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.

Table of Contents

Page

I. Identification of Claims for Which Reexamination is Requested 1
II. Overview of the '781 Patent 1
A. Summary of the Independent Claims 1
B. The '781 Patent Prosecution History Lacks Any Prior Art Rejections 1
III. The Level of Ordinary Skill in the Art 2
IV. Claim Construction 3
A. Claims 1-20 3
B. Claims 5-11 5
V. Other Supporting Evidence 5
A. Declaration of Mr. Anthony P. Shuber, MS 5
VI. Statement Pointing Out Each Substantial New Question of Patentability 6
A. Lapidus '178 13
B. Lapidus '650 14
C. Lapidus '178 in view of De Luca and Olson 14
D. Lapidus '650 in view of De Luca and Olson 15
E. Ahlquist in view of De Luca and Olson 15
F. O'Neill in view of De Luca and Olson 15
G. Lapidus '178 in view of De Luca, Olson, and Leung 16
H. Lapidus '650 in view of De Luca, Olson, and Leung 16
I. Ahlquist in view of De Luca, Olson, and Leung 16
J. O'Neill in view of De Luca, Olson, and Leung 17
K. Lapidus '178 in view of De Luca, Olson, and Hoepffner 17
L. Lapidus '650 in view of De Luca, Olson, and Hoepffner 17
M. Ahlquist in view of De Luca, Olson, and Hoepffner 18
N. O'Neill in view of De Luca, Olson, and Hoepffner 18
VII. Detailed Explanation under 37 C.F.R. § 1.510(b) 18
A. Independent Claim 1 23
B. Dependent Claim 2 108
C. Dependent Claim 3 114
D. Dependent Claim 4 185
E. Dependent Claim 5 196

F. Dependent Claim 6 201
G. Dependent Claim 7 204
H. Dependent Claim 8 207
I. Dependent Claim 9 211
J. Dependent Claim 10 217
K. Dependent Claim 11 221
L. Dependent Claim 12 225
M. Dependent Claim 13 237
N. Dependent Claim 14 210
O. Dependent Claim 15 250
P. Dependent Claim 16 260
Q. Dependent Claim 17 265
R. Dependent Claim 18 269
S. Dependent Claim 19 273
T. Dependent Claim 20 278
VIII. Conclusion 282

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.

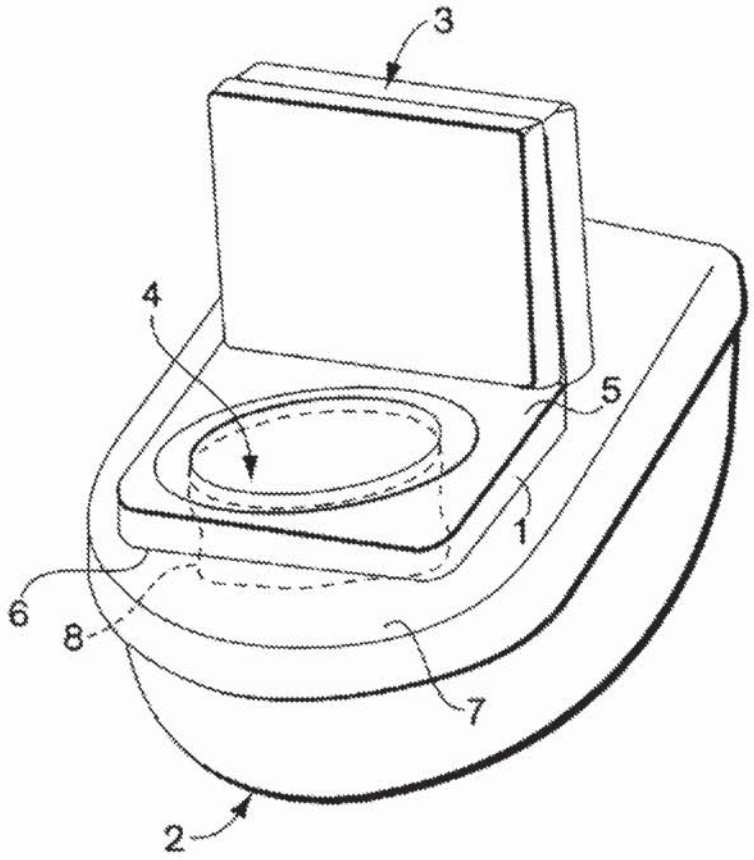
As explained in Section IV. *supra*, the preamble of claim 1 is not a limitation. However, even if the preamble of claim 1 was determined to be a limitation, Lapidus '178 describes this limitation. Lapidus '178 describes a stool (a fecal sample) voided by a patient into a receptacle that is transported 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.

