufficient inhibitor to produce at least the minimum number of DNA molecules in the sample. Methods for calculating the minimum number of DNA molecules necessary to overcome the effects of stochastic processes, such as PCR, are presented below.

A model useful to generate sufficient DNA molecules for accurate measurement operates by iterating stochastic processes over a number of rounds of PCR. In the context of molecular disease diagnostics, the model dictates the number of molecules that must be presented to the PCR in order to reliably ensure amplification of desired target DNA. The model incorporates a preset PCR efficiency (established to meet separate specificity requirements), and a preset ratio of mutant DNA to total DNA in the sample to be analyzed (which is a property of the disease to be detected and the nature of the sample). Based upon those input values, the model predicts the number of molecules that must be presented to the PCR in order to ensure, within a predefined level of statistical confidence, that a low-frequency (target) molecule will be amplified and detected. Once the number of molecules is determined, the skilled artisan can determine the sample size to be used (*e.g.*, the weight, volume, etc.), depending on the characteristics of the sample (*e.g.*, its source, molecular makeup, etc.). The model dictates the number of molecules that must be presented to the PCR in order to reliably ensure amplification and detection.

The exemplary model simulates selection of DNA for amplification through several rounds of PCR. For purposes of the model, a sample is chosen that contains a ratio of mutant-to-total DNA of 1:100, which is assumed to lie at the clinical threshold for disease. For example, in colorectal cancer 1% of the human DNA in a specimen (*e.g.*, stool) is mutated (*i.e.*, has a deletion, substitution, rearrangement, inversion, or other sequence that is different than a corresponding wild-type sequence). Over a large number of PCR rounds, both the mutant and

wild-type molecules will be selected (*i.e.*, amplified) according to their ratio in the specimen (here, nominally 1 in 100), assuming there are any abnormal molecules in the sample. However, in any one round, the number of each species that is amplified is determined according to a Poisson distribution. Over many rounds, the process is subject to stochastic errors that reduce the ability to detect low-frequency mutant DNA. However, the earlier rounds of PCR (principally, the first two rounds) are proportionately more important when a low-frequency species is to be detected, and any rounds after round 10 are virtually unimportant. Thus, the model determines the combined probability of (1) sufficient mutant molecules being presented to the PCR, and (2) the effects of stochastic amplification on those molecules so that at the output of the PCR there will be a sufficient number of molecules and a sufficient ratio of mutant to total molecules to assure reliable detection.

The model used to run the number of molecules necessary at the first round of PCR was generated as a "Monte Carlo" simulation of a thousand experiments, each experiment consisting of 10 cycles of PCR operating on each molecule in the sample. The simulation analyzed (1) taking a sample from the specimen; and (2) each round of PCR iteratively to determine whether, for each round, a mutant DNA if present in the sample was amplified. Upon completion of the iterative sampling, the model determined the percent of rounds in which a mutant strand was amplified, the percent of mutants exceeding a predetermined threshold for detection (in this example 0.5% based upon the mutant:total ratio of 1%), the coefficient of variation (CV) for stochastic sampling in each round alone, and the coefficient of variance for stochastic sampling and PCR in combination.

Stochastic noise is created in PCR if the PCR efficiency is anything other than 0% or 100% (these two cases represent either there is no amplification at all or perfect fidelity of

specific amplification). The noise, or background, signal level in a PCR that is between 0% and 100% varies with the efficiency of the PCR. The standard deviation of stochastic noise, S, in a PCR is given by the equation, $S = \sqrt{npq}$, where n is the number of molecules in the sample, p is the efficiency of PCR, and q is 1-p. Table 1 presents results obtained for iterative samplings with PCR efficiency set at 100% and 20%, and a mutant:total ratio of 0.5%.

Table 1 represents output from the model in 12 experiments conducted under various conditions. The first row shows the nominal number of molecules entering the first round of PCR (i.e., the total number of molecules available for amplification). The second row shows the percent of molecules (DNA) in the biological specimen that is expected to be mutant. For colorectal cancer indicia in DNA recovered from stool, the threshold for clinical relevance in the detection of early stage cancer is 1%. That is, 1% of the DNA in a sample derived from a heterogeneous specimen (e.g., stool) contains a mutation associated with colorectal cancer. The 6th row is the threshold of detection of the assay used to measure PCR product after completion of PCR. That number is significant, as will be seen below, because sufficient mutant DNA must be produced by PCR to be detectable over aberrant signal from wild-type and random background noise. Under the heading "Outputs", the first line provides the likelihood that at least one mutant molecule is presented to the first round of PCR. The second line under the Output heading provides the likelihood of detection of mutants (after PCR) above the predetermined threshold for detection. For example, in experiment 4, the results indicate that in 87.9% of experiments run under the conditions specified for experiment 4, the number of mutants will exceed the threshold number for detection. Finally, the last two rows provide the coefficient of variation for sampling, and for the combination of sampling and PCR.

TABLE 1

	100% Efficiency PCR						20% Efficiency PCR					
Inputs	Exp 1	Exp 2	Exp 3	Exp 4	Exp 5	Exp 6	Exp 7	Exp 8	Exp 9	Exp 10	Exp 11	Exp 12
Nominal number of Molecules going into PCR	50	100	200	500	1,000	10,000	50	100	200	500	1,000	10,000
Percent of molecules that are mutant	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
Number of PCR Rounds	10	10	10	10	10	10	10	10	10	10	10	10
Efficiency of PCR per round	100%	100%	100%	100%	100%	100%	20%	20%	20%	20%	20%	20%
Number of experiments modeled	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000
M:Wr ratio which can be reliably detected by assay	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%
Outputs												
% of Experiments each with the number of mutan cells > 0	39.30%	64.40%	87.30%	99.40%	100%	100%	39.10%	63.50%	86.10%	99.60%	100%	100%
% of Experiments each with number of mutant cells exceeding threshold	39.30%	64.40%	87.30%	87.90%	97.10%	100%	36.20%	52.40%	63.30%	63.30%	91.60%	100%
Stochastic Sampling CV	143.20%	100%	70%	44.10%	32.10%	9.90%	144.60%	101.80%	72.00%	44.20%	32.00%	10%
Stochastic Sampling and Stochastic PCR CV	143.20%	100%	70%	44.10%	32.10%	9.90%	179.70%	123.10%	92.10%	56.40%	40.30%	12.70%

As shown in Table 1, even at 100% PCR efficiency, mutant DNA is detected in only 97.1% of the samples when 1000 input molecules are used (*i.e.*, 1000 DNA molecules are available for priming at the initial PCR cycle), even though 100% of the DNA is amplified in any given round of PCR. When 10,000 molecules are presented, it is virtually certain that the mutant DNA will be amplified and detected, as shown in the results for experiment 6 in Table 1. Stochastic errors due to variation in the number of input molecules become less significant at about 500 input molecules and higher (*i.e.*, the CV for stochastic variations is about the same regardless of whether PCR efficiency is 20% or 100%). At lower PCR efficiency (20% in Table 1), the model shows that introducing 50, 100, 200, 500, or even 1000 molecules into the PCR does not assure either amplification or detection. As shown in experiment 12, introducing 10,000 molecules results in amplification of the mutant target, and a high likelihood of its subsequent detection. Thus, even with 100% efficient PCR, significant false negative events occur when input molecules fall below 500.

The foregoing analysis shows that there is a unique range for the number of molecules that must be presented to a PCR in order to achieve amplification of a low-frequency DNA, and to allow its detection. That range is a function of the PCR efficiency, and the percentage of low-frequency (mutant) DNA in the sample, and the detection threshold. The aforementioned model was developed and run in Visual Basic for Applications code (Microsoft, Office 97) to simulate a PCR as described above. The statistical confidence level within which results were measured was held constant at approximately 99%. Only the PCR efficiency and percent mutant DNA were varied. As discussed above, the model iteratively samples DNA in a "Monte Carlo" simulation over a thousand experiments, each experiment consisting of 10 rounds of PCR. The results are shown below in Table 2.

TABLE 2

	Number of molecules needed			
PCR Efficiency	1% Mutant	2% Mutant	5% Mutant	10% Mutant
10%	3,000			
20%	2,500			
50%	2,200			
100%	1,600			
10%		1,500		
20%		1,200		
50%		1,000		
100%		800		
10%			500	
20%			450	
50%			400	
100%			300	
10%				225
20%				200
50%				150
100%				125

Regression of the data obtained using the model as described above produced the set of curves set forth below in Figure 5.

Using Figure 5, the optimal number of molecules to be presented to the PCR is determined by selecting a PCR efficiency (or determining the efficiency by empirical means), and selecting a percentage of the sample suspected to be mutant DNA associated with disease. This, in turn, dictates a threshold of detection. Not all detection strategies have similar underlying detection thresholds, so an appropriate technology must be selected. The percentage mutant DNA may be determined by clinical considerations as outlined above for colorectal cancer.

One may determine the PCR efficiency and percent expected mutant in order to maximize the probability of obtaining amplified, detectable mutant DNA. For example, one may select N, the number of input molecules from the "1%" curve in Figure 5, when 5% of the

sample is expected to be mutant DNA in order to increase the confidence of the assay result.

This model, and particularly Figure 5, are useful when determining optimal concentrations of a DNA degradation inhibitor. If PCR is used to analyze DNA after the DNA sample is exposed to a DNA inhibitor, Figure 5, will indicate how many molecules of target DNA need to be preserved in order to have sufficient analyzable DNA. Thus, the optimal amount of any DNA degradation inhibitor may be determined as that amount, or range of amounts, of inhibitor that produce a sufficient number of analyzable DNA according to Figure 5. Of course, this modeling system may be applied to DNA detection techniques other than PCR. Specifically, those skilled in the art can apply this modeling system to any process and/or detection technique in which stochastic noise is problematic. Thus, the optimal amount of any DNA degradation inhibitor can be determined based upon the number of DNA molecules that are sufficient to produce analyzable DNA.

Once the number of molecules for input to the PCR is determined, a sample comprising that number of molecules (or greater) is prepared for PCR according to standard methods. The number of molecules in a sample may be determined directly by, for example, enumerative methods such as those taught in U.S. Patent No. 5,670,325, incorporated by reference herein. Alternatively, the number of molecules in a complex sample may be determined by molar concentration, molecular weight, or by other means known in the art. The amount of DNA in a sample may be determined by mass spectrometry, optical density, or other means known in the art. The number of molecules in a sample derived from a biological specimen may be determined by numerous means in the art, including those disclosed in U.S. Patent Nos. 5,741,650 and 5,670,325, both of which are incorporated by reference herein.

Methods as described above are used to determine minimum or optimal amounts of DNA

degradation inhibitors for use in any DNA isolation, detection, or amplification process in which stochastic processes occur. Using the above-described model for determining the minimum number of molecules that must be measured to reliably detect a low-frequency species, one can empirically determine how much of any given inhibitor should be used.

II. Example - Detection of DNA in Stool with EDTA as a DNA Degradation Inhibitor

A. Introduction

Methods of the invention are useful for analyzing DNA from stool to detect colorectal cancer. If colorectal cancer is diagnosed early, it may be treated effectively by surgical removal of the cancerous tissue. Colorectal cancers originate in the colorectal epithelium, and typically are not extensively vascularized (and therefore not invasive) during the early stages of development. The transition to a highly vascularized, invasive and ultimately metastatic cancer which spreads throughout the body commonly takes ten years or longer. If the cancer is detected prior to invasion, surgical removal of the cancerous tissue is an effective cure. However, colorectal cancer is often detected only upon manifestation of clinical symptoms, such as pain and black tarry stool. Generally, such symptoms are present only when the disease is well established, often after metastasis has occurred, and the prognosis for the patient is poor, even after surgical resection of the cancerous tissue. Early detection of colorectal cancer, therefore, is important because early detection may significantly reduce patient morbidity.

B. Experiments

The following experiments demonstrate that EDTA, an inhibitor of DNase, increases the yield of high-integrity DNA from a stool sample with a concomitant increase in the amount of amplifiable DNA. In these experiments, three aliquots of stool (5 g each) were homogenized in buffer (0.5 M Tris, 10 mM NaCl, EDTA). The buffer to stool ratio was 7:1; thus, 35 ml of buffer

was used for each 5 g of stool. The buffer contained either 0 mM EDTA, 16 mM EDTA, or 96 mM EDTA. Each of the three aliquots was then diluted with additional buffer (not containing EDTA) to a final buffer to stool ratio of 20:1. Each aliquot was then centrifuged, and the supernatant, which carried the active DNA degrading fraction, was removed to a clean tube. Then, a DNA mixture of 2 µg *E. coli* DNA and 100 ng human genomic DNA was added to each tube. Each tube was incubated for 75 minutes at 37°C. Then, 42 µl of Proteinase K and 250 µl of 10% SDS (sodium dodecyl sulfate) were added to each tube followed by an overnight incubation at 37°C. After the overnight incubation, the DNA in each sample was prepared by standard techniques. *See, e.g.*, SHORT PROTOCOLS IN MOLECULAR BIOLOGY §§ 2.1-2.4 (Ausubel *et al.*, 3d ed., 1995). Generally, a phenol extraction, a phenol/chloroform extraction, and a phenol extraction were performed prior to isolating the DNA. Then, the isolated DNA was placed into a standard Tris buffer.

Three experiments were conducted on the isolated DNA. The first experiment demonstrated that the DNA degrading activity present in homogenized stool supernatant is inhibited by optimal amounts of EDTA, increasing the amount of high-integrity DNA. In this experiment, DNA was isolated from homogenized stool supernatant which was taken from aliquots of stool homogenized in buffer having 0 mM, 16 mM, or 96 mM EDTA. Total nucleic acid was run on a separation gel. Results are shown in Figure 2, where arrows identify the location of the smear (or lack thereof) containing the DNA of interest.

Lanes 4, 5, and 6 represent samples of DNA added to homogenized stool supernatant, obtained from stool homogenized in buffers containing 0 mM, 16 mM, or 96 mM EDTA, respectively, that was subsequently isolated. Note that each lane shows a high molecular weight band which represents endogenous DNA from the stool sample and a smear from the exogenous

DNA. The intensity of the band and smear in the photograph (which correlates with the amount of DNA in the band, a greater intensity corresponding to a greater amount of DNA) increased as the concentration of EDTA in the original buffer increased. Lanes 7-9 and 10-12 are replicates of lanes 4-6. The increasing intensity of the bands and the smears as EDTA concentration increased indicated that DNA integrity was preserved as the concentration of EDTA in the buffer increased. Thus, the DNA degrading activity of the homogenized stool supernatant was inhibited by the EDTA in a roughly dose-dependent manner.

Lanes 1, 2 and 3 and lanes 13, 14 and 15 were control samples containing 2 μg *E. coli* DNA and 100 ng exogenous human DNA in buffer made with 16 mM EDTA. As expected, each lane showed a smear representative of the added DNA.

In a second experiment, the isolated DNA as described above was captured and amplified. The results of this experiment demonstrated that EDTA not only inhibits the DNA degrading activity present in stool supernatant but also increases the amount of amplifiable DNA. In this experiment, after preparing the DNA as described above, a standard hybrid capture was performed using Kras-specific capture probes to capture Kras DNA. The Kras DNA then was PCR amplified. Figure 3 shows the effect of EDTA on the preservation of Kras DNA. The location of the band (or lack thereof) representing Kras DNA is identified with an arrow.

Lanes 4, 5, and 6 represent Kras DNA that was amplified from template DNA that was added to homogenized stool supernatant obtained from stool homogenized in buffer containing 0 mM, 16 mM, or 96 mM EDTA, respectively. Note that the Kras band in lane 4 was nearly absent, while the Kras band grew in intensity (representing an increase in the amount of Kras DNA actually present) in lanes 5 and 6 as the concentration of EDTA in the buffer increased. Lanes 7-9 are replicates of lanes 4-6 and show a similar increase in band intensity (an increase in

the amount of DNA present) as the concentration of EDTA in the original buffer increased. Thus, more Kras DNA was amplified, resulting in a more robust signal at higher concentrations of EDTA.

Additionally, in the population, levels of DNA which can be amplified from stool vary across individuals. These individuals have been characterized in groups from A to F, with A being the highest level of DNA and F being an undetectable level of DNA. The high levels of DNA in group A are due to low DNA degradation activity in their stool ("high-integrity stool"). Adding EDTA to the buffer in which a stool aliquot from a Group A individual is homogenized would not be expected to produce a large effect because Group A stool has little DNA degrading activity. In fact, when Kras DNA was amplified from template DNA that was added to homogenized stool supernatant obtained from Group A stool homogenized in buffer containing 0 mM, 16 mM, or 96 mM EDTA, little difference in the amount of amplified Kras DNA was observed (lanes 10, 11, and 12, respectively). Only a slight increase in Kras band intensity can be seen between 0 mM EDTA and 16 mM or 96 mM EDTA, representing only a slight increase in the amount of Kras DNA at inhibitory concentrations of EDTA.

Lanes 1-3 as well as lanes 13-15 represent samples of amplified Kras DNA that was not exposed to homogenized stool supernatant. As expected, those control lanes show a band of equal intensity across lanes representing Kras DNA. Lanes 16 and 17 are negative controls and, as expected, show no band representing Kras, indicating that any observed Kras DNA is due to captured DNA and not to contamination. Lane 18 is a negative control, and, as expected, has no band representing the Kras gene, indicating that the PCR products are from the sample and not from contamination. Lanes 19-21 are positive controls where 50 pg, 100 pg, or 200 pg of human

DNA is amplified in a background of *E. coli* DNA, indicating that human DNA can be amplified in an *E. coli* background in this model system. Finally, lane 22 is a molecular weight marker.

In a third experiment, the same protocol was used as in the second experiment except human genomic DNA was added into each sample after capture. Kras DNA was again amplified by PCR. Thus, an excess of template DNA was available for PCR. This experiment demonstrated that the varying levels of PCR amplification in the second experiment were not due to EDTA interfering with or enhancing normal PCR but were due to varying levels of template DNA available to be amplified resulting from various levels of DNA degradation inhibition by EDTA. Figure 4 shows the results of this experiment. The location of the band (or lack thereof) representing Kras is identified with an arrow. Lanes 1-6 and 8-13 correspond with lanes 1-12 in the second experiment (*i.e.*, lanes 1-3 were controls, lanes 4-6 and 8-10 were excess Kras DNA amplified in samples exposed to homogenized stool supernatant from stool homogenized in 0 mM, 16 mM, or 96 mM EDTA, and lanes 11-13 were excess Kras DNA amplified in samples exposed to homogenized stool supernatant from high-integrity stool homogenized in 0 mM, 16 mM, or 96 mM EDTA). As expected, lanes 1-6 and 8-13 show a PCR product of roughly equal intensity because an excess of template DNA is available. The EDTA does not interfere with or enhance normal PCR. This result indicates that the varying levels of PCR amplification in the 0 mM, 16 mM, or 96 mM EDTA samples in the second experiment was due to varying levels of template DNA and not to inhibitor. Lane 14 shows a sample of human genomic DNA. Lanes 15-18 are the same controls as lanes 17 and 19-21 in the second experiment.

From the experimental data described above, the amount of EDTA required to inhibit DNase was calculated. The concentration of EDTA in the various buffers used in the three

experiments was normalized as grams of EDTA per gram of stool. Generally, the concentration of EDTA was multiplied by the molecular weight of EDTA and by the volume of buffer in which the stool was homogenized. The product was divided by the amount of stool that was homogenized. For example, the following equations were used to normalize EDTA concentration.

For 16 mM EDTA:

(0.016 EDTA M/L x 372.2 g/M x 0.035L) ÷ 5g = 0.042 g EDTA per gram of stool

For 96 mM EDTA:

(0.096 EDTA M/L x 372.2 g/M x 0.035L) ÷ 5g = 0.250 g EDTA per gram of stool

Thus, for any amount of stool to be homogenized, at least about 0.042 g EDTA per gram of stool should be used in the homogenization buffer in order to maximize yield of DNA. The range of EDTA which may be used is from about 0.042 g EDTA per gram of stool to about 0.782 g EDTA per gram of stool. More preferably, about 0.250 g EDTA per gram of stool to about 0.521 g EDTA per gram of stool is used. Most preferably, about 0.391 g EDTA per gram of stool is used.

These calculations indicate that at commonly used buffer volumes and stool amounts, the amount of EDTA present in the homogenized sample is a more important factor than the final concentration of EDTA in the homogenized sample. However, as one skilled in the art realizes, at some point, although the amount of EDTA will remain the same in a given volume, the volume may become so large that the effect of EDTA on DNA integrity is diluted. When examining a stool sample within commonly used parameters, this dilution effect is not seen. However, in alternative embodiments, the concentration of EDTA is a relevant factor. In these embodiments, from about 16 mM EDTA to about 300 mM EDTA is useful. More preferably,

from about 100 mM EDTA to about 200 mM EDTA is useful. Most preferably, about 150 mM EDTA is useful.

What is claimed is:

1. A method for preserving the integrity of DNA in a stool sample, the method comprising:

exposing the stool sample to an amount of an inhibitor of DNA degradation sufficient to produce a critical number of molecules of analyzable DNA.

2. The method of claim 1 wherein the inhibitor comprises an ion chelator.

3. The method of claim 2 wherein the ion chelator comprises a divalent ion chelator.

4. The method of claim 3 wherein the divalent ion chelator is selected from the group consisting of EDTA and EGTA.

5. The method of claim 1 wherein the step of exposing the stool sample to an amount of an inhibitor of DNA degradation comprises providing EDTA in a range from 0.042 g EDTA per gram of stool to 0.782 g EDTA per gram of stool.

6. The method of claim 1 wherein the inhibitor of DNA degradation comprises an enzyme inhibitor.

7. The method of claim 1 further comprising a step of extracting a target DNA.

8. The method of claim 7 wherein the step of extracting comprises a phenol-chloroform extraction.

9. A method for preserving the integrity of DNA in a sample containing exfoliated cells, the method comprising:

exposing the sample to a minimum amount of an inhibitor of DNA degradation sufficient to produce a critical number of molecules of analyzable DNA.

10. The method of claim 9 wherein the sample is obtained from stool.

11. The method of claim 9 wherein the inhibitor comprises an ion chelator.

12. The method of claim 11 wherein the ion chelator comprises a divalent ion chelator.

13. The method of claim 12 wherein the divalent ion chelator is selected from the group consisting of EDTA and EGTA.

14. The method of claim 10 wherein the step of exposing the sample to a minimum amount of an inhibitor of DNA degradation comprises providing EDTA in a range from 0.042 g EDTA per gram of stool to 0.782 g EDTA per gram of stool.

15. The method of claim 9 further comprising extracting a target DNA.

16. The method of claim 9 wherein the step of extracting comprises a phenol-chloroform extraction.

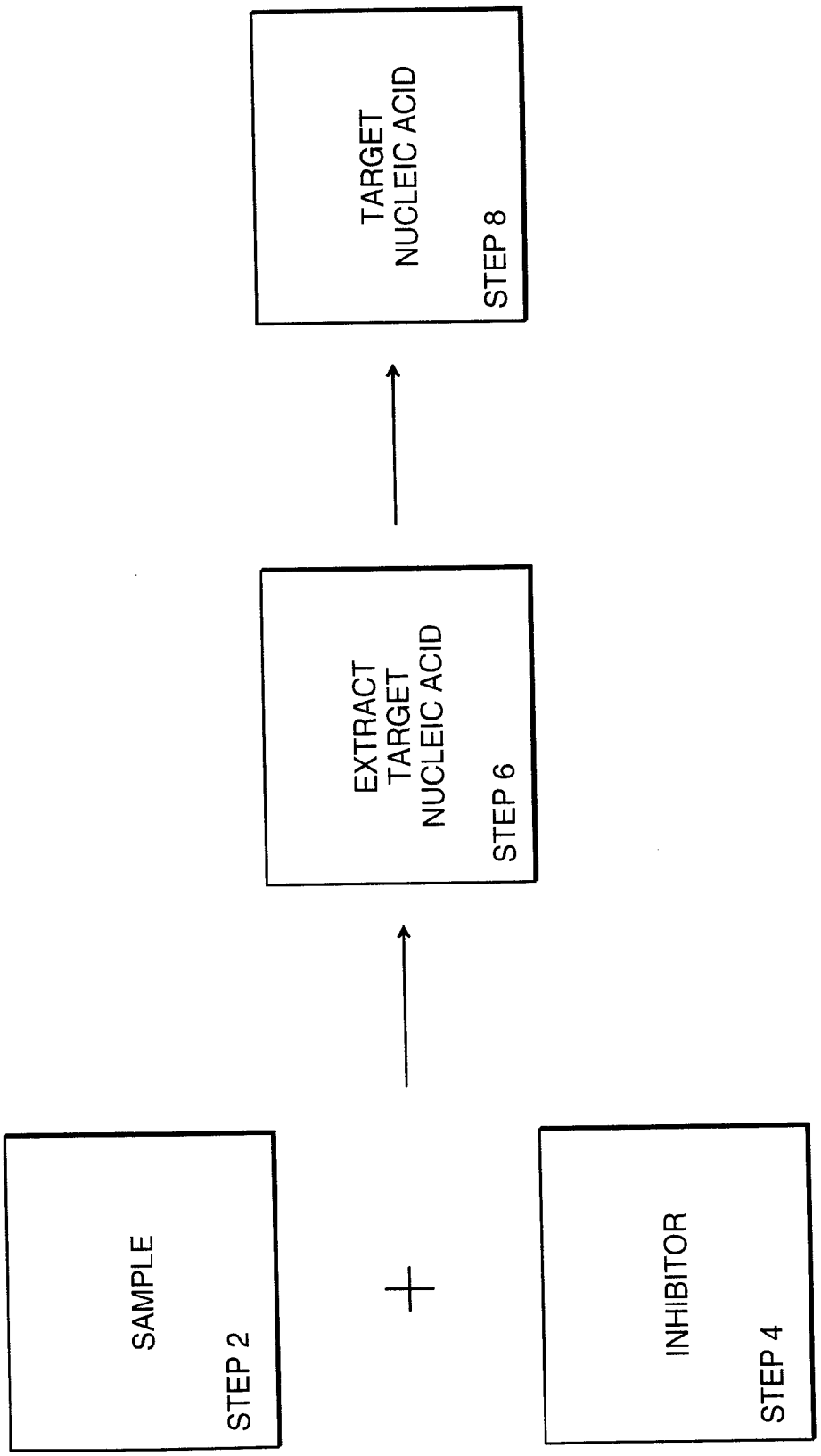

SAMPLE
STEP 2
+
INHIBITOR
STEP 4
EXTRACT TARGET NUCLEIC ACID
STEP 6
TARGET NUCLEIC ACID
STEP 8

FIG. 1

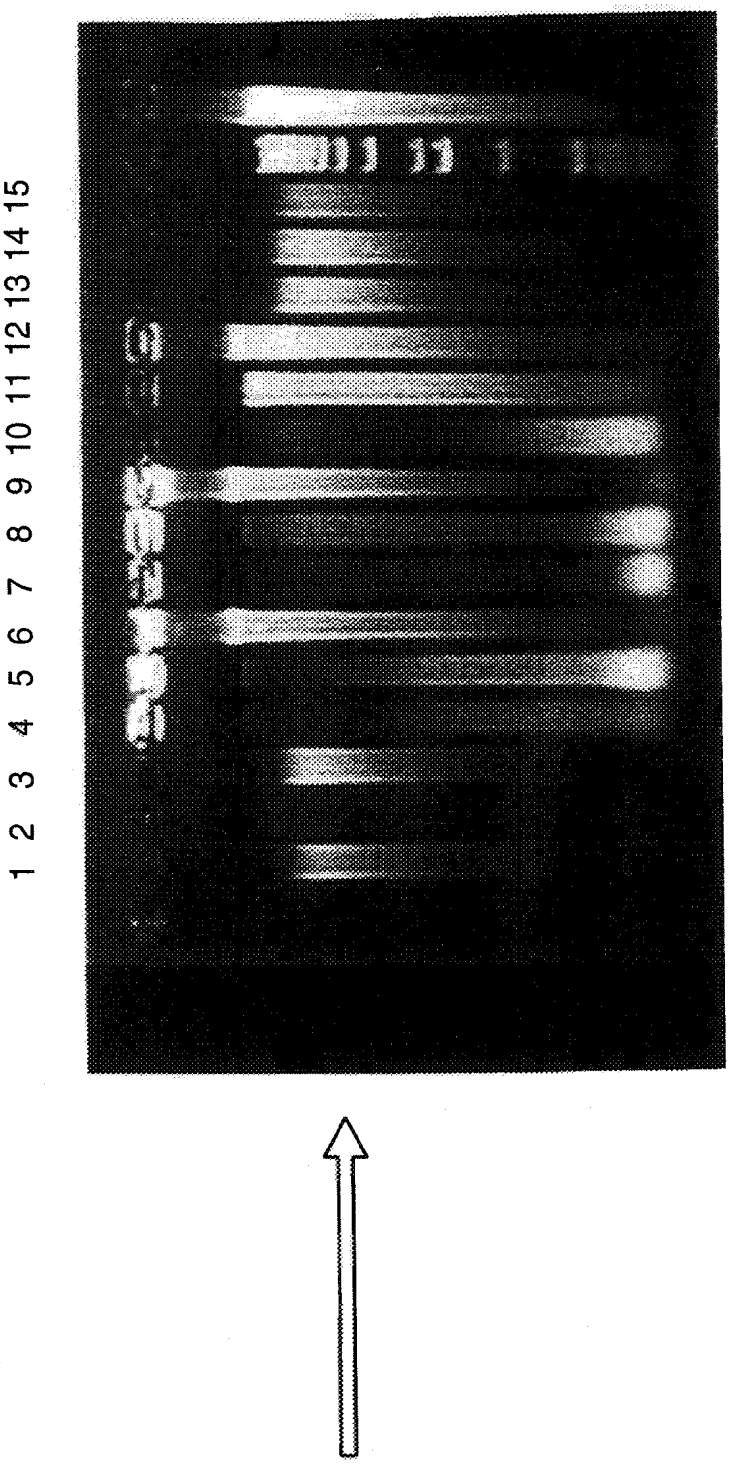


FIG. 2

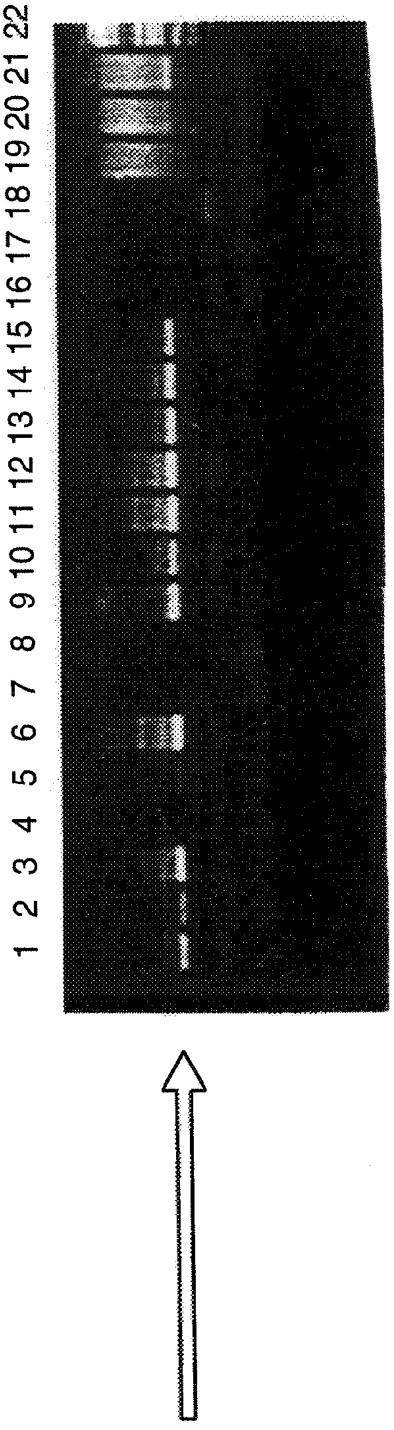


FIG. 3

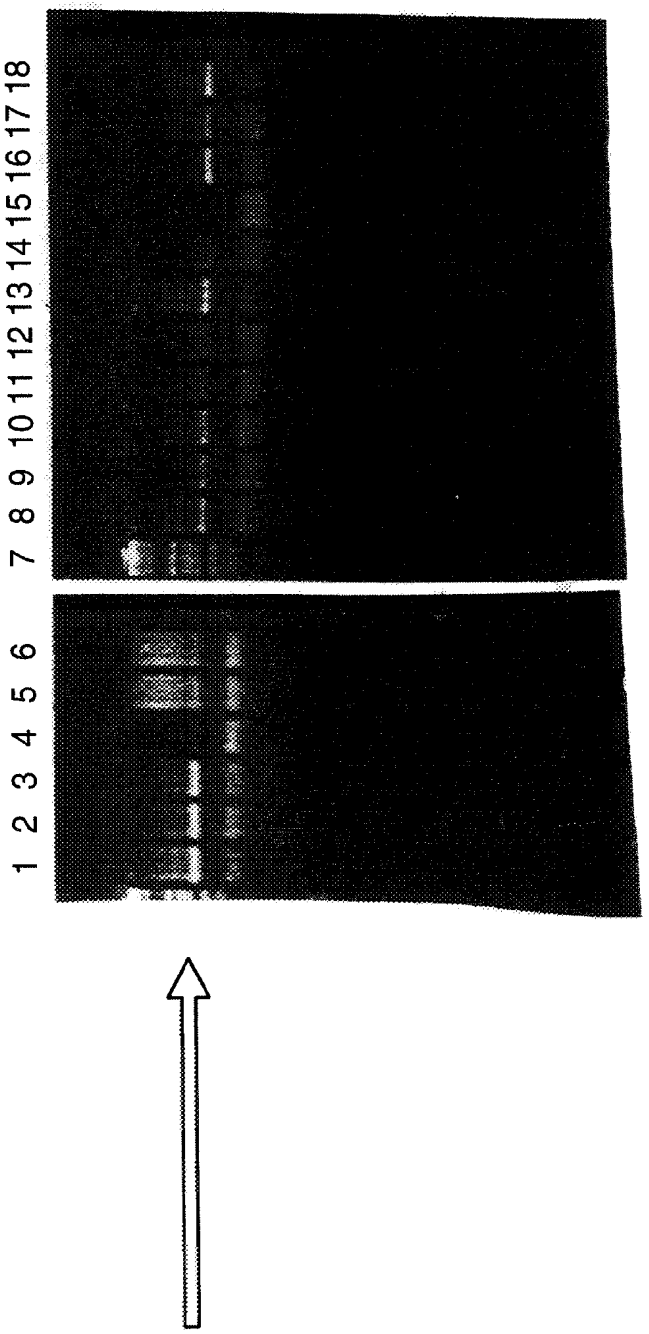


FIG. 4

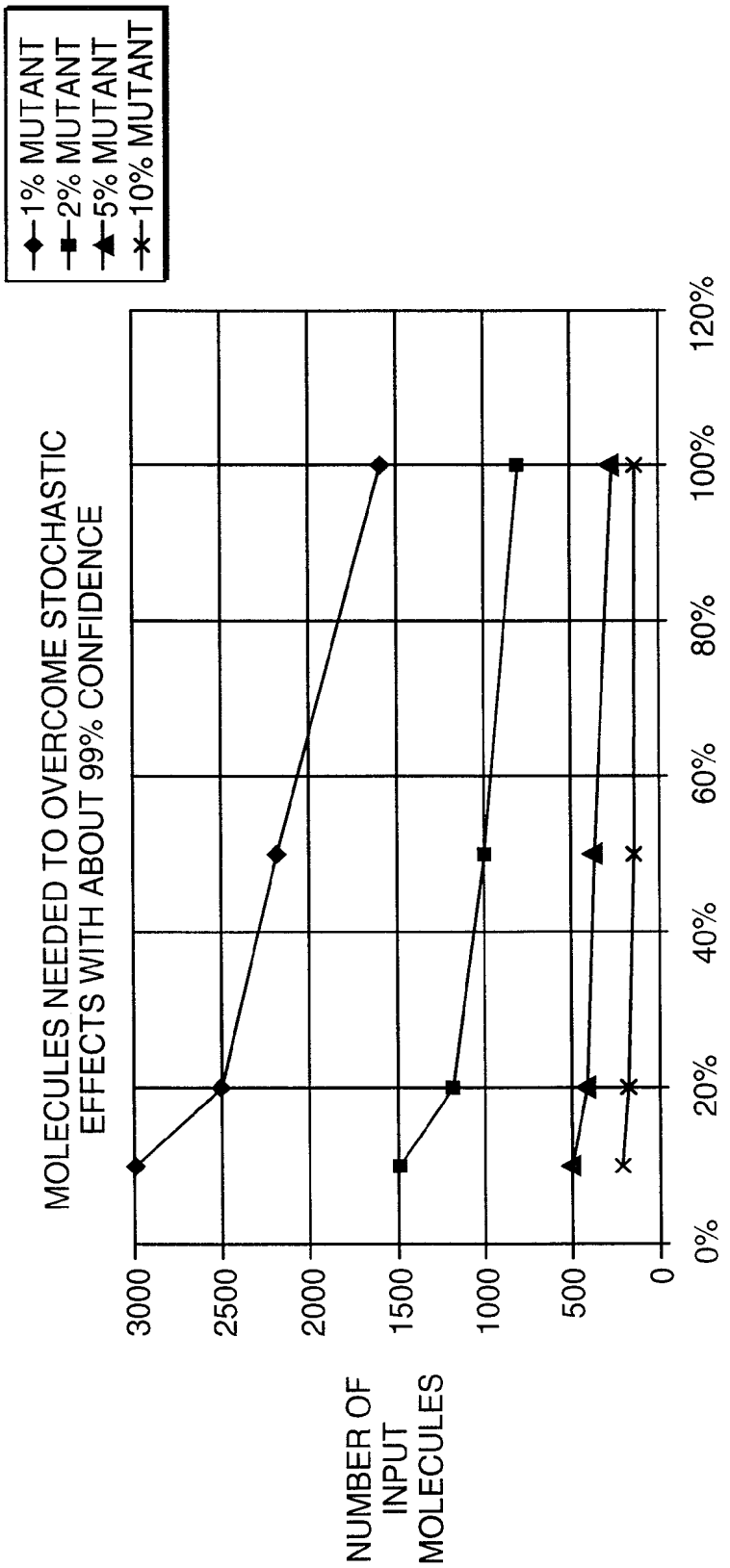

1% MUTANT
2% MUTANT
5% MUTANT
10% MUTANT
MOLECULES NEEDED TO OVERCOME STOCHASTIC EFFECTS WITH ABOUT 99% CONFIDENCE
NUMBER OF INPUT MOLECULES
3000
2500
2000
1500
1000
500
0
0%
20%
40%
60%
80%
100%
120%
PCR EFFICIENCY

FIG. 5

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/US 00/01759

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 20235 A (UNIV JOHNS HOPKINS MED) 14 October 1993 (1993-10-14) the whole document ---	1-16
X	WO 98 58081 A (EXACT LAB INC) 23 December 1998 (1998-12-23) the whole document ---	1-16
X	DE 195 30 132 A (MAX PLANCK GESELLSCHAFT) 20 February 1997 (1997-02-20) the whole document --- -/--	1-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 June 2000	04/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hagenmaier, S

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/01759

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CALDAS C ET AL: "DETECTION OF K-RAS MUTATIONS IN THE STOOL OF PATIENTS WITH PANCREATIC ADENOCARCINOMA AND PANCREATIC DUCTAL HYPERPLASIA" CANCER RESEARCH,US,AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, vol. 54, 1 July 1994 (1994-07-01), pages 3568-3573, XP002050203 ISSN: 0008-5472 the whole document ---	1-16
X	SIDRANSKY ET AL.: "IDENTIFICATION OF RAS ONCOGENE MUTATIONS IN THE STOOL OF PATIENTS WITH CURABLE COLORECTAL TUMORS" SCIENCE, vol. 256, 1992, pages 102-105, XP000605488 the whole document -----	1-16

1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ational Application No
PCT/US 00/01759

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9320235 A	14-10-1993	CA 2132874 A	14-10-1993
		EP 0672181 A	20-09-1995
		JP 8504081 T	07-05-1996
		US 5910407 A	08-06-1999
WO 9858081 A	23-12-1998	AU 7816898 A	04-01-1999
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		AU 6821696 A	12-03-1997
		CA 2228769 A	27-02-1997
		WO 9707239 A	27-02-1997
		EP 0851937 A	08-07-1998
		JP 11511020 T	28-09-1999

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	15/634,607
				Filing Date	06/27/2017
				First Named Inventor	JOOST LOUWAGIE
				Art Unit	1634
				Examiner Name	WHISENANT
Sheet	1	of	2	Attorney Docket Number	EXCTD-35239.304

U.S. PATENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		6761702	2004-07-13	SMITH	

U.S. PUBLISHED PATENT APPLICATIONS

Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] (if known)	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		20020096469	2002-07-25	FAULKNER	
		20030086869	2003-05-08	STALLINGS	
		20040019298	2004-01-29	ZHOU	
		20050075543	2005-04-07	CALABRESE	
		20050244836	2005-11-03	TSANG	
		20070072214	2007-03-29	GARVIN	

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[5] Number[6] Kind Code[7] (if known)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Translation[8]
		WO 2000/050640	2000-08-31	EXACT LABORATORIES, INC.		
		WO 2005/014154	2005-02-17	LOOTS LIMITED		

NONPATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and-or country where published.	Translation[6]

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	15/634,607
				Filing Date	06/27/2017
				First Named Inventor	JOOST LOUWAGIE
				Art Unit	1634
				Examiner Name	WHISENANT
Sheet	2	of	2	*Attorney Docket Number*	EXCTD-35239.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

☐ Documents not provided herewith have been previously cited in parent U.S. patent application number ____ filed on_____. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Mary Ann D. Brow/	Date (YYYY-MM-DD)	2023-02-06
Name/Print	Mary Ann D. Brow	Registration Number	42363

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Patent Owner's Ex. 2003, Page 816

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
15/634,607	02/06/2023 03:43:08 PM ET	EXCTD-35239.304

Title of Invention

FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1874	FILED BY	Stephanie Filandrinos
PATENT CENTER #	61551831	AUTHORIZED BY	Mary Ann Brow
CUSTOMER #	173254	FILING DATE	06/27/2017
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Joost Louwagie

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0638	E202326F43572961	Stephanie Filandrinos

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1801	REQUEST FOR CONTINUED EXAMINATION (RCE) - 1ST REQUEST (SEE 37 CFR 1.114)	1360.00	1	1360.00
			TOTAL AMOUNT:	$1,360.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 February 2005 (17.02.2005)

PCT

(10) International Publication Number
WO 2005/014154 A1

(51) International Patent Classification[7]: B01F 11/00, C12Q 1/68, A61B 10/00, G01N 33/574

(21) International Application Number: PCT/GB2004/003434

(22) International Filing Date: 9 August 2004 (09.08.2004)

(25) Filing Language: English

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0318702.8 8 August 2003 (08.08.2003) GB

(71) Applicant *(for all designated States except US)*: **LOOTS LIMITED**; PO BOX 293, GRANITE HOUSE, LA GRANDE RUE, ST MARTIN GUERNSEY GY1 3RS (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **O'NEILL, IAN** [GB/GB]; 5 RED HILL CLOSE, GREAT SHELFORD, CAMBRIDGE Cambridgeshire CB2 5JP (GB).

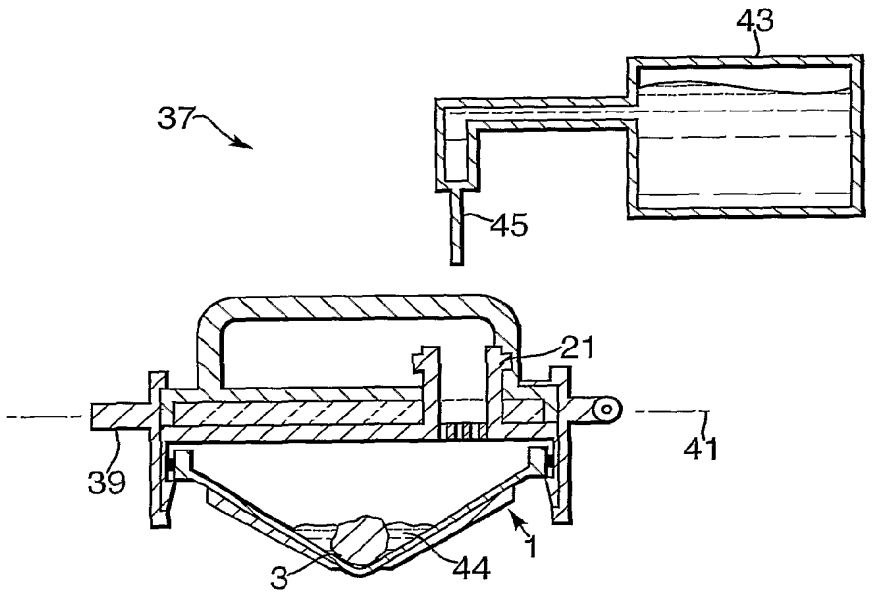
(74) Agents: **GILL, Stephen** et al.; Mewburn Ellis LLP, York House, 23 Kingsway, London Greater London WC2B 6HP (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: METHOD AND APPARATUS FOR REMOVING CELLULAR MATERIAL FROM FAECAL STOOLS AND CONTAINER FOR COLLECTING FAECAL STOOLS



(57) Abstract: A method of removing cellular material from the surface of a faecal stool comprises the steps of: a) supporting the stool in a container having a channel along which the stool extends; b) cooling the stool to a temperature below its gel greezing point; c) introducing wash liquid into the container whilst maintaining the stool at a temperature below its gel freezing point; and d) moving the container to cause the liquid to run back and forth along the channel thereby washing the cellular material from the surface of the stool. Further disclosed are an apparatus (4) for removing cellular material from. the surface of a faecal stool and a container for collecting faecal stools (3b) .

WO 2005/014154 A1

WO 2005/014154 A1

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

METHOD AND APPARATUS FOR REMOVING CELLULAR MATERIAL FROM FAECAL STOOLS AND CONTAINER FOR COLLECTING FAECAL STOOLS

Field of the Invention

The present invention relates to a method and apparatus for removing cellular material from faecal stools and a container for collecting faecal stools.

Background

Faecal stools are the residue of digestive products in the gastrointestinal tract, and contain not only bacteria and undigested food residues, but also residual products from the body's metabolism and structure such as exfoliated epithelial cells from the lining of the gastrointestinal tract.

Exfoliated epithelial cells consist of cellular components, such as DNA, RNA and proteins, which potentially provide a multiplicity of approaches to identifying and monitoring unhealthy conditions of the epithelium as exemplified by colorectal cancer, polyps and ulcerative colitis. The facile recovery of such cells makes possible the application of a wide variety of test procedures for qualitative and/or quantitative analysis of, for example, DNA alterations, gene expression and enzyme activity. A. Loktionov *et al.*, in *Clinical Cancer Research*, Vol. 4, 337-342, (1998), describe a non-invasive screening test for early detection of colorectal cancer which is based on a quantitative comparison of the DNA concentrations derived from exfoliated epithelial cells isolated from the surface of stools from healthy and tumour-bearing persons. In this isolation procedure, cells on the surface of the stool were predominantly clustered and had varying degrees of intactness and damage. In the present specification by "cells" and "cellular material" we mean all such material irrespective of degree of clustering or intactness.

In our earlier patent application, WO 97/09600, we describe a method of isolating cells (especially exfoliated epithelial cells) from the surface of faecal stools, comprising cooling a stool to a temperature (preferably of -80°C to 15°C, preferably -10°C to 15°C, preferably -10°C to 10°C, more preferably 0°C to 5°C) below its gel freezing point and removing the cells from the cooled stool by agitating the stool in an aqueous solution (which may be pre-cooled to a temperature below the gel freezing point, and is preferably ice-cold). The cooled condition creates a much more physically robust hard gel state that helps to prevent the stool from breaking up or rapidly eroding so that non-surface material is largely prevented from entering the aqueous solution.

Stool surface layers provide a particularly rich source of exfoliated cells suitable for isolation. Typically between one-sixth and one third of colonic epithelial cells are exfoliated per day (D. Sidransky *et al.* (1992), *Science* 256, 102-105 and W. C. MacDonald, J. S. Trier, N. B. Everett, *Gastroenterology* (1964) 46, 405). It is believed that some of these exfoliated cells, together with mucus, may be envisaged as forming a "sheath" around a stool, containing a low proportion of bacterial cells and other faecal matter. It is further believed that the viability of the cells in the surface layers (i.e. the layer of faecal material within 1.0 mm, and preferably 0.25 mm, of the stool surface) of the stool is facilitated by i) a tendency of the cells to agglomerate into plaques (which helps to prevent apoptosis), ii) the availability of oxygen at the surface of the stool and iii) the unique ability of colonic epithelial cells to utilise as fuel the butyrate formed locally in high concentrations by microfloral fermentation (J. H. Cummings (1981) *Gut* 22, 763-799 and W. E. W. Roediger (1980) *Gut* 21, 793-798). Oxidation of butyrate is believed to provide fuel for the cells in the

absence of blood-borne nourishment following exfoliation. It has been found that isolation of cells from stool surface layers provides significant advantages in yield, purity and ease of recovery over isolation of cells from homogenised stools.

Summary of the Invention

Although the method described in WO 97/09600 is effective for isolating cells from the surfaces of faecal stools, in order to make the method more suitable for high throughput screening of e.g. hundreds or thousands of samples per day, problems remain of washing the stools in a standard and reproducible way that maximises the amount of surface cells extracted from the stools but minimises the risk of breaking up the stools.

Consequently, in a first aspect, the present invention provides a method of removing cellular material from the surface of a faecal stool comprising the steps of:

a) supporting the stool in a container having a channel along which the stool extends;

b) cooling the stool to a temperature below its gel freezing point;

c) introducing wash liquid into the container whilst maintaining the stool at a temperature below its gel freezing point; and

d) moving the container to cause the liquid to run back and forth along the channel thereby washing the cellular material from the surface of the stool. A minority of stools are very soft when excreted, such that on cooling they do not reach the gel freezing point, but do become sufficiently viscous to be washed with minimal entry into the wash liquid of sub-surface material. Thus, for that minority of stools, by "gel freezing point" we mean the temperature at which the stools become sufficiently viscous to be washed with negligible entry of sub-surface material into the wash liquid.

The method promotes the reproducible and gentle washing of the stool, which facilitates the quantitative comparison of cellular material between individuals.

Human faecal stools are typically elongate and approximately cylindrical in shape. So the channel significantly reduces the likelihood that sections of the stool will break off when the stool is being washed because the channel walls substantially prevent side-to-side rolling motion of the stool and, for a wide range of rocking angles and speeds, friction largely prevents the stool from sliding along the channel. Preferably the container is moved to cause a wash frequency of from 5 to 40 back and forth cycles per minute, and more preferably from 15 to 25 cycles per minute. The stool may be pre-soaked (for e.g. 3 minutes) in the wash liquid prior to step d), in which case preferably the container is moved for a total time of from 10 seconds to 1 minute. Without a pre-soak, preferably the container is moved for a total time of from 30 seconds to 5 minutes. With or without pre-soaking it is advantageous to limit the exposure of the stool to the wash liquid so as to avoid localised depletion of wash reagents or over-enrichment of released cellular material. The channel may have a V or U-shaped transverse section.

An advantage of the container motion, is that the wash liquid is channelled back and forth along the length of the stool so that, compared with e.g. circular agitation by an orbital shaker of the wash liquid relative to the stool (which we have found in any event tends to break up the stool), less liquid is required to wash the cells from the surface of the stool. Clearly the less liquid that is used to wash the stool, the higher the resulting concentration of cells in the liquid, which can in turn improve the accuracy of screening tests which may be subsequently performed on the liquid. Also smaller volumes of liquid

reduce cost and disposal problems. Preferably from 30 to 150 ml of liquid is used in steps c) and d). This is generally sufficient to wash a typical 100 g stool while minimising losses due to residual wetting of the container and stool. Most preferably a fixed ratio of liquid to stool is used so that all stools experience a similar degree of wetting. This ratio may be in the range 0.5 to 1.0 ml of liquid per gram of stool.

In one embodiment, step d) comprises rocking the container about a horizontal axis perpendicular to the channel so that the liquid runs back and forth under gravity. In another embodiment, step d) comprises displacing the container back and forth in the direction in which the channel extends.

Preferably the container is of fixed shape, e.g. by being formed of rigid material.

In a second aspect, the present invention provides an apparatus for removing cellular material from the surface of a faecal stool, comprising:

mounting means for mounting a container having a channel along which, in use, the stool extends; and

motion imparting means for moving the container so that, when wash liquid is introduced into the container, the liquid runs back and forth along the channel thereby washing cellular material from the surface of the stool.

In one embodiment, the motion imparting means rocks the container about a horizontal axis perpendicular to the channel so that the liquid runs back and forth under gravity. In another embodiment, the motion imparting means displaces the container back and forth in the direction in which the channel extends.

The apparatus may further comprise control means to control e.g. the rocking angle, rocking or displacement frequency and/or total time of movement of the container, preferred ranges for some of these parameters being

provided above in respect of the first aspect of the invention. The control means may further control a sequence of stationary and mobile periods for the container, so that e.g. stationary exposure of the stool to the wash liquid allows the liquid to penetrate the stool and loosen its surface layers prior to active washing when the container is moved.

With such an apparatus, stool washing can be performed in a repeatable, standardised manner, and with a relatively high stool sample throughput. These are significant advantages if the wash liquid is to provide the material for a screening test based on e.g. a quantitative comparison of amounts of epithelial cell components.

The apparatus may further comprise cooling means for cooling the stool to a temperature (preferably of -80°C to 15°C, preferably -10°C to 15°C, preferably -10°C to 10°C, more preferably 0°C to 5°C) below its gel freezing point.

In one embodiment the apparatus further comprises a filter means such as a sieve, so that, when wash liquid is removed from the container, the cells are retained in the liquid but food residues from the stool are filtered from the liquid.

The apparatus may further comprise a metering device for introducing a metered dose (e.g. 50 to 150 ml, or an amount which is related to the stool weight) of wash liquid into the container, and/or a wash liquid pre-cooler for cooling the wash liquid to a temperature below the gel point of the stool before the wash liquid is introduced into the container. This temperature is preferably about 0°C.

The apparatus may further comprise at least one and preferably a plurality of detachable sample receptacles into which wash liquid is transferable from the container, so that e.g. when stool washing is completed the wash liquid may be poured from the container into the

receptacles. These can then be detached from the apparatus and transferred to an automated liquid-handling system for high throughput processing of the liquid samples contained therein.

A third aspect of the invention provides a fixed shape container for collecting faecal stools which has an upper receiving mouth and a lower stool collection channel, the internal walls of the container narrowing from the mouth to the channel so that when a stool is deposited through the mouth the stool is encouraged to lie lengthways along the channel. The mouth can be of any suitable shape, e.g. rectangular or circular. The length of the channel is preferably in the range from 10 to 25cm, which corresponds to the size of a typical stool. The container may be used in the first or second aspect of the invention.

As faecal stool is generally regarded as disgusting material that people are reluctant to handle, even indirectly, the fixed shape container has several advantages as compared with, e.g. a flexible plastic specimen bag for collecting stool. For example, the mouth of the container cannot collapse as a stool is being deposited in the container, thereby making it easier for a user to excrete into the container. Also the container can be handled without, apart from the weight of the stool, any sensation that a stool is contained therein.

Furthermore the funnelling effect of the narrowing container walls guides a formed stool (which on defecation can be quite malleable) to a position in which it extends along the channel. This reduces or eliminates the need for the user to directly or indirectly manipulate the stool into that position prior to stool washing. Soft stools, and even diarrhoea, are also encouraged to align along the channel by the narrowing of the container walls.

A further advantage of the container is that it can serve both as the receptacle into which the stool is

excreted and as the container in which the stool is washed. So the stool does not need to be transferred to a different washing container, which avoids damage to the stool surface caused by such a transfer. Such damage would interfere with the accuracy of e.g. screening tests which may be performed on the stool.

If the stool is excreted into the container at home and then transported to e.g. a clinic for washing, the container has the further advantage of holding the stool reasonably securely in the channel so that transportation damage to the stool surface is reduced or avoided.

To avoid user embarrassment during transportation at least a majority of the container may be opaque (i.e. a stool inside the container is not visible through the opaque portions of the container, even if the material of the container transmits light to some degree), or an opaque transport casing may be provided for transporting the container. However, desirably at least a portion of the container permits viewing to the inside of the container so that e.g. after delivery of the container for stool processing a health professional can check the stool for gross abnormalities such as blood before the stool is processed and without opening the container.

The container may further have installation means (which may be detachable from the container) for removably installing the container on a toilet (e.g. below the toilet seat) with the receiving mouth opening upwardly and the collection channel extending horizontally beneath the mouth. This allows the user to produce the stool in the usual manner, which promotes user acceptability.

Typically, for hygiene reasons, at least the stool-contacting parts of the container are disposable. However, in one embodiment the internal walls of the container serve as a former for a bag which is reversibly fixable inside the container, whereby the bag assumes the shape of the

mouth and channel. In this embodiment the bag is typically disposed after use, but the container can be reused.

Preferably the container is made of plastics material such as polypropylene. Desirably the container has smooth internal surfaces which reduce damage to the surface of the stool as the stool passes from the mouth to the channel.

In one embodiment the container has cooling means, such as an outer jacket or bath, for cooling a stool deposited in the container. This means that the stool can be cooled immediately it is produced, which helps to preserve the surface layer cells and makes the stool robust for physical transport. The cooling means may be of material that can be pre-cooled in a domestic refrigerator or freezer. This is particularly convenient when the stool is produced at home, allowing the donor to defecate at a convenient time and in a minimally stressful setting and thereby promoting user acceptability. The cooling means may enable the stool to be cooled to a temperature below its gel freezing point.

The cooling means may be detachable from the container so that the cooling means can be pre-cooled before fitting to the container. Also, if the container is disposable, the cooling means can still be reused.

Anaerobic bacteria in stools produce damaging radicals when exposed to atmospheric oxygen (C. F. Babbs (1990) *Free Radical Biology and Medicine*, 8, 191-200). Such oxygen also oxidises the mucus on the surface of stools and encourages the growth of aerobic bacteria. So preferably the container is hermetically sealable to reduce the exposure to atmospheric oxygen of a stool deposited therein. The seal may be achieved by means of a lid or cover (e.g. having a snap-fit or screw fitting) for the mouth. A sealed container rapidly becomes anaerobic due to the high concentration of anaerobic bacteria in the stool, and this apparently largely prevents the growth of aerobic

bacteria on the stool surface, helping to preserve the stool. We have found that sealed containers allow stools to be stored at 0°C for a number of weeks apparently without significant degradation. To promote user acceptability, the seal should also eliminate any odour from the stool escaping from the container, particularly if the stool is produced at home and then transported before washing.

The container may also have a liquid port which allows wash liquid to be removed from the container while maintaining the stool in the container. For example the diameter of the port may be sized to prevent a typical-sized stool from exiting via the port, or a foraminous screen over the port may serve the same function. The port may include closure means such as a valve or a cap which allows the liquid to be poured or sucked out of the container but at other times maintains an airtight seal. The same or another port may be used to introduce wash liquid into the container.

A further aspect of the invention provides a kit of parts comprising the container of the previous aspect with the installation means and/or the cooling means and/or the transport casing.

Another aspect of the invention provides a method of screening for unhealthy condition(s) of the epithelium (such as colorectal cancer, polyps and ulcerative colitis) in a plurality of subjects (which are typically human subjects, but may be other animal species such as dogs and cats), the method comprising the steps of:

a) providing to the subjects respective containers (e.g. according to the third aspect of the invention) for defecation of a stool sample thereinto at the convenience of the subject (which is typically when the subject is "at home" or in a domestic setting);

b) collecting the filled containers from the subjects at a central location (which may be a doctor's surgery or a hospital out-patients clinic);

c) removing a specimen of cellular material from the surface of each stool sample (e.g. according to the first aspect of the invention); and

d) testing each specimen for unhealthy condition(s) of the epithelium (e.g. as described by A. Loktionov *et al.*, referenced above).

Brief Description of the Drawings

The present invention is now described in respect of a specific embodiment and with reference to the accompanying drawings in which:

Figs. 1a and b show schematically and respectively a cross section through and a plan view of a receptacle for collecting a faecal stool, and Fig. 1c shows a plan view of an alternative form of the receptacle;

Fig. 2 shows the same cross section as Fig. 1a except that a lid is fixed to the receptacle;

Fig. 3a shows a schematic cross section of the receptacle of Fig. 1a fixed inside a transport unit, and Fig. 3b shows the receptacle of Fig. 1c fixed in another version of the transport unit;

Fig. 4 shows schematically a stool washing apparatus with the receptacle of Fig. 1a positioned in a sample rack; and

Fig. 5 shows the apparatus of Fig. 4 with the sample rack pivoted to pour wash liquid out of the receptacle.

Detailed Description

Figs. 1a and b show respectively a cross section through and a plan view of a transparent plastic receptacle 1 having a V-shaped cross-section for collecting a faecal stool 3 produced by a user. The receptacle has a mouth 5 and a straight stool collection channel 7 (which extends perpendicularly to the plane of the paper in Fig. 1a). The

receptacle is removably installed inside a toilet bowl 9 by a support web 11 which is attached over the rim of the toilet and has a central hole 12 to receive the receptacle so that channel 7 is horizontal and mouth 5 is directly above channel 7. The smoothly sloping walls 14 of the receptacle guide the stool to the bottom of channel 7 and encourage the deposited stool to align with the longitudinal direction of the channel.

Fig. 1c shows an alternative form of the receptacle which has a U-shaped channel cross-section, and which is capable of receiving larger specimens.

Once the stool is collected in the receptacle, a lid 13 (see Fig. 2) is used to close mouth 5 and is releasably fixed to the receptacle by a snap-fit mechanism 16. A sealing ring 15 seals the receptacle from the external atmosphere.

Lid 13 includes a carrying handle 17, thermally insulated upper wall 19 and wash liquid entry/exit port 21. The port is sealed by closure cap 23 and has a foraminous screen 25 at its inner end which prevents the stool from entering the port when (as described below) wash liquid is decanted from the receptacle, and a coarse sieve 25a to retain particles of e.g. greater than 2 mm in diameter.

The receptacle is lifted by handle 17 from web 11 and fixed inside a transport unit 27 by a snap-fit mechanism 29 (see Fig. 3a). The transport unit has thermally insulated walls 31 and contains a cooling block 33 of pre-cooled ice or chemical cooling medium contained under a shaped divider 35. The cooling block is brought into close proximity with the outer wall of receptacle 1. Ring 15a maintains the position of channel relative to the cooling block. The cooling block cools stool 3 to a temperature preferably in the range from 0 to 5°C, which is below the gel freezing point of the stool.

Fig. 3b shows the receptacle of Fig. 1c fixed in another version of the transport unit. In this version divider 35 forms an air space around the receptacle. The air space and divider 35 prevent the cooling block cooling the stool so rapidly as may damage the outer surface layers of the stool.

The stool is then transported in the transport unit to e.g. a clinic where stool washing is performed. The walls of the transport unit and lid are opaque so that the stools are not visible inside the unit, and lid 13 prevents odours from escaping the unit. Channel 7 also reduces movement of the stool during transportation which prevents significant damage to the surface of the stool.

At the clinic, the receptacle 1 and lid 13 are removed from the transport unit. As the receptacle is transparent visual inspection of the stool is possible without removing the lid. At this stage the stool sample may be rejected if, for example, it is too small or runny. also any gross evidence of disease, such as blood, may be noted. However, if the stool is acceptable, the receptacle and lid are positioned into the sample rack 39 (i.e. receiving means) of a stool-washing apparatus 37 shown in Fig. 4. Collection channel 7 is aligned perpendicular to axis 41 about which rack 39 is pivotable and which at this stage is horizontal.

Cooling means (not shown), such as a cold air jet, refrigerator unit or coolant bath, keeps or brings the stool to a temperature in the range 0 to 5°C so that it is below its gel freezing point.

Apparatus 37 has a reservoir 43 of chilled wash liquid, such as a buffered aqueous solution containing N-acetylcysteine, bovine serum albumin and sodium butyrate which has been found (see WO 97/09600) to improve recovery of exfoliated cells. When the stool is sufficiently cool, closure cap 23 is removed and a metered dose of wash liquid

44 is injected into the receptacle via an injector 45 and port 21. The liquid may alternatively be injected through an air-tight septum at port 21. Afterwards injector 45 is swung away from the sample rack.

Rocking means (not shown), which is e.g. an electric motor and associated drive, then rocks the sample rack and receptacle backwards and forwards about axis 41. A control unit (also not shown) which controls the rocking means defines a wash programme consisting of rocking angle, rocking frequency and total exposure and rocking time experienced by the stool. As receptacle 1 moves, gravity causes wash liquid 44 in the receptacle to run back and forth along channel 7 so that intimate contact with the stool is achieved and surface cells from the stool are washed into the liquid. To a significant extent friction prevents the stool from moving during the rocking procedure.

When the wash programme ends, the sample rack is pivoted about pivot 47 to bring axis 41 into a vertical position (see Fig. 5). Almost all of wash liquid 44 is then decanted out of receptacle 1 via port 21, foraminous screen 25 substantially preventing larger food residues or other broken off pieces from the stool exiting with the liquid. Coarse sieve 25a removes smaller pieces from the liquid. Finer downstream sieves (not shown) further limit the maximum particle size in the liquid. The liquid is then be divided into standard volumes and received into a plurality of removable (e.g. clip-on) sample receptacles (not shown). The sample receptacles may be a strip of tubes each of e.g. 0.1-0.5 ml volume as can be removed and clipped into a standard microplate format used for clinical analyses. Alternatively the sample receptacles may be individual tubes each of e.g. 1-2 ml volume. The sample rack is then returned to its horizontal position and receptacle 1 is removed and safely disposed of.

In this way, the apparatus converts a typical total 100-500 g mass of stool and wash liquid into aliquots of cell-suspension of typically only 50-1000 mg (i.e. a thousand-fold reduction in scale). The aliquots can be made representative by preventing the cells from settling out during the decanting process the aliquots. One method of preventing settling out is to provide mixing channels (not shown) through which the liquid flows on its way to the sample receptacles. Alternatively a stirrer (also not shown) can be provided to stir the wash liquid. Fine sieves (e.g. of water wettable material such as nylon, and/or having a mesh size in the range 50-400 μm, preferably 100-250 μm, more preferably 125-200 μm) may be provided over the entrances to the receptacles to further filter the liquid. The excess liquid flows to waste.

The samples may be used for e.g. DNA assays as described in WO 97/09600 and A. Loktionov *et al.*, *Clinical Cancer Research*, Vol. 4, 337-342, (1998).

The entire procedure, from when the receptacle is positioned in the sample rack to when the wash liquid exits the receptacle, can be automated, with standard wash programme settings being used. Also no manual contact with or manipulation of the stool required, which promotes good hygiene. So the present invention allows a large number of stool samples to be processed in a safe and reproducible manner.

In an experimental study, stools were collected into re-sealable bags and stored at 0°C from no more than a few minutes after excretion. The bags were transparent, which allowed visual inspection of the stools during testing. For stool washing, a wash solution was poured into each bag and the bag was located inside a rigid rocking channel of a stool washer apparatus, the channel being 40-45mm wide and perforated so as to permit intimate cooling by surrounding

ice-water held in an insulated container equipped with a submersible pump. Rocking caused a gravity-imposed back and forth circulation of the wash solution along the channel and also promoted cooling of the stool by the surrounding ice-water. A frequency of 3 seconds per rocking cycle was chosen.

The wash solution was as previously described by A. Loktionov *et al.* (referenced above), but the stool wash was passed through a 250 µm instead of a 125 µm sieve. Cell clean-up was performed robotically on a TECAN™ Genesis RSP 150 and then DNA was released by mechanical cell disruption in the presence of 0.9%SDS as lysing agent. Following dilution to prevent quenching, fluorimetric DNA assay was performed with a TECAN™ Spectrafluor Plus using PicoGreen (Molecular Probes™) to yield the stool DNA index (SDNAI, defined as nanograms of DNA per ml of stool wash).

The effects of pre-soaking, rocking angle, mechanical and bacterial damage, stool age, and wash volume were studied, and the results are given below.

Effect of pre-soaking on SDNAI

The following SDNAI data from the stool washer (using a +/-45deg rocking angle) demonstrate the advantage of a period of pre-soaking. Presoaking appears to promote a more or less equilibrated suspension state of cellular material in the wash solution, which thereby helps to prevent the chance dynamic release of cellular material.

Rocking time	SDNAI (ng/ml) with no pre-soak			SDNAI (ng/ml) with 3 min pre-soak		
	stool 1	stool 2	stool 3	stool 4	stool 5	stool 6
30-40 sec	34	12	29	115	206	217
1 min	118	43	21	101	221	294
3 min	100	80	75	125	216	338

Effect of Rocking Angle

If too small a rocking angle was used or the channel became obstructed by the stool, the wash liquid tended to form non-flowing pools that failed to contact the stool surface so that unacceptable variations in washing condition were experienced. However, under favourable conditions, reproducible and relatively constant results could be obtained over a range of rocking angles. For example in three different experiments the same stool was given a 3 minute pre-soak followed by a 1 minute of wash at different rocking angles in a visibly free flow of liquid in a channel 40-45 mm wide and using a wash liquid to stool ratio of 0.7 ml per gram. The rocking angles for the three experiments were +/-30, 45 and 60° from the horizontal and the respective SDNAI measurements were 263, 254 and 260 ng/ml.

Effects of Damage to Stool Surface Layer and of Stool Age

Sometimes stored stools were found to be accidentally squashed, or stored in improperly sealed containers as evidenced by smalls amount of white bacterial over-growth on the stools. The following data (using different stools all washed for 1 minute after a 3 min pre-soak at a wash solution/stool weight ratio of 0.7) demonstrate the importance of protecting the stool surface layer during storage. However, they also demonstrate that under favourable conditions storage durations of up to several weeks have no particular effect on measured SDNAI values. The squashed stools had SDNAI values significantly above the 700 ng/ml value which is considered to be the upper limit for healthy persons.

Stool age (days) donor A	1	4	7	11[s]	15	19	81[s]
SDNAI	203	192	90	1,400	218	585	987

Stool age (days) donor B	14	29[b]	29[b]	31	42[b]	73	101
SDNAI	255	23	50	177	78	261	515

[s] indicates the stool was squashed

[b] indicates the stool had bacterial over-growth

Effect of Wash Solution Volume

Each of a series of undamaged stools from one donor was washed (with a 3 min pre-soak and a 3 min wash at +/- 45° rocking angles) with both a fixed 50 ml volume of wash solution and a variable volume of wash solution based on a 0.5 ml/gram wash/stool ratio. For successive stools of the series, washing first was alternated between the fixed and variable volume. The variable volume based on the 0.5 ratio resulted on average in the use of a 64% greater volume of wash solution which visibly appeared to wet the whole stool better and produced a 21% greater DNA concentration. The second washes gave a 54% higher on average DNA yield than the first washes (largely irrespective of whether the fixed or variable wash solution volume was used first) which was presumably due to the pre-softening effect of the first washes. In general therefore the fixed ratio wash took better account of the stool weight without significantly influencing the DNA result. As shown above, stool age had an insignificant effect on the results.

stool age (days)	1	5	9	20	60	70
stool weight (g)	89	141	103	232	274	146
SDNAI from 50 ml wash	1st 55	2nd 167	1st 234	2nd 300	2nd 256	1st 49
SDNAI from 0.5 ratio wash	2nd 139	1st 92	2nd 220	1st 262	1st 207	2nd 65

Claims:

1. A method of removing cellular material from the surface of a faecal stool comprising the steps of:

a) supporting the stool in a container having a channel along which the stool extends;

b) cooling the stool to a temperature below its gel freezing point;

c) introducing wash liquid into the container whilst maintaining the stool at a temperature below its gel freezing point; and

d) moving the container to cause the liquid to run back and forth along the channel thereby washing the cellular material from the surface of the stool.

2. A method of removing cellular material according to claim 1, wherein step d) comprises rocking the container about a horizontal axis perpendicular to the channel so that the liquid runs back and forth under gravity.

3. A method of removing cellular material according to claim 1, wherein step d) comprises displacing the container back and forth in the direction in which the channel extends.

4. A method of removing cellular material according to any one of claims 1 to 3, wherein the container has a fixed shape.

5. An apparatus for removing cellular material from the surface of a faecal stool, comprising:

mounting means for mounting a container having a channel along which, in use, the stool extends; and

motion imparting means for moving the container so that, when wash liquid is introduced into the container,

the liquid runs back and forth along the channel thereby washing cellular material from the surface of the stool.

6. An apparatus for removing cellular material according to claim 5, wherein the motion imparting means rocks the container about a horizontal axis perpendicular to the channel so that the liquid runs back and forth under gravity.

7. An apparatus for removing cellular material according to claim 5, wherein the motion imparting means displaces the container back and forth in the direction in which the channel extends.

8. An apparatus for removing cellular material according to any one of claims 5 to 7, further comprising cooling means for cooling the stool to a temperature below its gel freezing point.

9. An apparatus for removing cellular material according to any one of claims 5 to 8, further comprising filter means which filters food residues from the stool but retains the cellular material in the wash liquid when the liquid is removed from the container.

10. An apparatus for removing cellular material according to any one of claims 5 to 9, in which the container is mounted at the mounting means.

11. A container for collecting faecal stools which has a fixed shape and has an upper receiving mouth and a lower stool collection channel, the internal walls of the container narrowing from the mouth to the channel so that when a stool is deposited through the mouth the stool is encouraged to lie lengthways along the channel.

12. A container according to claim 12, further having installation means for removably installing the container on a toilet with the receiving mouth opening upwardly and the collection channel extending horizontally beneath the mouth.

13. A container according to claim 11 or 12, further having cooling means for cooling a stool deposited in the container.

14. A container according to any one of claims 11 to 13, which is hermetically sealable to reduce the exposure to atmospheric oxygen of a stool deposited therein.

Fig.1a.

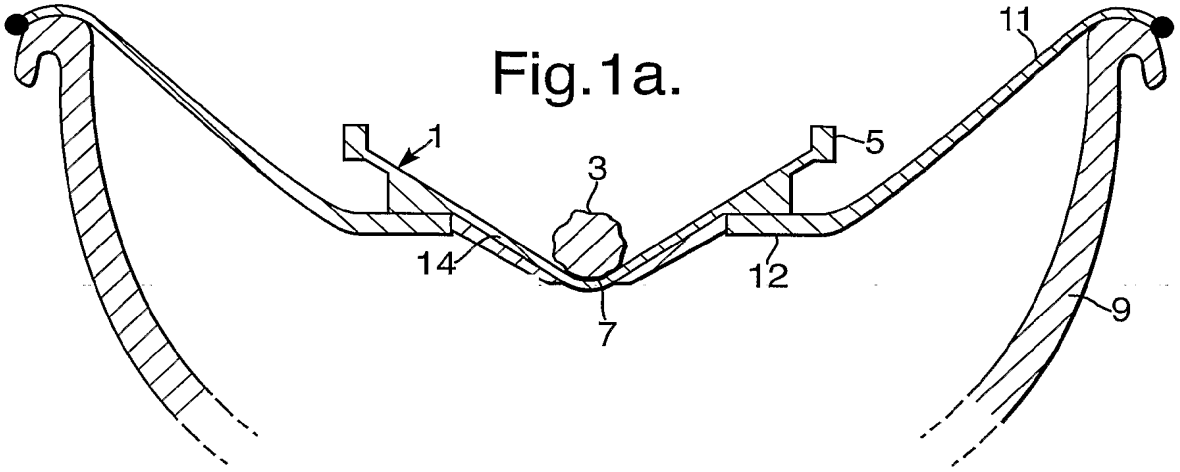


Fig.1b.

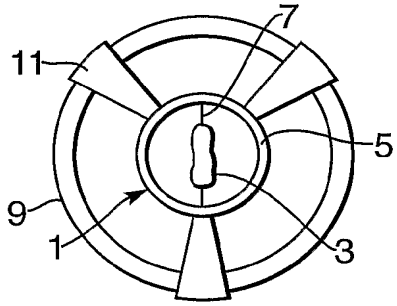


Fig.2.

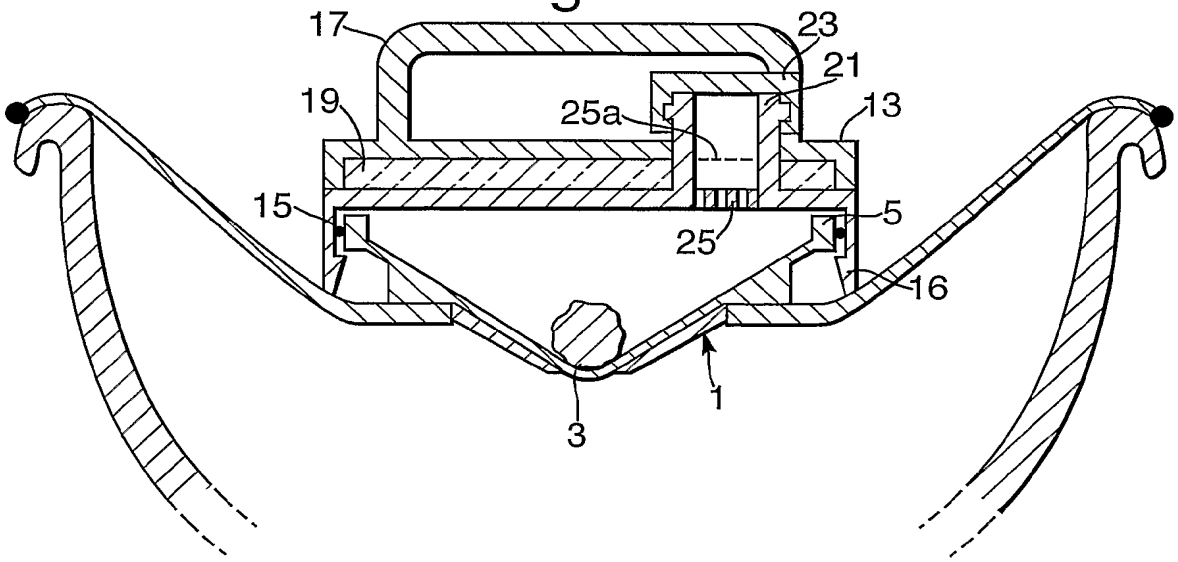


Fig.1c.

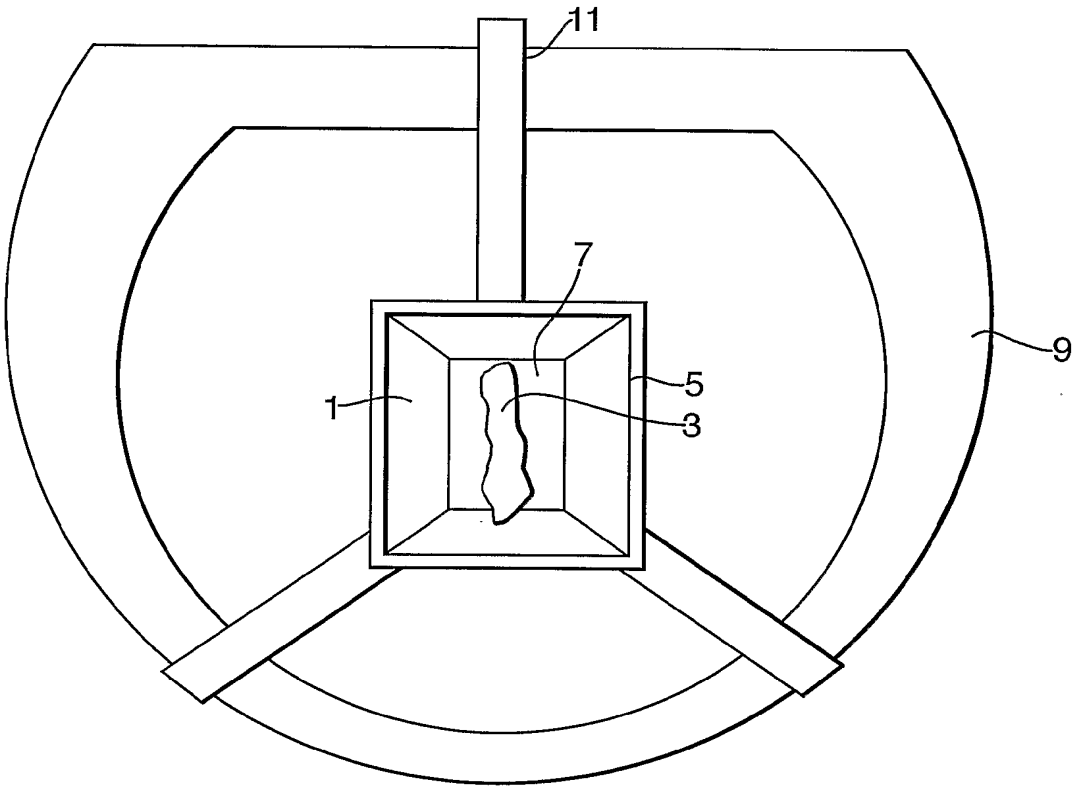


Fig.3a.

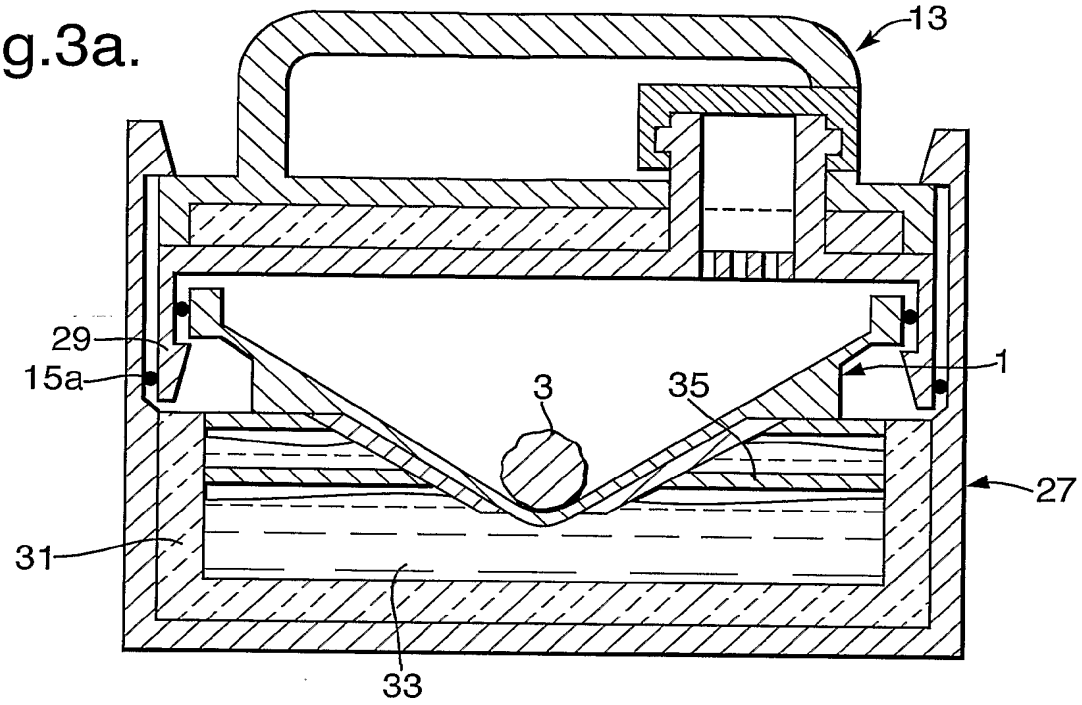

13
29
15a
3
35
1
27
31
33

Fig.3b.

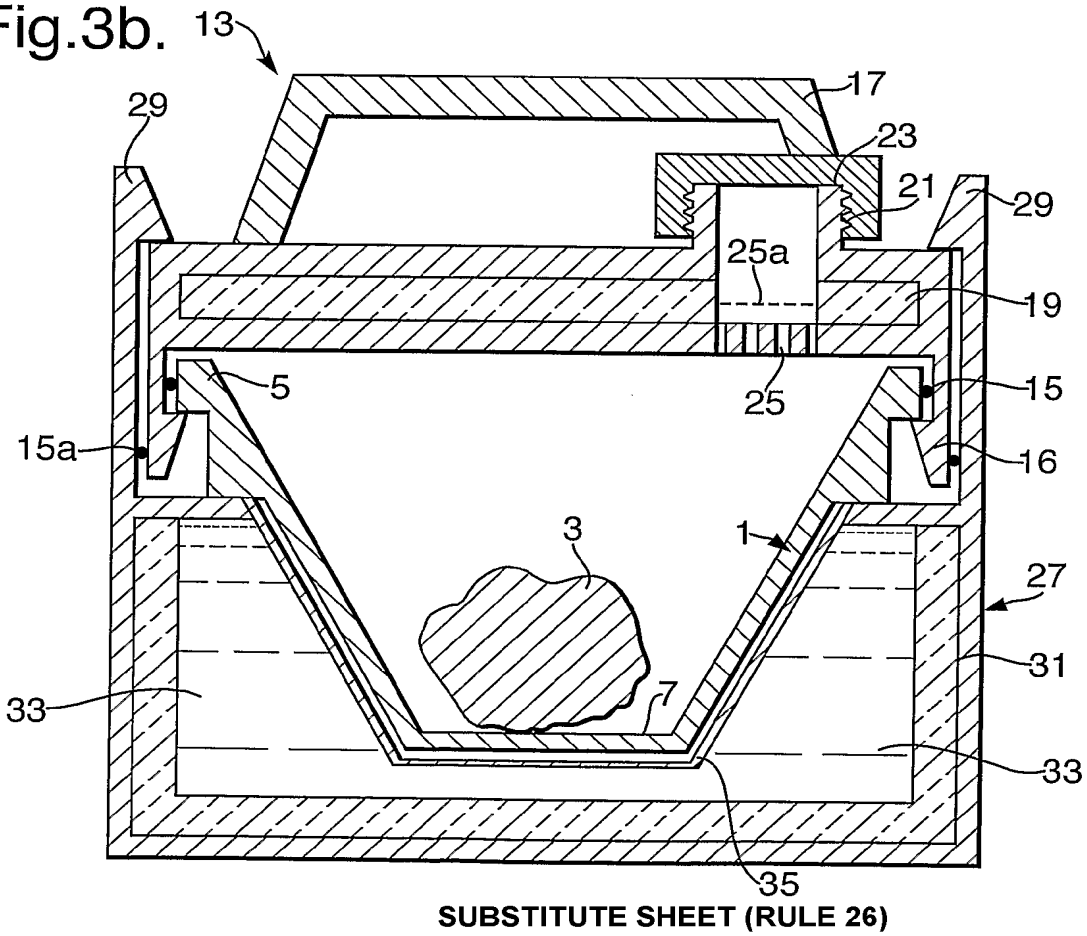

13
17
29
23
21
29
25a
19
5
25
15
15a
16
3
1
27
31
33
7
33
35

Fig.5.

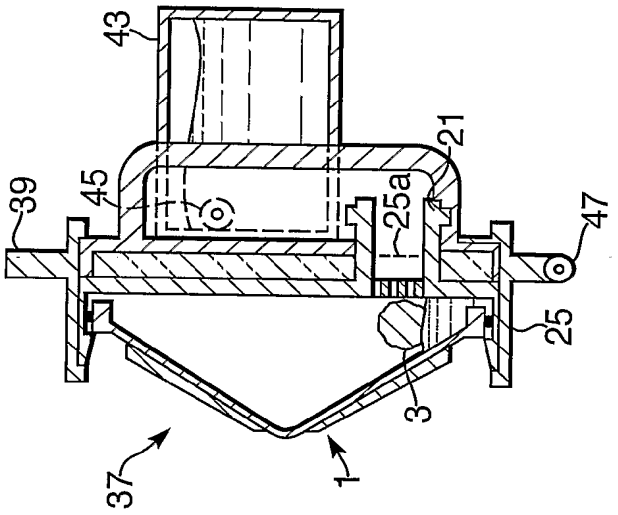
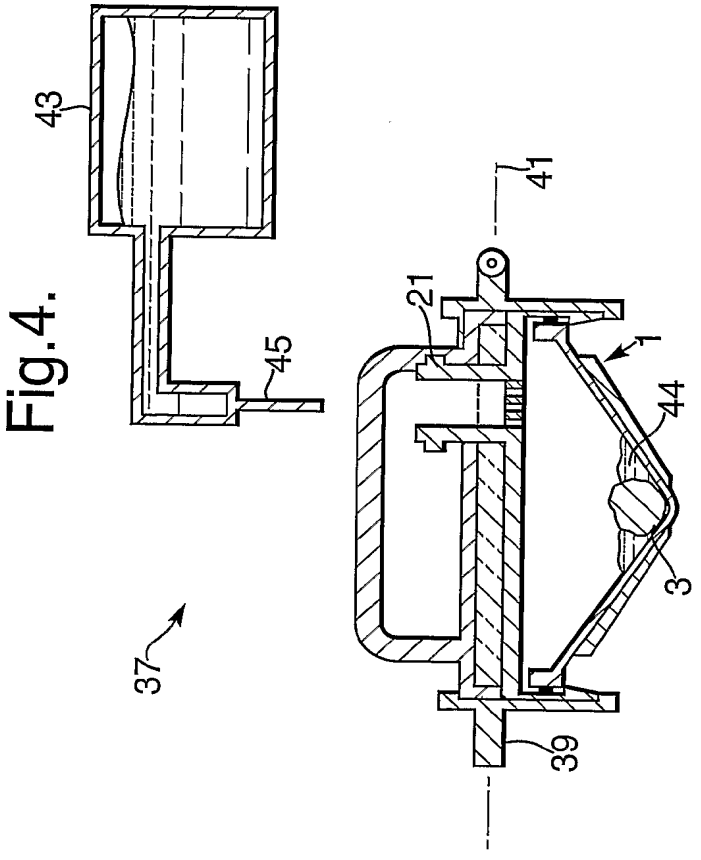


Fig.4.



INTERNATIONAL SEARCH REPORT

nal Application No
B2004/003434

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01F11/00 C12Q1/68 A61B10/00 G01N33/574

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01F C12Q A61B G01N A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 187 546 B1 (LOKTIONOV ALEXANDRE ET AL) 13 February 2001 (2001-02-13) cited in the application column 4, line 47 - column 5, line 9 column 13	1-4
X	US 2001/002985 A1 (KLEINSASSER JONATHAN) 7 June 2001 (2001-06-07) paragraphs '0052! - '0058!; figures 6,7	5,6,8,10
X	DE 15 98 515 A (GERHARDT FABRIK UND LAGER CHEM) 27 May 1971 (1971-05-27) the whole document	5,7,10
A	US 2002/119472 A1 (LAPIDUS STANLEY N ET AL) 29 August 2002 (2002-08-29) paragraph '0038!	1-4

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 October 2004	11/11/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Herberhold, C

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Int[illegible]al Application No
PCT/GB2004/003434

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 456 507 A (BRACONNIER THERESE) 12 December 1980 (1980-12-12)	11,14
Y	figure 1	13
Y	DE 199 10 836 A (KERNFORSCHUNGSANLAGE JUELICH) 21 September 2000 (2000-09-21) abstract	13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
IB2004/003434

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 6187546	B1	13-02-2001	AU	6883096 A	27-03-1997
			EP	0873502 A2	28-10-1998
			WO	9709600 A2	13-03-1997
			JP	11511982 T	19-10-1999
US 2001002985	A1	07-06-2001	AU	1574102 A	18-06-2002
			WO	0245619 A2	13-06-2002
			CA	2430758 A1	13-06-2002
DE 1598515	A	27-05-1971	DE	1598515 A1	27-05-1971
US 2002119472	A1	29-08-2002	US	6303304 B1	16-10-2001
			US	5952178 A	14-09-1999
			US	5741650 A	21-04-1998
			AU	3491999 A	01-11-1999
			CA	2328616 A1	21-10-1999
			EP	1073898 A1	07-02-2001
			JP	2002511585 T	16-04-2002
			WO	9953316 A1	21-10-1999
			AT	246806 T	15-08-2003
			AU	704696 B2	29-04-1999
			AU	2240697 A	22-08-1997
			CA	2215263 A1	07-08-1997
			DE	69629363 D1	11-09-2003
			DE	69629363 T2	09-06-2004
			DK	817968 T3	01-12-2003
			EP	1291657 A2	12-03-2003
			EP	0817968 A1	14-01-1998
			ES	2202497 T3	01-04-2004
			JP	2002515973 T	28-05-2002
			WO	9728450 A1	07-08-1997
FR 2456507	A	12-12-1980	FR	2456507 A1	12-12-1980
DE 19910836	A	21-09-2000	DE	19910836 A1	21-09-2000

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
15/634,607	**02/06/2023 03:43:08 PM ET**	**EXCTD-35239.304**

Title of Invention

FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1874	FILED BY	Stephanie Filandrinos
PATENT CENTER #	61551831	FILING DATE	06/27/2017
CUSTOMER #	173254	FIRST NAMED INVENTOR	Joost Louwagie
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Mary Ann Brow

Documents

TOTAL DOCUMENTS: 5

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2023-02-06_RCE-Form_EXCTD-003USCON2-35239_35239-304.pdf	3	Request for Continued Examination (RCE)	1628 KB
2023-02-06_IDS-SB08_EXCTD-003USCON2.35239_35239.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	162 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
sb0439.pdf	2	Internet Communications Authorization	190 KB

WO2000050640A1.pdf	33	Foreign Reference	1298 KB
WO2005014154A1.pdf	31	Foreign Reference	1267 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2023-02-06_RCE-Form_EXCTD-003USCON2-35239_35239-304.pdf	881AA3676B7B3159CA1ED186EA6F0C0971AFD27BFE8EDFF9CE1C701C4C65775543FDE582B6691389BE1E388A1884E491271D59FA0C9F91A6A8F4A219E91C874B
2023-02-06_IDS-SB08_EXCTD-003USCON2.35239_35239.pdf	A864DC87C9ADE278C70F113D87E6CDDFB9B8670C8DDA3D01EC9F586DD2FBD04C099640AA8A916137DFAFE2304BD374945A61852305D8E88114E175C3D931C9E3
sb0439.pdf	4507870AB0FCC5A80565B6682A1EB8E96756EDD4E8AC27A3C610D4BB5350E66E7623B301FBF6E7AC96DD80D4511E0ACCC12AA4B53E2B181BB7FCABA0565CDBBE
WO2000050640A1.pdf	3DAA5D5C9CC7BFA6A290F203990508685728 1DC6F61B6FE6A535DFE23693D254A47F8F50A92ABA4F67C1CBFB31726459B0F584211208893E8695681A0B6E8738
WO2005014154A1.pdf	4B1DF29ED26D4CC3058416C4362B64078ABBF42DE5F58CFFD7E661EC34B459B324D7E831F702FD7D241AD48CF3A159914FD8DEE6DC57F79554A188D53785C9A1

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: ECOMM.AUTH/ECOMM.WTDW
Doc Description: Internet Communications Authorization/Internet Communications Authorization Withdrawal

PTO/SB/439 (11-15)

AUTHORIZATION FOR INTERNET COMMUNICATIONS IN A PATENT APPLICATION OR REQUEST TO WITHDRAW AUTHORIZATION FOR INTERNET COMMUNICATIONS		
	Application No.	15/634,607
	Filing Date	06/27/2017
	First Named Inventor	JOOST LOUWAGIE
	Art Unit	1634
	Examiner Name	ETHAN WHISENANT
	Practitioner Docket No.	EXCT-34706.303

To: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I. To authorize permission for Internet Communications.

☒ Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned and practitioners in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via video conferencing, instant messaging, or electronic mail. I understand that a copy of these communications will be made of record in the application file. (MPEP 502.03)

II. To withdraw authorization for Internet Communications.

☐ The authorization given on _____, to the USPTO to communicate with the undersigned and any practitioner in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via Internet communications such as video conferencing, instant messaging, or electronic mail is hereby withdrawn. I understand that the withdrawal is effective when approved rather than when received.