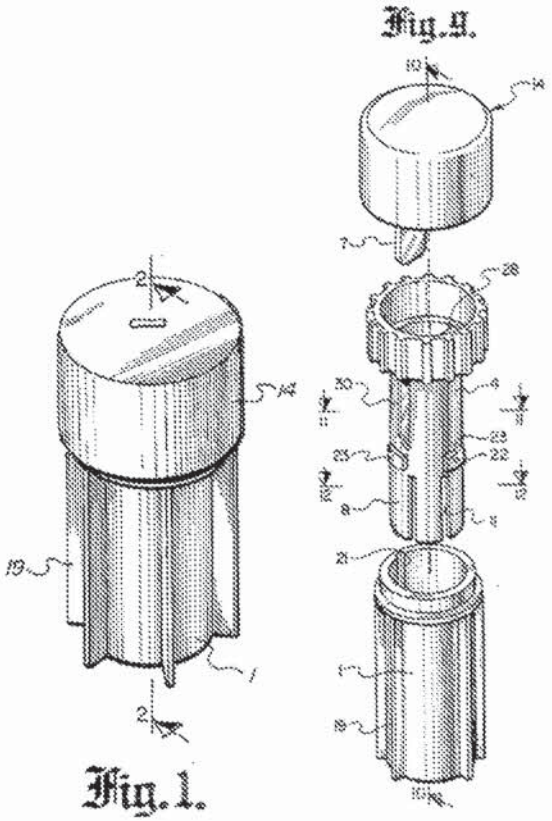
Given the removal of a cross-sectional, circumferential surface, and/or layer of the voided stool sample, logic dictates that Lapidus '178 describes a 'remaining portion' of the fecal sample that is left over following such removal. *In re Johnson*, 558 F.2d at 1019. A person of ordinary skill in the 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:



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.

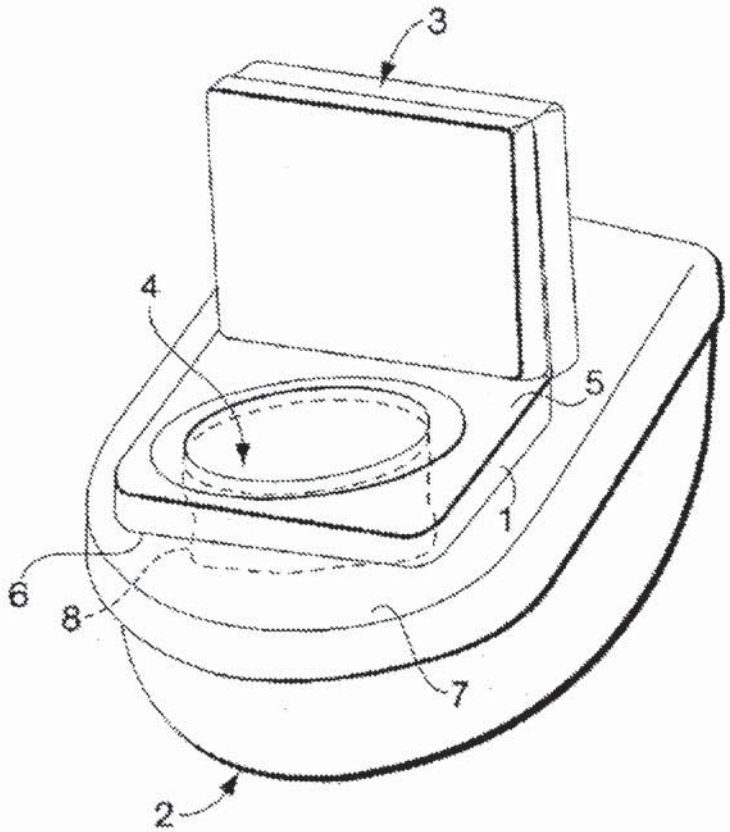
Moreover, U.S. Patent No. 5,196,167 (Ex. 1011) is incorporated by reference into Lapidus '650 at column 6, lines 30-31. In pertinent part, U.S. Patent No. 5,196,167 describes a test sheet product used for identification of blood in a patient stool and states that "[a]fter the patient has completed a 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.