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 42363.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Mary Ann D. Brow/ — Signature

02/06/2023 — Date

Mary Ann D. Brow — Typed or printed name

608-662-1277 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Juristic entities must be represented by a patent practitioner (see 37 CFR 1.31, which is applicable to any paper filed on or after September 16, 2012, that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below*.

☒ * Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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NOTICE OF ALLOWANCE AND FEE(S) DUE

173254 7590 03/29/2023

CASIMIR JONES, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

EXAMINER	
WHISENANT, ETHAN C	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/29/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/634,607	06/27/2017	Joost Louwagie	EXCTD-35239.304	1874

TITLE OF INVENTION: FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	06/29/2023

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

173254 7590 03/29/2023

CASIMIR JONES, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/634,607	06/27/2017	Joost Louwagie	EXCTD-35239.304	1874

TITLE OF INVENTION: FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	06/29/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
WHISENANT, ETHAN C	1634	435-006110

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via Patent Center or EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/634,607	06/27/2017	Joost Louwagie	EXCTD-35239.304	1874

173254 7590 03/29/2023

CASIMIR JONES, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

EXAMINER	
WHISENANT, ETHAN C	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/29/2023

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	**Application No.** 15/634,607	**Applicant(s)** Louwagie, Joost	
	Examiner Ethan C Whisenant	**Art Unit** 1634	**AIA (FITF) Status** No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 06 FEB 2023.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 82,84,87,89-94 and 96-100 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 06 FEB 2023.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ETHAN C WHISENANT/
Primary Examiner, Art Unit 1634

NOTICE OF ALLOWABILITY

► A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed on 06 FEB 2023 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Claims 82, 84, 87, 89-94 and 96-100 are pending.

► The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

REASON(S) FOR ALLOWANCE

► **Claim(s) 82, 84, 87, 89-94 and 96-100** is/are deemed to be allowable for the reason(s) of record , see the NOA mailed 02 DEC 2022. The Claims have now been renumbered as Claims 1-14 in the same order as presented by the applicant.

CONCLUSION

C. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ethan Whisenant whose telephone number is (571) 272-0754. The examiner can normally be reached Monday-Friday from 8:30 am -5:30 pm EST or any time via voice mail. If repeated attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731.

The Central Fax number for the USPTO is (571) 273-8300. Please note that the faxing of papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ETHAN C WHISENANT/
Primary Examiner, Art Unit 1634
ethan.whisenant@uspto.gov

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	**Art Unit**
	Ethan C Whisenant	1634

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/25/2023								
	1	-								
	2	-								
	3	-								
	4	-								
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	39	-								
	40	-								
	41	-								
	42	-								

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	Art Unit
	Ethan C Whisenant	1634

CLAIM		DATE								
Final	Original	03/25/2023								
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4	89	=								
5	90	=								
6	91	=								
7	92	=								
8	93	=								
9	94	=								

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	**Art Unit**
	Ethan C Whisenant	1634

CLAIM		DATE								
Final	Original	03/25/2023								
	95	-								
10	96	=								
11	97	=								
12	98	=								
13	99	=								
14	100	=								

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	**Art Unit**
	Ethan C Whisenant	1634

CPC - Searched*		
Symbol	**Date**	**Examiner**
C12Q 16886	11/22/2022	ECW
G01N 33/574	11/22/2022	ECW
Updated Search	03/24/2023	ECW

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

/ETHAN C WHISENANT/ Primary Examiner, Art Unit 1634	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	**Art Unit**
	Ethan C Whisenant	1634

Search Notes		
Search Notes	**Date**	**Examiner**
EAST (see transcript for databases and search terms)	06/23/2019	B. L. S.
Reviewed 15/010436 & 13/147570	06/23/2019	B. L. S.
EAST (see transcript for databases and search terms)	01/14, 15/2020	B. L. S.
STN (see transcript for databases and search terms)	01/14/2020	B. L. S.
EAST (updated)	08/04/2020	B. L. S.
EAST	06/16/2021	B. L. S.
EAST	03/22/2022	B. L. S.
PE2E Search	06/09/2022	B. L. S.
See the Examiner's Search Notes on the last pg of the NOA	11/22/2022	ECW
Updated Search	03/24/2023	ECW

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
C12Q	1/6886	11/22/2022	ECW
G01N	33/574	11/22/2022	ECW
Updated	Search	03/24/2023	ECW

/ETHAN C WHISENANT/ Primary Examiner, Art Unit 1634	

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	**Art Unit**
	Ethan C Whisenant	1634

CPC						
Symbol					**Type**	**Version**
C12Q	/	1	/	6886	F	2013-01-01
G01N	/	33	/	57446	I	2013-01-01
C12Q	/	2600	/	106	A	2013-01-01
C12Q	/	2600	/	154	A	2013-01-01
C12Q	/	2600	/	158	A	2013-01-01
G01N	/	2800	/	50	A	2013-01-01
G01N	/	2800	/	52	A	2013-01-01
G01N	/	2333	/	805	A	2013-01-01

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	14	
/ETHAN C WHISENANT/ Primary Examiner, Art Unit 1634	24 March 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20230325

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	**Art Unit**
	Ethan C Whisenant	1634

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C12Q1/6886	/	1	/	6886
G01N33/574	/	33	/	574

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	14	
/ETHAN C WHISENANT/ Primary Examiner, Art Unit 1634	24 March 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20230325

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/634,607	Louwagie, Joost
	Examiner	**Art Unit**
	Ethan C Whisenant	1634

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		14		27		40		53		66		79	7	92
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	9		22		35		48		61		74	3	87	14	100
	10		23		36		49		62		75		88		
	11		24		37		50		63		76	4	89		
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NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 14	
/ETHAN C WHISENANT/ Primary Examiner, Art Unit 1634 (Primary Examiner)	24 March 2023 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	15/634,607
				Filing Date	06/27/2017
				First Named Inventor	JOOST LOUWAGIE
				Art Unit	1634
				Examiner Name	WHISENANT
Sheet	1	of	2	Attorney Docket Number	EXCTD-35239.304

U.S. PATENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		6761702	2004-07-13	SMITH	

U.S. PUBLISHED PATENT APPLICATIONS

Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] (if known)	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		20020096469	2002-07-25	FAULKNER	
		20030086869	2003-05-08	STALLINGS	
		20040019298	2004-01-29	ZHOU	
		20050075543	2005-04-07	CALABRESE	
		20050244836	2005-11-03	TSANG	
		20070072214	2007-03-29	GARVIN	

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[5] Number[6] Kind Code[7] (if known)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Translation[8]
		WO 2000/050640	2000-08-31	EXACT LABORATORIES, INC.		
		WO 2005/014154	2005-02-17	LOOTS LIMITED		

NONPATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and-or country where published.	Translation[6]

Examiner Signature	/ETHAN C WHISENANT/	Date Considered	03/25/2023

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /E.C.W/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	15/634,607
				Filing Date	06/27/2017
				First Named Inventor	JOOST LOUWAGIE
				Art Unit	1634
				Examiner Name	WHISENANT
Sheet	2	of	2	*Attorney Docket Number*	EXCTD-35239.304

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

☐ Documents not provided herewith have been previously cited in parent U.S. patent application number ____ filed on_____. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Mary Ann D. Brow/	Date (YYYY-MM-DD)	2023-02-06
Name/Print	Mary Ann D. Brow	Registration Number	42363

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /E.C.W/

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[2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

[3] Applicant's unique citation designation number (optional).
[4] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.
[5] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).
[6] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[7] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible.
[8] Applicant is to place a check mark here if English language Translation is attached.
This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /E.C.W/

To: DOCKETING@CASIMIRJONES.COM,Genomic_docketing@cardinal-ip.com,
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Cc: PAIR_eOfficeAction@uspto.gov
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Mar 29, 2023 03:32:55 AM

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CASIMIR JONES, S.C.
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Application	Document	Mailroom Date	Attorney Docket No.
15634607	NOA	03/29/2023	EXCTD-35239.304
	1449	03/29/2023	EXCTD-35239.304

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Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

EXHIBIT 1009
Patent Owner's Ex. 2003, Page 874

Alimentary Pharmacology & Therapeutics

Comparative evaluation of a new bedside faecal occult blood test in a prospective multicentre study

N. HOEPFFNER*[1], Y. M. SHASTRI*[1], E. HANISCH†, W. RÖSCH‡, J. MÖSSNER§, W. F. CASPARY* & J. STEIN*

*Department of Medicine I, ZAFES, Centre of Internal Medicine, Johann Wolfgang Goethe University, Frankfurt/Main; †Asklepiosklinik, Dreieich-Langen; ‡Department of Medicine II, Hospital Nordwest, Frankfurt/Main; §Department of Medicine II, University Hospital Leipzig, Leipzig, Germany

Correspondence to:
Dr J. Stein, Department of Medicine I, ZAFES, J. W. Goethe University Frankfurt, Theodor-Stern-Kai 7, D - 60590 Frankfurt/Main, Germany.
E-mail: j.stein@em.uni-frankfurt.de

[1]These authors contributed equally to this study.

Publication data
Submitted 23 August 2005
First decision 12 September 2005
Resubmitted 29 September 2005
Accepted 29 September 2005

SUMMARY

Background
Faecal occult blood testing is an established method of colorectal neoplasia screening. Guaiac-based tests are limited by poor patient compliance, low sensitivity, specificity and positive predictive value. Newer immunochemical-based tests, accurate but tedious, require a well-established laboratory set up. There is need for simpler immunochemical tests that can be performed at the out-patient clinic.

Aim
To compare the performance characteristics of a new bedside immunological test strip device with a sensitive Guaiac-based and established immunochemical test for detection of faecal occult blood in patients undergoing colonoscopy.

Methods
A total of 389 consecutive patients from four centres who were referred for colonoscopy also provided the stool samples for detection of occult blood without dietary restrictions. Stool tests performed were (i) Guaiac-based, (ii) immunochemical enzyme-linked immunosorbent assay and (iii) bedside immunochemical strip test.

Results
At the optimal threshold level, the sensitivity and specificity of the beside immunochemical strip test for detection of significant colorectal neoplasia (adenomas >1.0 cm and carcinomas) were 60% and 95%, respectively.

Conclusions
This bedside immunochemical strip test proved to be a simple, convenient, non-cumbersome and accurate tool with similar performance characteristics for detection of any bleeding lesion including colorectal neoplasia when compared with an established immunochemical faecal occult blood test.

Aliment Pharmacol Ther **23**, 145–154

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doi:10.1111/j.1365-2036.2006.02702.x

Patent Owner's Ex. 2003, Page 875

INTRODUCTION

Colorectal cancer (CRC) accounted for about 1 million new cases in 2002; its worldwide prevalence is only second to that of breast cancer. It is one of the leading causes of cancer death in western societies with 25-fold variation in its occurrence across the globe.[1] In Europe, there were estimated to be 376 400 new cases of CRC amounting to 203 700 deaths in 2004[2] while in the US there are expected to be 145 200 CRC registrations and 56 290 deaths this year.[3] It is estimated that about half of these deaths could have been prevented if patients would have undergone CRC screening.[4] It has been observed that most cases of sporadic CRC arise from pre-existing adenomatous polyps.

The metastatic CRC [stage IV tumour node metastasis (TNM)] has a dismal survival of <5% when compared with early CRC (stage I TNM).[5] The prevalence of the disease, with the proven ability of screening to reduce mortality makes population-wide screening of CRC a lucrative health goal. An ideal screening test must be non-invasive, acceptable to patients, simple, have high sensitivity and specificity, inexpensive, cost-effective, easy to implement across a large population and should be effective in reducing morbidity and mortality from CRC in the screened population.[6]

The most widely accepted non-invasive method for detecting CRC is faecal occult blood testing (FOBT). It is routinely used world over for CRC screening and surveillance and has been in use now for more than three decades. Screening in asymptomatic populations with FOBTs followed by colonoscopy if tested positive have reduced mortality rates by 15–33%.[7–10] However, sensitivity of FOBTs ranges from 26% to 69% for detecting CRC.[11–14]

There are two main types of commercially available FOBTs: 'Guaiac-based tests' in which Guaiac blue colour change occurs because of the pseudoperoxidase activity of haeme in the stool; 'immunochemical tests' which detect globin portion of human haemoglobin (Hb) in the stool using anti-Hb antibodies.[15] A major disadvantage of Guaiac tests is the fact that they are not specific for human blood and can produce false-positive results when meat, fruit, or vegetables containing peroxidase have been ingested. Also bleeding in the upper gastrointestinal (GI) tract secondary to aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) can produce false-positive Guaiac-based tests.[16] This may lead to contraindicate colonoscopic examinations thus increasing the cost and risk of screening programmes. False-negative tests may occur with ingestion of high doses of vitamin C, which will prevent detection of cancer and will provide a false sense of security to the patient. Because of these shortcomings Guaiac-based tests are being replaced by immunochemical faecal occult blood tests (IFOBTs), despite being more expensive.

The IFOBTs, which are widely used as screening tests in Japan, have been shown to be superior to the Guaiac-based tests in sensitivities, with similar specificity, as reported both in known CRC[17] and in asymptomatic populations.[13, 18] This is because IFOBTs do not detect blood from the upper GI tract, do not react with plant peroxidases and animal Hb. Thus, there is no need of dietary or medical restriction. One of the studies has shown 66% increase in patient participation with the elimination of dietary restrictions.[19] Furthermore, sensitivity of IFOBTs is high for adenomas,[17] intramucosal cancer[20] and Dukes A cancer.[21] On the basis of these reports, it is expected that screening with IFBOTs may provide larger effects on the incidence reduction of advanced CRC when compared with the Guaiac-based tests. However, most IFOBTs require a suitable well-equipped laboratory, i.e. an enzyme-linked immunosorbent assay (ELISA) reader, limiting their widespread use because of logistics and higher costs.

Colonoscopy is considered the gold standard for CRC screening. But it is expensive, requires skilled endoscopist and may lead to life-threatening complications like perforation (one in 300 procedures).[22] However, complication rate varies in different studies and one of the recent studies in which more than 22 000 patients underwent screening colonoscopies (only diagnostic) by experienced endoscopists without any major complication or mortality.[23]

In a recent pilot study, we demonstrated a new immunological test strip device (bedside IFOBT) for the rapid, quantitative detection of FOB (Prevent ID CC, Preventis GmbH, Bensheim, Germany) and compared it with a widely used Guaiac-FOBT keeping ELISA-IFOBT as the gold standard. We showed that this bedside IFOBT is much more sensitive (76% vs. 30%) for detection of FOB than Guaiac-based test whereas specificity of both tests were comparable.[24] However, we did not perform colonoscopy in these patients.

In the present prospective study, we have evaluated the performance characteristics of this new bedside test for detection of FOB in patients undergoing colonoscopy. Experienced endoscopists carefully examined

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the entire large bowel, recorded and reported the presence of any bleeding lesion that could cause positive FOBT. If any such lesion was found it was biopsied or snared if indicated. We also compared it with another established IFOBT (ELISA) and a sensitive Guaiac-based FOBT.

Our study is peculiar and different from previous studies in that the patient population was not only of CRC screening patients but also constituted the patients referred to or admitted with colonic symptoms and many of them had known clinical diagnosis. Thus, we evaluated performance characteristics of FOBT not only in detecting neoplasia but also in detecting presence of microscopic faecal blood whether it was because of neoplasia, inflammatory bowel disease (IBD) or dysentery.

MATERIAL AND METHODS

Ethics

The study protocol was approved by the ethics committee of Frankfurt University Hospital. Written informed consent was obtained from all participants before entering the study.

Patients and healthy controls

Patients from four different centres who were referred for colonoscopy were invited to participate in the study. There were 237 patients who either had known clinical diagnosis (e.g. IBD) or were symptomatic suggestive of colonic disease while as 150 healthy patients underwent CRC screening. Patients with active GI bleeding, menstruation and past history of total colectomy were not included in the study.

Patients given appointments for colonoscopy were asked to provide one stool sample for detecting faecal blood. No dietary restrictions were advised to the patients. Stool sample was collected before starting the bowel preparation in a sterile box for Guaiac and immunological tests whereas for the bedside IFOBT we provided patients with a simple stool-collecting device (see below). Stool samples of these patients with or without pathological findings were tested. In a standard questionnaire patient's clinical history was recorded.

After standard bowel wash colonoscopies were performed by the endoscopists, who were not aware of FOBT findings, till the caecum using the standard colonoscopes. Patients who were poorly prepared or in whom caecum could not be reached were not included in the study. Histology was obtained from the routine biopsies, polypectomies and/or from surgery. Adenomas were classified as large (>10 mm) or small (<10 mm) as judged during colonoscopies using biopsy forceps as measure to assess polyp size. All data were collected prospectively and recorded on standardized questionnaire forms. If a neoplastic obstructive lesion was found during colonoscopies, it was biopsied and the patient was included in the study despite colonoscopy not being complete.

Faecal occult blood tests

Stool samples were applied to the three windows of a Guaiac-FOBT Haemoccult (Beckman Coulter, Inc., Fullerton, CA, USA) and further processed without rehydration as indicated by the manufacturer. On an especially Guaiac resin impregnated filter paper stool sample was placed. Once it had dried alcohol-stabilized hydrogen peroxide was put on the paper. A positive test was indicated by colour change to blue after 60 s.

A human Hb ELISA (Immundiagnostik AG, Bensheim, Germany) was used as a highly sensitive IFOBT. This test is based on Hb antibodies-precoated microtitre plates. To 100 mg of faeces wash buffer was added, mixed and centrifuged. About 100 L of this solution was incubated on the microtitre plates precoated with anti-Hb antibodies. After washing anti-Hb a peroxidase-labelled antibody was added, and was incubated for 1 h. Then, the substrate was added and incubated for 20 min and finally the stop solution was added so the colour changed from blue to yellow. Absorption was determined with an ELISA reader at 450 nm against reference value. According to the manufacturer a cut-off level of ≤10 g Hb/mL of stool was used.

An immunological FOB test strip device (Prevent ID CC) was used. It is a one-step immunochromatographic assay for rapid quantitative detection of human faecal blood. One of its major advantages, which should make it more acceptable to the patients, is the simplicity and non-messy sample collection. Figure 1 demonstrates the convenience of this test. The stick of the sample collection device was sticked into the faeces (approximately 2 cm), it was then inserted into the collection device containing an extraction buffer solution and the assembly was shaken thoroughly. This procedure was repeated three times sampling the

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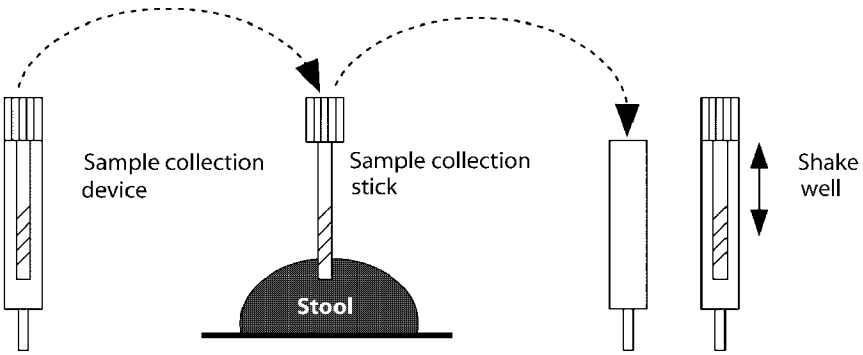


Figure 1. Sample collection for the bedside immunochemical faecal occult blood test (IFOBT; immunological test strip device; Prevent ID CC).

faeces from different sites. If the test was not performed within 1 day of sample collection it was stored at 2–8 C (as per the manufacturer's instructions). Two drops of this extracted sample were loaded into the sample opening of the test strip device, liquid faecal extract flows from the sample opening of the test device through the conjugate-release pad.

Principally it is a sandwich immunoassay in which gold-labelled anti-Hb antibodies bind to Hb (if present) in the sample. These complexes migrate over the test membrane until it passes the test zone, which consists of immobilized gold-labelled antibody–Hb complex and generates a violet band within 10 min (Figure 2a,b). To prevent false-negative an internal (control) line consisting of anti-IgG antibody has been added which indicates that the test has run properly. It has a very high sensitivity and can detect human Hb up to 10 g/mL.

The bedside FOBT was easy to use, and results did not depend on operator experience. All the three FOBTs were performed and reported by an experienced technician who was blinded to the patient's clinical profile.

Statistical analysis

For the statistical comparison of the non-parametrically distributed data, the Kruskall–Wallis ANOVA test was used (STATISTICA Version 5.0, StatSofts Inc., Tulsa, OK, USA). Sensitivity, specificity, positive predictive (PPV) and negative predictive (NPV) values of all the three FOBTs were determined.[25] Specificity was calculated for CR neoplasia as a whole group and not separately for adenoma and CRC. We used chi-square and Fisher's exact tests to compare differences in proportions amongst the tests. The *P*-values of <0.05 were considered as statistically significant (for sensitivity and specificity). Methods for proportions were used to calculate 95% confidence interval (CI).

RESULTS

A total of 387 consecutive patients underwent 407 tests, i.e. colonoscopies and FOBTs simultaneously. In 14 patients tests were repeated twice while in three patients they were repeated thrice. All the patients with repeat test were known cases of IBD. Their age ranged from 5 to 96 years (median age: 51 years). There was slight preponderance of females; 186 males and 201 females. The study duration was from January 2002 to December 2004. The major indications for colonoscopy were CRC screening, IBD, clinical suspicion of CR neoplasia or IBS, unexplained anaemia or diarrhoea, positive FOBT, etc. Comparative results of the test characteristics of asymptomatic screened patients and symptomatic patients are shown in Table 1. About 54 patients had evidence of CRC on colonoscopy (Table 2), the sensitivity of these tests to detect faecal Hb was 37.0%, 74.0% and 77.7% for the Guaiac-based test, the bedside IFOBT and the ELISA (cut-off <10 ng/mL) respectively (Table 3). Of 18 adenomas diagnosed, six were large (>10 mm) and 12 were small, i.e. <10 mm. The sensitivity of faecal Hb for any neoplasia (CR carcinoma plus large adenomas) was 29.1%, 59.7%, and 63.8% respectively (Table 3). Of 164 patients with normal colonic mucosa, 16 (9.7%) were positive with the Guaiac test, nine (5.5%) with the bedside IFOBT, whereas six (3.7%) were found positive with ELISA-IFOBT, i.e. false-positive.

About 141 (34.6%) patients revealed a lesion (bleeding) on colonoscopy which is fairly high when compared with screening population. This is because, ours was a hospital-based study, and mostly included symptomatic patients unlike the screening studies that usually includes asymptomatic healthy individuals. Active bleeding colonic lesions were found in 67 (43.2%) of total 155 IBD patients examined, 29 with

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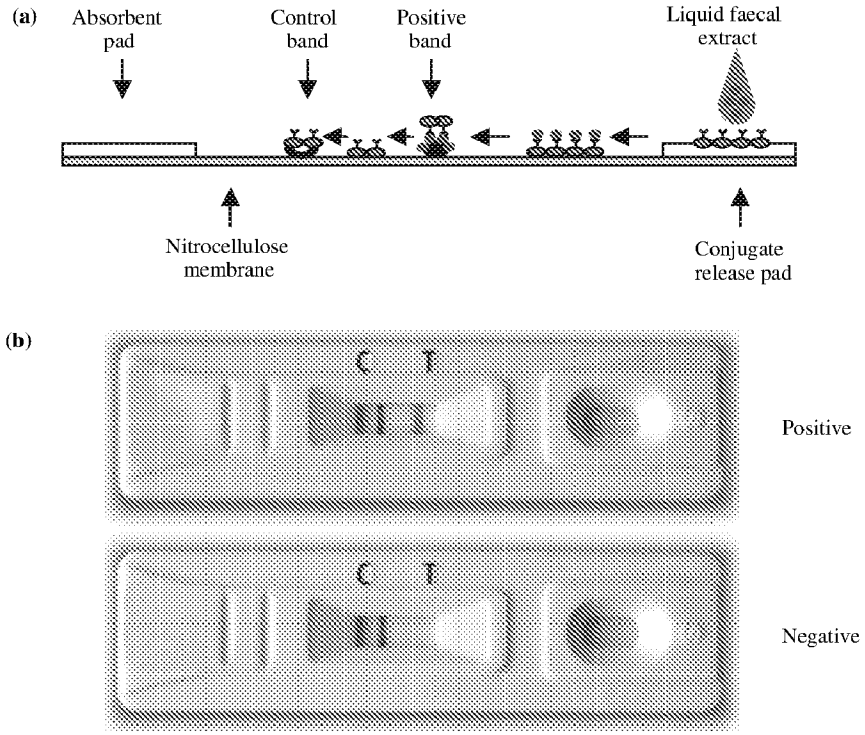


Figure 2. (a) Principle of the bedside immunochemical faecal occult blood test (IFOBT; immunological test strip device). After binding of faecal haemoglobin (blue dots) by antihaemoglobin antibodies, immuncomplexes are detected by a second nitrocellulose membrane-coupled antibody, resulting in the appearance of a positive band. The formation of a control band indicates the correct function of the test and unimpeded flow of faecal extracts through the device. (b) Photograph of Prevent ID CC test strips from a faecal specimen negative or positive for faecal occult blood.

Table 1. Test characteristics in screening and symptomatic patients

Diagnosis	*N*	Positive Guaiac-based test, *N* (%)	Positive bedside IFOBT, *N* (%)	Positive ELISA-IFOBT, *N* (%)
Screening patients				
Colorectal neoplasia*	6	2 (33.3)	4 (66.7)	4 (66.7)
Normal	150	17 (11.4)	8 (5.3)	5 (3.3)
Total	156	19 (12.2)	12 (7.7)	9 (5.8)
Symptomatic patients/patients with known disease				
Colorectal neoplasia*	66	19 (28.8)	39 (59)	42 (63.6)
IBD	155	39 (25.2)	68 (43.9)	68 (43.9)
Others	30	3 (10)	3 (10)	3 (10)
Total	251	61 (24.3)	110 (43.8)	113 (45.0)

* CRC + large adenomas.
CRC, colorectal cancer; IFOBT, immunochemical faecal occult blood test; IBD, inflammatory bowel disease; ELISA, enzyme-linked immunosorbent assay.

ulcerative colitis (UC) and 38 with Crohn's disease (CD). About 88 patients had inactive IBD (i.e. no evidence of bleeding lesion during colonoscopy), 22 UC and 66 CD. Two patients with pseudomembranous colitis had all the three FOBTs-positive in them. Sensitivity and specificity of rapid bedside test was found to be statistically significant in detecting any bleeding lesion (except adenomas) when compared with Guaiac-based tests.

DISCUSSION

The CRC and adenomas bleed intermittently[26] and positivity of FOBTs depend on degree of blood loss. Generally 2 mL of blood is necessary in stool to produce positive Guaiac-based tests.[5] When compared with CRC, adenomas bleed less frequently and also the bleeding is small in amount,[27] i.e. why sensitivity to detect them is lower. Also in the present study, the

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Table 2. Endoscopic diagnoses in 407 consecutive patients

Diagnosis	Total number	Positive Guaiac-based test, *N* (%)	Positive bedside IFOBT, *N* (%)	Positive ELISA-IFOBT, *N* (%)
Normal*	164	16 (9.7)	9 (5.5)	6 (3.7)
Colorectal cancer	54	20 (37.0)	40 (74.0)	42 (77.7)
Adenoma	18	1 (5.6)	3 (16.7)	4 (22.2)
Large (>10 mm)	6	1 (16.6)	2 (33.3)	3 (50.0)
Small (<10 mm)	12	0 (0)	0 (0)	0 (0)
IBD	155	39 (25.2)	68 (43.9)	68 (43.9)
UC	51			
Active	29	14 (48.3)	27 (93.1	28 (96.6)
Inactive	22	2 (9.1)	1 (4.5)	1 (4.5)
CD	104			
Active	38	16 (42.1)	36 (94.7)	36 (94.7)
Inactive	66	7 (10.6)	4 (6.0)	3 (4.5)
Diverticulosis	10	2 (20)	0 (0)	0 (0)
Pseudomembranous colitis	2	2 (100)	2 (100)	2 (100)
Hyperplastic polyps	4	0 (0)	0 (0)	0 (0)

* Includes 13 patients with irritable bowel syndrome and 15 patients with unexplained diarrhoea.
IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; IFOBT, immunochemical faecal occult blood test; ELISA, enzyme-linked immunosorbent assay.

Table 3. Sensitivities, specificities, PPV and NPV of three FOBTs in the different diagnostic groups

Parameters	Guaiac-based test	Bedside IFOBT	ELISA-IFOBT
Sensitivity (%)			
Adenoma	5.56 (0.14–27.29)	18.9 (3.58–41.42)	22.2* (6.41–47.64)
Cancer	37.0 (24.29–51.26)	74.0* (60.35–85.04)	77.7* (64.40–87.96)
Cancer + adenoma	29.1 (19.05–41.07)	59.7* (47.50–71.12)	63.8* (51.71–74.88)
Ulcerative colitis	48.2 (29.45–67.47)	93.1 (77.23–99.15)	96.5 (82.24–99.91)
Crohn's disease	42.1 (26.31–59.18)	94.7* (82.25–99.36)	94.7* (82.25–99.36)
Specificity (%)			
Cancer + adenoma	90.2 (84.64–94.32)	94.5 (89.84–97.46)	96.3* (92.21–98.65)
Ulcerative colitis	90.9 (70.84–98.88)	95.4* (77.16–99.88)	95.4 (77.16–99.88)
Crohn's disease	89.3 (79.36–95.63)	93.9* (85.20–98.32)	95.4* (87.29–99.05)
PPV (%)			
Adenoma	5.9 (0.15–28.69)	25.0 (5.49–57.19)	40.0 (12.16–73.76)
Cancer	55.6 (38.10–72.06)	81.6 (67.98–91.24)	87.5 (74.75–95.27)
Cancer + adenoma	56.7 (39.49–72.90)	82.6 (69.67–91.77)	88.4 (76.56–95.65)
Ulcerative colitis	87.5 (61.65–98.45)	96.4 (81.65–99.91)	96.6 (82.24–99.91)
Crohn's disease	69.6 (47.08–86.79)	90.0 (76.34–97.21)	92.3 (79.13–98.38)
NPV (%)			
Adenoma	89.7 (84.02–93.88)	91.2 (85.86–94.98)	91.9 (86.72–95.48)
Cancer	81.3 (74.89–86.70)	91.7 (86.49–95.40)	92.9 (87.99–96.30)
Cancer + adenoma	74.4 (67.72–80.28)	84.2 (78.16–89.18)	85.9 (79.99–90.56)
Ulcerative colitis	57.1 (39.35–73.68)	91.3 (71.96–98.93)	95.4 (77.16–99.88)
Crohn's disease	72.8 (61.81–82.13)	96.9 (89.16–99.62)	96.7 (89.32–99.63)

* $P < 0.05$ compared with Guaiac-based test.
Values in parentheses indicate 95% CI.
IFOBT, immunochemical faecal occult blood test; PPV, positive predictive value; NPV, negative predictive value; ELISA, enzyme-linked immunosorbent assay; CI, confidence interval.

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sensitivity and specificity of all the three FOBTs performed were lowest for detecting adenomas when compared with all the other lesions.

The results of IFOBT performed on 1 day of stool sample has been shown to be almost as specific as Guaiac-based testing performed on 3 days of stool sample.[21] We have also used 1-day stool sample for conducting FOBTs. Faecal Hb loses its antigenicity at room temperature mostly because of its degradation by faecal flora,[28] so we stored stool samples at 4 C before testing.

One of the studies has demonstrated an increase in sensitivity by 7.4% but worsening of specificity by 7.3% with rehydration of stool sample with Guaiac-based tests.[7] We also did not rehydrate the stool sample before performing the Guaiac-based test. There is a broad range of variation in the sensitivity of Guaiac-based tests. According to Ahlquist and Shuber in a review of eight prospective Guaiac-based tests against colonoscopy, in screening population, showed that sensitivity for diagnosing CRC was 26% while for large adenomas it was 12%.[29] We observed the sensitivity of Guaiac-based test for detecting CRC to be 37% and for large adenomas 16.6%. Although the specificity for Guaiac-based tests lies in the range of 88–98% actually it is misleading as false-positives outnumber the true positives. Only one in 10 subjects with a positive Guaiac-based test harbour a CRC.[15] Thus, despite high specificity PPV is low.

The clinical value of technically comparable test strip devices for the rapid qualitative detection of other human proteins, e.g. cardiac troponin T or prostate-specific antigen, has already been proven.[30, 31] Here, we have utilized the same principle for detection of FOB using an immunological test strip device.

We found the performance characteristics of the bedside IFOBT in detecting CRCs to be comparable with ELISA-IFOBT. The sensitivity of this new bedside IFOBT for diagnosing CR neoplasia was 59.7% vs. 63.8% (P 0.29) for ELISA-IFOBT whereas the specificity of these two tests were 94.5 vs. 96.3 (P 0.38) respectively. Thus, the sensitivity and specificity of bedside IFOBT was lower than that of ELISA-IFOBT, but not statistically significant.

The sensitivity of both IFOBTs in the present study was in the same range or even better than that reported by other authors, and far higher than the values reported for Guaiac tests without rehydration.[32, 33] A large screening study revealed sensitivity of IFOBT for detecting advanced neoplasia and cancer to be 27% and 66% respectively.[23]

Upon comparison of rate of positive CR neoplasia in earlier large studies we noticed that the positivity rate of FOBT varied significantly (Table 4). These differences could be because of varied study populations and also inherent biases of these studies. As some of them were conducted in asymptomatic screening populations whereas others were performed in patients who were diseased. Also it is well evident that there is a wide range of variation in the rate of positivity of FOBT in detecting CR neoplasia, e.g. the range of HemOccult positivity is 47–84% while that of HemeSelect is 49–91%. Immunochemical tests were shown to be more sensitive than Guaiac-based tests.

In a study using a simple brush sampling technique for collection of stool for immunochemical 'Insure FOBT' demonstrated improved compliance by 66%. About 82% patients preferred brush over the

Table 4. Comparison of positive FOBTs in patients with CR neoplasia (CRC and adenoma >10 mm; modified from Ref.[34])

		Rate of positive lesions* (%)				
Reference	Lesions	HO	SENSA	HS	ELISA-IFOBT	Bedside IFOBT
Ahlquist *et al.*[12]	102	19	–	–	–	–
St John *et al.*[44]	152	75	84	91	–	–
Gopalswamy *et al.*[45]	9	60	78	89	–	–
Allison *et al.*[13]	142	38	47	49	–	–
Greenberg *et al.*[34]	55	38	47	49	–	–
Our study	60	35	–	–	76	71

* Positive test in patients with lesion documented by endoscopy.
HO, HemOccult II; SENSA, HemOccult II SENSA; HS, HemSelect; IFOBT, immunochemical faecal occult blood test; CRC, colorectal cancer; ELISA, enzyme-linked immunosorbent assay.

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traditional sampling method using the spatula for performing FOBT.[19] Similarly in this bedside IFOBT also the sample preparation is very simple with minimal stool handling, so we hope that it will improve patient acceptability for FOBTs.

Specificity is an important determinant of the cost of FOB screening. Even small changes in test specificity result in large effects on the number of false-positives in a screening study, which are responsible for unnecessary colonoscopic examinations. In our study the specificity defined by false-positive results if a normal colonic mucosa and no other cause of GI bleeding were shown to be between 89.3% and 90.9% for the Guaiac test, 93.9% and 95.4% for bedside IFOBT and 95.4% and 96.3% for the ELISA-IFOBT which is comparable with earlier reports in the literature.

One peculiar feature of our study is that subjects with variety of symptoms and with suspected or known clinical or endoscopic findings were included and underwent these tests. As the real focus of our work was to evaluate the relative performance characteristics of each of these three tests in diagnosing positive FOB irrespective of clinical diagnosis (whether because of CR neoplasia or active IBD) unlike previous studies which had excluded patients with known clinical diagnosis-like IBD, etc.[34, 35] Non-malignant bleeding lesions were diagnosed in 69 of total 141 patients showing positive bleeding lesions on colonoscopy.

There are mainly two large reports in the literature mentioning diagnosis of IBD in patients undergoing FOBTs. Actually in these studies asymptomatic IBD were diagnosed upon performing colonoscopy in patients detected positive with FOBTs during CRC screening in large sample population.[36, 37]

On comparing the costs of these tests, Guaiac-based FOBT costs around 1 €, ELISA-FOBT cost 15–20 € whereas for bedside IFOBT one has to pay 3–5 € for each test performed.

Newer promising non-invasive methods for CRC screening include detection of stool DNA for mutations-like p53, K-ras, APC, BAT-26, etc. However, initial enthusiasm with these tests could not be realized in large trials comparing it with Guaiac-based tests.[38–41] The major drawbacks of it are lower sensitivities, exorbitant costs (up to 800$), compliance issue as patient needs to send an entire bowel movement with a minimum weight of 30 g to be sent to the laboratory, which may not be acceptable to many patients and last but not the least anxiety associated with false-positive tests.

The inherent limitations of our study include, at first that a highly selected population undergoing colonoscopy for several 'high-risk' indications were included, and so care should be taken when applying our results to an average-risk asymptomatic population. Nevertheless, we feel that useful information was obtained about the feasibility and relative specificity of this new bedside IFOBT in our population. And secondly the use of endoscopy as the standard for the presence of bleeding lesion. Though colonoscopy is widely considered as the gold standard for detection of colonic bleeding lesions, miss rates of up to 6% in detection of adenomatous polyps are documented.[42, 43] This might have caused underestimation of results of FOBT in our study.

The biggest advantages of this new bedside IFOBT are its simplicity, rapidity (needs just about 10 min), convenience, no need of cumbersome ELISA readers and the fact that it can be performed at the patient bedside or in doctor's office by any health care personnel. Thus, performing FOBT may become as simple as doing serum blood glucose determination using glucometer. This advance should make screening for CRC an attainable goal and should increase patient compliance.

To conclude, FOBT is the only method of CRC screening whose efficacy has been established in randomized-controlled trials. We have shown that the new bedside IFOBT, is more specific and appears to be more accurate than the Guaiac-based HemOccult test for the detection of significant colonic bleeding lesions including CR neoplasia. Although this constitutes a pilot study only, it provides some guidance as to which type of FOBT may be appropriate for large-scale screening programmes. Future larger-scale screening studies are required to evaluate it over a large asymptomatic sample size.

CONFLICT OF INTEREST

The authors have no conflicts of interest with the device manufacturers.

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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	15/634,607	Filing Date	2017-06-27	Docket Number (if applicable)	EXCTD-35239.304	Art Unit	1634
First Named Inventor	JOOST LOUWAGIE			Examiner Name	WHISENANT		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☐ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 504302

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

Signature of Registered U.S. Patent Practitioner			
Signature	/Mary Ann D. Brow/	Date (YYYY-MM-DD)	2023-06-28
Name	Mary Ann D. Brow	Registration Number	42363

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	*Ex Parte* Reexamination of U.S. Patent No. 11,634,781
Issued:	April 25, 2023
App. Ser. No.:	17/936,335
Filing Date:	September 28, 2022
Named Inventor:	Joost Louwagie
Title:	FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD

Mail Stop: *Ex Parte* Reexam
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR EX PARTE REEXAMINATION UNDER 37 C.F.R. § 1.510

Dear Commissioner:

Ex parte reexamination under 35 U.S.C. §§ 302-307 and 37 C.F.R. § 1.510 is requested of U.S. Patent No. 11,634,781 ("the '781 Patent"). Reexamination is requested of claims 1-20 as these claims are anticipated and/or obvious in view of the prior art identified in the citation of prior art under 37 C.F.R. §1.501 submitted herewith. The Rule 501 citation includes a PTO form PTO/SB/08a and copies of all prior art relied upon.

Requestor, as confirmed by the undersigned attorney, hereby certifies that the statutory estoppel provisions of 35 U.S.C. § 315(e)(1) and 35 U.S.C. § 325(e)(1) do not prohibit Requester from filing this *ex parte* reexamination request.

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Exhibits

Exhibit 1001: U.S. Patent No. 11,634,781 ("the '781 Patent")

Exhibit 1002: U.S. Patent No. 5,952,178 to Lapidus et al. ("Lapidus '178")

Exhibit 1003: U.S. Patent No. 5,741,650 to Lapidus et al. ("Lapidus '650")

Exhibit 1004: Ahlquist et al., "Stool DNA and Occult Blood Testing for Screen Detection of Colorectal Neoplasia," *Ann Intern Med.*, 149(7):441-W81 (published in final form October 7, 2008) ("Ahlquist")

Exhibit 1005: Patent Cooperation Treaty (PCT) Publication No. WO 2005/014154 to O'Neill ("O'Neill")

Exhibit 1006: European Patent Application Publication No. EP1366715A1 to De Luca et al. ("De Luca")

Exhibit 1007: Olson et al., "DNA Stabilization Is Critical for Maximizing Performance of Fecal DNA-Based Colorectal Cancer Tests," *Diagn Mol Pathol*, 14:183–191 (published September 2005) ("Olson")

Exhibit 1008: Leung et al., "Detection of Hypermethylated DNA or Cyclooxygenase-2 Messenger RNA in Fecal Samples of Patients With Colorectal Cancer or Polyps," *Am J Gastroenterol*, 102:1070–1076 (2007) ("Leung")

Exhibit 1009: Hoepffner et al., "Comparative evaluation of a new bedside faecal occult blood test in a prospective multicentre study," *Aliment Pharmacol Ther*, 23, 145–154 (published 2006) ("Hoepffner")

Exhibit 1010: U.S. Patent No. 4,859,610 to Maggio ("Maggio")

Exhibit 1011: U.S. Patent No. 5,196,167 to Guandagno et al. ("Guandagno")

Exhibit 1012: U.S. Patent No. 5,137,806 to LeMaistre et al. ("LeMaistre")

Exhibit 1013: U.S. Patent No. 5,527,676 to Vogelstein et al. ("Vogelstein")

Exhibit 1014: Declaration of Mr. Anthony P. Shuber, MS

I. Identification of Claims for Which Reexamination is Requested

In accordance with 37 C.F.R. § 1.510, reexamination of claims 1-20 of the '781 Patent is requested, in view of the references cited herein.

II. Overview of the '781 Patent

A. Summary of the Independent Claims

The '781 Patent issued on April 25, 2023 and includes one independent claim. As discussed below, independent claim 1 and its respective dependent claims are known in the prior art.

Claim 1 is the sole independent claim as shown below:

1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:

a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject by defecation directly into a sealable collection vessel;

b) removing a portion of the fecal sample to a separate sealable container to produce a removed portion and a remaining portion of the fecal sample;

c) combining the removed portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container; and

d) combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, and sealing the sealable collection vessel.

B. The '781 Patent Prosecution History Lacks Any Prior Art Rejections

The application for the '781 Patent was filed by Exact Sciences Corporation on September 28, 2022. As shown on the face of the '781 Patent (Ex. 1001), the '781 Patent claims priority to i) U.S. Patent Application No. 15/634,607, filed June 27, 2017, ii) U.S. Patent Application No. 15/010,436, filed January 29, 2016, iii) U.S. Patent Application No. 13/147,570, filed March 12, 2012, iv) PCT International Application No. PCT/GB2010/000180, filed February 3, 2010, and v) U.S. Provisional Patent Application No. 61/149,581, filed February 3, 2009.

The Office examined the application that resulted in the '781 Patent under the pre-AIA "first to invent" provisions as stated in the prosecution history of the '781 Patent. Requestor does not concede that the '781 Patent should be afforded this status but provides the anticipation and obviousness assertions herein according to the pre-AIA "first to invent" provisions as determined by the Office. However, if the '781 Patent is subject to the AIA's "first inventor to file" provisions, then Requestor notes that each prior art reference cited herein would qualify as prior art under AIA 35 U.S.C. § 102(a)(1).

Notably, the prosecution history of the application that resulted in the '781 Patent is ***completely devoid*** of prior-art based rejections, other than a provisional nonstatutory double patenting rejection over a co-pending Exact Sciences application related to the '781 Patent (i.e., co-pending U.S. Patent Application No. 15/634,607) and a provisional nonstatutory double patenting rejection over the co-pending Exact Sciences application in view of Ohlsson et al. (*Br J Cancer*, 2006; 95(2):218–225). The provisional nonstatutory double patenting rejections were made in an Office Action issued on January 11, 2023. In response, the applicant filed a Terminal Disclaimer on January 24, 2023. Thereafter, the provisional nonstatutory double patenting rejections were withdrawn.

The application was subsequently allowed on February 16, 2023. On pages 2-3 of the Notice of Allowance, the Examiner provided a statement of reasons for allowance, the entirety of which is quoted below:

> Claim(s) 1-20 is/are deemed to be allowable in light of the paper(s) filed 23 JAN 2023 and the persuasive argument(s) therein.

The application subsequently issued as the '781 Patent on April 25, 2023. Ex. 1001. As discussed below, the claimed subject matter in the '781 Patent was known in the prior art and lacks novelty and/or would have been obvious to one of ordinary skill in the art.

III. The Level of Ordinary Skill in the Art

As set forth above, the '781 Patent issued from an application claiming priority from a provisional application filed on February 3, 2009. As such, the earliest possible effective filing date that could be accorded the '781 Patent is February 3, 2009. Requestor does not concede that any or all claims of the '781 Patent should be afforded an effective filing date of February 3, 2009, but has nevertheless treated this date as the effective filing date of all claims solely for purposes of this Request.

The relevant field of "the invention of the '781 Patent is the field of processing and evaluating fecal samples. Ex. 1014 at paragraph 18. A person of ordinary skill in this field:

> would have had at least a Bachelor of Science degree in Biology (or a similar major) and several years of experience in the processing of biological samples, such as fecal samples from a human. Such a person would have been well-acquainted with methods of collecting fecal samples, preserving proteins and/or nucleic acids, including hemoglobin, DNA, and RNA, and subsequently evaluating the fecal samples for proteins and/or nucleic acids, including hemoglobin, DNA, and RNA, as of February 3, 2009.

Id. at paragraph 20.

IV. Claim Construction

During reexamination, claims are given the broadest reasonable interpretation consistent with the specification and limitations in the specification are not read into the claims. MPEP § 2258.

A. Claims 1-20

1. The Preamble of Independent Claim 1 is Not a Limitation

Requestor respectfully submits that the preamble of claim 1 is not a limitation. The Federal Circuit has held:

> In general, a preamble limits the invention if it recites essential structure or steps, or if it is necessary to give life, meaning, and vitality to the claim. Conversely, a preamble is not limiting where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention. No litmus test defines when a preamble limits claim scope. Some guideposts, however, have emerged from various cases discussing the preamble's effect on claim scope. For example, this court has held that Jepson claiming generally indicates intent to use the preamble to define the claimed invention, thereby limiting claim scope. Additionally, dependence on a particular disputed preamble phrase for antecedent basis may limit claim scope because it indicates a reliance on both the preamble and claim body to define the claimed invention. Likewise, when the preamble is essential to understand limitations or terms in the claim body, the preamble limits claim scope. Further, when reciting additional structure or steps underscored as important by the specification, the preamble may operate as a claim limitation. Moreover, clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention. Without such reliance, however, a preamble generally is not limiting when the claim body describes a structurally complete invention such that deletion of the

> preamble phrase does not affect the structure or steps of the claimed invention. Thus, preamble language merely extolling benefits or features of the claimed invention does not limit the claim scope without clear reliance on those benefits or features as patentably significant.

Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc., 289 F.3d 801, 808–09 (Fed. Cir. 2002) (internal quotations and citations omitted).

The preamble of claim 1 of the '781 Patent does not recite any essential structure or steps and is not necessary to give life, meaning, or vitality to the claim. Instead, claim 1 defines a complete method in the claim body and uses the preamble only to state a purpose or intended use for the alleged invention. Further, claim 1 of the '781 Patent is not drafted in Jepson format. Additionally, the preamble of claim 1 of the '781 Patent does not establish dependence on a particular disputed preamble phrase for antecedent basis as there is no apparent reliance on both the preamble and claim body to define the claimed invention, nor is the preamble of claim 1 of the '781 Patent essential to understand limitations or terms in the claim body. The preamble of claim 1 of the '781 Patent does not recite additional structure or steps underscored as important by the specification. Finally, there is no clear reliance on the preamble of claim 1 of the '781 Patent during prosecution to distinguish the claimed invention from the prior art. In summary, the preamble of claim 1 of the '781 Patent merely extols benefits or features of the claimed invention and Requestor asserts that the preamble of claim 1 is not a limitation.

2. "Without Freezing" Refers to a Temperature or Temperature Range Above 0°C (32°F)

All claims require that a fecal sample is processed "without freezing." The ordinary meaning of "freezing" is "being at or below the temperature at which water freezes" according to Merriam-Webster's Medical Dictionary (*available at* https://www.merriam-webster.com/dictionary/freezing). The temperature at which water freezes is known to be 0°C (32°F). Ex. 1014 at paragraph 27. Therefore, any temperature above 0°C (32°F), or a temperature range that includes a temperature above 0°C (32°F), would be understood as "without freezing" by those of ordinary skill in the art. *Id.*

3. "At Home" Refers to a Location Other Than a Testing Facility

All claims require that the fecal sample is collected "at home." The '781 Patent uses this term primarily to distinguish the location of collection from the testing facility. For instance, the '781 Patent states that "[f]ollowing collection of the sample and suitable processing, the method may further comprise forwarding or otherwise delivering the removed portion of the collected faecal sample *to a laboratory* for performing step (a) of the method, as defined herein, on the removed portion of the collected faecal sample." *Id.* at column 18, lines 32-35 (emphasis added). Similarly, dependent claim 2 of the '781 Patent indicates that the method of claim 1 *further comprises* "delivering the [fecal sample collected at home] to a medical diagnostics laboratory." *Id.* at column 45, lines 39-44.

Therefore, a person of ordinary skill in the art would understood "at home", as used in the '781 Patent, to refer to a location other than the testing facility. Ex. 1014 at paragraph 28.

B. Claims 5-11

1. "Epigenetic Modification" is an Alteration in DNA

Regarding claims 5-11, the '781 Patent defines "epigenetic modification" such that it includes "any alteration in the DNA, generally resulting in diminished gene expression, which is mediated by mechanisms other than alterations in the primary nucleotide sequence of a gene." Ex. 1001 at column 12, lines 35-39. For instance, the '781 patent describes that "[i]n specific embodiments, the epigenetic modification is methylation." *Id.* at column 12, line 46-47. This definition of "epigenetic modification" provided by the '781 Patent is consistent with the definition of "epigenetic modification" as understood by those of ordinary skill in the art. Ex. 1014 at paragraph 29.

V. Other Supporting Evidence

A. Declaration of Mr. Anthony P. Shuber, MS

The Declaration of Mr. Anthony P. Shuber, MS is being submitted with this Request as Exhibit 1014 to "explain the contents or pertinent dates of prior art patents or printed publications in more detail." See MPEP § 2258(I)(E). Mr. Shuber has extensive experience in the fields of diagnostics and applied genomics, including a Bachelor of Science degree in Biology and a Master of Science degree in Molecular and Developmental Biology from

Marquette University in Milwaukee, Wisconsin. *See* Mr. Anthony P. Shuber curriculum vitae (Ex. 1014).

Mr. Shuber's work in the field includes developing several DNA diagnostics tests as well as diagnostics in oncology, with a focus on the early detection of cancer. He is currently the Chief Innovation Officer at Harbinger Health. Mr. Shuber is a named inventor or author on several prior art references cited herein, including Ex. 1002, Ex. 1003, and Ex. 1007.

His declaration provides factual evidence regarding the level of skill in the art, the prior art references, the scope and content of the prior art, and technical information relevant to the '781 Patent, as well as explaining why the claimed invention would have been obvious to a person of ordinary skill in the art.

VI. Statement Pointing Out Each Substantial New Question of Patentability

This Section addresses the substantial new questions of patentability and is organized by cited references.

As explained above, the Office did not issue prior art-based rejections during the examination that resulted in the '781 Patent. Moreover, with the exception of O'Neill, ***none of the prior art references identified below and discussed herein were cited*** by the Patentee or by the Office in the course of examination that resulted in the '781 Patent. Although O'Neill was cited by the Patentee, it was not utilized in any prior-art based rejection during the examination that resulted in the '781 Patent.

Accordingly, the following prior art references (except O'Neill) are ***newly cited*** in this reexamination request and raise substantial new questions of patentability because they are highly relevant to the claims of the '781 Patent as shown below and have not been substantively considered by the USPTO:

Prior Art Citation	Ex. No.	Summary
U.S. Patent No. 5,952,178 to Lapidus et al. ("**Lapidus '178**")	1002	Lapidus '178 is a granted U.S. patent and discloses methods for processing and testing a fecal sample, including evaluation of proteins and nucleic acids. *Id.* at, *e.g.,* column 7, line 59 – column 9, line 50. Fecal samples are collected from a human subject,

		separated into two or more portions, and combined with buffers. Lapidus '178 was patented on September 14, 1999 and therefore is prior art under pre-AIA 35 U.S.C. § 102(b) against the challenged claims.
U.S. Patent No. 5,741,650 to Lapidus et al. ("**Lapidus '650**")	1003	Lapidus '650 is a granted U.S. patent and discloses methods for processing and testing a fecal sample, including evaluation of proteins and nucleic acids. *Id.* at, *e.g.,* column 7, line 12 – column 8, line 25. Fecal samples are collected from a human subject, separated into two or more portions, and combined with buffers. Lapidus '650 was patented on April 21, 1998 and therefore is prior art under pre-AIA 35 U.S.C. § 102(b) against the challenged claims.
Ahlquist et al., "Stool DNA and Occult Blood Testing for Screen Detection of Colorectal Neoplasia," *Ann Intern Med.*, 149(7):441-W81 (published in final form October 7, 2008) ("**Ahlquist**")	1004	**Ahlquist** is a journal article and discloses collection of stool and comparison of stool DNA and fecal blood testing for detection of colorectal neoplasia. *Id.* at Abstract. Fecal samples are collected from a human subject, separated into two or more portions, and analyzed for both nucleic acids and blood proteins. Ahlquist was published and publicly available at least as early as October 7, 2008. Ex. 1014 at paragraph 37. Therefore, Ahlquist is at least prior art under pre-AIA 35 U.S.C. § 102(a) against the challenged claims.
Patent Cooperation Treaty (PCT) Publication No. WO 2005/014154 to O'Neill ("**O'Neill**")	1005	**O'Neill** is a published PCT application and discloses a method of removing cellular material from the surface of a fecal stool in a container. *Id.* at Abstract. The patient collects a fecal sample at home by defecation directly into a sealable container and then a portion of the fecal sample

		(cellular material) is removed for analysis of DNA, RNA, proteins, and the like. O'Neill was published and publicly available on February 17, 2005, and therefore is at least prior art under pre-AIA 35 U.S.C. § 102(b) against the challenged claims.
European Patent Application Publication No. EP1366715A1 to De Luca et al. ("**De Luca**")	1006	**De Luca** is a published European patent application and discloses an extraction tube for collection of fecal samples and combination with a buffer. *Id.* at [0019]. The extraction tube contains a sealable cap and the tube is utilized for laboratory immunological tests, such as for qualitative or quantitative determination of hemoglobin. De Luca was published and publicly available on December 3, 2003, and therefore is at least prior art under pre-AIA 35 U.S.C. § 102(b) against the challenged claims.
Olson et al., "DNA Stabilization Is Critical for Maximizing Performance of Fecal DNA-Based Colorectal Cancer Tests," *Diagn Mol Pathol*, 14:183–191 (published September 2005) ("**Olson**")	1007	**Olson** is a journal article and discloses collection of stool and detection of fecal DNA. *Id.* at Abstract. Fecal samples are collected from a human subject and a stabilizing buffer was added to the samples. Addition of the stabilizing buffer was shown to provide a significant increase in recovery of DNA from fecal samples. *Id.* Olson was published and publicly available in September 2005. Ex. 1014 at paragraph 40. Therefore, Olson is at least prior art under pre-AIA 35 U.S.C. § 102(b) against the challenged claims.
Leung et al., "Detection of Hypermethylated DNA or Cyclooxygenase-2 Messenger RNA in Fecal Samples of	1008	**Leung** is a journal article and discloses collection of stool and detection of fecal DNA. *Id.* at Abstract. Fecal samples are collected from a human subject and analyzed for hypermethylated DNA via

Patients With Colorectal Cancer or Polyps," *Am J Gastroenterol*, 102:1070–1076 (2007) ("**Leung**")		PCR and for mRNA via RT-PCR. Leung was published and publicly available in 2007. Ex. 1014 at paragraph 41. Therefore, Leung is at least prior art under pre-AIA 35 U.S.C. § 102(b) against the challenged claims.
Hoepffner et al., "Comparative evaluation of a new bedside faecal occult blood test in a prospective multicentre study," *Aliment Pharmacol Ther*, 23, 145–154 (published 2006) ("**Hoepffner**")	1009	**Hoepffner** is a journal article and discloses a comparison of characteristics of a new bedside immunological test strip device with a sensitive Guaiac-based and established immunochemical test for detection of faecal occult blood in patients. *Id.* at Abstract. The concentrations of hemoglobin in nanograms/milliliter (ng/ml) resulting in a positive blood test in fecal samples is discussed. Hoepffner was published and publicly available in 2006. Ex. 1014 at paragraph 42. Therefore, Hoepffner is at least prior art under pre-AIA 35 U.S.C. § 102(b) against the challenged claims.
U.S. Patent No. 4,859,610 to Maggio **("Maggio")**	1010	**Maggio** is a granted U.S. patent and discloses a device that is used for homogenizing and analyzing fecal samples. *Id.* at, *e.g.,* column 4, lines 7-8. Fecal sample and phosphate buffered saline are homogenized in a separate sealable container (i.e., vessel) that contains a cap and seal. Maggio was patented on August 22, 1989 and therefore is prior art under pre-AIA 35 U.S.C. § 102(b) against the challenged claims. Maggio is cited herein as an evidentiary reference only.

This Request seeks reexamination based on the following proposed rejections that raise substantial new questions of patentability for all claims of the '781 Patent. The specific application of the newly cited prior art references to such claims is detailed in Section VIII:

Claim	Prior Art Rendering Claims Anticipated Under 35 USC § 102(b)
1	Lapidus '178 (Ex. 1002)
	Lapidus '650 (Ex. 1003)
2	Lapidus '178
	Lapidus '650
3	Lapidus '178
	Lapidus '650
4	Lapidus '178
	Lapidus '650
12	Lapidus '178
	Lapidus '650

Claim	Prior Art Combinations Rendering Claims Obvious Under 35 USC § 103(a)
1	Lapidus '178
	Lapidus '650
	Lapidus '178 in view of De Luca (Ex. 1006) and Olson (Ex. 1007)
	Lapidus '650 in view of De Luca and Olson
	Ahlquist (Ex. 1004) in view of De Luca and Olson
	O'Neill (Ex. 1005) in view of De Luca and Olson
2	Lapidus '178
	Lapidus '650
	Lapidus '178 in view of De Luca and Olson
	Lapidus '650 in view of De Luca and Olson
	Ahlquist in view of De Luca and Olson
	O'Neill in view of De Luca and Olson
3	Lapidus '178
	Lapidus '650
	Lapidus '178 in view of De Luca and Olson
	Lapidus '650 in view of De Luca and Olson

	Ahlquist in view of De Luca and Olson
	O'Neill in view of De Luca and Olson
4	Lapidus '178
	Lapidus '650
	Lapidus '178 in view of De Luca and Olson
	Lapidus '650 in view of De Luca and Olson
	Ahlquist in view of De Luca and Olson
	O'Neill in view of De Luca and Olson
5	Lapidus '178 in view of De Luca, Olson, and Leung
	Lapidus '650 in view of De Luca, Olson, and Leung
	Ahlquist in view of De Luca and Olson
	O'Neill in view of De Luca, Olson, and Leung
6	Lapidus '178 in view of De Luca, Olson, and Leung
	Lapidus '650 in view of De Luca, Olson, and Leung
	Ahlquist in view of De Luca and Olson
	O'Neill in view of De Luca, Olson, and Leung
7	Lapidus '178 in view of De Luca, Olson, and Leung
	Lapidus '650 in view of De Luca, Olson, and Leung
	Ahlquist in view of De Luca, Olson, and Leung
	O'Neill in view of De Luca, Olson, and Leung
8	Lapidus '178 in view of De Luca, Olson, and Leung
	Lapidus '650 in view of De Luca, Olson, and Leung
	Ahlquist in view of De Luca, Olson, and Leung
	O'Neill in view of De Luca, Olson, and Leung
9	Lapidus '178 in view of De Luca, Olson, and Leung
	Lapidus '650 in view of De Luca, Olson, and Leung
	Ahlquist in view of De Luca, Olson, and Leung
	O'Neill in view of De Luca, Olson, and Leung
10	Lapidus '178 in view of De Luca, Olson, and Leung
	Lapidus '650 in view of De Luca, Olson, and Leung

	Ahlquist in view of De Luca, Olson, and Leung
	O'Neill in view of De Luca, Olson, and Leung
11	Lapidus '178 in view of De Luca, Olson, and Leung
	Lapidus '650 in view of De Luca, Olson, and Leung
	Ahlquist in view of De Luca, Olson, and Leung
	O'Neill in view of De Luca, Olson, and Leung
12	Lapidus '178
	Lapidus '650
	Lapidus '178 in view of De Luca, Olson, and Leung
	Lapidus '650 in view of De Luca, Olson, and Leung
	Ahlquist in view of De Luca, Olson, and Leung
	O'Neill in view of De Luca, Olson, and Leung
13	Lapidus '178 in view of De Luca, Olson, and Leung
	Lapidus '650 in view of De Luca, Olson, and Leung
	Ahlquist in view of De Luca, Olson, and Leung
	O'Neill in view of De Luca, Olson, and Leung
14	Lapidus '178 in view of De Luca and Olson
	Lapidus '650 in view of De Luca and Olson
	Ahlquist in view of De Luca, Olson, and Leung
	O'Neill in view of De Luca and Olson
15	Lapidus '178 in view of De Luca and Olson
	Lapidus '650 in view of De Luca and Olson
	Ahlquist in view of De Luca and Olson
	O'Neill in view of De Luca and Olson
16	Lapidus '178 in view of De Luca, Olson, and Hoepffner (Ex. 1009)
	Lapidus '650 in view of De Luca, Olson, and Hoepffner
	Ahlquist in view of De Luca, Olson, and Hoepffner
	O'Neill in view of De Luca, Olson, and Hoepffner
17	Lapidus '178 in view of De Luca, Olson, and Hoepffner
	Lapidus '650 in view of De Luca, Olson, and Hoepffner

	Ahlquist in view of De Luca, Olson, and Hoepffner
	O'Neill in view of De Luca, Olson, and Hoepffner
18	Lapidus '178 in view of De Luca, Olson, and Hoepffner
	Lapidus '650 in view of De Luca, Olson, and Hoepffner
	Ahlquist in view of De Luca, Olson, and Hoepffner
	O'Neill in view of De Luca, Olson, and Hoepffner
19	Lapidus '178 in view of De Luca, Olson, and Hoepffner
	Lapidus '650 in view of De Luca, Olson, and Hoepffner
	Ahlquist in view of De Luca, Olson, and Hoepffner
	O'Neill in view of De Luca, Olson, and Hoepffner
20	Lapidus '178 in view of De Luca, Olson, and Hoepffner
	Lapidus '650 in view of De Luca, Olson, and Hoepffner
	Ahlquist in view of De Luca, Olson, and Hoepffner
	O'Neill in view of De Luca, Olson, and Hoepffner

Section VIII. provides a further explanation of each of the references discussed in this Section. As explained below, the prior art references relied on here disclose all of the limitations of claims 1-20 of the '781 Patent. In view of the prior art, the challenged claims are anticipated "if each and every element as set forth in the claim[s] is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, (Fed. Cir. 1987). Furthermore, in view of this prior art, and taking into account the knowledge, experience, and creativity of a person of ordinary skill in the art, such a person would have found the challenged claims to be "a predictable use of prior art elements according to their established functions," *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 417 (2007), and therefore obvious. Requestor, therefore, respectfully submits that substantial new questions of patentability have been raised by the prior art cited herein.

A. Lapidus '178

Lapidus '178 (Ex. 1002) is a granted U.S. patent owned by Exact Sciences Corporation and discloses methods for processing and testing a fecal sample, including evaluation of proteins and nucleic acids. *Id.* at, *e.g.,* column 7, line 59 – column 9, line 50. Fecal samples are collected

from a human subject and were sealed in a container, separated into two or more portions, and combined with buffers. Lapidus '178 was patented on September 14, 1999 and therefore is prior art under pre-AIA 35 U.S.C. § 102(b) against the challenged claims. Lapidus '178 was not cited during prosecution of the '781 Patent.

As discussed fully in Section VIII. below, Lapidus '178 anticipates the elements of certain claims. Thus, the technological teachings of Lapidus '178 alone raise a substantial new question of patentability at least with respect to claims 1, 2, 3, 4, and 12 of the '781 Patent.

B. Lapidus '650

Lapidus '650 (Ex. 1003) is a granted U.S. patent owned by Exact Sciences Corporation and discloses methods for processing and testing a fecal sample, including evaluation of proteins and nucleic acids. *Id.* at, *e.g.,* column 7, line 12 – column 8, line 25. Fecal samples are collected from a human subject and were sealed in a container, separated into two or more portions, and combined with buffers. Lapidus '650 was patented on April 21, 1998 and therefore is prior art under pre-AIA 35 U.S.C. § 102(b) against the challenged claims. Lapidus '650 was not cited during prosecution of the '781 Patent.

As discussed fully in Section VIII. below, Lapidus '650 anticipates the elements of certain claims. Thus, the technological teachings of Lapidus '650 alone raise a substantial new question of patentability at least with respect to claims 1, 2, 3, 4, and 12 of the '781 Patent.

C. Lapidus '178 in view of De Luca and Olson

Lapidus '178 is discussed briefly above. De Luca (Ex. 1006) is a published European patent application and discloses an extraction tube for collection of fecal samples and combination with a buffer. *Id.* at [0019]. The extraction tube contains a sealable cap and the tube is utilized for laboratory immunological tests, such as for qualitative or quantitative determination of hemoglobin. De Luca was published and publicly available on December 3, 2003, and therefore is at least prior art under pre-AIA 35 U.S.C. § 102(b) against the challenged claims. De Luca was not cited during prosecution of the '781 Patent.

Olson (Ex. 1007) is a journal article and discloses collection of stool and detection of fecal DNA. *Id.* at Abstract. Fecal samples are collected from a human subject and a stabilizing buffer was added to the samples. Addition of the stabilizing buffer was shown to provide a significant increase in recovery of DNA from fecal samples. *Id.* Olson was published and

publicly available in September 2005 and therefore is at least prior art under pre-AIA 35 U.S.C. § 102(b) against the challenged claims. Olson was not cited during prosecution of the '781 Patent.

As discussed fully in Section VIII. below, the combined teachings of Lapidus '178, De Luca, and Olson render certain claims to be obvious. Thus, the technological teachings of Lapidus '178, De Luca, and Olson raise a substantial new question of patentability at least with respect to claims 1-4 and 14-15 of the '781 Patent.

D. Lapidus '650 in view of De Luca and Olson

Lapidus '650, De Luca, and Olson are discussed briefly above. As discussed fully in Section VIII. below, the combined teachings of Lapidus '650, De Luca, and Olson render certain claims to be obvious. Thus, the technological teachings of Lapidus '650, De Luca, and Olson raise a substantial new question of patentability at least with respect to claims 1-4 and 14-15 of the '781 Patent.

E. Ahlquist in view of De Luca and Olson

Ahlquist is a journal article and discloses collection of stool and comparison of stool DNA and fecal blood testing for detection of colorectal neoplasia. *See* Abstract. Fecal samples are collected from a human subject, separated into two or more portions, and analyzed for both nucleic acids and blood proteins. Ahlquist was published and publicly available at least as early as October 7, 2008 and therefore is at least prior art under pre-AIA 35 U.S.C. § 102(a) against the challenged claims. Ahlquist was not cited during prosecution of the '781 Patent.

De Luca and Olson are discussed briefly above. As discussed fully in Section VIII. below, the combined teachings of Ahlquist, De Luca, and Olson render certain claims to be obvious. Thus, the technological teachings of Ahlquist, De Luca, and Olson raise a substantial new question of patentability at least with respect to claims 1-6 and 15 of the '781 Patent.

F. O'Neill in view of De Luca and Olson

O'Neill (Ex. 1005) is a published PCT application and discloses a method of removing cellular material from the surface of a fecal stool in a container. *Id.* at Abstract. The patient collects a fecal sample at home by defecation directly into a sealable container and then a portion

of the fecal sample (cellular material) is removed for analysis of DNA, RNA, proteins, and the like. O'Neill was published and publicly available on February 17, 2005, and therefore is at least prior art under pre-AIA 35 U.S.C. § 102(b) against the challenged claims. O'Neill was cited during prosecution of the '781 Patent but was not included in any prior art rejection.

De Luca and Olson are discussed briefly above. As discussed fully in Section VIII. below, the combined teachings of O'Neill, De Luca, and Olson render certain claims to be obvious. Thus, the technological teachings of O'Neill, De Luca, and Olson raise a substantial new question of patentability at least with respect to claims 1-4, 14, and 15 of the '781 Patent.

G. Lapidus '178 in view of De Luca, Olson, and Leung

The teachings of Lapidus '178, De Luca, and Olson are briefly described above.

Leung is a journal article and discloses collection of stool and detection of fecal DNA. *Id.* at Abstract. Fecal samples are collected from a human subject and analyzed for hypermethylated DNA via PCR and for mRNA via RT-PCR. Leung was published and publicly available in 2007 and therefore is at least prior art under pre-AIA 35 U.S.C. § 102(b) against the challenged claims. Leung was not cited during prosecution of the '781 Patent.

As discussed fully in Section VIII. below, the combined teachings of Lapidus '178, De Luca, Olson, and Leung render certain claims to be obvious. Thus, the technological teachings of Lapidus '178, De Luca, Olson, and Leung raise a substantial new question of patentability at least with respect to claims 5-13 of the '781 Patent.

H. Lapidus '650 in view of De Luca, Olson, and Leung

The teachings of Lapidus '650, De Luca, Olson, and Leung are discussed briefly above. As discussed fully in Section VIII. below, the combined teachings of Lapidus '650, De Luca, Olson, and Leung render certain claims to be obvious. Thus, the technological teachings of Lapidus '650, De Luca, Olson, and Leung raise a substantial new question of patentability at least with respect to claims 5-13 of the '781 Patent.

I. Ahlquist in view of De Luca, Olson, and Leung

The teachings of Ahlquist, De Luca, Olson, and Leung are discussed briefly above. As discussed fully in Section VIII. below, the combined teachings of Ahlquist, De Luca, Olson, and

Leung render certain claims to be obvious. Thus, the technological teachings of Ahlquist, De Luca, Olson, and Leung raise a substantial new question of patentability at least with respect to claims 7-14 of the '781 Patent.

J. O'Neill in view of De Luca, Olson, and Leung

The teachings of O'Neill, De Luca, Olson, and Leung are discussed briefly above. As discussed fully in Section VIII. below, the combined teachings of O'Neill, De Luca, Olson, and Leung render certain claims to be obvious. Thus, the technological teachings of O'Neill, De Luca, Olson, and Leung raise a substantial new question of patentability at least with respect to claims 5-13 of the '781 Patent.

K. Lapidus '178 in view of De Luca, Olson, and Hoepffner

The teachings of Lapidus '178, De Luca, and Olson are discussed briefly above.

Hoepffner is a journal article and discloses a comparison of characteristics of a new bedside immunological test strip device with a sensitive Guaiac-based and established immunochemical test for detection of faecal occult blood in patients. *Id.* at Abstract. The concentrations of hemoglobin in nanograms/milliliter (ng/ml) resulting in a positive blood test in fecal samples is discussed. Hoepffner was published and publicly available in 2006 and therefore is at least prior art under pre-AIA 35 U.S.C. § 102(b) against the challenged claims. Hoepffner was not cited during prosecution of the '781 Patent.

As discussed fully in Section VIII. below, the combined teachings of Lapidus '178, De Luca, Olson, and Hoepffner render certain claims to be obvious. Thus, the technological teachings of Lapidus '178, De Luca, Olson, and Hoepffner raise a substantial new question of patentability at least with respect to claims 16-20 of the '781 Patent.

L. Lapidus '650 in view of De Luca, Olson, and Hoepffner

Lapidus '650, De Luca, Olson, and Hoepffner are discussed briefly above. As discussed fully in Section VIII. below, the combined teachings of Lapidus '650, De Luca, Olson, and Hoepffner render certain claims to be obvious. Thus, the technological teachings of Lapidus '650, De Luca, Olson, and Hoepffner raise a substantial new question of patentability at least with respect to claims 16-20 of the '781 Patent.

M. Ahlquist in view of De Luca, Olson, and Hoepffner

Ahlquist, De Luca, Olson, and Hoepffner are discussed briefly above. As discussed fully in Section VIII. below, the combined teachings of Ahlquist, De Luca, Olson, and Hoepffner render certain claims to be obvious. Thus, the technological teachings of Ahlquist, De Luca, Olson, and Hoepffner raise a substantial new question of patentability at least with respect to claims 16-20 of the '781 Patent.

N. O'Neill in view of De Luca, Olson, and Hoepffner

O'Neill, De Luca, Olson, and Hoepffner are discussed briefly above. As discussed fully in Section VIII. below, the combined teachings of O'Neill, De Luca, Olson, and Hoepffner render certain claims to be obvious. Thus, the technological teachings of O'Neill, De Luca, Olson, and Hoepffner raise a substantial new question of patentability at least with respect to claims 16-20 of the '781 Patent.

VII. Detailed Explanation under 37 C.F.R. § 1.510(b)

As discussed more fully below, certain challenged claims are anticipated by either Lapidus '178 or Lapidus '650 because each reference describes each and every element of the challenged claims. See, *e.g.,* Ex. 1014 at paragraphs 89 and 91. Specifically, Lapidus '178 and Lapidus '650 describe methods for processing and testing a fecal sample, including evaluation of proteins and nucleic acids. Fecal samples are collected from a human subject and were sealed in a container, separated into two or more portions, and combined with buffers.

In the alternative, certain challenged claims would have been obvious to one of ordinary skill in the art based on Lapidus '178 or Lapidus '650 because each reference discloses methods for processing and testing a fecal sample, including evaluation of proteins and nucleic acids as noted above. See, *e.g.,* Ex. 1014 at paragraphs 90 and 92.

As discussed more fully below, certain challenged claims would have been obvious to one of ordinary skill in the art, based on a combination of Lapidus '178/Lapidus '650, De Luca, and Olson, because the references disclose methods for processing and testing a fecal sample. See, *e.g.,* Ex. 1014 at paragraphs 93-94. Specifically, Lapidus '178 and Lapidus '650 disclose collection and separation of a fecal sample into containers and combining fecal samples with buffers. De Luca discloses combining a portion of a removed fecal sample and buffer in a

separate, sealable container for analyzing a blood protein such as hemoglobin. Olson discloses combining a portion of a fecal sample and buffer in a sealable container for analyzing human nucleic acid such as DNA.

A person of ordinary skill in the art would have been motivated to combine the teachings of Lapidus '178/Lapidus '650 with De Luca and Olsen to protect the fecal samples for improved capabilities of diagnostic tests in human patients. De Luca and Olsen specifically teach the advantages of separating fecal samples and stabilizing the fecal samples with buffers for improving diagnostic testing. See, *e.g.,* Ex. 1014 at paragraphs 65 and 83. Furthermore, modifying the methods of Lapidus '178/Lapidus '650 to include the features of De Luca and Olsen would have required only minor changes to general methods to stabilize fecal samples with buffer in sealable containers, all of which were well within the knowledge and technical grasp of a person of ordinary skill in the art, who would therefore have a reasonable expectation of success. *Id.*

A person of ordinary skill in the art would have been motivated by the express teachings of De Luca to modify the Lapidus '178/Lapidus '650 methods by combining a portion of a removed fecal sample and buffer in a separate, sealable container for analyzing a blood protein such as hemoglobin. *Id.* at paragraph 66. Specifically, De Luca discloses that its invention provides "an extraction and sampling tube for the collection of faeces samples that is practical for the patient and simple to use for the laboratory technician." Ex. 1006 at [0015].

Moreover, a person of ordinary skill in the art would also have been motivated by the express teachings of Olson to modify the Lapidus '178/Lapidus '650 methods by combining a portion of a removed fecal sample and buffer in a separate, sealable container for analyzing human nucleic acid such as DNA. See, *e.g.,* Ex. 1014 at paragraph 84. Olson explicitly sates that "[t]he goals of this investigation are to establish how sample handling conditions affect the stability of DNA in stool, thereby potentially limiting clinical sensitivity, and to determine conditions to ameliorate DNA degradation." Ex. 1007 at Abstract. Further, Olson concludes that "DNA can be stabilized by addition of buffer to the sample, leading to increased assay sensitivity." *Id.*

Accordingly, modifying the Lapidus '178/Lapidus '650 methods according to the advantages taught by De Luca and Olson would have been a "predictable use of prior art elements according to their established functions," yielding "predictable results." *KSR, supra,*

550 U.S. at 417. Because Lapidus '178/Lapidus '650 in combination with De Luca and Olson discloses all of the limitations of certain claims of the '781 Patent as explained herein, such claims would have been obvious to a person of ordinary skill in view of this prior art and unpatentable under 35 U.S.C. § 103. See, *e.g.,* Ex. 1014 at paragraphs 93-94.

As discussed more fully below, certain challenged claims would have been obvious to one of ordinary skill in the art, based on a combination of Ahlquist, De Luca, and Olson, because the references disclose methods for processing and testing a fecal sample. *Id.* at paragraph 95. Specifically, Ahlquist disclose collection and separation of a fecal sample into containers and combining fecal samples with buffers. De Luca discloses combining a portion of a removed fecal sample and buffer in a separate, sealable container for analyzing a blood protein such as hemoglobin. Olson discloses combining a portion of a fecal sample and buffer in a sealable container for analyzing human nucleic acid such as DNA.

A person of ordinary skill in the art would have been motivated to combine the teachings of Ahlquist with De Luca and Olsen to protect the fecal samples for improved diagnostic power of cancer screening in human patients. De Luca and Olsen specifically teach the advantages of separating fecal samples and stabilizing the fecal samples with buffers for improving diagnostic testing. See, *e.g.,* Ex. 1014 at paragraphs 65 and 83. Furthermore, modifying the methods of Ahlquist include the features of De Luca and Olsen would have required only minor changes to general methods to stabilize fecal samples with buffer in sealable containers, all of which were well within the knowledge and technical grasp of a person of ordinary skill in the art, who would therefore have a reasonable expectation of success. *Id.* at paragraphs 68, 76, and 86.

A person of ordinary skill in the art would have been motivated by the express teachings of De Luca to modify the Ahlquist methods by combining a portion of a removed fecal sample and buffer in a separate, sealable container for analyzing a blood protein such as hemoglobin. *Id.* at paragraph 68. Specifically, De Luca discloses that its invention provides "an extraction and sampling tube for the collection of faeces samples that is practical for the patient and simple to use for the laboratory technician." Ex. 1006 at [0015].

Moreover, a person of ordinary skill in the art would also have been motivated by the express teachings of Olson to modify the Ahlquist methods by combining a portion of a removed fecal sample and buffer in a separate, sealable container for analyzing human nucleic acid such as DNA. Ex. 1014 at paragraph 86. Olson explicitly sates that "[t]he goals of this investigation

are to establish how sample handling conditions affect the stability of DNA in stool, thereby potentially limiting clinical sensitivity, and to determine conditions to ameliorate DNA degradation." Ex. 1007 at Abstract. Further, Olson concludes that "DNA can be stabilized by addition of buffer to the sample, leading to increased assay sensitivity." *Id.*

Accordingly, modifying the Ahlquist methods according to the advantages taught by De Luca and Olson would have been a "predictable use of prior art elements according to their established functions," yielding "predictable results." *KSR, supra,* 550 U.S. at 417. Because Ahlquist in combination with De Luca and Olson discloses all of the limitations of certain claims of the '781 Patent as explained herein, such claims would have been obvious to a person of ordinary skill in view of this prior art and unpatentable under 35 U.S.C. § 103. See, *e.g.,* Ex. 1014 at paragraph 95.

As discussed more fully below, certain challenged claims would have been obvious to one of ordinary skill in the art, based on a combination of O'Neill, De Luca, and Olson, because the references disclose methods for processing and testing a fecal sample. See, *e.g.,* Ex. 1014 at paragraph 96. Specifically, O'Neill disclose collection and separation of a fecal sample into containers and combining fecal samples with buffers. De Luca discloses combining a portion of a removed fecal sample and buffer in a separate, sealable container for analyzing a blood protein such as hemoglobin. Olson discloses combining a portion of a fecal sample and buffer in a sealable container for analyzing human nucleic acid such as DNA.

A person of ordinary skill in the art would have been motivated to combine the teachings of O'Neill with De Luca and Olsen to protect the fecal samples for improved diagnostic power of cancer screening in human patients. De Luca and Olsen specifically teach the advantages of separating fecal samples and stabilizing the fecal samples with buffers for improving diagnostic testing. See, *e.g., id.* at paragraphs 65 and 83. Furthermore, modifying the methods of O'Neill include the features of De Luca and Olsen would have required only minor changes to general methods to stabilize fecal samples with buffer in sealable containers, all of which were well within the knowledge and technical grasp of a person of ordinary skill in the art, who would therefore have a reasonable expectation of success. *Id.* at paragraphs 70, 77, 87, and 88.

A person of ordinary skill in the art would have been motivated by the express teachings of De Luca to modify the O'Neill methods by combining a portion of a removed fecal sample and buffer in a separate, sealable container for analyzing a blood protein such as hemoglobin. *Id.*

at paragraph 70. Specifically, De Luca discloses that its invention provides "an extraction and sampling tube for the collection of faeces samples that is practical for the patient and simple to use for the laboratory technician." Ex. 1006 at [0015].

Moreover, a person of ordinary skill in the art would also have been motivated by the express teachings of Olson to modify the O'Neill methods by combining a portion of a removed fecal sample and buffer in a separate, sealable container for analyzing human nucleic acid such as DNA. Ex. 1014 at paragraphs 77 and 88. Olson explicitly sates that "[t]he goals of this investigation are to establish how sample handling conditions affect the stability of DNA in stool, thereby potentially limiting clinical sensitivity, and to determine conditions to ameliorate DNA degradation." Ex. 1007 at Abstract. Further, Olson concludes that "DNA can be stabilized by addition of buffer to the sample, leading to increased assay sensitivity." *Id.*

Accordingly, modifying the O'Neill methods according to the advantages taught by De Luca and Olson would have been a "predictable use of prior art elements according to their established functions," yielding "predictable results." *KSR, supra,* 550 U.S. at 417. Because O'Neill in combination with De Luca and Olson discloses all of the limitations of certain claims of the '781 Patent as explained herein, such claims would have been obvious to a person of ordinary skill in view of this prior art and unpatentable under 35 U.S.C. § 103. See, *e.g.,* Ex. 1014 at paragraph 96.

Moreover, Leung describes collection of stool and detection of fecal DNA and its analysis for hypermethylated DNA via PCR and for mRNA via RT-PCR. Ex. 1008 at Abstract. One skilled in the art would have been motivated to utilize the teachings Leung as additional testing that could have increased the predictive power of diagnosing colorectal cancer in human patients. *Id.* at paragraphs 171 and 191. Accordingly, modifying the teachings of i) Lapidus '178/Lapidus '650, De Luca, and Olson, ii) Ahlquist, De Luca, and Olson, and iii) O'Neill, De Luca, and Olson to incorporate the methods of Leung would have been a "predictable use of prior art elements according to their established functions," yielding "predictable results." *KSR*, supra, 550 U.S. at 417. Thus, because Leung in combination with i) Lapidus '178/Lapidus '650, De Luca, and Olson, ii) Ahlquist, De Luca, and Olson, and/or iii) O'Neill, De Luca, and Olson discloses all of the limitations of certain claims of the '781 Patent as explained herein, such claims would have been obvious to a person of ordinary skill in view of this prior art and unpatentable under 35 U.S.C. § 103. See, *e.g.,* Ex. 1014 at paragraphs 165 and 173.

Finally, Hoepffner describes concentrations of hemoglobin in nanograms per milliliter (ng/ml) resulting in a positive blood test in fecal samples. Ex. 1009 at p. 148, second column, first full paragraph. One skilled in the art would be motivated to utilize the teachings of Hoepffner in order to use the disclosed hemoglobin concentration as an indicator of a 'positive' test for blood in a fecal sample. Ex. 1014 at paragraph 219. Accordingly, modifying the teachings of i) Lapidus '178/Lapidus '650, De Luca, and Olson, ii) Ahlquist, De Luca, and Olson, and iii) O'Neill, De Luca, and Olson to incorporate the methods of Hoepffner would have been a "predictable use of prior art elements according to their established functions," yielding "predictable results." *KSR*, supra, 550 U.S. at 417. Thus, because Hoepffner in combination with i) Lapidus '178/Lapidus '650, De Luca, and Olson, ii) Ahlquist, De Luca, and Olson, and/or iii) O'Neill, De Luca, and Olson discloses all of the limitations of certain claims of the '781 Patent as explained herein, such claims would have been obvious to a person of ordinary skill in view of this prior art and unpatentable under 35 U.S.C. § 103. See, *e.g.,* Ex. 1014 at paragraphs 220-223.

A. Independent Claim 1

1. Lapidus '178 Anticipates Claim 1

'781 Patent, Claim 1, Preamble	Lapidus '178
1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:	**Lapidus '178** describes processing of "a stool voided by a patient" in Example 1, entitled "Preparation of a Stool Sample." Ex. 1002 at column 7, lines 58-62. Further, "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 63-64.

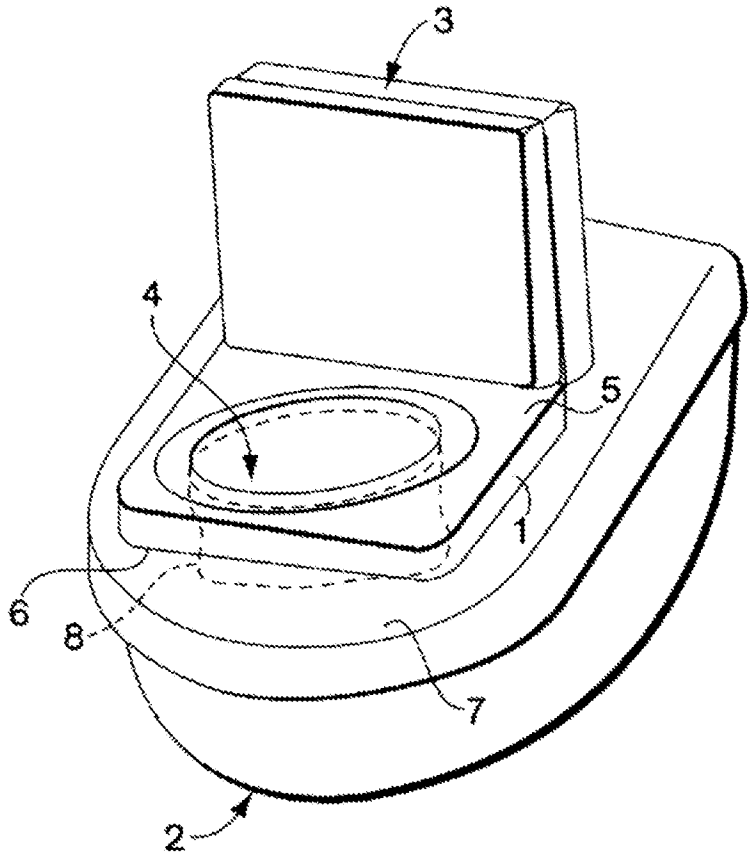
As explained in Section IV. *supra*, the preamble of claim 1 is not a limitation. However, even if the preamble of claim 1 was determined to be a limitation, Lapidus '178 describes this limitation. Lapidus '178 describes a stool (a fecal sample) voided by a patient into a receptacle that is transported to a testing facility.

Further, Lapidus '178 describes the method of processing a "freshly-collected" fecal sample "without freezing" specified by the preamble. Lapidus '178 describes that in "a preferred embodiment a stool is frozen prior to processing." *Id.* at column 9, lines 21-22. According to well-established law, the alternative (i.e., a stool NOT being frozen prior to processing) is also described by Lapidus '178. For instance, *In re Johnson* holds that if alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See 558 F.2d 1008, 1019 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984). Accordingly, one skilled in the art would recognize Lapidus '178 describes the method of processing a "freshly-collected" fecal sample "without freezing" specified by the preamble. Ex. 1014 at paragraph 45.

'781 Patent, Claim 1, First Limitation	**Lapidus '178**
a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject by defecation directly into a sealable collection vessel;	**Lapidus '178** describes collecting "a stool voided by a patient." Ex. 1002 at column 7, lines 61-62. Lapidus '178 describes that a "[s]tool is voided [by the patient] into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 63-64. Lapidus '178 describes that "[t]he receptacle may be fitted to a conventional toilet such that the receptacle accepts stool voided in a conventional manner." *Id.* at column 7, lines 64-66. Lapidus '178 describes that "[t]he receptacle, whether adapted to fit a toilet or simply adapted for receiving the voided stool sample, should include sealing means sufficient to contain the voided stool sample…". *Id.* at column 8, lines 17-20.

Lapidus '178 describes collecting a fecal sample from a human subject. Lapidus '178 describes that "[t]he receptacle may be fitted to a conventional toilet such that the receptacle accepts stool voided in a conventional manner." *Id.* at column 7, lines 64-66. This passage in Lapidus '178 provides evidence that the fecal sample is collected from a human subject, since only humans use conventional toilets to void stool in a conventional manner.

Furthermore, Lapidus '178 describes that the fecal sample is collected in a receptacle that can be adapted to fit a toilet, thus demonstrating that the human subject defecates "directly" into the receptacle. As shown in Figure 2, the receptacle is a "sealable" receptacle comprising an articulating **cover 3** that can be utilized in "a closed position (not shown) for sealing voided stool within the receptacle." *Id.* at column 8, lines 24-27. Figure 2 of Lapidus '178 is shown below:



Finally, Lapidus '178 describes that the stool can be collected at home according to the broadest reasonable interpretation of the claims consistent with the specification. As discussed above, the broadest reasonable interpretation of "collected at home" in the '781 Patent is collected at a location other than a testing facility. Lapidus '178 describes that the sealable receptacle containing the fecal sample "is preferably small enough to be transported to a testing

facility," meaning that the fecal sample is collected at *a location different than the testing facility.* Further, Lapidus '178 describes that the toilet onto which the receptacle may be fitted is "a conventional toilet such that the receptacle accepts stool voided in a conventional manner." This indicates that a fecal sample is collected at home by the patient since the "conventional manner" for voiding stool is on a toilet in one's home. A person skilled in the art would understand that Lapidus '178 effectively describes collection of a stool at home, given that "home" is not a testing facility such a medical diagnostics laboratory. Ex. 1014 at paragraph 53.

Therefore, one skilled in the art would recognize that Lapidus '178 describes all of the requirements for the collecting step contained in the first limitation of claim 1 of the '781 Patent. *Id.*

'781 Patent, Claim 1, Second Limitation	**Lapidus '178**
b) removing a portion of the fecal sample to a separate sealable container to produce a removed portion and a remaining portion of the fecal sample;	**Lapidus '178** describes that "a cross-sectional portion is removed from the voided stool by making one or more sagittal or coronal section through the stool." Ex. 1002 at column 8, lines 45-47. Lapidus '178 describes that "[a]lternatively, a circumferential surface of a stool is prepared by taking the entire surface layer of the stool, or the entire surface layer of a cross-sectional portion of the stool." *Id.* at column 8, lines 49-52. Lapidus '178 describes that "[a]lternatively, the stool sample is rolled along the surface of the sampling device, and the layer of stool that adheres to the surface is then processed as described herein." *Id.* at column 9, lines 10-12.

	Referring to Figure 2, Lapidus '178 describes that "[m]eans 8 may be fixedly attached to the support frame 1 or may be removably attached for removal subsequent to deposition of stool. Means 8 may comprise a further means for removing at least a circumferential surface or cross-sectional portion from the voided stool." *Id.* at column 8, lines 33-37. Lapidus '178 describes that "[o]nce obtained, the entire circumference or cross-sectional sample of stool is homogenized in an appropriate buffer, such as phosphate buffered saline." *Id.* at column 9, lines 30-32. Lapidus '178 describes "[o]nce a circumferential surface or cross-sectional sample of stool is obtained, it may be homogenized by known methods to distribute cells and cellular debris throughout the sample. An assay then is performed on the homogenate, or an extract of the homogenate, to detect the presence of cells and/or cellular debris in the sample. The assay may be any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation such as a protein, or DNA-based assays for detecting mutations or genetic characteristics indicative of colorectal cancer." *Id.* at column 6, lines 45-56.

Lapidus '178 describes removing a portion of the fecal sample to produce a removed portion and a remaining portion of the fecal sample. According to Lapidus '178, the 'removed portion' could take a number of forms, including removal of a cross-sectional portion of the voided stool sample, a circumferential surface portion of the voided stool sample, or a layer of the voided stool sample that adheres to the surface of a sampling device. In these scenarios, the cross-sectional portion, the circumferential surface portion, or the layer portion described by Lapidus '178 corresponds to the 'removed portion' of the fecal sample in independent claim 1.

Given the removal of a cross-sectional, circumferential surface, and/or layer of the voided stool sample, logic dictates that Lapidus '178 describes a 'remaining portion' of the fecal sample that is left over following such removal. *In re Johnson*, 558 F.2d at 1019. A person of ordinary skill in the art would recognize and understand that Lapidus '178 describes the 'remaining portion' according to independent claim 1. Ex. 1014 at paragraphs 60-63.

Moreover, Lapidus '178 describes that the 'removed portion' of the fecal sample is obtained upon collection of the fecal sample. Again referring to Figure 2 above, Lapidus '178 describes that "Means 8 may be fixedly attached to the support frame 1 or may be removably attached for removal subsequent to deposition of stool. Means 8 may comprise a further means for removing at least a circumferential surface or cross-sectional portion from the voided stool." This provides evidence that the 'removed portion' of the fecal sample (e.g., a circumferential surface or cross-sectional portion from the voided stool) can be obtained in the conventional toilet upon collection of the voided stool. Ex. 1014 at paragraphs 60-63.

Finally, Lapidus '178 describes that the 'removed portion' of the fecal sample is in a separate sealable container. Lapidus '178 describes that the 'removed portion' (e.g., a circumferential surface or cross-sectional sample of stool) is placed in a buffer such as phosphate buffered saline according to "means and materials" that are generally known in the art in order to assay the 'removed portion'. At the time of filing Lapidus '178, it was well known in the art that a fecal sample was homogenized in appropriate buffers for the purpose of assaying would be done in a separate sealable container. For instance, U.S. Patent No. 4,859,610 to Maggio (Ex. 1010) describes a device that is "particularly useful for homogenizing and analyzing fecal samples." Ex. 1010 at column 4, lines 7-8. Maggio describes that the device includes a vessel for placement of a fecal sample and that "[a]fter a measured portion of [fecal sample] is secured

by the scoop (8) and introduced into the vessel (1), 2 mils of phosphate buffered saline, pH 7.4 (PBS) is added to the vessel (1)." *Id.* at column 8, lines 39-42.