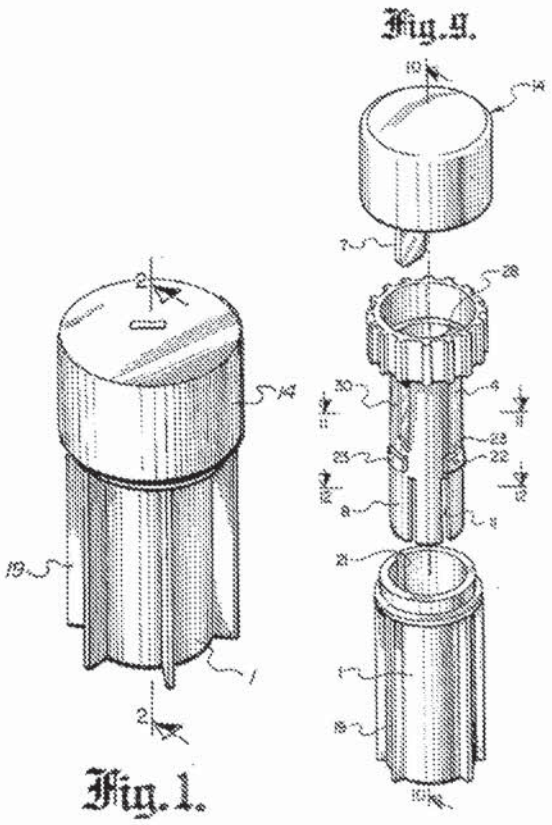
Given the removal of a cross-sectional sample, logic dictates that Lapidus '650 describes a 'remaining portion' of the fecal sample that is left over following such removal. *In re Johnson*, 558 F.2d at 1019. A person of ordinary skill in the art would recognize and understand that

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

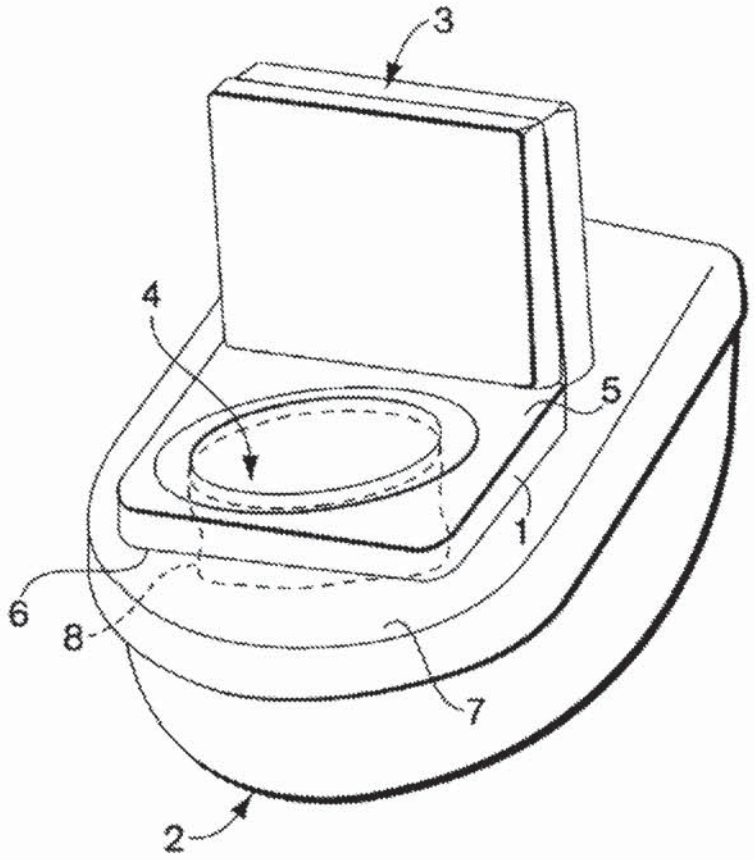
recognize Lapidus '178 discloses the method of processing a "freshly-collected" fecal sample "without freezing" specified by the preamble. Ex. 1014 at paragraph 45.

'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.