Maggio later describes that "FIG. 1 is a perspective view of a preferred embodiment of the immunoassay incubation device." *Id.* at column 3, lines 33-34. Furthermore, Maggio describes that "FIG. 9 is an exploded view in perspective of another alternative embodiment of the immunoassay incubation device illustrating a valve for controlling the flow of homogenized sample from the extractor into the incubation chamber." *Id.* at column 3, lines 60-64. Figures 1 and 9 of Maggio, presented below, clearly depict a separate sealable container that is configured to contain a fecal sample and a homogenizing buffer:

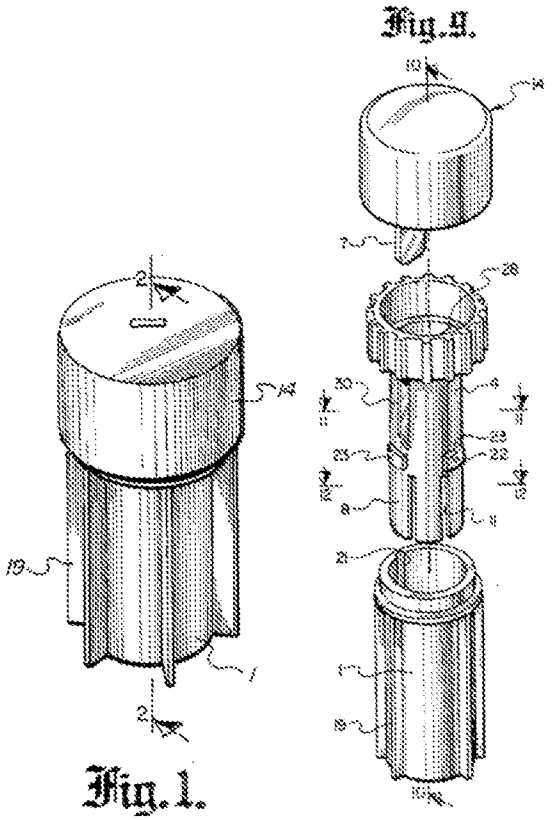


Fig. 1.

Therefore, one skilled in the art would recognize that Lapidus '178 describes all of the requirements for the removing step contained in the second limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraphs 60-63.

'781 Patent, Claim 1, Third Limitation	**Lapidus '178**
c) combining the removed portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container; and	**Lapidus '178** describes that "[o]nce obtained, the entire circumference or cross-sectional sample of stool is homogenized in an appropriate buffer, such as phosphate buffered saline. Homogenization means and materials for homogenization are generally known in the art. Thus, particular homogenization methods may be selected by the skilled artisan and may depend upon the assay to be employed. The buffer may contain detergent, salt, proteinase, inhibitors of DNA and RNA degrading enzymes. The composition of the buffer will depend on the type of assay to be performed. If a fecal occult blood assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for detecting the presence of fecal occult blood are known in the art. If a test is to be performed for the presence of a particular protein, the buffer should not contain a proteinase capable of degrading such tumor marking antigens." Ex. 1002 at column 9, lines 30-36.

Lapidus '178 describes combining the removed portion of the fecal sample (e.g., the cross-sectional portion, the circumferential surface portion, or the layer portion) with a buffer. Lapidus '178 describes such buffers as any buffer known to the skilled artisan, such as those that contain detergents and salts, which are well known for preservation of proteins. Ex. 1014 at

paragraphs 72-73. Lapidus '178 further notes that to prevent the denaturation or degradation of blood proteins found in the sample, it would be important to specifically avoid including a proteinase in the buffer that would contain detergents and salts.

Again, Lapidus '178 describes that the cross-sectional portion, circumferential surface portion, or layer portion of the fecal sample can be homogenized in a buffer according to "means and materials" that are generally known in the art. This indicates that the removed portion is added to a buffer for further processing. As discussed *supra,* at the time of filing Lapidus, it was well known in the art that a fecal sample was homogenized in appropriate buffers for the purpose of assaying would be done in a separate sealable container. See, *e.g.,* Maggio (Ex. 1010) as evidence of the state of the art at the time of filing Lapidus '178. Accordingly, the combination of the removed portion of the fecal sample and buffer is placed in a separate container and sealed according to methods known in the art.

Therefore, one skilled in the art would recognize that Lapidus '178 describes all of the requirements for the combining step contained in the third limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraph 73.

'781 Patent, Claim 1, Fourth Limitation	**Lapidus '178**
d) combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, and sealing the sealable collection vessel.	**Lapidus '178** describes that "[m]ethods of the invention also comprise obtaining a representative (i.e., cross-sectional) ***sample of stool*** and homogenizing ***the stool*** in a buffer, such as a buffer comprising a detergent and a proteinase and optionally a DNase inhibitor. Ex. 1002 at column 3, lines 11-15 (emphasis added). Lapidus '178 describes that "the receptacle [containing the stool] may comprise means for introducing homogenization buffer or one or more preservatives, such as alcohol, a solution of high salt concentration, antibiotics, and chaotropic salts in order to neutralize bacteria

	present in the stool sample. The homogenization buffer may be a physiologically compatible buffer such as phosphate buffered saline, and may comprise salt such as 20-100 mM NaCl or KCl. The homogenization buffer may also comprise a detergent, such as 1-10% SDS or triton, and/or a proteinase, such as proteinase K. The buffer may also contain inhibitors of DNA and RNA degrading enzymes. The receptacle, whether adapted to fit a toilet or simply adapted for receiving the voided stool sample, should include sealing means sufficient to contain the voided stool sample and any solution added thereto and to prevent the emanation of odors." *Id.* at column 8, lines 5-21.

Lapidus '178 describes combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer. As discussed *supra*, given removal of a cross-sectional, circumferential surface, and/or layer of the stool, logic dictates that Lapidus '178 describes a 'remaining portion' of the fecal sample that is left over following such removal. *In re Johnson*, 558 F.2d at 1019. A person of ordinary skill in the art would recognize and understand that Lapidus '178 describes the 'remaining portion' according to independent claim 1. Ex. 1014 at paragraph 79.

The 'remaining portion' of the fecal sample corresponds to the stool and Lapidus '178 describes that the stool is contained in the receptacle, which corresponds to the "sealable collection vessel." Further, Lapidus '178 describes that homogenization buffer can be added to the receptacle containing the stool. Lapidus '178 states that "[m]ethods of the invention also comprise obtaining a representative (i.e., cross-sectional) ***sample of stool*** and homogenizing ***the stool*** in a buffer, such as a buffer comprising a detergent and a proteinase and optionally a DNase

inhibitor. Ex. 1002 at column 3, lines 11-15 (emphasis added). This sentence is interpreted to describe two different parts of fecal material – the 'removed portion' ***sample of stool*** and also the 'remaining portion' of ***the stool***. This sentence of Lapidus '178 describes addition of a buffer to the 'remaining portion' of ***the stool***.

Lapidus '178 describes that the buffer can contain phosphate buffered saline, NaCl or KCl, a detergent such as SDS or triton, and inhibitors of DNA and/or RNA degrading enzymes. A person of ordinary skill in the art would recognize such buffer as a "stabilizing buffer." Ex. 1014 at paragraph 80.

Finally, Lapidus '178 describes that the receptacle includes sealing means and that it should be sealed "to contain the voided stool sample and any solution added thereto and to prevent the emanation of odors."

Therefore, one skilled in the art would recognize that Lapidus '178 describes all of the requirements for the combining step contained in the fourth limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraphs 79-81.

2. Lapidus '650 Anticipates Claim 1

'781 Patent, Claim 1, Preamble	**Lapidus '650**
1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:	**Lapidus '650** describes processing of "a stool voided by a patient" in Example 1, entitled "Preparation of a Stool Sample." Ex. 1003 at column 7, lines 12-17. Further, "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 24-26.

As explained in Section IV. *supra*, the preamble of claim 1 is not a limitation. However, even if the preamble of claim 1 was determined to be a limitation, Lapidus '650 describes this limitation. Lapidus '650 describes a stool (a fecal sample) voided by a patient into a receptacle that is transported to a testing facility.

Further, Lapidus '650 describes the method of processing a "freshly-collected" fecal sample "without freezing" specified by the preamble. Lapidus '650 does not describe the concept of freezing fecal samples. Thus, Lapidus explicitly describes collecting a fecal sample "without freezing" to meet the language of the preamble.

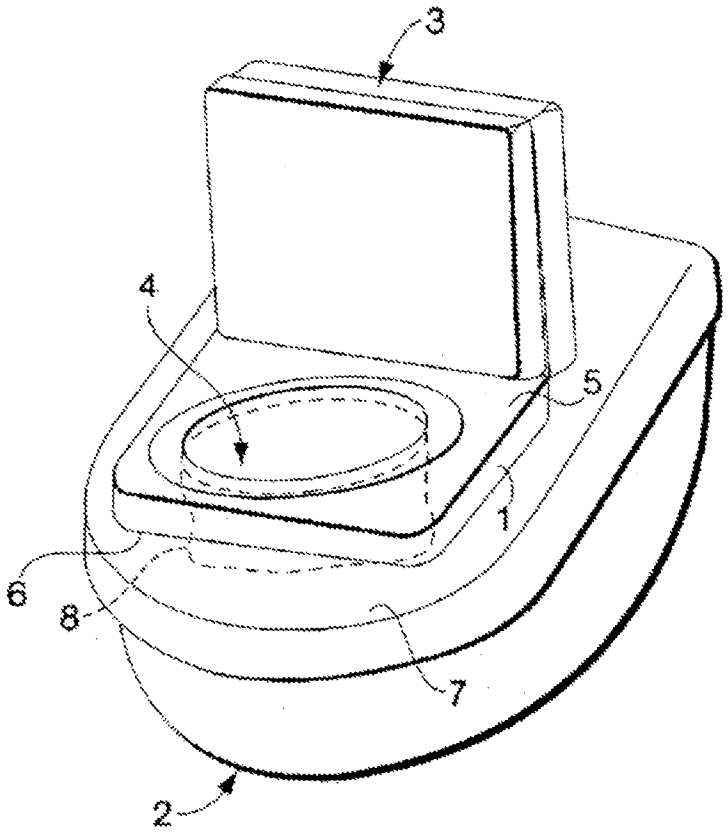
Moreover, U.S. Patent No. 5,196,167 (Ex. 1011) is incorporated by reference into Lapidus '650 at column 6, lines 30-31. In pertinent part, U.S. Patent No. 5,196,167 describes a test sheet product used for identification of blood in a patient stool and states that "[a]fter the patient has completed a bowel movement, the test sheet is merely dropped into the toilet bowl." Ex. 1011 at column 6, lines 65-67. Further, U.S. Patent No. 5,196,167 describes that "[a]fter the results of the test have been visually observed, the test sheet is disposed of by merely flushing the toilet bowl." *Id.* at column 7, lines 7-9. Accordingly, one skilled in the art would recognize Lapidus '650 describes the method of processing a "freshly-collected" fecal sample "without freezing" specified by the preamble because U.S. Patent No. 5,196,167 (incorporated by reference into Lapidus '650) clearly describes a method in which a "freshly-collected" fecal sample is collected and processed "without freezing". Ex. 1014 at paragraph 46.

'781 Patent, Claim 1, First Limitation	**Lapidus '650**
a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject by defecation directly into a sealable collection vessel;	**Lapidus '650** describes collecting "a stool voided by a patient." Ex. 1003 at column 7, lines 12-17. Further, "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 24-26. Lapidus '650 describes that "[t]he receptacle may be fitted to a conventional toilet such that the receptacle accepts stool voided in a conventional manner." *Id.* at column 7, lines 26-28. Lapidus '650 describes that "[t]he receptacle, whether adapted to fit a toilet or simply adapted for receiving the voided stool

	sample, should include sealing means sufficient to contain the voided stool sample…". *Id.* at column 7, lines 45-49.

Lapidus '650 describes collecting a fecal sample from a human subject. Lapidus '650 describes that "[t]he receptacle may be fitted to a conventional toilet such that the receptacle accepts stool voided in a conventional manner." *Id.* at column 7, lines 26-28. This passage in Lapidus '650 provides evidence that the fecal sample is collected from a human subject, since only humans use conventional toilets to void stool in a conventional manner.

Furthermore, Lapidus '650 describes that the fecal sample is collected in a receptacle that can be adapted to fit a toilet, thus demonstrating that the human subject defecates "directly" into the receptacle. As shown in Figure 2, the receptacle is a "sealable" receptacle comprising an articulating **cover 3** that can be utilized in "a closed position (not shown) for sealing voided stool within the receptacle." *Id.* at column 7, lines 54-55. Figure 2 of Lapidus '650 is shown below:



Finally, Lapidus '650 describes that the stool can be collected at home according to the broadest reasonable interpretation of the claims consistent with the specification. As discussed above, the broadest reasonable interpretation of "collected at home" in the '781 Patent is collected at a location other than a testing facility such a medical diagnostics laboratory. Lapidus '650 describes that the sealable receptacle containing the fecal sample "is preferably small enough to be transported to a testing facility," meaning that the fecal sample is collected at *a location different than the testing facility.* Further, Lapidus '650 describes that the toilet onto which the receptacle may be fitted is "a conventional toilet such that the receptacle accepts stool voided in a conventional manner." This indicates that a fecal sample is collected at home by the patient since the "conventional manner" for voiding stool is on a toilet in one's home. A person skilled in the art would understand that Lapidus '650 effectively describes collection of a stool at home, given that "home" is not a testing facility such a medical diagnostics laboratory. Ex. 1014 at paragraph 53.

Therefore, one skilled in the art would recognize that Lapidus '650 describes all of the requirements for the collecting step contained in the first limitation of claim 1 of the '781 Patent. *Id.*

'781 Patent, Claim 1, Second Limitation	**Lapidus '650**
b) removing a portion of the fecal sample to a separate sealable container to produce a removed portion and a remaining portion of the fecal sample;	**Lapidus '650** describes that "a cross-sectional portion is removed from the voided stool by making one or more sagittal or coronal section through the stool." Ex. 1003 at column 7, lines 17-19. Referring to Figure 2, Lapidus '650 describes that "[m]eans 8 may be fixedly attached to the support frame 1 or may be removably attached for removal subsequent to deposition of stool. Means 8 may comprise a further means for removing at least a circumferential surface or cross-

	sectional portion from the voided stool." *Id.* at column 7, lines 61-65. Lapidus '650 describes that "[o]nce obtained, the cross-sectional stool sample is homogenized in an appropriate buffer, such as phosphate buffered saline." *Id.* at column 8, lines 5-7. Lapidus '650 describes "[o]nce a cross-sectional stool sample is obtained, it may be homogenized by known methods to distribute cells and cellular debris throughout the sample. An assay then is performed on the homogenate, or an extract of the homogenate, to detect the presence of cells and/or cellular debris in the sample. The assay may be any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation such as a protein, or DNA-based assays for detecting mutations or genetic characteristics indicative of colorectal cancer". *Id.* at column 6, lines 1-11.

Lapidus '650 describes removing a portion of the fecal sample to produce a removed portion and a remaining portion of the fecal sample. According to Lapidus '650, the cross-sectional portion corresponds to the 'removed portion' of the fecal sample in independent claim 1.

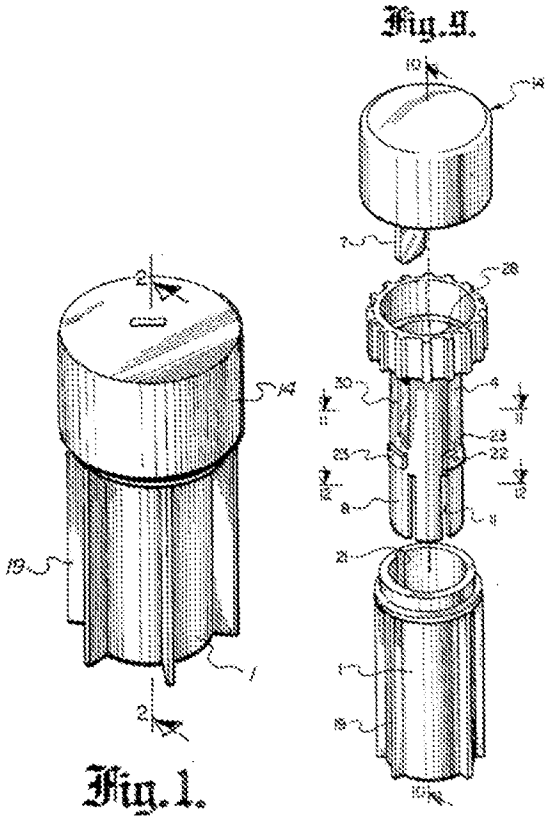
Given the removal of a cross-sectional sample, logic dictates that Lapidus '650 describes a 'remaining portion' of the fecal sample that is left over following such removal. *In re Johnson*, 558 F.2d at 1019. A person of ordinary skill in the art would recognize and understand that

Lapidus '650 describes the 'remaining portion' according to independent claim 1. Ex. 1014 at paragraphs 60-63.

Moreover, Lapidus '650 describes that the 'removed portion' of the fecal sample is obtained upon collection of the fecal sample. Again referring to Figure 2 above, Lapidus '650 describes that "[m]eans 8 may be fixedly attached to the support frame 1 or may be removably attached for removal subsequent to deposition of stool. Means 8 may comprise a further means for removing at least a circumferential surface or cross-sectional portion from the voided stool." *Id.* at column 7, lines 61-65. This provides evidence that the 'removed portion' of the fecal sample (e.g., a cross-sectional portion from the voided stool) can be obtained in the conventional toilet upon collection of the voided stool.

Finally, Lapidus '650 describes that the 'removed portion' of the fecal sample is in a separate sealable container. Lapidus '650 describes that the 'removed portion' (e.g., a cross-sectional sample of stool) is placed in a buffer such as phosphate buffered saline according to "means and materials" that are generally known in the art in order to assay the 'removed portion'. At the time of filing Lapidus '650, it was well known in the art that a fecal sample was homogenized in appropriate buffers for the purpose of assaying would be done in a separate sealable container. For instance, U.S. Patent No. 4,859,610 to Maggio (Ex. 1010) describes a device that is "particularly useful for homogenizing and analyzing fecal samples." Ex. 1010 at column 4, lines 7-8. Maggio describes that the device includes a vessel for placement of a fecal sample and that "[a]fter a measured portion of [fecal sample] is secured by the scoop (8) and introduced into the vessel (1), 2 mils of phosphate buffered saline, pH 7.4 (PBS) is added to the vessel (1)." *Id.* at column 8, lines 39-42.

Maggio later describes that "FIG. 1 is a perspective view of a preferred embodiment of the immunoassay incubation device." *Id.* at column 3, lines 33-34. Furthermore, Maggio describes that "FIG. 9 is an exploded view in perspective of another alternative embodiment of the immunoassay incubation device illustrating a valve for controlling the flow of homogenized sample from the extractor into the incubation chamber." *Id.* at column 3, lines 60-64. Figures 1 and 9 of Maggio, presented below, clearly depict a separate sealable container that is configured to contain a fecal sample and a homogenizing buffer:



Therefore, one skilled in the art would recognize that Lapidus '650 describes all of the requirements for the removing step contained in the second limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraphs 60-63.

'781 Patent, Claim 1, Third Limitation	**Lapidus '650**
c) combining the removed portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container; and	**Lapidus '650** describes that "[o]nce obtained, the cross-sectional stool sample is homogenized in an appropriate buffer, such as phosphate buffered saline. Homogenization means and materials for homogenization are generally known in the art. Thus, particular homogenization methods may be selected by the skilled artisan and may depend upon the assay to be employed. The buffer may contain detergent, salt, proteinase, inhibitors of DNA

	and RNA degrading enzymes. The composition of the buffer will depend on the type of assay to be performed. If a fecal occult blood assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for detecting the presence of fecal occult blood are known in the art. If a test is to be performed for the presence of a particular protein, the buffer should not contain a proteinase capable of degrading such tumor marking antigens." Ex. 1003 at column 8, lines 5-21.

Lapidus '650 describes combining the removed portion of the fecal sample (e.g., the cross-sectional portion) with a buffer. Lapidus '650 describes such buffers as any buffer known to the skilled artisan, such as those that contain detergents and salts, which are well known for preservation of proteins. Ex. 1014 at paragraphs 72-73. Lapidus '650 further notes that to prevent the denaturation or degradation of blood proteins found in the sample, it would be important to specifically avoid including a proteinase in the buffer that would contain detergents and salts.

Again, Lapidus '650 describes that the cross-sectional portion of the fecal sample can be homogenized in a buffer according to "means and materials" that are generally known in the art. This indicates that the removed portion is added to a buffer for further processing. As discussed *supra,* at the time of filing Lapidus, it was well known in the art that a fecal sample was homogenized in appropriate buffers for the purpose of assaying would be done in a separate sealable container. See, *e.g.,* Maggio (Ex. 1010) as evidence of the state of the art at the time of filing Lapidus '650. Accordingly, the combination of the removed portion of the fecal sample and buffer is placed in a separate container and sealed according to methods known in the art.

Therefore, one skilled in the art would recognize that Lapidus '650 describes all of the requirements for the combining step contained in the third limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraph 73.

'781 Patent, Claim 1, Fourth Limitation	**Lapidus '650**
d) combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, and sealing the sealable collection vessel.	**Lapidus '650** describes that "[m]ethods of the invention also comprise obtaining a representative (i.e., cross-sectional) ***sample of stool*** and homogenizing ***the stool*** in a buffer, such as a buffer comprising a detergent and a proteinase and optionally a DNase inhibitor. Ex. 1003 at column 2, line 66 – column 3, line 3 (emphasis added). Lapidus '650 describes that "the receptacle [containing the stool] may comprise means for introducing homogenization buffer or one or more preservatives, such as alcohol, a solution of high salt concentration, antibiotics, and chaotropic salts in order to neutralize bacteria present in the stool sample. The homogenization buffer may be a physiologically compatible buffer such as phosphate buffered saline, and may comprise salt such as 20-100 mM NaCl or KCl. The homogenization buffer may also comprise a detergent, such as 1-10% SDS or triton, and/or a proteinase, such as proteinase K. The buffer may also contain inhibitors of DNA and RNA degrading enzymes. The receptacle, whether adapted to fit a toilet or simply adapted for receiving the voided stool

	sample, should include sealing means sufficient to contain the voided stool sample and any solution added thereto and to prevent the emanation of odors." *Id.* at column 7, lines 31-49.

Lapidus '650 describes combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer. As discussed *supra*, given removal of a cross-sectional sample of stool, logic dictates that Lapidus '650 describes a 'remaining portion' of the fecal sample that is left over following such removal. *In re Johnson*, 558 F.2d at 1019. A person of ordinary skill in the art would recognize and understand that Lapidus '650 describes the 'remaining portion' according to independent claim 1. Ex. 1014 at paragraph 79.

The 'remaining portion' of the fecal sample corresponds to the stool and Lapidus '650 describes that the stool is contained in the receptacle, which corresponds to the "sealable collection vessel." Further, Lapidus '650 describes that homogenization buffer can be added to the receptacle containing the stool. Lapidus '650 states that "[m]ethods of the invention also comprise obtaining a representative (i.e., cross-sectional) ***sample of stool*** and homogenizing ***the stool*** in a buffer, such as a buffer comprising a detergent and a proteinase and optionally a DNase inhibitor. Ex. 1003 at column 2, line 66 – column 3, line 3 (emphasis added). This sentence is interpreted to describe two different parts of fecal material – the 'removed portion' ***sample of stool*** and also the 'remaining portion' of ***the stool***. This sentence of Lapidus '650 describes addition of a buffer to the 'remaining portion' of ***the stool***.

Lapidus '650 describes that the buffer can contain phosphate buffered saline, NaCl or KCl, a detergent such as SDS or triton, and inhibitors of DNA and/or RNA degrading enzymes. A person of ordinary skill in the art would recognize such buffer as a "stabilizing buffer." Ex. 1014 at paragraph 80.

Finally, Lapidus '650 describes that the receptacle includes sealing means and that it should be sealed "to contain the voided stool sample and any solution added thereto and to prevent the emanation of odors."

Therefore, one skilled in the art would recognize that Lapidus '650 describes all of the requirements for the combining step contained in the fourth limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraphs 79-81.

3. Lapidus '178 Renders Claim 1 Obvious

'781 Patent, Claim 1, Preamble	Lapidus '178
1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:	**Lapidus '178** discloses processing of "a stool voided by a patient" in Example 1, entitled "Preparation of a Stool Sample." Ex. 1002 at column 7, lines 58-62. Further, "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 63-64.

In the alternative to the assertion that Lapidus '178 anticipates claim 1, Lapidus '178 further renders claim 1 obvious.

As explained in Section IV. *supra*, the preamble of claim 1 is not a limitation. However, even if the preamble of claim 1 was determined to be a limitation, Lapidus '178 discloses this limitation. Lapidus '178 discloses a stool (a fecal sample) voided by a patient into a receptacle that is transported to a testing facility.

Further, Lapidus '178 discloses the method of processing a "freshly-collected" fecal sample "without freezing" specified by the preamble. Lapidus '178 discloses that in "a preferred embodiment a stool is frozen prior to processing." *Id.* at column 9, lines 21-22. According to well-established law, the alternative (i.e., a stool NOT being frozen prior to processing) is also described by Lapidus. For instance, *In re Johnson* holds that if alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See 558 F.2d 1008, 1019 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984). Accordingly, one skilled in the art would

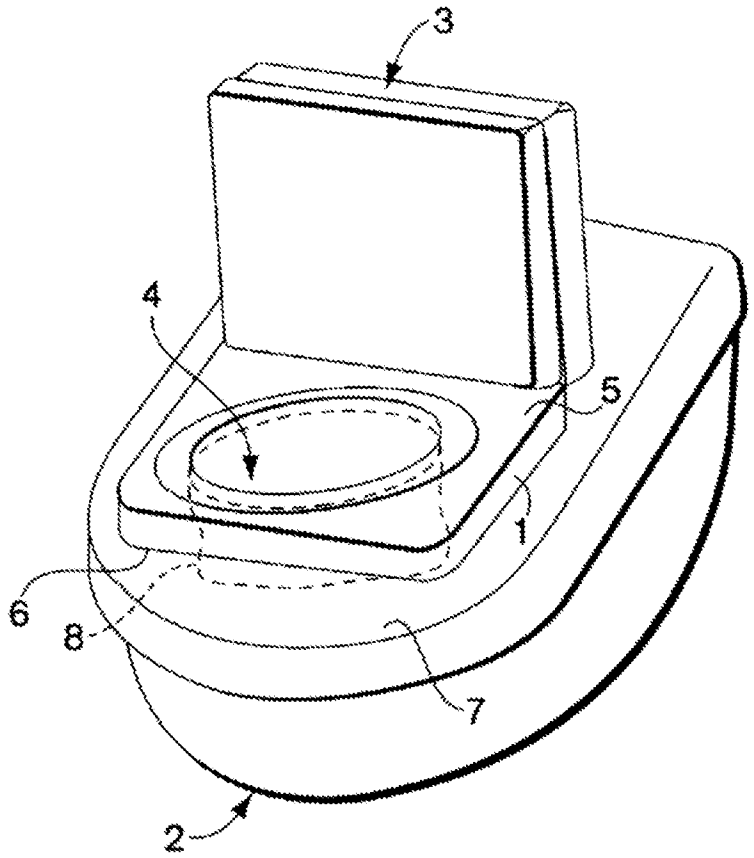
recognize Lapidus '178 discloses the method of processing a "freshly-collected" fecal sample "without freezing" specified by the preamble. Ex. 1014 at paragraph 45.

'781 Patent, Claim 1, First Limitation	**Lapidus '178**
a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject by defecation directly into a sealable collection vessel;	**Lapidus '178** discloses collecting "a stool voided by a patient." Ex. 1002 at column 7, lines 61-62. Lapidus '178 discloses that a "[s]tool is voided [by the patient] into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 63-64. Lapidus '178 discloses that "[t]he receptacle may be fitted to a conventional toilet such that the receptacle accepts stool voided in a conventional manner." *Id.* at column 7, lines 64-66. Lapidus '178 discloses that "[t]he receptacle, whether adapted to fit a toilet or simply adapted for receiving the voided stool sample, should include sealing means sufficient to contain the voided stool sample…". *Id.* at column 8, lines 17-20.

Lapidus '178 discloses collecting a fecal sample from a human subject. Lapidus '178 discloses that "[t]he receptacle may be fitted to a conventional toilet such that the receptacle accepts stool voided in a conventional manner." *Id.* at column 7, lines 64-66. This passage in Lapidus '178 provides evidence that the fecal sample is collected from a human subject, since only humans use conventional toilets to void stool in a conventional manner.

Furthermore, Lapidus '178 discloses that the fecal sample is collected in a receptacle that can be adapted to fit a toilet, thus demonstrating that the human subject defecates "directly" into the receptacle. As shown in Figure 2, the receptacle is a "sealable" receptacle comprising an

articulating **cover 3** that can be utilized in "a closed position (not shown) for sealing voided stool within the receptacle." *Id.* at column 8, lines 24-27. Figure 2 of Lapidus '178 is shown below:



Finally, Lapidus '178 discloses that the stool can be collected at home according to the broadest reasonable interpretation of the claims consistent with the specification. As discussed above, the broadest reasonable interpretation of "collected at home" in the '781 Patent is collected at a location other than a testing facility. Lapidus '178 discloses that the sealable receptacle containing the fecal sample "is preferably small enough to be transported to a testing facility," meaning that the fecal sample is collected at *a location different than the testing facility.* Further, Lapidus '178 discloses that the toilet onto which the receptacle may be fitted is "a conventional toilet such that the receptacle accepts stool voided in a conventional manner." This indicates that a fecal sample is collected at home by the patient since the "conventional manner" for voiding stool is on a toilet in one's home. A person skilled in the art would understand that Lapidus '178 effectively describes collection of a stool at home, given that "home" is not a testing facility such a medical diagnostics laboratory. Ex. 1014 at paragraph 53.

Therefore, one skilled in the art would recognize that Lapidus '178 discloses all of the requirements for the collecting step contained in the first limitation of claim 1 of the '781 Patent. *Id.* Accordingly, Lapidus '178 renders this portion of claim 1 obvious.

'781 Patent, Claim 1, Second Limitation	**Lapidus '178**
b) removing a portion of the fecal sample to a separate sealable container to produce a removed portion and a remaining portion of the fecal sample;	**Lapidus '178** discloses that "a cross-sectional portion is removed from the voided stool by making one or more sagittal or coronal section through the stool." Ex. 1002 at column 8, lines 45-47. Lapidus '178 discloses that "[a]lternatively, a circumferential surface of a stool is prepared by taking the entire surface layer of the stool, or the entire surface layer of a cross-sectional portion of the stool." *Id.* at column 8, lines 49-52. Lapidus '178 discloses that "[a]lternatively, the stool sample is rolled along the surface of the sampling device, and the layer of stool that adheres to the surface is then processed as described herein." *Id.* at column 9, lines 10-12. Referring to Figure 2, Lapidus '178 describes that "[m]eans 8 may be fixedly attached to the support frame 1 or may be removably attached for removal subsequent to deposition of stool. Means 8 may comprise a further means for removing at least a circumferential surface or cross-sectional portion from the voided stool." *Id.* at column 8, lines 33-37.

	Lapidus '178 discloses that "[o]nce obtained, the entire circumference or cross-sectional sample of stool is homogenized in an appropriate buffer, such as phosphate buffered saline." *Id.* at column 9, lines 30-32. Lapidus '178 discloses "[o]nce a circumferential surface or cross-sectional sample of stool is obtained, it may be homogenized by known methods to distribute cells and cellular debris throughout the sample. An assay then is performed on the homogenate, or an extract of the homogenate, to detect the presence of cells and/or cellular debris in the sample. The assay may be any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation such as a protein, or DNA-based assays for detecting mutations or genetic characteristics indicative of colorectal cancer." *Id.* at column 6, lines 45-56.

Lapidus '178 discloses removing a portion of the fecal sample to produce a removed portion and a remaining portion of the fecal sample. According to Lapidus '178, the 'removed portion' could take a number of forms, including removal of a cross-sectional portion of the voided stool sample, a circumferential surface portion of the voided stool sample, or a layer of the voided stool sample that adheres to the surface of a sampling device. In these scenarios, the cross-sectional portion, the circumferential surface portion, or the layer portion described by Lapidus '178 corresponds to the 'removed portion' of the fecal sample in independent claim 1.

Given the removal of a cross-sectional, circumferential surface, and/or layer of the voided stool sample, it would be obvious that Lapidus '178 discloses a 'remaining portion' of the fecal sample that is left over following such removal. A person of ordinary skill in the art would recognize and understand that Lapidus '178 discloses the 'remaining portion' according to independent claim 1. Ex. 1014 at paragraphs 60-63.

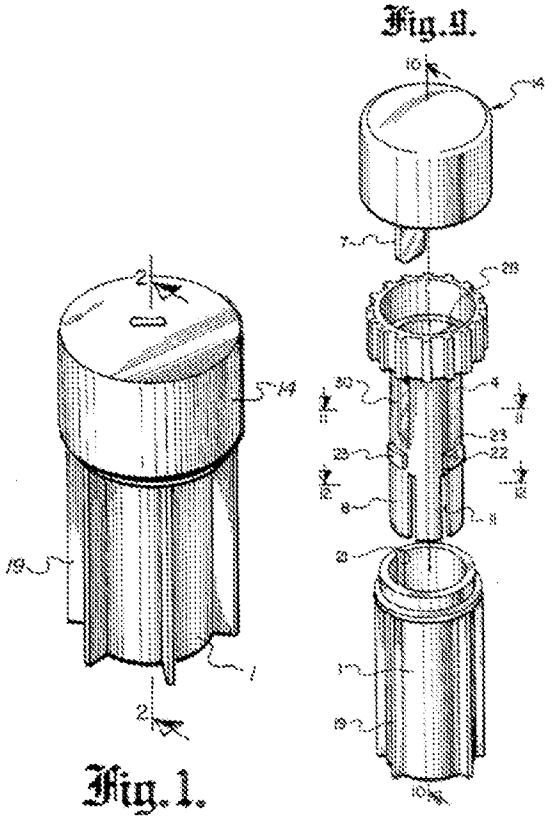
Moreover, Lapidus '178 discloses that the 'removed portion' of the fecal sample is obtained upon collection of the fecal sample. Again referring to Figure 2 above, Lapidus '178 discloses that "Means 8 may be fixedly attached to the support frame 1 or may be removably attached for removal subsequent to deposition of stool. Means 8 may comprise a further means for removing at least a circumferential surface or cross-sectional portion from the voided stool." This provides evidence that the 'removed portion' of the fecal sample (e.g., a circumferential surface or cross-sectional portion from the voided stool) can be obtained in the conventional toilet upon collection of the voided stool.

Finally, Lapidus '178 discloses that the 'removed portion' of the fecal sample is in a separate sealable container. Lapidus '178 discloses that the 'removed portion' (e.g., a circumferential surface or cross-sectional sample of stool) is placed in a buffer such as phosphate buffered saline according to "means and materials" that are generally known in the art in order to assay the 'removed portion'. It would have been obvious that placement of the removed portion in a buffer would result in stabilization of the material in the portion for subsequent testing.

Further, at the time of filing Lapidus, it was well known in the art that a fecal sample was homogenized in appropriate buffers for the purpose of assaying would be done in a separate sealable container. For instance, U.S. Patent No. 4,859,610 to Maggio (Ex. 1010) describes a device that is "particularly useful for homogenizing and analyzing fecal samples." Ex. 1010 at column 4, lines 7-8. Maggio describes that the device includes a vessel for placement of a fecal sample and that "[a]fter a measured portion of [fecal sample] is secured by the scoop (8) and introduced into the vessel (1), 2 mils of phosphate buffered saline, pH 7.4 (PBS) is added to the vessel (1)." *Id.* at column 8, lines 39-42.

Maggio later describes that "FIG. 1 is a perspective view of a preferred embodiment of the immunoassay incubation device." *Id.* at column 3, lines 33-34. Furthermore, Maggio describes that "FIG. 9 is an exploded view in perspective of another alternative embodiment of the immunoassay incubation device illustrating a valve for controlling the flow of homogenized

sample from the extractor into the incubation chamber." *Id.* at column 3, lines 60-64. Figures 1 and 9 of Maggio, presented below, clearly depict a separate sealable container that is configured to contain a fecal sample and a homogenizing buffer:



Therefore, one skilled in the art would recognize that Lapidus '178 discloses all of the requirements for the removing step contained in the second limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraphs 60-63. Accordingly, Lapidus '178 renders this portion of claim 1 obvious.

'781 Patent, Claim 1, Third Limitation	**Lapidus '178**
c) combining the removed portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container; and	**Lapidus '178** discloses that "[o]nce obtained, the entire circumference or cross-sectional sample of stool is homogenized in an appropriate buffer, such as phosphate buffered saline. Homogenization means and materials for homogenization are generally

	known in the art. Thus, particular homogenization methods may be selected by the skilled artisan and may depend upon the assay to be employed. The buffer may contain detergent, salt, proteinase, inhibitors of DNA and RNA degrading enzymes. The composition of the buffer will depend on the type of assay to be performed. If a fecal occult blood assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for detecting the presence of fecal occult blood are known in the art. If a test is to be performed for the presence of a particular protein, the buffer should not contain a proteinase capable of degrading such tumor marking antigens." Ex. 1002 at column 9, lines 30-36.

Lapidus '178 discloses combining the removed portion of the fecal sample (e.g., the cross-sectional portion, the circumferential surface portion, or the layer portion) with a buffer. Lapidus '178 discloses such buffers as any buffer known to the skilled artisan, such as those that contain detergents and salts, which are well known for preservation of proteins. Ex. 1014 at paragraphs 72-73.

Again, Lapidus '178 discloses that the cross-sectional portion, circumferential surface portion, or layer portion of the fecal sample can be homogenized in a buffer according to "means and materials" that are generally known in the art. This indicates that the removed portion is added to a buffer for further processing. As discussed *supra,* at the time of filing Lapidus, it was well known in the art that a fecal sample was homogenized in appropriate buffers for the purpose of assaying would be done in a separate sealable container. See, *e.g.,* Maggio (Ex. 1010) as

evidence of the state of the art at the time of filing Lapidus. Accordingly, the combination of the removed portion of the fecal sample and buffer is placed in a separate container and sealed according to methods known in the art.

Therefore, one skilled in the art would recognize that Lapidus '178 discloses all of the requirements for the combining step contained in the third limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraph 73. Accordingly, Lapidus '178 renders this portion of claim 1 obvious.

'781 Patent, Claim 1, Fourth Limitation	**Lapidus '178**
d) combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, and sealing the sealable collection vessel.	**Lapidus '178** discloses that "[m]ethods of the invention also comprise obtaining a representative (i.e., cross-sectional) ***sample of stool*** and homogenizing ***the stool*** in a buffer, such as a buffer comprising a detergent and a proteinase and optionally a DNase inhibitor. Ex. 1002 at column 3, lines 11-15 (emphasis added). Lapidus '178 discloses that "the receptacle [containing the stool] may comprise means for introducing homogenization buffer or one or more preservatives, such as alcohol, a solution of high salt concentration, antibiotics, and chaotropic salts in order to neutralize bacteria present in the stool sample. The homogenization buffer may be a physiologically compatible buffer such as phosphate buffered saline, and may comprise salt such as 20-100 mM NaCl or KCl. The homogenization buffer may also comprise a detergent, such as 1-10% SDS or triton, and/or a proteinase, such as proteinase K. The

	buffer may also contain inhibitors of DNA and RNA degrading enzymes. The receptacle, whether adapted to fit a toilet or simply adapted for receiving the voided stool sample, should include sealing means sufficient to contain the voided stool sample and any solution added thereto and to prevent the emanation of odors." *Id.* at column 8, lines 5-21.

Lapidus '178 discloses combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer. As discussed *supra*, given removal of a cross-sectional, circumferential surface, and/or layer of the stool, logic dictates that Lapidus '178 discloses a 'remaining portion' of the fecal sample that is left over following such removal. *In re Johnson*, 558 F.2d at 1019. A person of ordinary skill in the art would recognize and understand that Lapidus '178 discloses the 'remaining portion' according to independent claim 1. Ex. 1014 at paragraph 79.

The 'remaining portion' of the fecal sample corresponds to the stool and Lapidus '178 discloses that the stool is contained in the receptacle, which corresponds to the "sealable collection vessel." Further, Lapidus '178 discloses that homogenization buffer can be added to the receptacle containing the stool. Lapidus '178 states that "[m]ethods of the invention also comprise obtaining a representative (i.e., cross-sectional) ***sample of stool*** and homogenizing ***the stool*** in a buffer, such as a buffer comprising a detergent and a proteinase and optionally a DNase inhibitor. Ex. 1002 at column 3, lines 11-15 (emphasis added). This sentence is interpreted ti describe two different parts of fecal material – the 'removed portion' ***sample of stool*** and also the 'remaining portion' of ***the stool***. This sentence of Lapidus '178 discloses addition of a buffer to the 'remaining portion' of ***the stool***.

Lapidus '178 discloses that the buffer can contain phosphate buffered saline, NaCl or KCl, a detergent such as SDS or triton, and inhibitors of DNA and/or RNA degrading enzymes. A person of ordinary skill in the art would recognize such buffer as a "stabilizing buffer." Ex. 1014 at paragraph 80.

Finally, Lapidus '178 discloses that the receptacle includes sealing means and that it should be sealed "to contain the voided stool sample and any solution added thereto and to prevent the emanation of odors."

Therefore, one skilled in the art would recognize that Lapidus '178 discloses all of the requirements for the combining step contained in the fourth limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraphs 79-81. Accordingly, Lapidus '178 renders this portion of claim 1 obvious.

4. Lapidus '650 Renders Claim 1 Obvious

'781 Patent, Claim 1, Preamble	Lapidus '650
1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:	**Lapidus '650** discloses processing of "a stool voided by a patient" in Example 1, entitled "Preparation of a Stool Sample." Ex. 1003 at column 7, lines 58-62. Further, "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 63-64.

In the alternative to the assertion that Lapidus '650 anticipates claim 1, Lapidus '650 further renders claim 1 obvious.

As explained in Section IV. *supra*, the preamble of claim 1 is not a limitation. However, even if the preamble of claim 1 was determined to be a limitation, Lapidus '650 discloses this limitation. Lapidus '650 discloses a stool (a fecal sample) voided by a patient into a receptacle that is transported to a testing facility.

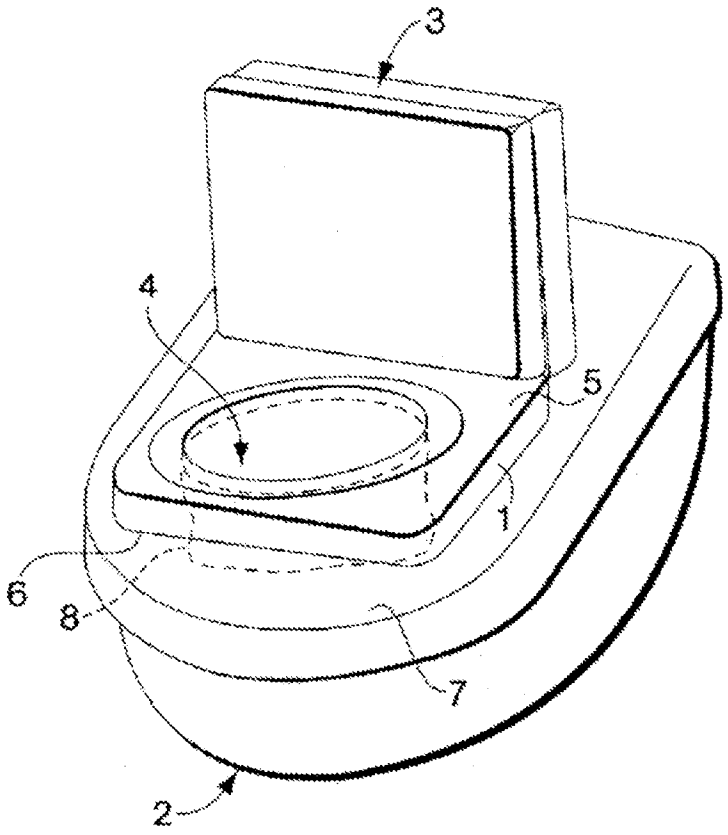
Further, Lapidus '650 discloses the method of processing a "freshly-collected" fecal sample "without freezing" specified by the preamble. Lapidus '650 does not disclose the concept of freezing fecal samples. Thus, Lapidus explicitly discloses collecting a fecal sample "without freezing" to meet the language of the preamble.

Moreover, U.S. Patent No. 5,196,167 (Ex. 1011) is incorporated by reference into Lapidus '650 at column 6, lines 30-31. In pertinent part, U.S. Patent No. 5,196,167 discloses a test sheet product used for identification of blood in a patient stool and states that "[a]fter the patient has completed a bowel movement, the test sheet is merely dropped into the toilet bowl." Ex. 1011 at column 6, lines 65-67. Further, U.S. Patent No. 5,196,167 discloses that "[a]fter the results of the test have been visually observed, the test sheet is disposed of by merely flushing the toilet bowl." *Id.* at column 7, lines 7-9. Accordingly, one skilled in the art would recognize Lapidus '650 discloses the method of processing a "freshly-collected" fecal sample "without freezing" specified by the preamble because U.S. Patent No. 5,196,167 (incorporated by reference into Lapidus '650) clearly discloses a method in which a "freshly-collected" fecal sample is collected and processed "without freezing". Ex. 1014 at paragraph 45.

'781 Patent, Claim 1, First Limitation	**Lapidus '650**
a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject by defecation directly into a sealable collection vessel;	**Lapidus '650** discloses collecting "a stool voided by a patient." Ex. 1003 at column 7, lines 61-62. Lapidus '650 discloses that a "[s]tool is voided [by the patient] into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 63-64. Lapidus '650 discloses that "[t]he receptacle may be fitted to a conventional toilet such that the receptacle accepts stool voided in a conventional manner." *Id.* at column 7, lines 64-66. Lapidus '650 discloses that "[t]he receptacle, whether adapted to fit a toilet or simply adapted for receiving the voided stool sample, should include sealing means sufficient to contain the voided stool sample…". *Id.* at column 8, lines 17-20.

Lapidus '650 discloses collecting a fecal sample from a human subject. Lapidus '650 discloses that "[t]he receptacle may be fitted to a conventional toilet such that the receptacle accepts stool voided in a conventional manner." *Id.* at column 7, lines 26-28. This passage in Lapidus '650 provides evidence that the fecal sample is collected from a human subject, since only humans use conventional toilets to void stool in a conventional manner.

Furthermore, Lapidus '650 discloses that the fecal sample is collected in a receptacle that can be adapted to fit a toilet, thus demonstrating that the human subject defecates "directly" into the receptacle. As shown in Figure 2, the receptacle is a "sealable" receptacle comprising an articulating **cover 3** that can be utilized in "a closed position (not shown) for sealing voided stool within the receptacle." *Id.* at column 7, lines 54-55. Figure 2 of Lapidus '650 is shown below:



Finally, Lapidus '650 discloses that the stool can be collected at home according to the broadest reasonable interpretation of the claims consistent with the specification. As discussed above, the broadest reasonable interpretation of "collected at home" in the '781 Patent is collected at a location other than a testing facility such a medical diagnostics laboratory. Lapidus

'650 discloses that the sealable receptacle containing the fecal sample "is preferably small enough to be transported to a testing facility," meaning that the fecal sample is collected at *a location different than the testing facility.* Further, Lapidus '650 discloses that the toilet onto which the receptacle may be fitted is "a conventional toilet such that the receptacle accepts stool voided in a conventional manner." This indicates that a fecal sample is collected at home by the patient since the "conventional manner" for voiding stool is on a toilet in one's home. A person skilled in the art would understand that Lapidus '650 effectively discloses collection of a stool at home, given that "home" is not a testing facility such a medical diagnostics laboratory. Ex. 1014 at paragraph 53.

Therefore, one skilled in the art would recognize that Lapidus '650 discloses all of the requirements for the collecting step contained in the first limitation of claim 1 of the '781 Patent. *Id.* Accordingly, Lapidus '650 renders this portion of claim 1 obvious.

a.

'781 Patent, Claim 1, Second Limitation	**Lapidus '650**
b) removing a portion of the fecal sample to a separate sealable container to produce a removed portion and a remaining portion of the fecal sample;	**Lapidus '650** discloses that "a cross-sectional portion is removed from the voided stool by making one or more sagittal or coronal section through the stool." Ex. 1003 at column 8, lines 45-47. Lapidus '650 discloses that "[a]lternatively, a circumferential surface of a stool is prepared by taking the entire surface layer of the stool, or the entire surface layer of a cross-sectional portion of the stool." *Id.* at column 8, lines 49-52. Lapidus '650 discloses that "[a]lternatively, the stool sample is rolled along the surface of the sampling device, and the layer of stool that adheres to the surface is then processed as described herein." *Id.* at column 9, lines 10-12.

	Referring to Figure 2, Lapidus '650 describes that "[m]eans 8 may be fixedly attached to the support frame 1 or may be removably attached for removal subsequent to deposition of stool. Means 8 may comprise a further means for removing at least a circumferential surface or cross-sectional portion from the voided stool." *Id.* at column 8, lines 33-37. Lapidus '650 discloses that "[o]nce obtained, the entire circumference or cross-sectional sample of stool is homogenized in an appropriate buffer, such as phosphate buffered saline." *Id.* at column 9, lines 30-32. Lapidus '650 discloses "[o]nce a circumferential surface or cross-sectional sample of stool is obtained, it may be homogenized by known methods to distribute cells and cellular debris throughout the sample. An assay then is performed on the homogenate, or an extract of the homogenate, to detect the presence of cells and/or cellular debris in the sample. The assay may be any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation such as a protein, or DNA-based assays for detecting mutations or genetic characteristics

	indicative of colorectal cancer. *Id.* at column 6, lines 45-56.

Lapidus '650 discloses removing a portion of the fecal sample to produce a removed portion and a remaining portion of the fecal sample. According to Lapidus '650, the cross-sectional portion corresponds to the 'removed portion' of the fecal sample in independent claim 1.

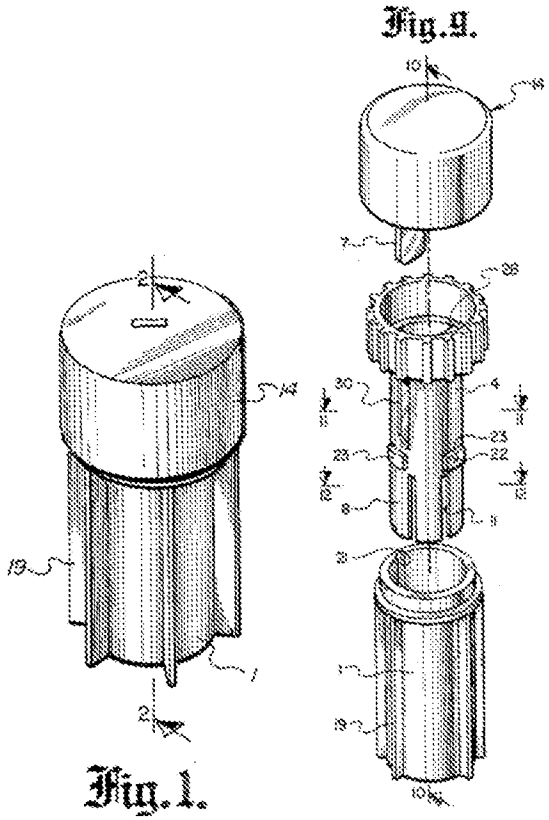
Given the removal of a cross-sectional sample, logic dictates that Lapidus '650 discloses a 'remaining portion' of the fecal sample that is left over following such removal. *In re Johnson*, 558 F.2d at 1019. A person of ordinary skill in the art would recognize and understand that Lapidus '650 discloses the 'remaining portion' according to independent claim 1. Ex. 1014 at paragraphs 60-63.

Moreover, Lapidus '650 discloses that the 'removed portion' of the fecal sample is obtained upon collection of the fecal sample. Again referring to Figure 2 above, Lapidus '650 discloses that "[m]eans 8 may be fixedly attached to the support frame 1 or may be removably attached for removal subsequent to deposition of stool. Means 8 may comprise a further means for removing at least a circumferential surface or cross-sectional portion from the voided stool." *Id.* at column 7, lines 61-65. This provides evidence that the 'removed portion' of the fecal sample (e.g., a cross-sectional portion from the voided stool) can be obtained in the conventional toilet upon collection of the voided stool.

Finally, Lapidus '650 discloses that the 'removed portion' of the fecal sample is in a separate sealable container. Lapidus '650 discloses that the 'removed portion' (e.g., a cross-sectional sample of stool) is placed in a buffer such as phosphate buffered saline according to "means and materials" that are generally known in the art in order to assay the 'removed portion'. At the time of filing Lapidus '650, it was well known in the art that a fecal sample was homogenized in appropriate buffers for the purpose of assaying would be done in a separate sealable container. For instance, U.S. Patent No. 4,859,610 to Maggio (Ex. 1010) discloses a device that is "particularly useful for homogenizing and analyzing fecal samples." Ex. 1010 at column 4, lines 7-8. Maggio discloses that the device includes a vessel for placement of a fecal sample and that "[a]fter a measured portion of [fecal sample] is secured by the scoop (8) and

introduced into the vessel (1), 2 mils of phosphate buffered saline, pH 7.4 (PBS) is added to the vessel (1)." *Id.* at column 8, lines 39-42.

Maggio later discloses that "FIG. 1 is a perspective view of a preferred embodiment of the immunoassay incubation device." *Id.* at column 3, lines 33-34. Furthermore, Maggio discloses that "FIG. 9 is an exploded view in perspective of another alternative embodiment of the immunoassay incubation device illustrating a valve for controlling the flow of homogenized sample from the extractor into the incubation chamber." *Id.* at column 3, lines 60-64. Figures 1 and 9 of Maggio, presented below, clearly depict a separate sealable container that is configured to contain a fecal sample and a homogenizing buffer:



Therefore, one skilled in the art would recognize that Lapidus '650 discloses all of the requirements for the removing step contained in the second limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraphs 60-63. Accordingly, Lapidus '650 renders this portion of claim 1 obvious.

'781 Patent, Claim 1, Third Limitation	**Lapidus '650**
c) combining the removed portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container; and	**Lapidus '650** discloses that "[o]nce obtained, the entire circumference or cross-sectional sample of stool is homogenized in an appropriate buffer, such as phosphate buffered saline. Homogenization means and materials for homogenization are generally known in the art. Thus, particular homogenization methods may be selected by the skilled artisan and may depend upon the assay to be employed. The buffer may contain detergent, salt, proteinase, inhibitors of DNA and RNA degrading enzymes. The composition of the buffer will depend on the type of assay to be performed. If a fecal occult blood assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for detecting the presence of fecal occult blood are known in the art. If a test is to be performed for the presence of a particular protein, the buffer should not contain a proteinase capable of degrading such tumor marking antigens." Ex. 1003 at column 9, lines 30-36.

Lapidus '650 discloses combining the removed portion of the fecal sample (e.g., the cross-sectional portion) with a buffer. Lapidus '650 discloses such buffers as any buffer known to the skilled artisan, such as those that contain detergents and salts, which are well known for preservation of proteins. Ex. 1014 at paragraphs 72-73. Lapidus '650 further notes that to

prevent the denaturation or degradation of blood proteins found in the sample, it would be important to specifically avoid including a proteinase in the buffer that would contain detergents and salts.

Again, Lapidus '650 discloses that the cross-sectional portion of the fecal sample can be homogenized in a buffer according to "means and materials" that are generally known in the art. This indicates that the removed portion is added to a buffer for further processing. As discussed *supra,* at the time of filing Lapidus, it was well known in the art that a fecal sample was homogenized in appropriate buffers for the purpose of assaying would be done in a separate sealable container. See, *e.g.,* Maggio (Ex. 1010) as evidence of the state of the art at the time of filing Lapidus '650. Accordingly, the combination of the removed portion of the fecal sample and buffer is placed in a separate container and sealed according to methods known in the art.

Therefore, one skilled in the art would recognize that Lapidus '650 discloses all of the requirements for the combining step contained in the third limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraph 73. Accordingly, Lapidus '650 renders this portion of claim 1 obvious.

'781 Patent, Claim 1, Fourth Limitation	**Lapidus '650**
d) combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, and sealing the sealable collection vessel.	**Lapidus '650** discloses that "[m]ethods of the invention also comprise obtaining a representative (i.e., cross-sectional) ***sample of stool*** and homogenizing ***the stool*** in a buffer, such as a buffer comprising a detergent and a proteinase and optionally a DNase inhibitor. Ex. 1003 at column 3, lines 11-15 (emphasis added). Lapidus '650 discloses that "the receptacle [containing the stool] may comprise means for introducing homogenization buffer or one or more preservatives, such as alcohol, a solution of high salt concentration, antibiotics, and chaotropic salts in order to neutralize bacteria

	present in the stool sample. The homogenization buffer may be a physiologically compatible buffer such as phosphate buffered saline, and may comprise salt such as 20-100 mM NaCl or KCl. The homogenization buffer may also comprise a detergent, such as 1-10% SDS or triton, and/or a proteinase, such as proteinase K. The buffer may also contain inhibitors of DNA and RNA degrading enzymes. The receptacle, whether adapted to fit a toilet or simply adapted for receiving the voided stool sample, should include sealing means sufficient to contain the voided stool sample and any solution added thereto and to prevent the emanation of odors." *Id.* at column 8, lines 5-21.

Lapidus '650 discloses combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer. As discussed *supra*, given removal of a cross-sectional sample of stool, logic dictates that Lapidus '650 discloses a 'remaining portion' of the fecal sample that is left over following such removal. *In re Johnson*, 558 F.2d at 1019. A person of ordinary skill in the art would recognize and understand that Lapidus '650 discloses the 'remaining portion' according to independent claim 1. Ex. 1014 at paragraph 79.

The 'remaining portion' of the fecal sample corresponds to the stool and Lapidus '650 discloses that the stool is contained in the receptacle, which corresponds to the "sealable collection vessel." Further, Lapidus '650 discloses that homogenization buffer can be added to the receptacle containing the stool. Lapidus '650 states that "[m]ethods of the invention also comprise obtaining a representative (i.e., cross-sectional) ***sample of stool*** and homogenizing ***the stool*** in a buffer, such as a buffer comprising a detergent and a proteinase and optionally a DNase inhibitor. Ex. 1003 at column 2, line 66 – column 3, line 3 (emphasis added). This sentence is

interpreted to disclose two different parts of fecal material – the 'removed portion' ***sample of stool*** and also the 'remaining portion' of ***the stool***. This sentence of Lapidus '650 discloses addition of a buffer to the 'remaining portion' of ***the stool***.

Lapidus '650 discloses that the buffer can contain phosphate buffered saline, NaCl or KCl, a detergent such as SDS or triton, and inhibitors of DNA and/or RNA degrading enzymes. A person of ordinary skill in the art would recognize such buffer as a "stabilizing buffer." Ex. 1014 at paragraph 80.

Finally, Lapidus '650 discloses that the receptacle includes sealing means and that it should be sealed "to contain the voided stool sample and any solution added thereto and to prevent the emanation of odors."

Therefore, one skilled in the art would recognize that Lapidus '650 discloses all of the requirements for the combining step contained in the fourth limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraphs 79-81. Accordingly, Lapidus '650 renders this portion of claim 1 obvious.

5. Lapidus '178 in view of De Luca and Olson Renders Claim 1 Obvious

'781 Patent, Claim 1, Preamble	Lapidus '178 in view of De Luca and Olson
1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:	**Lapidus '178** discloses processing of "a stool voided by a patient" in Example 1, entitled "Preparation of a Stool Sample." Ex. 1002 at column 7, lines 58-62. Further, "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 63-64.

As explained in Section IV. *supra*, the preamble of claim 1 is not a limitation. However, even if the preamble of claim 1 was determined to be a limitation, Lapidus '178 discloses this limitation. Lapidus '178 discloses a stool (a fecal sample) voided by a patient into a receptacle that is transported to a testing facility.

Further, Lapidus '178 discloses the method of processing a "freshly-collected" fecal sample "without freezing" specified by the preamble. Lapidus '178 discloses that in "a preferred embodiment a stool is frozen prior to processing." *Id.* at column 9, lines 21-22. According to well-established law, the alternative (i.e., a stool NOT being frozen prior to processing) is also described by Lapidus. For instance, *In re Johnson* holds that if alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See 558 F.2d 1008, 1019 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984). Accordingly, one skilled in the art would recognize Lapidus '178 discloses the method of processing a "freshly-collected" fecal sample "without freezing" specified by the preamble. Ex. 1014 at paragraph 45.

'781 Patent, Claim 1, First Limitation	**Lapidus '178 in view of De Luca and Olson**
a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject by defecation directly into a sealable collection vessel;	**Lapidus '178** discloses collecting "a stool voided by a patient." Ex. 1002 at column 7, lines 61-62. Lapidus '178 discloses that a "[s]tool is voided [by the patient] into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 63-64. Lapidus '178 discloses that "[t]he receptacle may be fitted to a conventional toilet such that the receptacle accepts stool voided in a conventional manner." *Id.* at column 7, lines 64-66. Lapidus '178 discloses that "[t]he receptacle, whether adapted to fit a toilet or simply adapted for receiving the voided stool sample, should include sealing means sufficient to contain the voided stool sample…". *Id.* at column 8, lines 17-20.

Lapidus '178 discloses collecting a fecal sample from a human subject. Lapidus '178 discloses that "[t]he receptacle may be fitted to a conventional toilet such that the receptacle accepts stool voided in a conventional manner." *Id.* at column 7, lines 64-66. This passage in Lapidus '178 provides evidence that the fecal sample is collected from a human subject, since only humans use conventional toilets to void stool in a conventional manner.

Furthermore, Lapidus '178 discloses that the fecal sample is collected in a receptacle that can be adapted to fit a toilet, thus demonstrating that the human subject defecates "directly" into the receptacle. As shown in Figure 2, the receptacle is a "sealable" receptacle comprising an articulating **cover 3** that can be utilized in "a closed position (not shown) for sealing voided stool within the receptacle." *Id.* at column 8, lines 24-27. Figure 2 of Lapidus '178 is shown *supra.*

Finally, Lapidus '178 discloses that the stool can be collected at home according to the broadest reasonable interpretation of the claims consistent with the specification. As discussed above, the broadest reasonable interpretation of "collected at home" in the '781 Patent is collected at a location other than a testing facility. Lapidus '178 discloses that the sealable receptacle containing the fecal sample "is preferably small enough to be transported to a testing facility," meaning that the fecal sample is collected at *a location different than the testing facility.* Further, Lapidus '178 discloses that the toilet onto which the receptacle may be fitted is "a conventional toilet such that the receptacle accepts stool voided in a conventional manner." This indicates that a fecal sample is collected at home by the patient since the "conventional manner" for voiding stool is on a toilet in one's home. A person skilled in the art would understand that Lapidus '178 effectively describes collection of a stool at home, given that "home" is not a testing facility such a medical diagnostics laboratory. Ex. 1014 at paragraph 53.

Therefore, one skilled in the art would recognize that Lapidus '178 discloses all of the requirements for the collecting step contained in the first limitation of claim 1 of the '781 Patent. *Id.*

'781 Patent, Claim 1, Second Limitation	**Lapidus '178 in view of De Luca and Olson**
b) removing a portion of the fecal sample to a separate sealable container to produce a	**Lapidus '178** discloses that "a cross-sectional portion is removed from the voided stool by making one or more sagittal or coronal

removed portion and a remaining portion of the fecal sample;	section through the stool." Ex. 1002 at column 8, lines 45-47. Lapidus '178 discloses that "[a]lternatively, a circumferential surface of a stool is prepared by taking the entire surface layer of the stool, or the entire surface layer of a cross-sectional portion of the stool." *Id.* at column 8, lines 49-52. Lapidus '178 discloses that "[a]lternatively, the stool sample is rolled along the surface of the sampling device, and the layer of stool that adheres to the surface is then processed as described herein." *Id.* at column 9, lines 10-12. Referring to Figure 2, Lapidus '178 describes that "[m]eans 8 may be fixedly attached to the support frame 1 or may be removably attached for removal subsequent to deposition of stool. Means 8 may comprise a further means for removing at least a circumferential surface or cross-sectional portion from the voided stool." *Id.* at column 8, lines 33-37. Lapidus '178 discloses that "[o]nce obtained, the entire circumference or cross-sectional sample of stool is homogenized in an appropriate buffer, such as phosphate buffered saline." *Id.* at column 9, lines 30-32. Lapidus '178 discloses "[o]nce a circumferential surface or cross-sectional sample of stool is obtained, it may be

	homogenized by known methods to distribute cells and cellular debris throughout the sample. An assay then is performed on the homogenate, or an extract of the homogenate, to detect the presence of cells and/or cellular debris in the sample. The assay may be any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation such as a protein, or DNA-based assays for detecting mutations or genetic characteristics indicative of colorectal cancer." *Id.* at column 6, lines 45-56. **De Luca** discloses "an extraction and sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin, Helicobacter pylori and the like. Ex. 1006 at [0001]. De Luca discloses "an extraction and sampling tube for the collection of faeces samples that is practical for the patient and simple to use for the laboratory technician." *Id.* at [0015]. Further, De Luca discloses "[t]he extraction tube for collection of faeces samples, according to the invention, comprises a container body hollow on the inside for containing a buffer solution and faeces

	samples, a top cap applied to the top end of the container body and provided with a threaded small rod for sampling of faeces samples and a bottom cap applied removably to the bottom end of the container body. *Id.* at [0019]. De Luca discloses that on the extraction tube, "[a]n annular seal 55 is provided between the knurled part 44 and the threaded part 45 of the top cap." *Id.* at [0032].

Lapidus '178 discloses removing a portion of the fecal sample to produce a removed portion and a remaining portion of the fecal sample. According to Lapidus '178, the 'removed portion' could take a number of forms, including removal of a cross-sectional portion of the voided stool sample, a circumferential surface portion of the voided stool sample, or a layer of the voided stool sample that adheres to the surface of a sampling device. In these scenarios, the cross-sectional portion, the circumferential surface portion, or the layer portion described by Lapidus '178 corresponds to the 'removed portion' of the fecal sample in independent claim 1.

Given the removal of a cross-sectional, circumferential surface, and/or layer of the voided stool sample, it would be obvious that Lapidus '178 discloses a 'remaining portion' of the fecal sample that is left over following such removal. A person of ordinary skill in the art would recognize and understand that Lapidus '178 discloses the 'remaining portion' according to independent claim 1. Ex. 1014 at paragraphs 60-63.

Moreover, Lapidus '178 discloses that the 'removed portion' of the fecal sample is obtained upon collection of the fecal sample. Again referring to Figure 2 above, Lapidus '178 discloses that "Means 8 may be fixedly attached to the support frame 1 or may be removably attached for removal subsequent to deposition of stool. Means 8 may comprise a further means for removing at least a circumferential surface or cross-sectional portion from the voided stool." This provides evidence that the 'removed portion' of the fecal sample (e.g., a circumferential surface or cross-sectional portion from the voided stool) can be obtained in the conventional toilet upon collection of the voided stool.

Even if Lapidus '178 is determined to not specifically teach removal to a separate sealable container, De Luca removes this deficiency. De Luca discloses "an extraction and sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin…". Ex. 1006 at [0001]. Further, De Luca teaches that fecal samples are removed and placed in a separate sealable container to perform assays, such as fecal immunochemical blood tests. The extraction tube of De Luca includes a container body for containing a fecal sample with buffer solution and the container is sealed using a cap.

Thus, a person of ordinary skill in the art would have been motivated to utilize the separate sealable container of De Luca to place the 'removed portion' of the fecal sample obtained by Lapidus '178 with the requisite expectation of success. Therefore, one skilled in the art would recognize that Lapidus '178 in view of De Luca discloses all of the requirements for the removing step contained in the second limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraph 66.

'781 Patent, Claim 1, Third Limitation	**Lapidus '178 in view of De Luca and Olson**
c) combining the removed portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container; and	**Lapidus '178** discloses that "[o]nce obtained, the entire circumference or cross-sectional sample of stool is homogenized in an appropriate buffer, such as phosphate buffered saline. Homogenization means and materials for homogenization are generally known in the art. Thus, particular homogenization methods may be selected by the skilled artisan and may depend upon the assay to be employed. The buffer may contain detergent, salt, proteinase, inhibitors of DNA and RNA degrading enzymes. The composition of the buffer will depend on the type of assay to be performed. If a fecal occult blood assay is to be performed, the

	buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for detecting the presence of fecal occult blood are known in the art. If a test is to be performed for the presence of a particular protein, the buffer should not contain a proteinase capable of degrading such tumor marking antigens." Ex. 1002 at column 9, lines 30-36. **De Luca** discloses "an extraction and sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin, Helicobacter pylori and the like. Ex. 1006 at [0001]. De Luca discloses "an extraction and sampling tube for the collection of faeces samples that is practical for the patient and simple to use for the laboratory technician." *Id.* at [0015]. Further, De Luca discloses "[t]he extraction tube for collection of faeces samples, according to the invention, comprises a container body hollow on the inside for containing a buffer solution and faeces samples, a top cap applied to the top end of the container body and provided with a threaded small rod for sampling of faeces samples and a bottom cap applied removably

	to the bottom end of the container body. *Id.* at [0019]. De Luca discloses that on the extraction tube, "[a]n annular seal 55 is provided between the knurled part 44 and the threaded part 45 of the top cap." *Id.* at [0032].

Lapidus '178 discloses combining the removed portion of the fecal sample (e.g., the cross-sectional portion, the circumferential surface portion, or the layer portion) with a buffer. Lapidus '178 discloses such buffers as any buffer known to the skilled artisan, such as those that contain detergents and salts, which are well known for preservation of proteins. Ex. 1014 at paragraphs 72-73.

Again, Lapidus '178 discloses that the cross-sectional portion, circumferential surface portion, or layer portion of the fecal sample can be homogenized in a buffer according to "means and materials" that are generally known in the art. This indicates that the removed portion is added to a buffer for further processing.

Even if Lapidus '178 is determined to not specifically teach combining the removed portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container, De Luca removes this deficiency. De Luca discloses "an extraction and sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin…". Ex. 1006 at [0001]. The devices of De Luca are used for detection of blood proteins such as hemoglobin for use in fecal immunochemical blood tests. Further, De Luca teaches that fecal samples are removed and placed in a separate sealable container to perform the fecal immunochemical blood tests. The extraction tube of De Luca includes a container body for containing a buffer solution and fecal sample and the container is sealed using a cap.

Thus, a person of ordinary skill in the art would have been motivated to utilize the separate sealable container of De Luca to place the removed portion from the fecal sample of Lapidus '178. Based on De Luca, a person of ordinary skill in the art would combine the removed portion of the fecal sample in the separate sealable container with a buffer in the

extraction tube's container body to prevent denaturation or degradation of blood proteins so that a fecal immunochemical blood test could be performed. Ex. 1014 at paragraph 75. Further, De Luca teaches that the extraction tube is sealed using a top cap, rendering the extraction tube to be a "separate sealable container." Therefore, one skilled in the art would recognize that Lapidus '178 in view of De Luca discloses all of the requirements for the combining step contained in the third limitation of claim 1 of the '781 Patent. *Id.*

'781 Patent, Claim 1, Fourth Limitation	**Lapidus '178 in view of De Luca and Olson**
d) combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, and sealing the sealable collection vessel.	**Lapidus '178** discloses that "[m]ethods of the invention also comprise obtaining a representative (i.e., cross-sectional) ***sample of stool*** and homogenizing ***the stool*** in a buffer, such as a buffer comprising a detergent and a proteinase and optionally a DNase inhibitor. Ex. 1002 at column 3, lines 11-15 (emphasis added). Lapidus '178 discloses that "the receptacle [containing the stool] may comprise means for introducing homogenization buffer or one or more preservatives, such as alcohol, a solution of high salt concentration, antibiotics, and chaotropic salts in order to neutralize bacteria present in the stool sample. The homogenization buffer may be a physiologically compatible buffer such as phosphate buffered saline, and may comprise salt such as 20-100 mM NaCl or KCl. The homogenization buffer may also comprise a detergent, such as 1-10% SDS or triton, and/or a proteinase, such as proteinase K. The buffer may also contain inhibitors of DNA

	and RNA degrading enzymes. The receptacle, whether adapted to fit a toilet or simply adapted for receiving the voided stool sample, should include sealing means sufficient to contain the voided stool sample and any solution added thereto and to prevent the emanation of odors." *Id.* at column 8, lines 5-21. **Olson** discloses development of "a multitarget, fecal DNA screening assay that detects the presence of gene-specific mutations and long DNA fragments associated with colorectal cancer (CRC)." Ex. 1007 at Abstract. Olson discloses that "[t]he amount of DNA recovered from aliquots stored under the different conditions is based on quantification of a 200-bp DNA fragment (Table 3). Although the amount of recoverable DNA varies widely from sample to sample, at t0 the average recovery was 14,891 copies/10 mL, whereas after room temperature incubation, the average recovery was 1,955. Without buffer added to the samples, between 65% to 98% of the DNA was no longer recoverable (excluding sample GP-031), after incubation of samples at room temperature, compared with t0. The one exception, sample GP-031, maintained high DNA yield even without addition of stabilization buffer. Samples incubated with

	stabilization buffer maintained human DNA yields similar to the t0 samples (Table 3)." *Id.* at page 186, first column, second full paragraph. In conclusion, Olson states that "DNA can be stabilized by addition of buffer to the sample, leading to increased assay sensitivity. *Id.* at Abstract.

As discussed *supra*, Lapidus '178 discloses combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer. Even if Lapidus '178 is determined to not specifically teach combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, Olson removes this deficiency.

Olson discloses that addition of a stabilizing buffer (Exact buffer A) to stool samples provided a significant increase in recovery of DNA compared with samples incubated without buffer. This addition of a stabilizing buffer to DNA led to increased assay sensitivity.

Thus, a person of ordinary skill in the art would have been motivated to combine the remaining portion of the fecal sample with the stabilizing buffer taught by Olson. Olson discloses that DNA assays are greatly improved with addition of stabilizing buffer. Therefore, one skilled in the art would recognize that Lapidus '178 in view of Olson discloses all of the requirements for the combining step contained in the fourth limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraph 84.

In summary, Lapidus '178 in view of De Luca and Olson disclose the limitations of claim 1 of the '781 Patent. Consequently, claim 1 is obvious over Lapidus '178 in view of De Luca and Olson.

6. Lapidus '650 in view of De Luca and Olson Renders Claim 1 Obvious

'781 Patent, Claim 1, Preamble	**Lapidus '650 in view of De Luca and Olson**
1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:	**Lapidus '650** describes processing of "a stool voided by a patient" in Example 1, entitled "Preparation of a Stool Sample." Ex. 1003 at

	column 7, lines 12-17. Further, "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 24-26.

As explained in Section IV. *supra*, the preamble of claim 1 is not a limitation. However, even if the preamble of claim 1 was determined to be a limitation, Lapidus '650 discloses this limitation. Lapidus '650 discloses a stool (a fecal sample) voided by a patient into a receptacle that is transported to a testing facility.

Further, Lapidus '650 discloses the method of processing a "freshly-collected" fecal sample "without freezing" specified by the preamble. Lapidus '650 does not disclose the concept of freezing fecal samples. Thus, Lapidus explicitly discloses collecting a fecal sample "without freezing" to meet the language of the preamble.

Moreover, U.S. Patent No. 5,196,167 (Ex. 1011) is incorporated by reference into Lapidus '650 at column 6, lines 30-31. In pertinent part, U.S. Patent No. 5,196,167 discloses a test sheet product used for identification of blood in a patient stool and states that "[a]fter the patient has completed a bowel movement, the test sheet is merely dropped into the toilet bowl." Ex. 1011 at column 6, lines 65-67. Further, U.S. Patent No. 5,196,167 discloses that "[a]fter the results of the test have been visually observed, the test sheet is disposed of by merely flushing the toilet bowl." *Id.* at column 7, lines 7-9. Accordingly, one skilled in the art would recognize Lapidus '650 discloses the method of processing a "freshly-collected" fecal sample "without freezing" specified by the preamble because U.S. Patent No. 5,196,167 (incorporated by reference into Lapidus '650) clearly discloses a method in which a "freshly-collected" fecal sample is collected and processed "without freezing". Ex. 1014 at paragraph 45.

'781 Patent, Claim 1, First Limitation	**Lapidus '650 in view of De Luca and Olson**
a) collecting a fecal sample from a human subject, wherein the fecal sample is collected	**Lapidus '650** discloses collecting "a stool voided by a patient." Ex. 1003 at column 7, lines 12-17. Further, "[s]tool is voided into a

at home by the human subject by defecation directly into a sealable collection vessel;	receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 24-26. Lapidus '650 discloses that "[t]he receptacle may be fitted to a conventional toilet such that the receptacle accepts stool voided in a conventional manner." *Id.* at column 7, lines 26-28. Lapidus '650 discloses that "[t]he receptacle, whether adapted to fit a toilet or simply adapted for receiving the voided stool sample, should include sealing means sufficient to contain the voided stool sample…". *Id.* at column 7, lines 45-49.

Lapidus '650 discloses collecting a fecal sample from a human subject. Lapidus '650 discloses that "[t]he receptacle may be fitted to a conventional toilet such that the receptacle accepts stool voided in a conventional manner." *Id.* at column 7, lines 26-28. This passage in Lapidus '650 provides evidence that the fecal sample is collected from a human subject, since only humans use conventional toilets to void stool in a conventional manner.

Furthermore, Lapidus '650 discloses that the fecal sample is collected in a receptacle that can be adapted to fit a toilet, thus demonstrating that the human subject defecates "directly" into the receptacle. As shown in Figure 2, the receptacle is a "sealable" receptacle comprising an articulating **cover 3** that can be utilized in "a closed position (not shown) for sealing voided stool within the receptacle." *Id.* at column 7, lines 54-55. Figure 2 of Lapidus '650 is shown *supra.*

Finally, Lapidus '650 discloses that the stool can be collected at home according to the broadest reasonable interpretation of the claims consistent with the specification. As discussed above, the broadest reasonable interpretation of "collected at home" in the '781 Patent is collected at a location other than a testing facility such a medical diagnostics laboratory. Lapidus '650 discloses that the sealable receptacle containing the fecal sample "is preferably small enough to be transported to a testing facility," meaning that the fecal sample is collected at *a location different than the testing facility.* Further, Lapidus '650 discloses that the toilet onto

which the receptacle may be fitted is "a conventional toilet such that the receptacle accepts stool voided in a conventional manner." This indicates that a fecal sample is collected at home by the patient since the "conventional manner" for voiding stool is on a toilet in one's home. A person skilled in the art would understand that Lapidus '650 effectively discloses collection of a stool at home, given that "home" is not a testing facility such a medical diagnostics laboratory. Ex. 1014 at paragraph 53.

Therefore, one skilled in the art would recognize that Lapidus '650 discloses all of the requirements for the collecting step contained in the first limitation of claim 1 of the '781 Patent. *Id.*

'781 Patent, Claim 1, Second Limitation	**Lapidus '650 in view of De Luca and Olson**
b) removing a portion of the fecal sample to a separate sealable container to produce a removed portion and a remaining portion of the fecal sample;	**Lapidus '650** discloses that "a cross-sectional portion is removed from the voided stool by making one or more sagittal or coronal section through the stool." Ex. 1003 at column 7, lines 17-19. Referring to Figure 2, Lapidus '650 discloses that "[m]eans 8 may be fixedly attached to the support frame 1 or may be removably attached for removal subsequent to deposition of stool. Means 8 may comprise a further means for removing at least a circumferential surface or cross-sectional portion from the voided stool." *Id.* at column 7, lines 61-65. Lapidus '650 discloses that "[o]nce obtained, the cross-sectional stool sample is homogenized in an appropriate buffer, such as phosphate buffered saline." *Id.* at column 8, lines 5-7. Lapidus '650 discloses "[o]nce a

	cross-sectional stool sample is obtained, it may be homogenized by known methods to distribute cells and cellular debris throughout the sample. An assay then is performed on the homogenate, or an extract of the homogenate, to detect the presence of cells and/or cellular debris in the sample. The assay may be any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation such as a protein, or DNA-based assays for detecting mutations or genetic characteristics indicative of colorectal cancer". *Id.* at column 6, lines 1-11. **De Luca** discloses "an extraction and sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin, Helicobacter pylori and the like. Ex. 1006 at [0001]. De Luca discloses "an extraction and sampling tube for the collection of faeces samples that is practical for the patient and simple to use for the laboratory technician." *Id.* at [0015]. Further, De Luca discloses "[t]he extraction tube for collection of faeces samples, according to the invention, comprises a container body hollow on the inside for

	containing a buffer solution and faeces samples, a top cap applied to the top end of the container body and provided with a threaded small rod for sampling of faeces samples and a bottom cap applied removably to the bottom end of the container body. *Id.* at [0019]. De Luca discloses that on the extraction tube, "[a]n annular seal 55 is provided between the knurled part 44 and the threaded part 45 of the top cap." *Id.* at [0032].

Lapidus '650 discloses removing a portion of the fecal sample to produce a removed portion and a remaining portion of the fecal sample. According to Lapidus '650, the cross-sectional portion corresponds to the 'removed portion' of the fecal sample in independent claim 1.

Given the removal of a cross-sectional sample, logic dictates that Lapidus '650 discloses a 'remaining portion' of the fecal sample that is left over following such removal. *In re Johnson*, 558 F.2d at 1019. A person of ordinary skill in the art would recognize and understand that Lapidus '650 discloses the 'remaining portion' according to independent claim 1. Ex. 1014 at paragraphs 60-63.

Moreover, Lapidus '650 discloses that the 'removed portion' of the fecal sample is obtained upon collection of the fecal sample. Again referring to Figure 2 above, Lapidus '650 discloses that "[m]eans 8 may be fixedly attached to the support frame 1 or may be removably attached for removal subsequent to deposition of stool. Means 8 may comprise a further means for removing at least a circumferential surface or cross-sectional portion from the voided stool." *Id.* at column 7, lines 61-65. This provides evidence that the 'removed portion' of the fecal sample (e.g., a cross-sectional portion from the voided stool) can be obtained in the conventional toilet upon collection of the voided stool.

Even if Lapidus '650 is determined to not specifically teach removal to a separate sealable container, De Luca removes this deficiency. De Luca discloses "an extraction and

sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin…". Ex. 1006 at [0001]. Further, De Luca teaches that fecal samples are removed and placed in a separate sealable container to perform assays, such as fecal immunochemical blood tests. The extraction tube of De Luca includes a container body for containing a fecal sample with buffer solution and the container is sealed using a cap.

Thus, a person of ordinary skill in the art would have been motivated to utilize the separate sealable container of De Luca to place the 'removed portion' of the fecal sample obtained by Lapidus '650 with the requisite expectation of success. Therefore, one skilled in the art would recognize that Lapidus '650 in view of De Luca discloses all of the requirements for the removing step contained in the second limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraph 66.

'781 Patent, Claim 1, Third Limitation	**Lapidus '650 in view of De Luca and Olson**
c) combining the removed portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container; and	**Lapidus '650** discloses that "[o]nce obtained, the cross-sectional stool sample is homogenized in an appropriate buffer, such as phosphate buffered saline. Homogenization means and materials for homogenization are generally known in the art. Thus, particular homogenization methods may be selected by the skilled artisan and may depend upon the assay to be employed. The buffer may contain detergent, salt, proteinase, inhibitors of DNA and RNA degrading enzymes. The composition of the buffer will depend on the type of assay to be performed. If a fecal occult blood assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers

	useful for detecting the presence of fecal occult blood are known in the art. If a test is to be performed for the presence of a particular protein, the buffer should not contain a proteinase capable of degrading such tumor marking antigens." Ex. 1003 at column 8, lines 5-21. **De Luca** discloses "an extraction and sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin, Helicobacter pylori and the like. Ex. 1006 at [0001]. De Luca discloses "an extraction and sampling tube for the collection of faeces samples that is practical for the patient and simple to use for the laboratory technician." *Id.* at [0015]. Further, De Luca discloses "[t]he extraction tube for collection of faeces samples, according to the invention, comprises a container body hollow on the inside for containing a buffer solution and faeces samples, a top cap applied to the top end of the container body and provided with a threaded small rod for sampling of faeces samples and a bottom cap applied removably to the bottom end of the container body. *Id.* at [0019]. De Luca discloses that on the extraction tube, "[a]n annular seal 55 is

	provided between the knurled part 44 and the threaded part 45 of the top cap." *Id.* at [0032].

Lapidus '650 discloses combining the removed portion of the fecal sample (e.g., the cross-sectional portion) with a buffer. Lapidus '650 discloses such buffers as any buffer known to the skilled artisan, such as those that contain detergents and salts, which are well known for preservation of proteins. Ex. 1014 at paragraphs 72-73. Lapidus '650 further notes that to prevent the denaturation or degradation of blood proteins found in the sample, it would be important to specifically avoid including a proteinase in the buffer that would contain detergents and salts.

Again, Lapidus '650 discloses that the cross-sectional portion of the fecal sample can be homogenized in a buffer according to "means and materials" that are generally known in the art. This indicates that the removed portion is added to a buffer for further processing.

Even if Lapidus '650 is determined to not specifically teach combining the removed portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container, De Luca removes this deficiency. De Luca discloses "an extraction and sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin…". Ex. 1006 at [0001]. The devices of De Luca are used for detection of blood proteins such as hemoglobin for use in fecal immunochemical blood tests. Further, De Luca teaches that fecal samples are removed and placed in a separate sealable container to perform the fecal immunochemical blood tests. The extraction tube of De Luca includes a container body for containing a buffer solution and fecal sample and the container is sealed using a cap.

Thus, a person of ordinary skill in the art would have been motivated to utilize the separate sealable container of De Luca to place the removed portion from the fecal sample of Lapidus '650. Based on De Luca, a person of ordinary skill in the art would combine the removed portion of the fecal sample in the separate sealable container with a buffer in the extraction tube's container body to prevent denaturation or degradation of blood proteins so that a fecal immunochemical blood test could be performed. Ex. 1014 at paragraph 75. Further, De

Luca teaches that the extraction tube is sealed using a top cap, rendering the extraction tube to be a "separate sealable container." Therefore, one skilled in the art would recognize that Lapidus '650 in view of De Luca discloses all of the requirements for the combining step contained in the third limitation of claim 1 of the '781 Patent. *Id.*

'781 Patent, Claim 1, Fourth Limitation	**Lapidus '650 in view of De Luca and Olson**
d) combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, and sealing the sealable collection vessel.	**Lapidus '650** discloses that "[m]ethods of the invention also comprise obtaining a representative (i.e., cross-sectional) ***sample of stool*** and homogenizing ***the stool*** in a buffer, such as a buffer comprising a detergent and a proteinase and optionally a DNase inhibitor. Ex. 1003 at column 2, line 66 – column 3, line 3 (emphasis added). Lapidus '650 discloses that "the receptacle [containing the stool] may comprise means for introducing homogenization buffer or one or more preservatives, such as alcohol, a solution of high salt concentration, antibiotics, and chaotropic salts in order to neutralize bacteria present in the stool sample. The homogenization buffer may be a physiologically compatible buffer such as phosphate buffered saline, and may comprise salt such as 20-100 mM NaCl or KCl. The homogenization buffer may also comprise a detergent, such as 1-10% SDS or triton, and/or a proteinase, such as proteinase K. The buffer may also contain inhibitors of DNA and RNA degrading enzymes. The receptacle, whether adapted to fit a toilet or

	simply adapted for receiving the voided stool sample, should include sealing means sufficient to contain the voided stool sample and any solution added thereto and to prevent the emanation of odors." *Id.* at column 7, lines 31-49. **Olson** discloses development of "a multitarget, fecal DNA screening assay that detects the presence of gene-specific mutations and long DNA fragments associated with colorectal cancer (CRC)." Ex. 1007 at Abstract. Olson discloses that "[t]he amount of DNA recovered from aliquots stored under the different conditions is based on quantification of a 200-bp DNA fragment (Table 3). Although the amount of recoverable DNA varies widely from sample to sample, at t0 the average recovery was 14,891 copies/10 mL, whereas after room temperature incubation, the average recovery was 1,955. Without buffer added to the samples, between 65% to 98% of the DNA was no longer recoverable (excluding sample GP-031), after incubation of samples at room temperature, compared with t0. The one exception, sample GP-031, maintained high DNA yield even without addition of stabilization buffer. Samples incubated with stabilization buffer maintained human DNA yields similar to the t0 samples (Table 3)."

	Id. at page 186, first column, second full paragraph. In conclusion, Olson states that "DNA can be stabilized by addition of buffer to the sample, leading to increased assay sensitivity. *Id.* at Abstract.

As discussed *supra*, Lapidus '650 discloses combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer. Even if Lapidus '650 is determined to not specifically teach combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, Olson removes this deficiency.

Olson discloses that addition of a stabilizing buffer (Exact buffer A) to stool samples provided a significant increase in recovery of DNA compared with samples incubated without buffer. This addition of a stabilizing buffer to DNA led to increased assay sensitivity.

Thus, a person of ordinary skill in the art would have been motivated to combine the remaining portion of the fecal sample with the stabilizing buffer taught by Olson. Olson discloses that DNA assays are greatly improved with addition of stabilizing buffer. Therefore, one skilled in the art would recognize that Lapidus '650 in view of Olson discloses all of the requirements for the combining step contained in the fourth limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraph 84.

In summary, Lapidus '650 in view of De Luca and Olson disclose the limitations of claim 1 of the '781 Patent. Consequently, claim 1 is obvious over Lapidus '650 in view of De Luca and Olson.

7. Ahlquist in view of De Luca and Olson Renders Claim 1 Obvious

'781 Patent, Claim 1, Preamble	**Ahlquist in view of De Luca and Olson**
1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:	**Ahlquist** discloses "[p]atients collected 3 stools by using plastic buckets mounted to the toilet seat. Promptly after each individual collection, patients smeared stool onto both windows of their Hemoccult and

	HemoccultSensa cards and then express-shipped smeared cards and the whole stool (sealed in a bucket in an insulated container cooled with ice packs) to the Mayo Clinic in Rochester, Minnesota. Ex. 1004 at page 4, at 'Stool Collection and Processing' heading.

As explained in Section IV. *supra*, the preamble of claim 1 is not a limitation. However, even if the preamble of claim 1 was determined to be a limitation, Ahlquist discloses this limitation because Ahlquist teaches collection of stool (a fecal sample) into a plastic bucket. Further, Ahlquist indicates that the stools were frozen ***after*** they were received at the Mayo Clinic. This indicates that the stools were obtained without freezing and therefore a person of ordinary skill in the art would recognize Ahlquist discloses the method of processing a "freshly-collected" fecal sample "without freezing" specified by the preamble. Ex. 1014 at paragraph 48.

'781 Patent, Claim 1, First Limitation	**Ahlquist in view of De Luca and Olson**
a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject by defecation directly into a sealable collection vessel;	**Ahlquist** discloses "[p]atients collected 3 stools by using plastic buckets mounted to the toilet seat. Promptly after each individual collection, patients smeared stool onto both windows of their Hemoccult and HemoccultSensa cards and then express-shipped smeared cards and the whole stool (sealed in a bucket in an insulated container cooled with ice packs) to the Mayo Clinic in Rochester, Minnesota. Ex. 1004 at page 4, at 'Stool Collection and Processing' heading.

Ahlquist discloses collecting a fecal sample from a human subject as it teaches that human patients collected stools (a fecal sample) into a plastic bucket mounted to a toilet seat. This indicates that the human subject defecated directly into the plastic bucket, which is a

collection vessel. Further, Ahlquist teaches that the plastic bucket is a sealable collection vessel because the plastic bucket is later sealed upon shipping.

Further, Ahlquist discloses that the stool can be collected at home according to the broadest reasonable interpretation of the claims consistent with the specification. Ahlquist discloses that the stools are collected by patients and then express-shipped to the Mayo Clinic, meaning that the fecal sample was collected at *a location different than the Mayo Clinic testing facility.* This indicates that the stool can be collected in a toilet that is not located at a testing facility. A person skilled in the art would understand that Ahlquist effectively describes collection of a stool at home, given that "home" is not a testing facility such a medical diagnostics laboratory at the Mayo Clinic.

Therefore, one skilled in the art would recognize that Ahlquist discloses all of the requirements for the collecting step contained in the first limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraphs 55-56.

'781 Patent, Claim 1, Second Limitation	**Ahlquist in view of De Luca and Olson**
b) removing a portion of the fecal sample to a separate sealable container to produce a removed portion and a remaining portion of the fecal sample;	**Ahlquist** discloses "[p]atients collected 3 stools by using plastic buckets mounted to the toilet seat. Promptly after each individual collection, patients smeared stool onto both windows of their Hemoccult and HemoccultSensa cards and then express-shipped smeared cards and the whole stool (sealed in a bucket in an insulated container cooled with ice packs) to the Mayo Clinic in Rochester, Minnesota. Ex. 1004 at page 4, at 'Stool Collection and Processing' heading. Ahlquist discloses that "[w]e did not evaluate fecal immunochemical blood tests, and such tests may detect more adenomas than do

	guaiac tests, because of differences in relative detection rates. *Id.* at page 9, second full paragraph. (citations omitted). **De Luca** discloses "an extraction and sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin, Helicobacter pylori and the like. Ex. 1006 at [0001]. De Luca discloses "an extraction and sampling tube for the collection of faeces samples that is practical for the patient and simple to use for the laboratory technician." *Id.* at [0015]. Further, De Luca discloses "[t]he extraction tube for collection of faeces samples, according to the invention, comprises a container body hollow on the inside for containing a buffer solution and faeces samples, a top cap applied to the top end of the container body and provided with a threaded small rod for sampling of faeces samples and a bottom cap applied removably to the bottom end of the container body. *Id.* at [0019]. De Luca discloses that on the extraction tube, "[a]n annular seal 55 is provided between the knurled part 44 and the threaded part 45 of the top cap." *Id.* at [0032].

Ahlquist discloses removing a portion of the fecal sample to produce a removed portion and a remaining portion of the fecal sample. According to Ahlquist, the patients collected stool and then "smeared stool" onto Hemoccult and HemoccultSensa cards. This smeared stool sample corresponds to the 'removed portion' of the fecal sample in independent claim 1. The rest of the stool in the plastic bucket disclosed by Ahlquist corresponds to the 'remaining portion' of the fecal sample in independent claim 1.

Although Ahlquist utilizes the guaiac tests for detection of blood proteins, Ahlquist states that fecal immunochemical blood tests provide improved detection of adenomas compared to guaiac tests. Thus, a person of ordinary skill in the art reading Ahlquist would be motivated to substitute the guaiac tests of Ahlquist with means to perform fecal immunochemical blood tests because an improvement in detection would be achieved. Ex. 1014 at paragraph 68.

De Luca discloses "an extraction and sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin…". Ex. 1006 at [0001]. The devices of De Luca are fecal immunochemical blood tests indicated by Ahlquist to provide improved adenoma detection compared to guaiac tests.

Further, De Luca teaches that fecal samples can be removed and placed in a separate sealable container to perform the fecal immunochemical blood tests. The extraction tube of De Luca includes a container body for containing a buffer solution and fecal sample and the container is sealed using a cap.

Thus, a person of ordinary skill in the art would have been motivated to utilize the separate sealable container of De Luca for performing fecal immunochemical blood tests instead of the guaiac tests of Ahlquist with the requisite expectation of success. Therefore, one skilled in the art would recognize that Ahlquist in view of De Luca discloses all of the requirements for the removing step contained in the second limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraph 68.

'781 Patent, Claim 1, Third Limitation	**Ahlquist in view of De Luca and Olson**
c) combining the removed portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or	**Ahlquist** discloses "[p]atients collected 3 stools by using plastic buckets mounted to the toilet seat. Promptly after each individual

degradation of blood proteins found in a fecal sample, and sealing the sealable container; and	collection, patients smeared stool onto both windows of their Hemoccult and HemoccultSensa cards and then express-shipped smeared cards and the whole stool (sealed in a bucket in an insulated container cooled with ice packs) to the Mayo Clinic in Rochester, Minnesota. Ex. 1004 at page 4, at 'Stool Collection and Processing' heading. Ahlquist discloses that "[w]e did not evaluate fecal immunochemical blood tests, and such tests may detect more adenomas than do guaiac tests, because of differences in relative detection rates. *Id.* at page 9, second full paragraph. (citations omitted). **De Luca** discloses "an extraction and sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin, Helicobacter pylori and the like. Ex. 1006 at [0001]. De Luca discloses "an extraction and sampling tube for the collection of faeces samples that is practical for the patient and simple to use for the laboratory technician." *Id.* at [0015]. Further, De Luca discloses "[t]he extraction tube for collection of faeces samples, according to the invention, comprises a container body hollow on the inside for

	containing a buffer solution and faeces samples, a top cap applied to the top end of the container body and provided with a threaded small rod for sampling of faeces samples and a bottom cap applied removably to the bottom end of the container body. *Id.* at [0019]. De Luca discloses that on the extraction tube, "[a]n annular seal 55 is provided between the knurled part 44 and the threaded part 45 of the top cap." *Id.* at [0032].