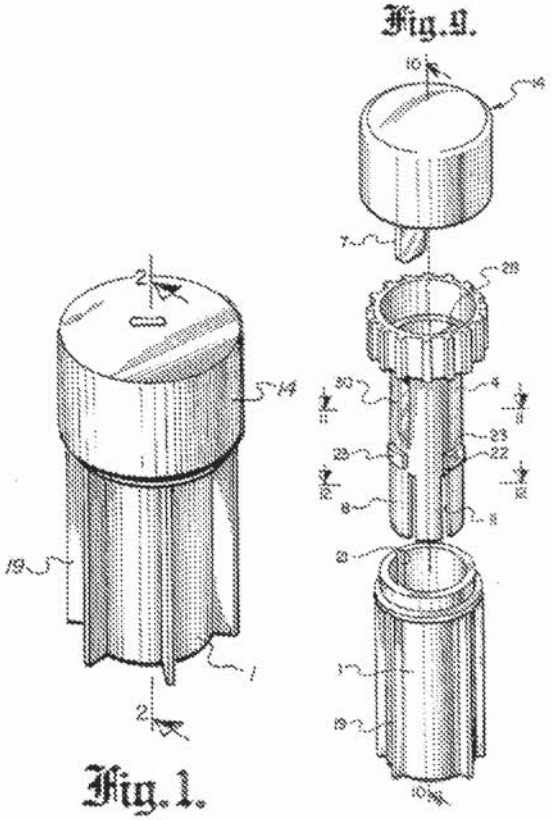
Moreover, Lapidus '178 discloses that the 'removed portion' of the fecal sample is obtained upon collection of the fecal sample. Again referring to Figure 2 above, Lapidus '178 discloses that "Means 8 may be fixedly attached to the support frame 1 or may be removably attached for removal subsequent to 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.

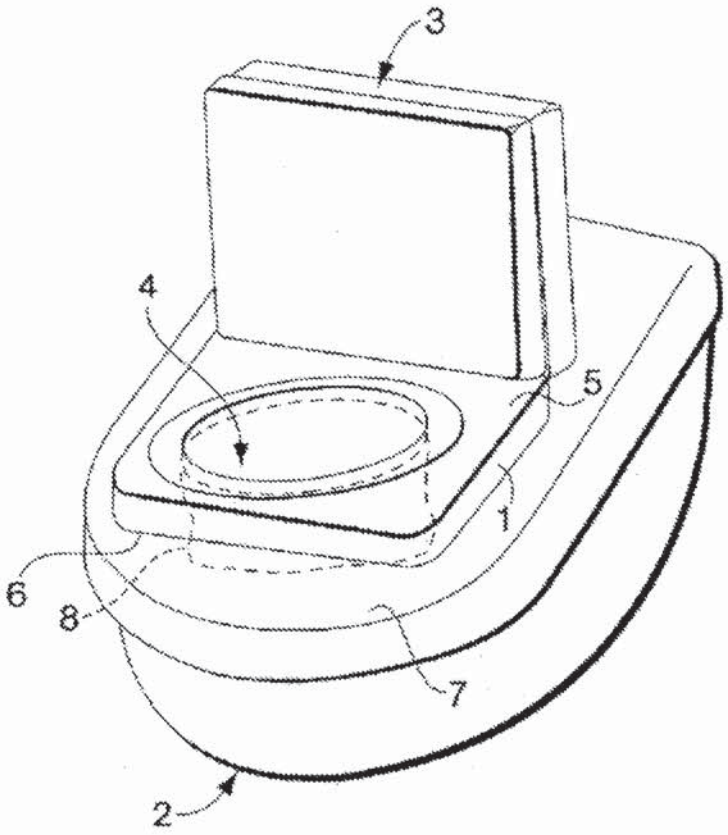
Further, Lapidus '650 discloses the method of processing a "freshly-collected" fecal sample "without freezing" specified by the preamble. Lapidus '650 does not disclose the concept of freezing fecal samples. Thus, Lapidus explicitly discloses collecting a fecal sample "without freezing" to meet the language 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.