As discussed *supra*, Ahlquist discloses removing a portion of the fecal sample by smearing stool onto the guaiac-based Hemoccult and HemoccultSensa cards. Ahlquist states that fecal immunochemical blood tests provide improved detection of adenomas compared to guaiac tests. Ex. 1004 at page 9, second full paragraph. Thus, a person of ordinary skill in the art reading Ahlquist would be motivated to substitute the guaiac tests of Ahlquist with means to perform fecal immunochemical blood tests because an improvement in detection would be achieved. Ex. 1014 at paragraph 76.

De Luca discloses "an extraction and sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin…". Ex. 1006 at [0001]. The devices of De Luca are fecal immunochemical blood tests indicated by Ahlquist to provide improved adenoma detection compared to guaiac tests.

Further, De Luca teaches that fecal samples can be removed and placed in a separate sealable container to perform the fecal immunochemical blood tests. The extraction tube of De Luca includes a container body for containing a buffer solution and fecal sample and the container is sealed using a cap.

Thus, a person of ordinary skill in the art would have been motivated to utilize the separate sealable container of De Luca in order to perform a fecal immunochemical blood test instead of the guaiac tests of Ahlquist. Based on De Luca, a person of ordinary skill in the art

would combine the removed portion of the fecal sample in the separate sealable container with a buffer in the extraction tube's container body to prevent denaturation or degradation of blood proteins so that a fecal immunochemical blood test could be performed. Ex. 1014 at paragraph 76. Further, De Luca teaches that the extraction tube is sealed using a top cap, rendering the extraction tube to be a "separate sealable container." Therefore, one skilled in the art would recognize that Ahlquist in view of De Luca discloses all of the requirements for the combining step contained in the third limitation of claim 1 of the '781 Patent. *Id.*

'781 Patent, Claim 1, Fourth Limitation	**Ahlquist in view of De Luca and Olson**
d) combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, and sealing the sealable collection vessel.	**Ahlquist** discloses "[p]atients collected 3 stools by using plastic buckets mounted to the toilet seat. Promptly after each individual collection, patients smeared stool onto both windows of their Hemoccult and HemoccultSensa cards and then express-shipped smeared cards and the whole stool (sealed in a bucket in an insulated container cooled with ice packs) to the Mayo Clinic in Rochester, Minnesota. Ex. 1004 at page 4, at 'Stool Collection and Processing' heading. Ahlquist states that "[t]echnical advances could improve DNA assay sensitivity" on the stools and that "[m]ethods to increase stool DNA capture are needed, and some have been reported." *Id.* at page 9, third full paragraph (citations omitted). Ahlquist states that its authors and other researchers "have shown that adding a preservative to stool at the time of defecation can prevent degradation of long DNA." *Id.*

	Olson discloses development of "a multitarget, fecal DNA screening assay that detects the presence of gene-specific mutations and long DNA fragments associated with colorectal cancer (CRC)." Ex. 1007 at Abstract. Olson discloses that "[t]he amount of DNA recovered from aliquots stored under the different conditions is based on quantification of a 200-bp DNA fragment (Table 3). Although the amount of recoverable DNA varies widely from sample to sample, at t0 the average recovery was 14,891 copies/10 mL, whereas after room temperature incubation, the average recovery was 1,955. Without buffer added to the samples, between 65% to 98% of the DNA was no longer recoverable (excluding sample GP-031), after incubation of samples at room temperature, compared with t0. The one exception, sample GP-031, maintained high DNA yield even without addition of stabilization buffer. Samples incubated with stabilization buffer maintained human DNA yields similar to the t0 samples (Table 3)." *Id.* at page 186, first column, second full paragraph. In conclusion, Olson states that "DNA can be stabilized by addition of buffer to the sample, leading to increased assay sensitivity. *Id.* at Abstract.

As discussed *supra*, Ahlquist discloses removing a portion of the fecal sample by smearing stool onto the guaiac-based Hemoccult and HemoccultSensa cards, corresponding to the "removed portion" of the fecal sample. After removing this portion, Ahlquist discloses that the remaining portion of the fecal sample is "sealed in a bucket" and express-shipped to the testing facility along with the Hemoccult and HemoccultSensa cards.

Although Ahlquist does not teach addition of a stabilizing buffer to the remaining portion of the fecal sample, Ahlquist states that "[t]echnical advances could improve DNA assay sensitivity" on the stools and that "[m]ethods to increase stool DNA capture are needed, and some have been reported." Ex. 1004 at page 9, third full paragraph (citations omitted). To this end, Ahlquist states that its authors and other researchers "have shown that adding a preservative to stool at the time of defecation can prevent degradation of long DNA." *Id.* Thus, a person of ordinary skill in the art reading Ahlquist would be motivated to add a preservative as a stabilizing buffer to the stool at the time of defecation in order to prevent degradation of nucleic acids. Ex. 1014 at paragraphs 85-86.

Olson discloses that addition of a stabilizing buffer (Exact buffer A) to stool samples provided a significant increase in recovery of DNA compared with samples incubated without buffer. This addition of a stabilizing buffer to DNA led to increased assay sensitivity.

Thus, a person of ordinary skill in the art would have been motivated to combine the remaining portion of the fecal sample with the stabilizing buffer taught by Olson instead of omitting the buffer as was done in Ahlquist. Olson discloses that DNA assays are greatly improved with addition of stabilizing buffer and Ahlquist provides express motivation to make this modification with the requisite expectation of success. Therefore, one skilled in the art would recognize that Ahlquist in view of Olson discloses all of the requirements for the combining step contained in the fourth limitation of claim 1 of the '781 Patent. *Id.*

In summary, Ahlquist in view of De Luca and Olson disclose the limitations of claim 1 of the '781 Patent. Consequently, claim 1 is obvious over Ahlquist in view of De Luca and Olson.

8. O'Neill in view of De Luca and Olson Renders Claim 1 Obvious

'781 Patent, Claim 1, Preamble	O'Neill in view of De Luca and Olson
1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:	**O'Neill** discloses "a fixed shape container for collecting faecal stools which has an upper receiving mouth and a lower stool collection channel, the internal walls of the container narrowing from the mouth to the channel so that when a stool is deposited through the mouth the stool is encouraged to lie lengthways along the channel." Ex. 1005 at page 7, lines 5-11. O'Neill discloses that the container "can serve both as the receptacle into which the stool is excreted and as the container in which the stool is washed. So the stool does not need to be transferred to a different washing container, which avoids damage to the stool surface caused by such a transfer. Such damage would interfere with the accuracy of e.g. screening tests which may be performed on the stool. If the stool is excreted into the container at home and then transported to e.g. a clinic for washing, the container has the further advantage of holding the stool reasonably securely in the channel so that transportation damage to the stool surface is reduced or avoided." *Id.* at page 7, line 34-page 8, line 11. O'Neill discloses that the container can be placed in an apparatus and that the "apparatus may further comprise cooling means for cooling the stool to a

	temperature (preferably of -80°C to 15°C, preferably -10°C to 15°C, preferably -10°C to 10°C, more preferably 0°C to 5°C) below its gel freezing point." *Id.* at page 6, lines 14-17.

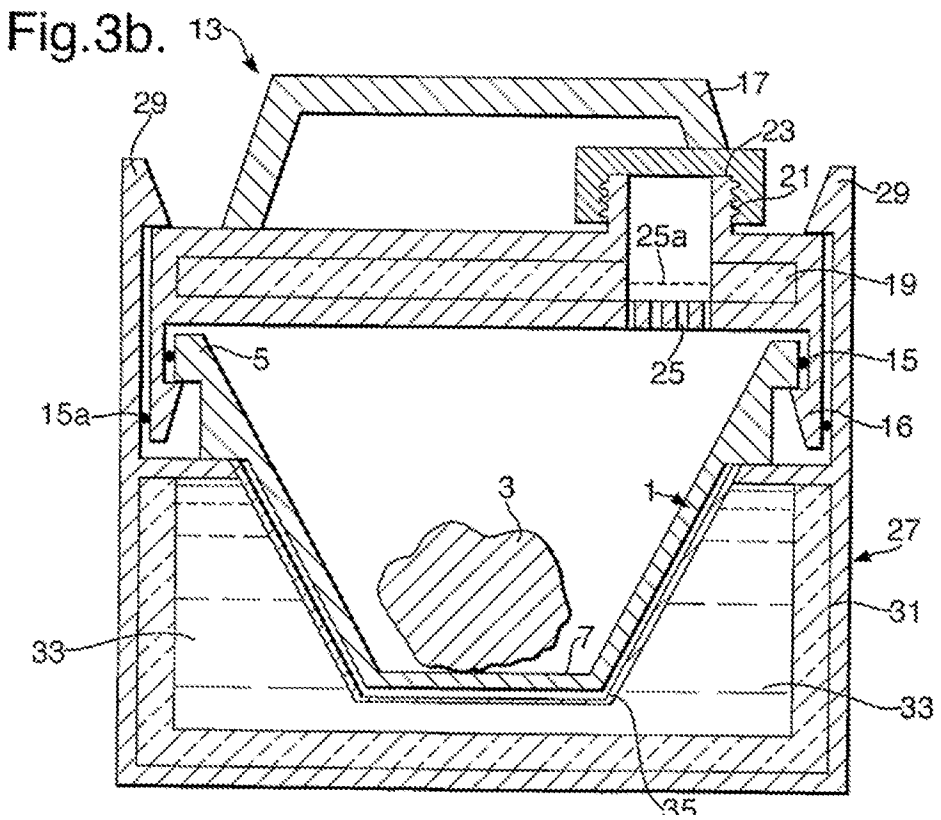
As explained in Section IV. *supra*, the preamble of claim 1 is not a limitation. However, even if the preamble of claim 1 was determined to be a limitation, O'Neill discloses this limitation because O'Neill teaches collection of stool (a fecal sample) into a container. Further, although O'Neill suggests that the stools can be cooled to a temperature "below its gel freezing point," this is simply one embodiment of the disclosure. Moreover, the temperature range of cooling the stool includes temperatures as high as 15°C (59°F). A person of ordinary skill in the art would understand that collection of a fecal sample at a temperature of 15°C (59°F) corresponds to processing "without freezing." Ex. 1014 at paragraph 49.

Accordingly, a person of ordinary skill in the art would recognize O'Neill discloses the method of processing a "freshly-collected" fecal sample "without freezing" specified by the preamble. *Id.*

'781 Patent, Claim 1, First Limitation	**O'Neill in view of De Luca and Olson**
a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject by defecation directly into a sealable collection vessel;	**O'Neill** discloses "a fixed shape container for collecting faecal stools which has an upper receiving mouth and a lower stool collection channel, the internal walls of the container narrowing from the mouth to the channel so that when a stool is deposited through the mouth the stool is encouraged to lie lengthways along the channel." Ex. 1005 at page 7, lines 5-11. O'Neill discloses that the container "can serve both as the receptacle into which the stool is excreted and as the container in which the stool is washed. … If

	the stool is excreted into the container at home and then transported to e.g. a clinic for washing, the container has the further advantage of holding the stool reasonably securely in the channel so that transportation damage to the stool surface is reduced or avoided." *Id.* at page 7, line 34- page 8, line 11. O'Neill discloses that "preferably the container is hermetically sealable to reduce the exposure to atmospheric oxygen of a stool deposited therein. The seal may be achieved by means of a lid or cover (e.g. having a snap-fit or screw fitting) for the mouth." *Id.* at page 9, lines 28-33.

O'Neill discloses collecting a fecal sample from a human subject as it teaches that human patients collected stools (a fecal sample) into a container that is positioned over a toilet. The container is a collection vessel and O'Neill teaches that the container is "the receptacle into which the stool is excreted." Figure 3b of O'Neill is presented below, showing the receptacle (1) of the container that includes an excreted stool (3).



O'Neill discloses that "the container is hermetically sealable to reduce the exposure to atmospheric oxygen of a stool deposited therein. The seal may be achieved by means of a lid or cover (e.g. having a snap-fit or screw fitting) for the mouth." This indicates that the container of O'Neill is a sealable collection vessel. Figure 3b of O'Neill shows the lid (13) that seals the container of the receptacle (1).

Further, O'Neill discloses that "the stool is excreted into the container at home and then transported to e.g. a clinic for washing." This indicates that the stool can be collected in a toilet that is not located at a testing facility.

Therefore, one skilled in the art would recognize that O'Neill discloses all of the requirements for the collecting step contained in the first limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraph 58.

'781 Patent, Claim 1, Second Limitation	**O'Neill in view of De Luca and Olson**
b) removing a portion of the fecal sample to a separate sealable container to produce a	**O'Neill** discloses "a method and apparatus for removing cellular material from faecal stools

removed portion and a remaining portion of the fecal sample;	and a container for collecting faecal stools." Ex. 1005 at page 1, lines 5-7. O'Neill discloses "a method of removing cellular material from the surface of a faecal stool" in a container that comprising the steps of "introducing wash liquid into the container whilst maintaining the stool at a temperature below its gel freezing point" and then "moving the container to cause the liquid to run back and forth along the channel thereby washing the cellular material from the surface of the stool." *Id.* at page 3, lines 16-27. Thereafter, O'Neill further discloses "[t]he apparatus may further comprise at least one and preferably a plurality of detachable sample receptacles into which wash liquid is transferable from the container, so that e.g. when stool washing is completed the wash liquid may be poured from the container into the receptacles. These can then be detached from the apparatus and transferred to an automated liquid-handling system for high throughput processing of the liquid samples contained therein." *Id.* at page 6, line 31 – page 7, line 4. Finally, O'Neill discloses that the wash liquid can "be divided into standard volumes and received into a plurality of removable (e.g. clip-on) sample receptacles (not shown) . The sample receptacles may be a strip of tubes each of e.g. 0.1-0.5 ml volume as can be removed and clipped into a standard

	microplate format used for clinical analyses. Alternatively the sample receptacles may be individual tubes each of e.g. 1-2 ml volume." *Id.* at page 14, lines 27-33. **De Luca** discloses "an extraction and sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin, Helicobacter pylori and the like. Ex. 1006 at [0001]. De Luca discloses "an extraction and sampling tube for the collection of faeces samples that is practical for the patient and simple to use for the laboratory technician." *Id.* at [0015]. Further, De Luca discloses "[t]he extraction tube for collection of faeces samples, according to the invention, comprises a container body hollow on the inside for containing a buffer solution and faeces samples, a top cap applied to the top end of the container body and provided with a threaded small rod for sampling of faeces samples and a bottom cap applied removably to the bottom end of the container body. *Id.* at [0019]. De Luca discloses that on the extraction tube, "[a]n annular seal 55 is provided between the knurled part 44 and the threaded part 45 of the top cap." *Id.* at [0032].

O'Neill discloses removing a portion of the fecal sample to produce a removed portion and a remaining portion of the fecal sample. According to O'Neill, cellular material is removed from a fecal sample. This cellular material corresponds to the 'removed portion' of the fecal sample in independent claim 1. The rest of the stool in the container disclosed by O'Neill corresponds to the 'remaining portion' of the fecal sample in independent claim 1.

O'Neill discloses that the cellular material is removed from the fecal sample via a wash liquid and teaches that the removed portion is placed into sample receptacles for subsequent analysis of DNA, RNA and proteins. In particular, O'Neill discloses that "[w]hen the wash programme ends, the sample rack is pivoted about pivot 47 to bring axis 41 into a vertical position (see Fig. 5). Almost all of wash liquid 44 is then decanted out of receptacle 1 via port 21, foraminous screen 25 substantially preventing larger food residues or other broken off pieces from the stool exiting with the liquid. Coarse sieve 25a removes smaller pieces from the liquid. Finer downstream sieves (not shown) further limit the maximum particle size in the liquid. The liquid is then be divided into standard volumes and received into a plurality of removable (e.g. clip-on) sample receptacles (not shown). The sample receptacles may be a strip of tubes each of e.g. 0.1-0.5 ml volume as can be removed and clipped into a standard microplate format used for clinical analyses. Alternatively the sample receptacles may be individual tubes each of e.g. 1-2 ml volume. The sample rack is then returned to its horizontal position and receptacle 1 is removed and safely disposed of." Ex. 1005 at page 14, lines 18-35. A person of ordinary skill in the art would understand that the individual tubes as described by O'Neill would include separate, sealable containers such as Eppendorf tubes that are used in the art. Ex. 1014 at paragraph 69.

Moreover, De Luca discloses "an extraction and sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin…". Ex. 1006 at [0001]. Further, De Luca teaches that fecal samples are removed and placed in a separate sealable container to perform assays, such as fecal immunochemical blood tests. The extraction tube of De Luca includes a container body for containing a fecal sample with buffer solution and the container is sealed using a cap.

Thus, a person of ordinary skill in the art would have been motivated to utilize the separate sealable container of De Luca to place the fecal cellular material/wash liquids obtained by O'Neill with the requisite expectation of success. Therefore, one skilled in the art would recognize that O'Neill in view of De Luca discloses all of the requirements for the removing step contained in the second limitation of claim 1 of the '781 Patent. Ex. 1014 at paragraph 70.

'781 Patent, Claim 1, Third Limitation	**O'Neill in view of De Luca and Olson**
c) combining the removed portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container; and	**O'Neill** discloses "a method and apparatus for removing cellular material from faecal stools and a container for collecting faecal stools." Ex. 1005 at page 1, lines 5-7. O'Neill discloses "a method of removing cellular material from the surface of a faecal stool" in a container that comprising the steps of "introducing wash liquid into the container whilst maintaining the stool at a temperature below its gel freezing point" and then "moving the container to cause the liquid to run back and forth along the channel thereby washing the cellular material from the surface of the stool." *Id.* at page 3, lines 16-27. Thereafter, O'Neill further discloses "[t]he apparatus may further comprise at least one and preferably a plurality of detachable sample receptacles into which wash liquid is transferable from the container, so that e.g. when stool washing is completed the wash liquid may be poured from the container into the receptacles. These can then be detached from the apparatus and transferred to an automated liquid-handling system for high

	throughput processing of the liquid samples contained therein." *Id.* at page 6, line 31 – page 7, line 4. Finally, O'Neill discloses that the wash liquid can "be divided into standard volumes and received into a plurality of removable (e.g. clip-on) sample receptacles (not shown) . The sample receptacles may be a strip of tubes each of e.g. 0.1-0.5 ml volume as can be removed and clipped into a standard microplate format used for clinical analyses. Alternatively the sample receptacles may be individual tubes each of e.g. 1-2 ml volume." *Id.* at page 14, lines 27-33. **De Luca** discloses "an extraction and sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin, Helicobacter pylori and the like. Ex. 1006 at [0001]. De Luca discloses "an extraction and sampling tube for the collection of faeces samples that is practical for the patient and simple to use for the laboratory technician." *Id.* at [0015]. Further, De Luca discloses "[t]he extraction tube for collection of faeces samples, according to the invention, comprises a container body hollow on the inside for containing a buffer solution and faeces samples, a top cap applied to the top end of

	the container body and provided with a threaded small rod for sampling of faeces samples and a bottom cap applied removably to the bottom end of the container body. *Id.* at [0019]. De Luca discloses that on the extraction tube, "[a]n annular seal 55 is provided between the knurled part 44 and the threaded part 45 of the top cap." *Id.* at [0032].

As discussed *supra*, O'Neill discloses removing a portion of the fecal sample by removing cellular material from the stool, for instance with a "chilled wash liquid, such as a buffered aqueous solution containing N-acetylcysteine, bovine serum albumin and sodium butyrate which has been found (see WO 97/09600) to improve recovery of exfoliated cells." Ex. 1005 at page 13, lines 30-34. O'Neill teaches that the removed portion is placed into sample receptacles for subsequent analysis of DNA, RNA and proteins. Ex. 1005 at page 1, lines 15-20. Thus, a person of ordinary skill in the art reading O'Neill would be motivated to stabilize the removed cellular material so that it could provide a more accurate assessment for patients. Ex. 1014 at paragraph 77.

De Luca discloses "an extraction and sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin…". Ex. 1006 at [0001]. The devices of De Luca are used for detection of blood proteins such as hemoglobin for use in fecal immunochemical blood tests. Further, De Luca teaches that fecal samples are removed and placed in a separate sealable container to perform the fecal immunochemical blood tests. The extraction tube of De Luca includes a container body for containing a buffer solution and fecal sample and the container is sealed using a cap.

Thus, a person of ordinary skill in the art would have been motivated to utilize the separate sealable container of De Luca to place the removed cellular material from the fecal sample of O'Neill. Based on De Luca, a person of ordinary skill in the art would combine the removed portion of the fecal sample in the separate sealable container with a buffer in the

extraction tube's container body to prevent denaturation or degradation of blood proteins so that a fecal immunochemical blood test could be performed. Ex. 1014 at paragraph 77. Further, De Luca teaches that the extraction tube is sealed using a top cap, rendering the extraction tube to be a "separate sealable container." Therefore, one skilled in the art would recognize that O'Neill in view of De Luca discloses all of the requirements for the combining step contained in the third limitation of claim 1 of the '781 Patent. *Id.*

'781 Patent, Claim 1, Fourth Limitation	**O'Neill in view of De Luca and Olson**
d) combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, and sealing the sealable collection vessel.	**O'Neill** discloses "a method and apparatus for removing cellular material from faecal stools and a container for collecting faecal stools." Ex. 1005 at page 1, lines 5-7. O'Neill discloses "a method of removing cellular material from the surface of a faecal stool" in a container that comprising the steps of "introducing wash liquid into the container whilst maintaining the stool at a temperature below its gel freezing point" and then "moving the container to cause the liquid to run back and forth along the channel thereby washing the cellular material from the surface of the stool." *Id.* at page 3, lines 16-27. Thereafter, O'Neill further discloses "[t]he apparatus may further comprise at least one and preferably a plurality of detachable sample receptacles into which wash liquid is transferable from the container, so that e.g. when stool washing is completed the wash liquid may be poured from the container into the receptacles. These can then be detached from the apparatus and transferred to an

	automated liquid-handling system for high throughput processing of the liquid samples contained therein." *Id.* at page 6, line 31 – page 7, line 4. Finally, O'Neill discloses that "the apparatus converts a typical total 100-500 g mass of stool and wash liquid into aliquots of cell-suspension of typically only 50-1000 mg (i.e. a thousand-fold reduction in scale)." *Id.* at page 15, lines 1-4. **Olson** discloses development of "a multitarget, fecal DNA screening assay that detects the presence of gene-specific mutations and long DNA fragments associated with colorectal cancer (CRC)." Ex. 1007 at Abstract. Olson discloses that "[t]he amount of DNA recovered from aliquots stored under the different conditions is based on quantification of a 200-bp DNA fragment (Table 3). Although the amount of recoverable DNA varies widely from sample to sample, at t0 the average recovery was 14,891 copies/10 mL, whereas after room temperature incubation, the average recovery was 1,955. Without buffer added to the samples, between 65% to 98% of the DNA was no longer recoverable (excluding sample GP-031), after incubation of samples at room temperature, compared with t0. The one exception, sample GP-031, maintained high DNA yield even without addition of

	stabilization buffer. Samples incubated with stabilization buffer maintained human DNA yields similar to the t0 samples (Table 3)." *Id.* at page 186, first column, second full paragraph. In conclusion, Olson states that "DNA can be stabilized by addition of buffer to the sample, leading to increased assay sensitivity. *Id.* at Abstract.

As discussed *supra*, O'Neill discloses removing a portion of the fecal sample by removing cellular material from the stool. After removing this portion, O'Neill discloses that the remaining portion of the fecal sample is still in the container. For instance, O'Neill states that a typical total stool has a mass of 100-500 grams and that the removed cellular material has a mass of about 50-1000 mg. Ex. 1005 at page 15, lines 1-4. Thus, a person of ordinary skill in the art would understand that O'Neill teaches a remaining portion of the stool of at least 99 grams. Ex. 1014 at paragraph 87. Although O'Neill does not teach addition of a stabilizing buffer to the remaining portion of the fecal sample, a person of ordinary skill in the art would be motivated to stabilize the remaining stool sample so that subsequent analyses could be made. Ex. 1014 at paragraphs 87-88.

Olson discloses that addition of a stabilizing buffer (Exact buffer A) to stool samples provided a significant increase in recovery of DNA compared with samples incubated without buffer. This addition of a stabilizing buffer to DNA led to increased assay sensitivity.

Thus, a person of ordinary skill in the art would have been motivated to combine the remaining portion of the fecal sample with the stabilizing buffer taught by Olson instead of omitting the buffer as was done in O'Neill. Olson discloses that DNA assays are greatly improved with addition of stabilizing buffer and O'Neill provides express motivation to make this modification with the requisite expectation of success. Therefore, one skilled in the art would recognize that O'Neill in view of Olson discloses all of the requirements for the combining step contained in the fourth limitation of claim 1 of the '781 Patent. *Id.*

In summary, O'Neill in view of De Luca and Olson disclose the limitations of claim 1 of the '781 Patent. Consequently, claim 1 is obvious over O'Neill in view of De Luca and Olson.

B. Dependent Claim 2

1. Lapidus '178 Anticipates Claim 2

'781 Patent, Claim 2	Lapidus '178
2. The method of claim 1, further comprising delivering the sealable container containing the removed portion of the fecal sample and said buffer and the sealable collection vessel containing the remaining portion of the fecal sample and said stabilizing buffer to a medical diagnostics laboratory.	Lapidus '178 describes that "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility." Ex. 1002 at column 7, lines 63-64.

As discussed above, Lapidus '178 describes the elements of claim 1 and further describes that the receptacle is "small enough to be transported to a testing facility." The testing facility according to the broadest reasonable interpretation of the claims consistent with the specification includes a testing facility (e.g., a medical diagnostics laboratory) that would perform the diagnostic assays on the stool sample. Further, Lapidus '178 describes transportation to a testing facility and a person of ordinary skill in the art would understand that such transportation would include the portions as provided in independent claim 1. Ex. 1014 at paragraph 98.

Lapidus '178 therefore describes the additional limitations of claim 2 of the '781 Patent. Because the other limitations of claim 2 are anticipated for the reasons explained above for claim 1, claim 2 is also anticipated by Lapidus '178.

2. Lapidus '650 Anticipates Claim 2

'781 Patent, Claim 2	Lapidus '650
2. The method of claim 1, further comprising delivering the sealable container containing the removed portion of the fecal sample and said buffer and the sealable collection vessel containing the remaining portion of the fecal	Lapidus '650 describes that "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility." Ex. 1003 at column 7, lines 24-26.

sample and said stabilizing buffer to a medical diagnostics laboratory.	

As discussed above, Lapidus '650 describes the elements of claim 1 and further describes that the receptacle is "small enough to be transported to a testing facility." The testing facility according to the broadest reasonable interpretation of the claims consistent with the specification includes a testing facility (e.g., a medical diagnostics laboratory) that would perform the diagnostic assays on the stool sample. Further, Lapidus '650 describes transportation to a testing facility and a person of ordinary skill in the art would understand that such transportation would include the portions as provided in independent claim 1. Ex. 1014 at paragraph 98.

Lapidus '650 therefore describes the additional limitations of claim 2 of the '781 Patent. Because the other limitations of claim 2 are anticipated for the reasons explained above for claim 1, claim 2 is also anticipated by Lapidus '650.

3. Lapidus '178 Renders Claim 2 Obvious

'781 Patent, Claim 2	**Lapidus '178**
2. The method of claim 1, further comprising delivering the sealable container containing the removed portion of the fecal sample and said buffer and the sealable collection vessel containing the remaining portion of the fecal sample and said stabilizing buffer to a medical diagnostics laboratory.	**Lapidus '178** discloses that "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility." Ex. 1002 at column 7, lines 63-64.

In the alternative to the assertion that Lapidus '178 anticipates claim 2, Lapidus '178 further renders claim 2 obvious.

As discussed above, Lapidus '178 discloses the elements of claim 1 and further describes that the receptacle is "small enough to be transported to a testing facility." The testing facility according to the broadest reasonable interpretation of the claims consistent with the specification includes a testing facility (e.g., a medical diagnostics laboratory) that would perform the

diagnostic assays on the stool sample. It would have been known to the person of ordinary skill in the art would understand that transportation according to Lapidus '178 would include delivery of the portions as provided in independent claim 1. Ex. 1014 at paragraph 99.

Lapidus '178 therefore discloses the additional limitations of claim 2 of the '781 Patent. Because the other limitations of claim 2 are obvious for the reasons explained above for claim 1, claim 2 is also obvious over Lapidus '178. Accordingly, Lapidus '178 renders claim 2 obvious.

4. Lapidus '650 Renders Claim 2 Obvious

'781 Patent, Claim 2	Lapidus '650
2. The method of claim 1, further comprising delivering the sealable container containing the removed portion of the fecal sample and said buffer and the sealable collection vessel containing the remaining portion of the fecal sample and said stabilizing buffer to a medical diagnostics laboratory.	**Lapidus '650** describes that "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility." Ex. 1003 at column 7, lines 24-26.

In the alternative to the assertion that Lapidus '650 anticipates claim 2, Lapidus '650 further renders claim 2 obvious.

As discussed above, Lapidus '650 discloses the elements of claim 1 and further describes that the receptacle is "small enough to be transported to a testing facility." The testing facility according to the broadest reasonable interpretation of the claims consistent with the specification includes a testing facility (e.g., a medical diagnostics laboratory) that would perform the diagnostic assays on the stool sample. It would have been known to the person of ordinary skill in the art would understand that transportation according to Lapidus '650 would include delivery of the portions as provided in independent claim 1. Ex. 1014 at paragraph 98.

Lapidus '650 therefore discloses the additional limitations of claim 2 of the '781 Patent. Because the other limitations of claim 2 are obvious for the reasons explained above for claim 1, claim 2 is also obvious over Lapidus '650. Accordingly, Lapidus '650 renders claim 2 obvious.

5. Lapidus '178 in view of De Luca and Olson Renders Claim 2 Obvious

'781 Patent, Claim 2	Lapidus '178 in view of De Luca and Olson
2. The method of claim 1, further comprising delivering the sealable container containing the removed portion of the fecal sample and said buffer and the sealable collection vessel containing the remaining portion of the fecal sample and said stabilizing buffer to a medical diagnostics laboratory.	**Lapidus '178** discloses that "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility." Ex. 1002 at column 7, lines 63-64.

As discussed *supra*, Lapidus '178 in view of De Luca and Olson disclose the limitations of claim 1, namely a sealable container containing the removed portion of the fecal sample and buffer and a sealable collection vessel containing the remaining portion of the fecal sample and stabilizing buffer.

Further, Lapidus '178 discloses delivering fecal sample-containing items to a clinic for analysis. A person of ordinary skill in the art would understand that a clinic in this context would contain a medical diagnostics laboratory. Ex. 1014 at paragraphs 98-99.

Lapidus '178 in view of De Luca and Olson therefore discloses the additional limitations of claim 2 of the '781 Patent. Because the other limitations of claim 2 are obvious for the reasons explained above for claim 1, claim 2 is also obvious over Lapidus '178 in view of De Luca and Olson.

6. Lapidus '650 in view of De Luca and Olson Renders Claim 2 Obvious

'781 Patent, Claim 2	Lapidus '650 in view of De Luca and Olson
2. The method of claim 1, further comprising delivering the sealable container containing the removed portion of the fecal sample and said buffer and the sealable collection vessel containing the remaining portion of the fecal	**Lapidus '650** describes that "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility." Ex. 1003 at column 7, lines 24-26.

sample and said stabilizing buffer to a medical diagnostics laboratory.	

As discussed *supra*, Lapidus '650 in view of De Luca and Olson disclose the limitations of claim 1, namely a sealable container containing the removed portion of the fecal sample and buffer and a sealable collection vessel containing the remaining portion of the fecal sample and stabilizing buffer.

Further, Lapidus '650 discloses delivering fecal sample-containing items to a testing facility (e.g., a medical diagnostics laboratory) for analysis. A person of ordinary skill in the art would understand that a testing facility in this context would contain a medical diagnostics laboratory. Ex. 1014 at paragraphs 98-99.

Lapidus '650 in view of De Luca and Olson therefore discloses the additional limitations of claim 2 of the '781 Patent. Because the other limitations of claim 2 are obvious for the reasons explained above for claim 1, claim 2 is also obvious over Lapidus '650 in view of De Luca and Olson.

7. Ahlquist in view of De Luca and Olson Renders Claim 2 Obvious

'781 Patent, Claim 2	**Ahlquist in view of De Luca and Olson**
2. The method of claim 1, further comprising delivering the sealable container containing the removed portion of the fecal sample and said buffer and the sealable collection vessel containing the remaining portion of the fecal sample and said stabilizing buffer to a medical diagnostics laboratory.	**Ahlquist** discloses "[p]atients collected 3 stools by using plastic buckets mounted to the toilet seat. Promptly after each individual collection, patients smeared stool onto both windows of their Hemoccult and HemoccultSensa cards and then express-shipped smeared cards and the whole stool (sealed in a bucket in an insulated container cooled with ice packs) to the Mayo Clinic in Rochester, Minnesota. Ex. 1004 at page 4, at 'Stool Collection and Processing' heading.

As discussed *supra*, Ahlquist in view of De Luca and Olson disclose the limitations of claim 1, namely a sealable container containing the removed portion of the fecal sample and buffer and a sealable collection vessel containing the remaining portion of the fecal sample and stabilizing buffer.

Further, Ahlquist discloses delivering fecal sample-containing items to a medical diagnostics laboratory. Ahlquist discloses that the items are express-shipped to the Mayo Clinic in Rochester, Minnesota. It is well known that the Mayo Clinic contains a medical diagnostics laboratory, and in fact Ahlquist further discloses diagnostic tests that are performed on the fecal samples that are mailed. Ex. 1014 at paragraph 100.

Ahlquist in view of De Luca and Olson therefore discloses the additional limitations of claim 2 of the '781 Patent. Because the other limitations of claim 2 are obvious for the reasons explained above for claim 1, claim 2 is also obvious over Ahlquist in view of De Luca and Olson.

8. O'Neill in view of De Luca and Olson Renders Claim 2 Obvious

'781 Patent, Claim 2	**O'Neill in view of De Luca and Olson**
2. The method of claim 1, further comprising delivering the sealable container containing the removed portion of the fecal sample and said buffer and the sealable collection vessel containing the remaining portion of the fecal sample and said stabilizing buffer to a medical diagnostics laboratory.	**O'Neill** discloses that "[i]f the stool is excreted into the container at home and then transported to e.g. a clinic for washing, the container has the further advantage of holding the stool reasonably securely in the channel so that transportation damage to the stool surface is reduced or avoided." *Id.* at page 8, lines 7-11.

As discussed *supra*, O'Neill in view of De Luca and Olson disclose the limitations of claim 1, namely a sealable container containing the removed portion of the fecal sample and buffer and a sealable collection vessel containing the remaining portion of the fecal sample and stabilizing buffer.

Further, O'Neill discloses delivering fecal sample-containing items to a clinic for analysis. A person of ordinary skill in the art would understand that a clinic in this context would contain a medical diagnostics laboratory. Ex. 1014 at paragraph 101.

O'Neill in view of De Luca and Olson therefore discloses the additional limitations of claim 2 of the '781 Patent. Because the other limitations of claim 2 are obvious for the reasons explained above for claim 1, claim 2 is also obvious over O'Neill in view of De Luca and Olson.

C. Dependent Claim 3

1. Lapidus '178 Anticipates Claim 3

'781 Patent, Claim 3, Preamble	Lapidus '178
3. A method of processing a fecal sample, the method comprising:	Lapidus '178 describes processing of "a stool voided by a patient" in Example 1, entitled "Preparation of a Stool Sample." Ex. 1002 at column 7, lines 58-62. Further, "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 63-64.

Assuming, without conceding, that the preamble of claim 3 is a limitation, Lapidus '178 describes this limitation because Lapidus '178 describes processing a stool (a fecal sample) voided by a patient into a receptacle that is transported to a testing facility for processing.

'781 Patent, Claim 3, First Limitation	Lapidus '178
a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising: i) a sealed sealable container containing a removed portion of a fecal sample and a buffer; and	Lapidus '178 describes obtaining a pair of portions of a fecal sample collected from a human subject, wherein the pair of portions are obtained by the method of claim 1. As discussed *supra* with respect to independent claim 1, Lapidus '178 describes each and every element of independent claim 1.

ii) a sealed sealable collection vessel containing a remaining portion of a fecal sample and a stabilizing buffer, the pair of portions obtained by the method of claim 1;	

Lapidus '178 describes obtaining a pair of portions of a fecal sample collected from a human subject, wherein the pair of portions are obtained by the method of claim 1. As discussed *supra*, one skilled in the art would recognize that Lapidus '178 describes all of the requirements for the obtaining step contained in the first limitation of claim 3 of the '781 Patent. Ex. 1014 at paragraphs 112-113.

'781 Patent, Claim 3, Second Limitation	**Lapidus '178**
b) testing the removed portion of the fecal sample for an amount of a blood protein present in the removed portion;	**Lapidus '178** describes that after "a circumferential surface or cross-sectional sample of stool is obtained, it may be homogenized by known methods to distribute cells and cellular debris throughout the sample. An assay then is performed on the homogenate, or an extract of the homogenate, to detect the presence of cells and/or cellular debris in the sample. The assay may be any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation such as a protein, or DNA-based assays for detecting mutations or genetic characteristics indicative of colorectal cancer." Ex. 1002 at

	column 6, lines 45-56. Lapidus '178 describes that "an assay performed on at least a circumferential surface or cross-sectional portion of stool may be an assay to detect the presence of elevated levels of carcinoembryonic antigen shed from cells lining the colon. Such an assay may also comprise detecting the presence of occult blood." *Id.* at column 3, lines 26-30. Lapidus '178 describes that "[i]f a fecal occult blood assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for detecting the presence of fecal occult blood are known in the art." *Id.* at column 9, lines 40-45.

Lapidus '178 describes removing a portion of the fecal sample to produce a removed portion. As discussed *supra*, the 'removed portion' could take a number of forms, a cross-sectional portion, a circumferential surface portion, and/or a layer of the voided stool sample. Lapidus '178 then describes that an assay can be performed on the removed portion to detect the presence of elevated levels of carcinoembryonic antigen (i.e., CEA), which is a known blood protein. Further, Lapidus '178 describes that an assay can be performed on the removed portion to detect the presence of occult blood. "Current non-invasive diagnostic methods involve assaying stool samples for the presence of fecal occult blood or for elevated levels of carcinoembryonic antigen, both of which are suggestive of the presence of colorectal cancer." *Id.* at column 1, lines 57-60.

Furthermore, Lapidus '178 describes that "[i]f a fecal occult blood assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for detecting the presence of fecal

occult blood are known in the art." A person of ordinary skill in the art would understand that such fecal occult blood assays test for an amount of a blood protein (hemoglobin) that is present in a sample. Ex. 1014 at paragraph 115.

Therefore, one skilled in the art would recognize that Lapidus '178 describes all of the requirements for the testing step contained in the second limitation of claim 3 of the '781 Patent. *Id.*

'781 Patent, Claim 3, Third Limitation	**Lapidus '178**
c) extracting nucleic acid from the remaining portion of the fecal sample; and	**Lapidus '178** describes that "a whole stool may be used for diagnostic assays. The stool or portion of stool that is obtained contains sufficient material to allow subsequent diagnostic assays to be performed." Ex. 1002 at column 9, lines 26-29. Lapidus '178 describes that the an illustrative "assay may be any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation such as a protein, or DNA-based assays for detecting mutations or genetic characteristics indicative of colorectal cancer. Known assay protocols, those disclosed herein or in U.S. Pat. No. 5,670,325 or assays hereafter developed may be used in the practice of the invention. Non-limiting examples of useful known assay protocols include those disclosed in U.S. Pat. Nos. 5,137,806 (detection of sequences in selected DNA molecules), 5,348,855 (assay for nucleic acid sequences), 5,512,441 (detection

	of mutant alleles), 5,272,057 and 5,380,645 (RFLP analysis), 5,527,676 (detection of p53 gene sequences), 5,330,892 (detection of MCC gene sequences), 5,352,775 (detection of APC gene sequences), 5,532,108 (detection of DCC gene sequences), and in WO96/08514 (monoclonal antibodies against human colon carcinoma-associated antigens), the disclosures of each of which are incorporated by reference herein." *Id.* at column 6, line 50 – column 7, line 2. Lapidus '178 describes "[m]ethods of the invention are used to prepare a stool sample followed by detection of a deletion or other mutation in the p53 tumor suppressor gene. … DNA or RNA may optionally be isolated from the sample according to methods known in the art." *Id.* at column 9, line 62 – column 10, line 6.

Lapidus '178 describes extracting nucleic acid from the remaining portion of the fecal sample. As discussed *supra*, it is logical that Lapidus '178 describes a 'remaining portion' of the fecal sample that is left over after removal of a cross-sectional, circumferential surface, and/or layer of the stool -- logic dictates that. *In re Johnson*, 558 F.2d at 1019. A person of ordinary skill in the art would recognize and understand that Lapidus '178 describes the 'remaining portion' according to independent claim 1. Ex. 1014 at paragraphs 124-125. Further, as discussed *supra*, Lapidus '178 describes two different parts of fecal material – the 'removed portion' ***sample of stool*** and also the 'remaining portion' of ***the stool***. See Ex. 1002 at column 3, lines 11-15.

Lapidus '178 contemplates that '[t]he ***stool*** or ***portion of stool*** that is obtained contains sufficient material to allow subsequent diagnostic assays to be performed." *Id.* at column 9, lines 27-29 (emphasis added). Such assays include those for the detection of sequences in selected

DNA molecules, detection of nucleic acid sequences, detection of mutant alleles, RFLP analysis, detection of p53 gene sequences, detection of MCC gene sequences, detection of APC gene sequences, and detection of DCC gene sequences, all of which are incorporated by reference into the specification of Lapidus '178. For instance, U.S. Patent No. 5,137,806 (Ex. 1012; incorporated by reference into Lapidus '178 at column 6, line 60) provides that it relates to methods and compositions for detecting the presence or absence of a target DNA sequence, such as a mutation, within an identified region of a selected DNA molecule, such as a gene." Furthermore, U.S. Patent No. 5,137,806 (Ex. 1012; incorporated by reference into Lapidus '178 at column 6, line 60) states that "[h]uman DNA specimens from SW480 and SW403 colon carcinoma cell lines and HL60 leukemia cell line were extracted by standard technique of proteinase K digestion and phenol/chloroform extraction (Ausubel, et al. Eds.: Current Protocols in Molecular Biology. Chapter 2, section 1 and 2. Greene Publishing Assoc. and Wiley-Interscience, New York, 1987)." A person of ordinary skill in the art understands that such assay involve extraction of nucleic acid in order to perform the assay. Ex. 1014 at paragraphs 124-125. Thus, Lapidus '178 describes assays that comprise extracting nucleic acid in order to perform the evaluation.

Furthermore, Lapidus '178 describes that DNA or RNA can be isolated from the sample according to methods known in the art, including those incorporated by reference in Smith-Ravin, et al., *Gut*, 36: 81-86 (1995). According to Smith-Ravin et al., "DNA was extracted from both the centrifugation pellet and supernatant fractions, as well as from endoscopy washings, using a conventional phenol chloroform extraction method and was then purified on glass milk or spin columns. The purified DNA was amplified using mitochondrial primers and analysed for ras mutations using a non-radioactive, allele specific mismatch method." Accordingly, it is well known to the skilled artisan that 'isolation' of nucleic acid refers to an extraction of nucleic acid. Ex. 1014 at paragraphs 124-125. Thus, Lapidus '178 describes an assay in which nucleic acid (e.g., DNA or RNA) is extracted.

Therefore, one skilled in the art would recognize that Lapidus '178 describes all of the requirements for the extracting step contained in the third limitation of claim 3 of the '781 Patent. *Id.*

'781 Patent, Claim 3, Fourth Limitation	**Lapidus '178**
d) testing the nucleic acid for an amount of a human nucleic acid.	**Lapidus '178** describes a protocol entitled "1. Method for Quantitation of Target and Reference Polynucleotides." Ex. 1002 at column 11, lines 19-20. Here, Lapidus '178 describes "[e]nhanced quantification of binding events between hybridization probes and target or reference is accomplished by coupling hybridization probes to particles, such as beads (hybridization beads). In order to obtain a precise quantitative measure of the amount of a polynucleotide in a sample, hybridization beads are constructed such that each bead has attached thereto a single oligonucleotide probe." *Id.* at column 7, lines 21-27.

Lapidus '178 describes testing the nucleic acid for an amount of a human nucleic acid. Example 2 of Lapidus '178 describes a procedure entitled "Method for Quantitation of Target and Reference Polynucleotides" and notes that a "precise quantitative measure of the amount of a polynucleotide in a sample" can be obtained. It is well known in the art that a 'polynucleotide is a synonym for a 'nucleic acid.' Ex. 1014 at paragraph 132. Thus, Lapidus '178 indicates that nucleic acids can be quantitated according to its described assays. A person of ordinary skill in the art would understand that the described nucleic acids are human nucleic acid. *Id.*

Therefore, one skilled in the art would recognize that Lapidus '178 describes all of the requirements for the testing step contained in the fourth limitation of claim 3 of the '781 Patent. *Id.*

Lapidus '178 therefore describes the additional limitations of claim 3 of the '781 Patent. Because the other limitations of claim 3 are anticipated for the reasons explained above for claim 1, claim 3 is also anticipated by Lapidus '178.

2. Lapidus '650 Anticipates Claim 3

'781 Patent, Claim 3, Preamble	Lapidus '650
3. A method of processing a fecal sample, the method comprising:	**Lapidus '650** describes processing of "a stool voided by a patient" in Example 1, entitled "Preparation of a Stool Sample." Ex. 1003 at column 7, lines 12-17. Further, "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 24-26.

Assuming, without conceding, that the preamble of claim 3 is a limitation, Lapidus '650 describes this limitation because Lapidus '650 describes processing a stool (a fecal sample) voided by a patient into a receptacle that is transported to a testing facility for processing.

'781 Patent, Claim 3, First Limitation	Lapidus '650
a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising: i) a sealed sealable container containing a removed portion of a fecal sample and a buffer; and ii) a sealed sealable collection vessel containing a remaining portion of a fecal sample and a stabilizing buffer, the pair of portions obtained by the method of claim 1;	Lapidus '650 describes obtaining a pair of portions of a fecal sample collected from a human subject, wherein the pair of portions are obtained by the method of claim 1. As discussed *supra* with respect to independent claim 1, Lapidus '650 describes each and every element of independent claim 1.

Lapidus '650 describes obtaining a pair of portions of a fecal sample collected from a human subject, wherein the pair of portions are obtained by the method of claim 1. As discussed *supra*, one skilled in the art would recognize that Lapidus '650 describes all of the requirements for the obtaining step contained in the first limitation of claim 3 of the '781 Patent. Ex. 1014 at paragraphs 112-113.

'781 Patent, Claim 3, Second Limitation	**Lapidus '650**
b) testing the removed portion of the fecal sample for an amount of a blood protein present in the removed portion;	**Lapidus '650** discloses that "[o]nce obtained, the cross-sectional stool sample is homogenized in an appropriate buffer, such as phosphate buffered saline." *Id.* at column 8, lines 5-7. Lapidus '650 discloses "[o]nce a cross-sectional stool sample is obtained, it may be homogenized by known methods to distribute cells and cellular debris throughout the sample. An assay then is performed on the homogenate, or an extract of the homogenate, to detect the presence of cells and/or cellular debris in the sample. The assay may be any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation such as a protein, or DNA-based assays for detecting mutations or genetic characteristics indicative of colorectal cancer". *Id.* at column 6, lines 1-11. Lapidus '650 describes that "an assay performed on at least a cross-sectional portion of stool may be an assay to detect the presence of elevated levels of

	carcinoembryonic antigen shed from cells lining the colon. Such an assay may also comprise detecting the presence of occult blood." *Id.* at column 3, lines 4-9. Lapidus '650 describes that "[i]f a fecal occult blood assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for detecting the presence of fecal occult blood are known in the art." *Id.* at column 8, lines 13-18.

Lapidus '650 describes removing a portion of the fecal sample to produce a removed portion. As discussed *supra*, the 'removed portion' could take a number of forms, a cross-sectional portion, a circumferential surface portion, and/or a layer of the voided stool sample. Lapidus '650 then describes that an assay can be performed on the removed portion to detect the presence of elevated levels of carcinoembryonic antigen (i.e., CEA), which is a known blood protein. Further, Lapidus '650 describes that an assay can be performed on the removed portion to detect the presence of occult blood. "Current non-invasive diagnostic methods involve assaying stool samples for the presence of fecal occult blood or for elevated levels of carcinoembryonic antigen, both of which are suggestive of the presence of colorectal cancer." *Id.* at column 1, lines 55-58.

Furthermore, Lapidus '650 describes that "[i]f a fecal occult blood assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for detecting the presence of fecal occult blood are known in the art." A person of ordinary skill in the art would understand that such fecal occult blood assays test for an amount of a blood protein (hemoglobin) that is present in a sample. Ex. 1014 at paragraph 115.

Therefore, one skilled in the art would recognize that Lapidus '650 describes all of the requirements for the testing step contained in the second limitation of claim 3 of the '781 Patent. *Id.*

'781 Patent, Claim 3, Third Limitation	**Lapidus '650**
c) extracting nucleic acid from the remaining portion of the fecal sample; and	Lapidus '650 describes that "a whole stool may be used [for diagnostic assays]. The portion contains sufficient material to allow subsequent diagnostic assays to be performed." Ex. 1003 at column 9, lines 21-24. Lapidus '650 describes that the an illustrative "assay may be any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation such as a protein, or DNA-based assays for detecting mutations or genetic characteristics indicative of colorectal cancer. Known assay protocols, those disclosed herein or in copending application serial number Co-owned U.S. patent application, Ser. No. 08/700,583 or assays hereafter developed may be used in the practice of the invention. Non-limiting examples of useful known assay protocols include those disclosed in U.S. Pat. No. 5,137,806 (detection of sequences in selected DNA molecules), U.S. Pat. No. 5,348,855 (assay for nucleic acid sequences), U.S. Pat. No. 5,512,441 (detection of mutant alleles), U.S. Pat. No. 5,272,057 and U.S. Pat.

	No. 5,380,645 (RFLP analysis), U.S. Pat. No. 5,527,676 (detection of p53 gene sequences), U.S. Pat. No. 5,330,892 (detection of MCC gene sequences), U.S. Pat. No. 5,352,775 (detection of APC gene sequences), U.S. Pat. No. 5,532,108 (detection of DCC gene sequences), and in WO96/08514 (monoclonal antibodies against human colon carcinoma-associated antigens), the disclosures of each of which are incorporated by reference herein." *Id.* at column 6, lines 6-28. Lapidus '650 describes "[m]ethods of the invention are used to prepare a stool sample followed by detection of a deletion or other mutation in the p53 tumor suppressor gene." … DNA or RNA may optionally be isolated from the sample according to methods known in the art." *Id.* at column 8, lines 39-50.

Lapidus '650 describes extracting nucleic acid from the remaining portion of the fecal sample. As discussed *supra*, it is logical that Lapidus '650 describes a 'remaining portion' of the fecal sample that is left over after removal of a cross-sectional, circumferential surface, and/or layer of the stool -- logic dictates that. *In re Johnson*, 558 F.2d at 1019. A person of ordinary skill in the art would recognize and understand that Lapidus '650 describes the 'remaining portion' according to independent claim 1. Ex. 1014 at paragraphs 124-125.

Lapidus '650 contemplates assays include those for the detection of sequences in selected DNA molecules, detection of nucleic acid sequences, detection of mutant alleles, RFLP analysis, detection of p53 gene sequences, detection of MCC gene sequences, detection of APC gene sequences, and detection of DCC gene sequences, all of which are incorporated by reference into the specification of Lapidus '650. For instance, U.S. Patent No. 5,137,806 (Ex. 1012; incorporated by reference into Lapidus '650 at column 6, line 17) provides that it relates to

methods and compositions for detecting the presence or absence of a target DNA sequence, such as a mutation, within an identified region of a selected DNA molecule, such as a gene." Furthermore, U.S. Patent No. 5,137,806 (Ex. 1012; incorporated by reference into Lapidus '650 at column 6, line 17) states that "[h]uman DNA specimens from SW480 and SW403 colon carcinoma cell lines and HL60 leukemia cell line were extracted by standard technique of proteinase K digestion and phenol/chloroform extraction (Ausubel, et al. Eds.: Current Protocols in Molecular Biology. Chapter 2, section 1 and 2. Greene Publishing Assoc. and Wiley-Interscience, New York, 1987)." A person of ordinary skill in the art understands that such assay involve extraction of nucleic acid in order to perform the assay. Ex. 1014 at paragraphs 124-125. Thus, Lapidus '650 describes assays that comprise extracting nucleic acid in order to perform the evaluation.

Furthermore, Lapidus '650 describes that DNA or RNA can be isolated from the sample according to methods known in the art, including those incorporated by reference in Smith-Ravin, et al., *Gut*, 36: 81-86 (1995). According to Smith-Ravin et al., "DNA was extracted from both the centrifugation pellet and supernatant fractions, as well as from endoscopy washings, using a conventional phenol chloroform extraction method and was then purified on glass milk or spin columns. The purified DNA was amplified using mitochondrial primers and analysed for ras mutations using a non-radioactive, allele specific mismatch method." Accordingly, it is well known to the skilled artisan that 'isolation' of nucleic acid refers to an extraction of nucleic acid. Ex. 1014 at paragraphs 124-125. Thus, Lapidus '650 describes an assay in which nucleic acid (e.g., DNA or RNA) is extracted.

Therefore, one skilled in the art would recognize that Lapidus '650 describes all of the requirements for the extracting step contained in the third limitation of claim 3 of the '781 Patent. *Id.*

'781 Patent, Claim 3, Fourth Limitation	**Lapidus '650**
d) testing the nucleic acid for an amount of a human nucleic acid.	Lapidus '650 describes a protocol entitled "1. Method for Quantitation of Target and Reference Polynucleotides." Ex. 1003 at column 9, lines 63-65. Here, Lapidus '650 describes "[e]nhanced quantification of

	binding events between hybridization probes and target or reference is accomplished by coupling hybridization probes to particles, such as beads (hybridization beads). In order to obtain a precise quantitative measure of the amount of a polynucleotide in a sample, hybridization beads are constructed such that each bead has attached thereto a single oligonucleotide probe." *Id.* at column 9, lines 66 – column 10, line 5.

Lapidus '650 describes testing the nucleic acid for an amount of a human nucleic acid. Example 2 of Lapidus '650 describes a procedure entitled "Method for Quantitation of Target and Reference Polynucleotides" and notes that a "precise quantitative measure of the amount of a polynucleotide in a sample" can be obtained. It is well known in the art that a 'polynucleotide is a synonym for a 'nucleic acid.' Ex. 1014 at paragraph 132. Thus, Lapidus '650 indicates that nucleic acids can be quantitated according to its described assays. A person of ordinary skill in the art would understand that the described nucleic acids are human nucleic acid. *Id.*

Therefore, one skilled in the art would recognize that Lapidus '650 describes all of the requirements for the testing step contained in the fourth limitation of claim 3 of the '781 Patent. *Id.*

Lapidus '650 therefore describes the additional limitations of claim 3 of the '781 Patent. Because the other limitations of claim 3 are anticipated for the reasons explained above for claim 1, claim 3 is also anticipated by Lapidus '650.

3. Lapidus '178 Renders Claim 3 Obvious

'781 Patent, Claim 3, Preamble	Lapidus '178
3. A method of processing a fecal sample, the method comprising:	**Lapidus '178** discloses processing of "a stool voided by a patient" in Example 1, entitled "Preparation of a Stool Sample." Ex. 1002 at

	column 7, lines 58-62. Further, "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 63-64.

In the alternative to the assertion that Lapidus '178 anticipates claim 3, Lapidus '178 further renders claim 3 obvious.

Assuming, without conceding, that the preamble of claim 3 is a limitation, Lapidus '178 discloses this limitation because Lapidus '178 discloses processing a stool (a fecal sample) voided by a patient into a receptacle that is transported to a testing facility for processing. Accordingly, Lapidus '178 renders this portion of claim 3 obvious.

'781 Patent, Claim 3, First Limitation	**Lapidus '178**
a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising: i) a sealed sealable container containing a removed portion of a fecal sample and a buffer; and ii) a sealed sealable collection vessel containing a remaining portion of a fecal sample and a stabilizing buffer, the pair of portions obtained by the method of claim 1;	**Lapidus '178** discloses obtaining a pair of portions of a fecal sample collected from a human subject, wherein the pair of portions are obtained by the method of claim 1. As discussed *supra* with respect to independent claim 1, Lapidus '178 describes each and every element of independent claim 1.

Lapidus '178 discloses obtaining a pair of portions of a fecal sample collected from a human subject, wherein the pair of portions are obtained by the method of claim 1. As discussed *supra*, one skilled in the art would recognize that Lapidus '178 discloses all of the requirements

for the obtaining step contained in the first limitation of claim 3 of the '781 Patent. x. 1014 at paragraphs 112-113. Accordingly, Lapidus '178 renders this portion of claim 3 obvious.

'781 Patent, Claim 3, Second Limitation	**Lapidus '178**
b) testing the removed portion of the fecal sample for an amount of a blood protein present in the removed portion;	**Lapidus '178** discloses that after "a circumferential surface or cross-sectional sample of stool is obtained, it may be homogenized by known methods to distribute cells and cellular debris throughout the sample. An assay then is performed on the homogenate, or an extract of the homogenate, to detect the presence of cells and/or cellular debris in the sample. The assay may be any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation such as a protein, or DNA-based assays for detecting mutations or genetic characteristics indicative of colorectal cancer." Ex. 1002 at column 6, lines 45-56. Lapidus '178 discloses that "an assay performed on at least a circumferential surface or cross-sectional portion of stool may be an assay to detect the presence of elevated levels of carcinoembryonic antigen shed from cells lining the colon. Such an assay may also comprise detecting the presence of occult blood." *Id.* at column 3, lines 26-30. Lapidus '178 discloses that "[i]f a fecal occult blood

	assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for detecting the presence of fecal occult blood are known in the art." *Id.* at column 9, lines 40-45.

Lapidus '178 discloses removing a portion of the fecal sample to produce a removed portion. As discussed *supra*, the 'removed portion' could take a number of forms, a cross-sectional portion, a circumferential surface portion, and/or a layer of the voided stool sample. Lapidus '178 then describes that an assay can be performed on the removed portion to detect the presence of elevated levels of carcinoembryonic antigen (i.e., CEA), which is a known blood protein and is evaluated to detect the presence of occult blood. Furthermore, Lapidus '178 discloses that "[i]f a fecal occult blood assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for detecting the presence of fecal occult blood are known in the art." A person of ordinary skill in the art would understand that such fecal occult blood assays test for an amount of a blood protein (hemoglobin) that is present in a sample. Ex. 1014 at paragraph 115.

Therefore, one skilled in the art would recognize that Lapidus '178 discloses all of the requirements for the testing step contained in the second limitation of claim 3 of the '781 Patent. *Id.* Accordingly, Lapidus '178 renders this portion of claim 3 obvious.

'781 Patent, Claim 3, Third Limitation	**Lapidus '178**
c) extracting nucleic acid from the remaining portion of the fecal sample; and	**Lapidus '178** discloses that "a whole stool may be used for diagnostic assays. The stool or portion of stool that is obtained contains sufficient material to allow subsequent diagnostic assays to be performed." Ex. 1002 at column 9, lines 26-29. Lapidus '178 discloses that the an illustrative "assay may be

	any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation such as a protein, or DNA-based assays for detecting mutations or genetic characteristics indicative of colorectal cancer. Known assay protocols, those disclosed herein or in U.S. Pat. No. 5,670,325 or assays hereafter developed may be used in the practice of the invention. Non-limiting examples of useful known assay protocols include those disclosed in U.S. Pat. Nos. 5,137,806 (detection of sequences in selected DNA molecules), 5,348,855 (assay for nucleic acid sequences), 5,512,441 (detection of mutant alleles), 5,272,057 and 5,380,645 (RFLP analysis), 5,527,676 (detection of p53 gene sequences), 5,330,892 (detection of MCC gene sequences), 5,352,775 (detection of APC gene sequences), 5,532,108 (detection of DCC gene sequences), and in WO96/08514 (monoclonal antibodies against human colon carcinoma-associated antigens), the disclosures of each of which are incorporated by reference herein." *Id.* at column 6, line 50 – column 7, line 2. Lapidus '178 discloses "[m]ethods of the invention are used to prepare a stool sample followed by detection of a deletion or other mutation in the p53 tumor suppressor gene. … DNA or RNA may

	optionally be isolated from the sample according to methods known in the art." *Id.* at column 9, line 62 – column 10, line 6.

Lapidus '178 discloses extracting nucleic acid from the remaining portion of the fecal sample. As discussed *supra*, it is logical that Lapidus '178 discloses a 'remaining portion' of the fecal sample that is left over after removal of a cross-sectional, circumferential surface, and/or layer of the stool. *In re Johnson*, 558 F.2d at 1019. A person of ordinary skill in the art would recognize and understand that Lapidus '178 discloses the 'remaining portion' according to independent claim 1. Ex. 1014 at paragraphs 124-125. Further, as discussed *supra*, Lapidus '178 discloses two different parts of fecal material – the 'removed portion' ***sample of stool*** and also the 'remaining portion' of ***the stool***. See Ex. 1002 at column 3, lines 11-15.

Lapidus '178 contemplates that '[t]he ***stool*** or ***portion of stool*** that is obtained contains sufficient material to allow subsequent diagnostic assays to be performed." *Id.* at column 9, lines 27-29 (emphasis added). Such assays include those for the detection of sequences in selected DNA molecules, detection of nucleic acid sequences, detection of mutant alleles, RFLP analysis, detection of p53 gene sequences, detection of MCC gene sequences, detection of APC gene sequences, and detection of DCC gene sequences, all of which are incorporated by reference into the specification of Lapidus '178. For instance, U.S. Patent No. 5,137,806 (Ex. 1012; incorporated by reference into Lapidus '178 at column 6, line 60) provides that it relates to methods and compositions for detecting the presence or absence of a target DNA sequence, such as a mutation, within an identified region of a selected DNA molecule, such as a gene." A person of ordinary skill in the art understands that such assay involve extraction of nucleic acid in order to perform the assay. Ex. 1014 at paragraphs 124-125. Thus, Lapidus '178 discloses assays comprise extracting nucleic acid in order to perform the evaluation.

Furthermore, Lapidus '178 discloses that DNA or RNA that can be isolated from the sample according to methods known in the art. It is well known to the skilled artisan that 'isolation' of nucleic acid refers to an extraction of nucleic acid. Ex. 1014 at paragraphs 124-125. Thus, Lapidus '178 discloses an assay in which nucleic acid (e.g., DNA or RNA) is extracted.

Therefore, one skilled in the art would recognize that Lapidus '178 discloses all of the requirements for the extracting step contained in the third limitation of claim 3 of the '781 Patent. *Id.* Accordingly, Lapidus '178 renders this portion of claim 3 obvious.

'781 Patent, Claim 3, Fourth Limitation	**Lapidus '178**
d) testing the nucleic acid for an amount of a human nucleic acid.	**Lapidus '178** discloses a protocol entitled "1. Method for Quantitation of Target and Reference Polynucleotides." Ex. 1002 at column 11, lines 19-20. Here, Lapidus '178 discloses "[e]nhanced quantification of binding events between hybridization probes and target or reference is accomplished by coupling hybridization probes to particles, such as beads (hybridization beads). In order to obtain a precise quantitative measure of the amount of a polynucleotide in a sample, hybridization beads are constructed such that each bead has attached thereto a single oligonucleotide probe." *Id.* at column 7, lines 21-27.

Lapidus '178 discloses testing the nucleic acid for an amount of a human nucleic acid. Example 2 of Lapidus '178 discloses a procedure entitled "Method for Quantitation of Target and Reference Polynucleotides" and notes that a "precise quantitative measure of the amount of a polynucleotide in a sample" can be obtained. It is well known in the art that a 'polynucleotide is a synonym for a 'nucleic acid.' Ex. 1014 at paragraph 132. Thus, Lapidus '178 indicates that nucleic acids can be quantitated according to its described assays. A person of ordinary skill in the art would understand that the described nucleic acids are human nucleic acid. *Id.*

Therefore, one skilled in the art would recognize that Lapidus '178 discloses all of the requirements for the testing step contained in the fourth limitation of claim 3 of the '781 Patent. *Id.*

Lapidus '178 therefore discloses the additional limitations of claim 3 of the '781 Patent. Because the other limitations of claim 3 are obvious the reasons explained above for claim 1, claim 3 is also obvious over Lapidus '178. Accordingly, Lapidus '178 renders this portion of claim 3 obvious.

4. Lapidus '650 Renders Claim 3 Obvious

'781 Patent, Claim 3, Preamble	Lapidus '650
3. A method of processing a fecal sample, the method comprising:	**Lapidus '650** describes processing of "a stool voided by a patient" in Example 1, entitled "Preparation of a Stool Sample." Ex. 1003 at column 7, lines 12-17. Further, "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 24-26.

In the alternative to the assertion that Lapidus '650 anticipates claim 3, Lapidus '650 further renders claim 3 obvious.

Assuming, without conceding, that the preamble of claim 3 is a limitation, Lapidus '650 discloses this limitation because Lapidus '650 discloses processing a stool (a fecal sample) voided by a patient into a receptacle that is transported to a testing facility for processing. Accordingly, Lapidus '650 renders this portion of claim 3 obvious.

'781 Patent, Claim 3, First Limitation	Lapidus '650
a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising: i) a sealed sealable container containing a removed portion of a fecal sample and a buffer; and	**Lapidus '650** discloses obtaining a pair of portions of a fecal sample collected from a human subject, wherein the pair of portions are obtained by the method of claim 1. As discussed *supra* with respect to independent

ii) a sealed sealable collection vessel containing a remaining portion of a fecal sample and a stabilizing buffer, the pair of portions obtained by the method of claim 1;	claim 1, Lapidus '650 describes each and every element of independent claim 1.

Lapidus '650 discloses obtaining a pair of portions of a fecal sample collected from a human subject, wherein the pair of portions are obtained by the method of claim 1. As discussed *supra*, one skilled in the art would recognize that Lapidus '650 discloses all of the requirements for the obtaining step contained in the first limitation of claim 3 of the '781 Patent. Ex. 1014 at paragraphs 112-113. Accordingly, Lapidus '650 renders this portion of claim 3 obvious.

'781 Patent, Claim 3, Second Limitation	**Lapidus '650**
b) testing the removed portion of the fecal sample for an amount of a blood protein present in the removed portion;	**Lapidus '650** discloses that "[o]nce obtained, the cross-sectional stool sample is homogenized in an appropriate buffer, such as phosphate buffered saline." *Id.* at column 8, lines 5-7. Lapidus '650 discloses "[o]nce a cross-sectional stool sample is obtained, it may be homogenized by known methods to distribute cells and cellular debris throughout the sample. An assay then is performed on the homogenate, or an extract of the homogenate, to detect the presence of cells and/or cellular debris in the sample. The assay may be any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation

	such as a protein, or DNA-based assays for detecting mutations or genetic characteristics indicative of colorectal cancer". *Id.* at column 6, lines 1-11. Lapidus '650 discloses that "an assay performed on at least a cross-sectional portion of stool may be an assay to detect the presence of elevated levels of carcinoembryonic antigen shed from cells lining the colon. Such an assay may also comprise detecting the presence of occult blood." *Id.* at column 3, lines 4-9. Lapidus '650 discloses that "[i]f a fecal occult blood assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for detecting the presence of fecal occult blood are known in the art." *Id.* at column 8, lines 13-18.

Lapidus '650 discloses removing a portion of the fecal sample to produce a removed portion. As discussed *supra*, the 'removed portion' could take a number of forms, a cross-sectional portion, a circumferential surface portion, and/or a layer of the voided stool sample. Lapidus '650 then discloses that an assay can be performed on the removed portion to detect the presence of elevated levels of carcinoembryonic antigen (i.e., CEA), which is a known blood protein. Further, Lapidus '650 discloses that an assay can be performed on the removed portion to detect the presence of occult blood. "Current non-invasive diagnostic methods involve assaying stool samples for the presence of fecal occult blood or for elevated levels of carcinoembryonic antigen, both of which are suggestive of the presence of colorectal cancer." *Id.* at column 1, lines 55-58.

Furthermore, Lapidus '650 discloses that "[i]f a fecal occult blood assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for detecting the presence of fecal occult blood are known in the art." A person of ordinary skill in the art would understand that such fecal occult blood assays test for an amount of a blood protein (hemoglobin) that is present in a sample. Ex. 1014 at paragraph 115.

Therefore, one skilled in the art would recognize that Lapidus '650 discloses all of the requirements for the testing step contained in the second limitation of claim 3 of the '781 Patent. *Id.* Accordingly, Lapidus '650 renders this portion of claim 3 obvious.

'781 Patent, Claim 3, Third Limitation	**Lapidus '650**
c) extracting nucleic acid from the remaining portion of the fecal sample; and	**Lapidus '650** discloses that "a whole stool may be used [for diagnostic assays]. The portion contains sufficient material to allow subsequent diagnostic assays to be performed." Ex. 1003 at column 9, lines 21-24. Lapidus '650 discloses that the an illustrative "assay may be any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation such as a protein, or DNA-based assays for detecting mutations or genetic characteristics indicative of colorectal cancer. Known assay protocols, those disclosed herein or in copending application serial number Co-owned U.S. patent application, Ser. No. 08/700,583 or assays hereafter developed may be used in the practice of the invention. Non-limiting examples of useful known assay

	protocols include those disclosed in U.S. Pat. No. 5,137,806 (detection of sequences in selected DNA molecules), U.S. Pat. No. 5,348,855 (assay for nucleic acid sequences), U.S. Pat. No. 5,512,441 (detection of mutant alleles), U.S. Pat. No. 5,272,057 and U.S. Pat. No. 5,380,645 (RFLP analysis), U.S. Pat. No. 5,527,676 (detection of p53 gene sequences), U.S. Pat. No. 5,330,892 (detection of MCC gene sequences), U.S. Pat. No. 5,352,775 (detection of APC gene sequences), U.S. Pat. No. 5,532,108 (detection of DCC gene sequences), and in WO96/08514 (monoclonal antibodies against human colon carcinoma-associated antigens), the disclosures of each of which are incorporated by reference herein." *Id.* at column 6, lines 6-28. Lapidus '650 discloses "[m]ethods of the invention are used to prepare a stool sample followed by detection of a deletion or other mutation in the p53 tumor suppressor gene." … DNA or RNA may optionally be isolated from the sample according to methods known in the art." *Id.* at column 8, lines 39-50.

Lapidus '650 discloses extracting nucleic acid from the remaining portion of the fecal sample. As discussed *supra*, it is logical that Lapidus '650 discloses a 'remaining portion' of the fecal sample that is left over after removal of a cross-sectional, circumferential surface, and/or layer of the stool -- logic dictates that. *In re Johnson*, 558 F.2d at 1019. A person of ordinary skill in the art would recognize and understand that Lapidus '650 discloses the 'remaining portion' according to independent claim 1. Ex. 1014 at paragraphs 124-125.

Lapidus '650 contemplates assays include those for the detection of sequences in selected DNA molecules, detection of nucleic acid sequences, detection of mutant alleles, RFLP analysis, detection of p53 gene sequences, detection of MCC gene sequences, detection of APC gene sequences, and detection of DCC gene sequences, all of which are incorporated by reference into the specification of Lapidus '650. For instance, U.S. Patent No. 5,137,806 (Ex. 1012; incorporated by reference into Lapidus '650 at column 6, line 17) provides that it relates to methods and compositions for detecting the presence or absence of a target DNA sequence, such as a mutation, within an identified region of a selected DNA molecule, such as a gene." Furthermore, U.S. Patent No. 5,137,806 (Ex. 1012; incorporated by reference into Lapidus '650 at column 6, line 17) states that "[h]uman DNA specimens from SW480 and SW403 colon carcinoma cell lines and HL60 leukemia cell line were extracted by standard technique of proteinase K digestion and phenol/chloroform extraction (Ausubel, et al. Eds.: Current Protocols in Molecular Biology. Chapter 2, section 1 and 2. Greene Publishing Assoc. and Wiley-Interscience, New York, 1987)." A person of ordinary skill in the art understands that such assay involve extraction of nucleic acid in order to perform the assay. Ex. 1014 at paragraphs 124-125. Thus, Lapidus '650 discloses assays that comprise extracting nucleic acid in order to perform the evaluation.

Furthermore, Lapidus '650 discloses that DNA or RNA can be isolated from the sample according to methods known in the art, including those incorporated by reference in Smith-Ravin, et al., *Gut*, 36: 81-86 (1995). According to Smith-Ravin et al., "DNA was extracted from both the centrifugation pellet and supernatant fractions, as well as from endoscopy washings, using a conventional phenol chloroform extraction method and was then purified on glass milk or spin columns. The purified DNA was amplified using mitochondrial primers and analysed for ras mutations using a non-radioactive, allele specific mismatch method." Accordingly, it is well known to the skilled artisan that 'isolation' of nucleic acid refers to an extraction of nucleic acid. Ex. 1014 at paragraphs 124-125. Thus, Lapidus '650 discloses an assay in which nucleic acid (e.g., DNA or RNA) is extracted.

Therefore, one skilled in the art would recognize that Lapidus '650 discloses all of the requirements for the extracting step contained in the third limitation of claim 3 of the '781 Patent. *Id.* Accordingly, Lapidus '650 renders this portion of claim 3 obvious.

'781 Patent, Claim 3, Fourth Limitation	**Lapidus '650**
d) testing the nucleic acid for an amount of a human nucleic acid.	**Lapidus '650** discloses a protocol entitled "1. Method for Quantitation of Target and Reference Polynucleotides." Ex. 1003 at column 9, lines 63-65. Here, Lapidus '650 discloses "[e]nhanced quantification of binding events between hybridization probes and target or reference is accomplished by coupling hybridization probes to particles, such as beads (hybridization beads). In order to obtain a precise quantitative measure of the amount of a polynucleotide in a sample, hybridization beads are constructed such that each bead has attached thereto a single oligonucleotide probe." *Id.* at column 9, lines 66 – column 10, line 5.

Lapidus '650 discloses testing the nucleic acid for an amount of a human nucleic acid. Example 2 of Lapidus '650 discloses a procedure entitled "Method for Quantitation of Target and Reference Polynucleotides" and notes that a "precise quantitative measure of the amount of a polynucleotide in a sample" can be obtained. It is well known in the art that a 'polynucleotide is a synonym for a 'nucleic acid.' Ex. 1014 at paragraph 132. Thus, Lapidus '650 indicates that nucleic acids can be quantitated according to its disclosed assays. A person of ordinary skill in the art would understand that the disclosed nucleic acids are human nucleic acid. *Id.*

Therefore, one skilled in the art would recognize that Lapidus '650 discloses all of the requirements for the testing step contained in the fourth limitation of claim 3 of the '781 Patent. *Id.*

Lapidus '650 therefore discloses the additional limitations of claim 3 of the '781 Patent. Because the other limitations of claim 3 are obvious the reasons explained above for claim 1, claim 3 is also obvious over Lapidus '650. Accordingly, Lapidus '650 renders this portion of claim 3 obvious.

5. Lapidus '178 in view of De Luca and Olson Renders Claim 3 Obvious

'781 Patent, Claim 3, Preamble	Lapidus '178 in view of De Luca and Olson
3. A method of processing a fecal sample, the method comprising:	**Lapidus '178** discloses processing of "a stool voided by a patient" in Example 1, entitled "Preparation of a Stool Sample." Ex. 1002 at column 7, lines 58-62. Further, "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 63-64.

Assuming, without conceding, that the preamble of claim 3 is a limitation, Lapidus '178 discloses this limitation because Lapidus '178 discloses processing a stool (a fecal sample) voided by a patient into a receptacle that is transported to a testing facility for processing. Furthermore, as discussed *supra*, Lapidus '178 discloses the "method of processing" of independent claim 1 from which claim 3 depends, should the preamble of claim 1 be determined to be a limitation.

'781 Patent, Claim 3, First Limitation	Lapidus '178 in view of De Luca and Olson
a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising: i) a sealed sealable container containing a removed portion of a fecal sample and a buffer; and ii) a sealed sealable collection vessel containing a remaining portion of a fecal sample and a stabilizing buffer,	**Lapidus '178** discloses obtaining a pair of portions of a fecal sample collected from a human subject, wherein the pair of portions are obtained by the method of claim 1. As discussed *supra* with respect to independent claim 1, Lapidus '178 describes each and every element of independent claim 1. **De Luca** discloses "an extraction and sampling device for collection of faeces

the pair of portions obtained by the method of claim 1;	samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin, Helicobacter pylori and the like. Ex. 1006 at [0001]. De Luca discloses "an extraction and sampling tube for the collection of faeces samples that is practical for the patient and simple to use for the laboratory technician." *Id.* at [0015]. Further, De Luca discloses "[t]he extraction tube for collection of faeces samples, according to the invention, comprises a container body hollow on the inside for containing a buffer solution and faeces samples, a top cap applied to the top end of the container body and provided with a threaded small rod for sampling of faeces samples and a bottom cap applied removably to the bottom end of the container body. *Id.* at [0019]. De Luca discloses that on the extraction tube, "[a]n annular seal 55 is provided between the knurled part 44 and the threaded part 45 of the top cap." *Id.* at [0032]. **Olson** discloses development of "a multitarget, fecal DNA screening assay that detects the presence of gene-specific mutations and long DNA fragments associated with colorectal cancer (CRC)." Ex. 1007 at Abstract. Olson discloses that

	"[t]he amount of DNA recovered from aliquots stored under the different conditions is based on quantification of a 200-bp DNA fragment (Table 3). Although the amount of recoverable DNA varies widely from sample to sample, at t0 the average recovery was 14,891 copies/10 mL, whereas after room temperature incubation, the average recovery was 1,955. Without buffer added to the samples, between 65% to 98% of the DNA was no longer recoverable (excluding sample GP-031), after incubation of samples at room temperature, compared with t0. The one exception, sample GP-031, maintained high DNA yield even without addition of stabilization buffer. Samples incubated with stabilization buffer maintained human DNA yields similar to the t0 samples (Table 3)." *Id.* at page 186, first column, second full paragraph. In conclusion, Olson states that "DNA can be stabilized by addition of buffer to the sample, leading to increased assay sensitivity. *Id.* at Abstract.

As discussed *supra*, Lapidus '178 in view of De Luca and Olson disclose obtaining a pair of portions of a fecal sample collected from a human subject. As discussed *supra*, Lapidus '178 in view of De Luca and Olson disclose the pair of portions are obtained by the method of claim 1. Accordingly, a person of ordinary skill in the art would recognize that Lapidus '178 in view of De Luca and Olson discloses all of the requirements for the obtaining step contained in the first limitation of claim 3 of the '781 Patent. Ex. 1014 at paragraphs 112-113.

'781 Patent, Claim 3, Second Limitation	Lapidus '178 in view of De Luca and Olson
b) testing the removed portion of the fecal sample for an amount of a blood protein present in the removed portion;	**Lapidus '178** discloses that after "a circumferential surface or cross-sectional sample of stool is obtained, it may be homogenized by known methods to distribute cells and cellular debris throughout the sample. An assay then is performed on the homogenate, or an extract of the homogenate, to detect the presence of cells and/or cellular debris in the sample. The assay may be any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation such as a protein, or DNA-based assays for detecting mutations or genetic characteristics indicative of colorectal cancer." Ex. 1002 at column 6, lines 45-56. Lapidus '178 discloses that "an assay performed on at least a circumferential surface or cross-sectional portion of stool may be an assay to detect the presence of elevated levels of carcinoembryonic antigen shed from cells lining the colon. Such an assay may also comprise detecting the presence of occult blood." *Id.* at column 3, lines 26-30. Lapidus '178 discloses that "[i]f a fecal occult blood assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for

	detecting the presence of fecal occult blood are known in the art." *Id.* at column 9, lines 40-45. **De Luca** discloses "collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin…". Ex. 1006 at [0001]. De Luca discloses "[t]he extraction tube for collection of faeces samples, according to the invention, comprises a container body hollow on the inside for containing a buffer solution and faeces samples, a top cap applied to the top end of the container body and provided with a threaded small rod for sampling of faeces samples and a bottom cap applied removably to the bottom end of the container body. *Id.* at [0019]. Further, De Luca discloses that "the extraction tube [] is positioned in a special housing [] of an automatic machine for immunological tests and then the bottom cap [] is removed so as to allow removal of the buffer solution [] containing the faeces samples by a probe of the automatic machine." *Id.* at [0048].

Lapidus '178 discloses removing a portion of the fecal sample to produce a removed portion. As discussed *supra*, the 'removed portion' could take a number of forms, a cross-sectional portion, a circumferential surface portion, and/or a layer of the voided stool sample.

Lapidus '178 then describes that an assay can be performed on the removed portion to detect the presence of elevated levels of carcinoembryonic antigen (i.e., CEA), which is a known blood protein and is evaluated to detect the presence of occult blood. Furthermore, Lapidus '178 discloses that "[i]f a fecal occult blood assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for detecting the presence of fecal occult blood are known in the art." A person of ordinary skill in the art would understand that such fecal occult blood assays test for an amount of a blood protein (hemoglobin) that is present in a sample. Ex. 1014 at paragraph 115.

Moreover, as discussed *supra*, a person of ordinary skill in the art would have been motivated to test the removed portion of the fecal sample for a blood protein by utilizing the fecal immunochemical blood tests taught by De Luca. Ex. 1014 at paragraph 117. To this end, De Luca also discloses testing a removed portion of the fecal sample for a blood protein, albeit with the more effective fecal immunochemical blood tests. Therefore, one skilled in the art would recognize that Lapidus '178 in view of De Luca disclose all of the requirements for the testing step contained in the second limitation of claim 3 of the '781 Patent. *Id.* at paragraph 118.

'781 Patent, Claim 3, Third Limitation	**Lapidus '178 in view of De Luca and Olson**
c) extracting nucleic acid from the remaining portion of the fecal sample; and	**Lapidus '178** discloses that "a whole stool may be used for diagnostic assays. The stool or portion of stool that is obtained contains sufficient material to allow subsequent diagnostic assays to be performed." Ex. 1002 at column 9, lines 26-29. Lapidus '178 discloses that the an illustrative "assay may be any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation such as a protein, or DNA-based assays for detecting mutations or

	genetic characteristics indicative of colorectal cancer. Known assay protocols, those disclosed herein or in U.S. Pat. No. 5,670,325 or assays hereafter developed may be used in the practice of the invention. Non-limiting examples of useful known assay protocols include those disclosed in U.S. Pat. Nos. 5,137,806 (detection of sequences in selected DNA molecules), 5,348,855 (assay for nucleic acid sequences), 5,512,441 (detection of mutant alleles), 5,272,057 and 5,380,645 (RFLP analysis), 5,527,676 (detection of p53 gene sequences), 5,330,892 (detection of MCC gene sequences), 5,352,775 (detection of APC gene sequences), 5,532,108 (detection of DCC gene sequences), and in WO96/08514 (monoclonal antibodies against human colon carcinoma-associated antigens), the disclosures of each of which are incorporated by reference herein." *Id.* at column 6, line 50 – column 7, line 2. Lapidus '178 discloses "[m]ethods of the invention are used to prepare a stool sample followed by detection of a deletion or other mutation in the p53 tumor suppressor gene. … DNA or RNA may optionally be isolated from the sample according to methods known in the art." *Id.* at column 9, line 62 – column 10, line 6. **Olson** discloses development of "a multitarget, fecal DNA screening assay that

	detects the presence of gene-specific mutations and long DNA fragments associated with colorectal cancer (CRC)." Ex. 1007 at Abstract. Olson discloses that "[t]he amount of DNA recovered from aliquots stored under the different conditions is based on quantification of a 200-bp DNA fragment (Table 3). Although the amount of recoverable DNA varies widely from sample to sample, at t0 the average recovery was 14,891 copies/10 mL, whereas after room temperature incubation, the average recovery was 1,955. Without buffer added to the samples, between 65% to 98% of the DNA was no longer recoverable (excluding sample GP-031), after incubation of samples at room temperature, compared with t0. The one exception, sample GP-031, maintained high DNA yield even without addition of stabilization buffer. Samples incubated with stabilization buffer maintained human DNA yields similar to the t0 samples (Table 3)." *Id.* at page 186, first column, second full paragraph. In conclusion, Olson states that "DNA can be stabilized by addition of buffer to the sample, leading to increased assay sensitivity. *Id.* at Abstract.

Lapidus '178 discloses extracting nucleic acid from the remaining portion of the fecal sample. As discussed *supra*, it is logical that Lapidus '178 discloses a 'remaining portion' of the fecal sample that is left over after removal of a cross-sectional, circumferential surface, and/or

layer of the stool. Lapidus '178 discloses testing DNA and RNA from cellular components of the fecal sample. It is well known in the art that these tests include extracting nucleic acid. Ex. 1014 at paragraphs 124-125.

Even if Lapidus '178 is determined to not specifically teach removal to a separate sealable container, Olson removes this deficiency. As discussed *supra*, a person of ordinary skill in the art would have been motivated to add a preservative as a stabilizing buffer to the stool at the time of defecation as taught by Olson in order to prevent degradation of nucleic acids. *Id.* at paragraphs 127-128. To this end, Olson also discloses extracting nucleic acid from a fecal sample and indicates that addition of a stabilizing buffer to stool led to increased DNA assay sensitivity. Therefore, one skilled in the art would recognize that Lapidus '178 in view of Olson disclose all of the requirements for the extracting step contained in the third limitation of claim 3 of the '781 Patent. *Id.* at paragraph 128.

'781 Patent, Claim 3, Fourth Limitation	**Lapidus '178 in view of De Luca and Olson**
d) testing the nucleic acid for an amount of a human nucleic acid.	**Lapidus '178** discloses a protocol entitled "1. Method for Quantitation of Target and Reference Polynucleotides." Ex. 1002 at column 11, lines 19-20. Here, Lapidus '178 discloses "[e]nhanced quantification of binding events between hybridization probes and target or reference is accomplished by coupling hybridization probes to particles, such as beads (hybridization beads). In order to obtain a precise quantitative measure of the amount of a polynucleotide in a sample, hybridization beads are constructed such that each bead has attached thereto a single oligonucleotide probe." *Id.* at column 7, lines 21-27.

	Olson discloses development of "a multitarget, fecal DNA screening assay that detects the presence of gene-specific mutations and long DNA fragments associated with colorectal cancer (CRC)." Ex. 1007 at Abstract. Olson discloses that "[t]he amount of DNA recovered from aliquots stored under the different conditions is based on quantification of a 200-bp DNA fragment (Table 3). Although the amount of recoverable DNA varies widely from sample to sample, at t0 the average recovery was 14,891 copies/10 mL, whereas after room temperature incubation, the average recovery was 1,955. Without buffer added to the samples, between 65% to 98% of the DNA was no longer recoverable (excluding sample GP-031), after incubation of samples at room temperature, compared with t0. The one exception, sample GP-031, maintained high DNA yield even without addition of stabilization buffer. Samples incubated with stabilization buffer maintained human DNA yields similar to the t0 samples (Table 3)." *Id.* at page 186, first column, second full paragraph. In conclusion, Olson states that "DNA can be stabilized by addition of buffer to the sample, leading to increased assay sensitivity. *Id.* at Abstract.

Lapidus '178 discloses testing the nucleic acid for an amount of a human nucleic acid. Example 2 of Lapidus '178 discloses a procedure entitled "Method for Quantitation of Target and Reference Polynucleotides" and notes that a "precise quantitative measure of the amount of a polynucleotide in a sample" can be obtained. It is well known in the art that a 'polynucleotide is a synonym for a 'nucleic acid.' Ex. 1014 at paragraph 132. Thus, Lapidus '178 indicates that nucleic acids can be quantitated according to its described assays. A person of ordinary skill in the art would understand that the described nucleic acids are human nucleic acid. *Id.*

Similarly, Olson also discloses testing the nucleic acid for an amount of a human nucleic acid. For instance, Table 1 of Olson lists "quantification of recoverable human DNA" in samples incubated with stabilization buffer. Therefore, a person of ordinary skill in the art would recognize that Lapidus '178 in view of Olson discloses all of the requirements for the testing step contained in the fourth limitation of claim 3 of the '781 Patent. *Id.* at paragraphs 128-129.

In summary, Lapidus '178 in view of De Luca and Olson therefore disclose the additional limitations of claim 3 of the '781 Patent. Because the other limitations of claim 3 are obvious for the reasons explained above for claim 1, claim 3 is also obvious over Lapidus '178 in view of De Luca and Olson.

6. Lapidus '650 in view of De Luca and Olson Renders Claim 3 Obvious

'781 Patent, Claim 3, Preamble	Lapidus '650 in view of De Luca and Olson
3. A method of processing a fecal sample, the method comprising:	**Lapidus '650** discloses processing of "a stool voided by a patient" in Example 1, entitled "Preparation of a Stool Sample." Ex. 1003 at column 7, lines 12-17. Further, "[s]tool is voided into a receptacle that is preferably small enough to be transported to a testing facility" for processing. *Id.* at column 7, lines 24-26.

Assuming, without conceding, that the preamble of claim 3 is a limitation, Lapidus '650 discloses this limitation because Lapidus '650 discloses processing a stool (a fecal sample) voided by a patient into a receptacle that is transported to a testing facility for processing. Furthermore, as discussed *supra*, Lapidus '650 discloses the "method of processing" of independent claim 1 from which claim 3 depends, should the preamble of claim 1 be determined to be a limitation.

'781 Patent, Claim 3, First Limitation	**Lapidus '650 in view of De Luca and Olson**
a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising: i) a sealed sealable container containing a removed portion of a fecal sample and a buffer; and ii) a sealed sealable collection vessel containing a remaining portion of a fecal sample and a stabilizing buffer, the pair of portions obtained by the method of claim 1;	**Lapidus '650** discloses obtaining a pair of portions of a fecal sample collected from a human subject, wherein the pair of portions are obtained by the method of claim 1. As discussed *supra* with respect to independent claim 1, Lapidus '650 describes each and every element of independent claim 1. **De Luca** discloses "an extraction and sampling device for collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin, Helicobacter pylori and the like. Ex. 1006 at [0001]. De Luca discloses "an extraction and sampling tube for the collection of faeces samples that is practical for the patient and simple to use for the laboratory technician." *Id.* at [0015]. Further, De Luca discloses "[t]he extraction tube for collection of faeces samples, according to the invention, comprises a container body hollow on the inside for

	containing a buffer solution and faeces samples, a top cap applied to the top end of the container body and provided with a threaded small rod for sampling of faeces samples and a bottom cap applied removably to the bottom end of the container body. *Id.* at [0019]. De Luca discloses that on the extraction tube, "[a]n annular seal 55 is provided between the knurled part 44 and the threaded part 45 of the top cap." *Id.* at [0032]. **Olson** discloses development of "a multitarget, fecal DNA screening assay that detects the presence of gene-specific mutations and long DNA fragments associated with colorectal cancer (CRC)." Ex. 1007 at Abstract. Olson discloses that "[t]he amount of DNA recovered from aliquots stored under the different conditions is based on quantification of a 200-bp DNA fragment (Table 3). Although the amount of recoverable DNA varies widely from sample to sample, at t0 the average recovery was 14,891 copies/10 mL, whereas after room temperature incubation, the average recovery was 1,955. Without buffer added to the samples, between 65% to 98% of the DNA was no longer recoverable (excluding sample GP-031), after incubation of samples at room temperature, compared with t0. The one

	exception, sample GP-031, maintained high DNA yield even without addition of stabilization buffer. Samples incubated with stabilization buffer maintained human DNA yields similar to the t0 samples (Table 3)." *Id.* at page 186, first column, second full paragraph. In conclusion, Olson states that "DNA can be stabilized by addition of buffer to the sample, leading to increased assay sensitivity. *Id.* at Abstract.

As discussed *supra*, Lapidus '650 in view of De Luca and Olson disclose obtaining a pair of portions of a fecal sample collected from a human subject. As discussed *supra*, Lapidus '650 in view of De Luca and Olson disclose the pair of portions are obtained by the method of claim 1. Accordingly, a person of ordinary skill in the art would recognize that Lapidus '650 in view of De Luca and Olson discloses all of the requirements for the obtaining step contained in the first limitation of claim 3 of the '781 Patent. Ex. 1014 at paragraphs 112-113.

'781 Patent, Claim 3, Second Limitation	**Lapidus '650 in view of De Luca and Olson**
b) testing the removed portion of the fecal sample for an amount of a blood protein present in the removed portion;	**Lapidus '650** discloses that "[o]nce obtained, the cross-sectional stool sample is homogenized in an appropriate buffer, such as phosphate buffered saline." *Id.* at column 8, lines 5-7. Lapidus '650 discloses "[o]nce a cross-sectional stool sample is obtained, it may be homogenized by known methods to distribute cells and cellular debris throughout the sample. An assay then is performed on the homogenate, or an extract of the homogenate, to detect the presence of cells and/or cellular

	debris in the sample. The assay may be any one or a combination of histological cellular assays, antibody based immunoassays (or other formats) designed to detect the presence of a molecule characteristic of transformation such as a protein, or DNA-based assays for detecting mutations or genetic characteristics indicative of colorectal cancer". *Id.* at column 6, lines 1-11. Lapidus '650 discloses that "an assay performed on at least a cross-sectional portion of stool may be an assay to detect the presence of elevated levels of carcinoembryonic antigen shed from cells lining the colon. Such an assay may also comprise detecting the presence of occult blood." *Id.* at column 3, lines 4-9. Lapidus '650 discloses that "[i]f a fecal occult blood assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for detecting the presence of fecal occult blood are known in the art." *Id.* at column 8, lines 13-18. **De Luca** discloses "collection of faeces samples, particularly for laboratory immunological tests, for qualitative or quantitative determination of one or more analytes, such as haemoglobin…". Ex. 1006 at [0001]. De Luca discloses "[t]he extraction

	tube for collection of faeces samples, according to the invention, comprises a container body hollow on the inside for containing a buffer solution and faeces samples, a top cap applied to the top end of the container body and provided with a threaded small rod for sampling of faeces samples and a bottom cap applied removably to the bottom end of the container body. *Id.* at [0019]. Further, De Luca discloses that "the extraction tube [] is positioned in a special housing [] of an automatic machine for immunological tests and then the bottom cap [] is removed so as to allow removal of the buffer solution [] containing the faeces samples by a probe of the automatic machine." *Id.* at [0048].

Lapidus '650 discloses removing a portion of the fecal sample to produce a removed portion. As discussed *supra*, the 'removed portion' is a cross-sectional portion and Lapidus '650 then describes that an assay can be performed on the removed portion to detect the presence of elevated levels of carcinoembryonic antigen (i.e., CEA), which is a known blood protein and is evaluated to detect the presence of occult blood. Furthermore, Lapidus '650 discloses that "[i]f a fecal occult blood assay is to be performed, the buffer may contain chemical compounds which react with blood to produce a color, the intensity of which can be measured. Buffers useful for detecting the presence of fecal occult blood are known in the art." A person of ordinary skill in the art would understand that such fecal occult blood assays test for an amount of a blood protein (hemoglobin) that is present in a sample. Ex. 1014 at paragraph 115.

Moreover, as discussed *supra*, a person of ordinary skill in the art would have been motivated to test the removed portion of the fecal sample for a blood protein by utilizing the fecal immunochemical blood tests taught by De Luca. Ex. 1014 at paragraph 117. To this end,