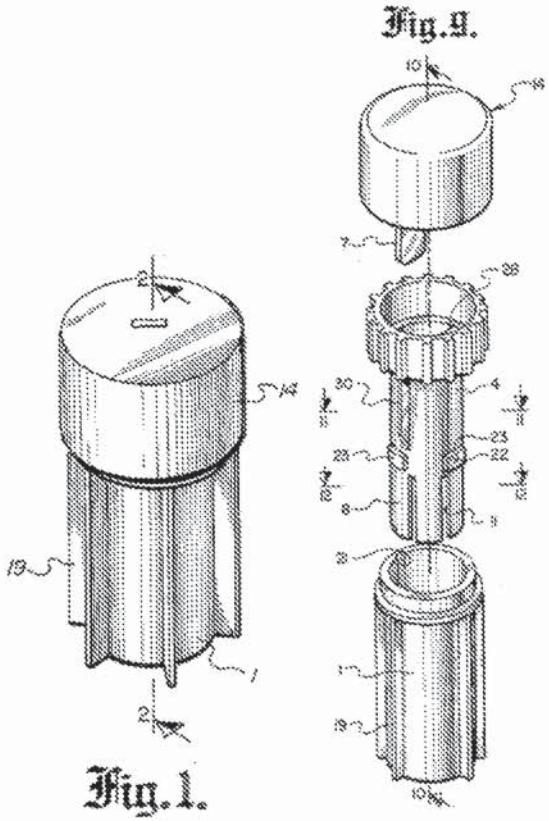
Given the removal of a cross-sectional sample, logic dictates that Lapidus '650 discloses a 'remaining portion' of the fecal sample that is left over following such removal. *In re Johnson*, 558 F.2d at 1019. A person of ordinary skill in the art would recognize and understand that Lapidus '650 discloses 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.

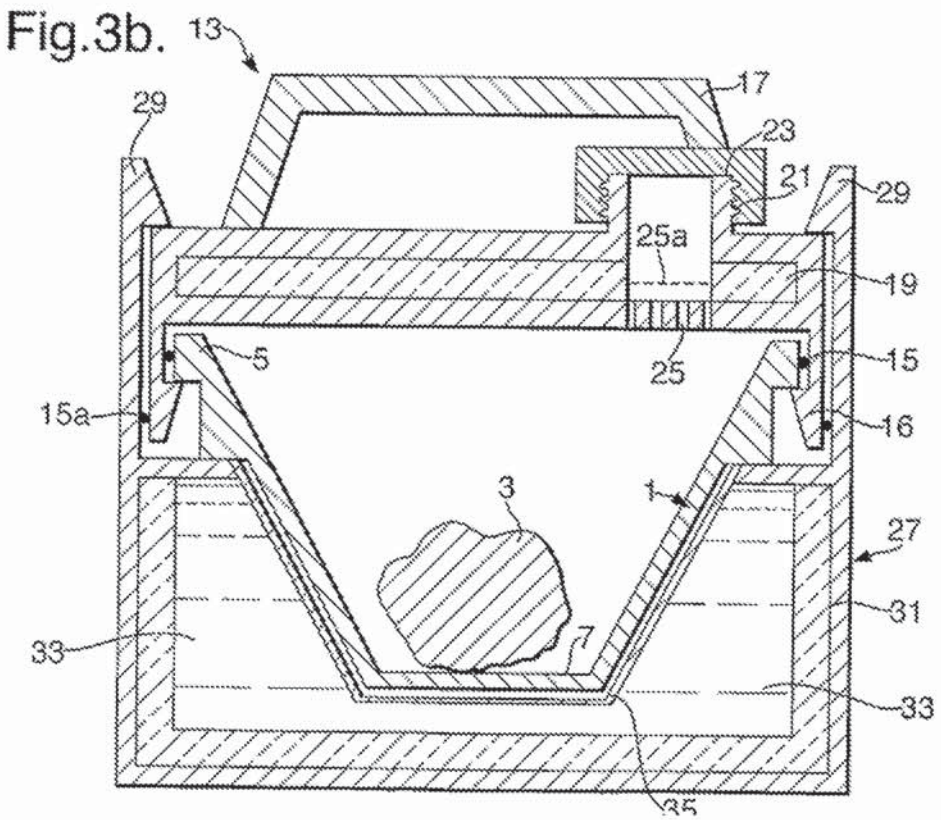
As explained in Section IV. *supra*, the preamble of claim 1 is not a limitation. However, even if the preamble of claim 1 was determined to be a limitation, O'Neill discloses this limitation because O'Neill teaches collection of stool (a fecal sample) into a container. Further, although O'Neill suggests 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.

Geneoscopy Exhibit 1021, Page 117

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.

Geneoscopy Exhibit 1021, Page 128

	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.*

Geneoscopy Exhibit 1021, Page 137

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,

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 '650 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 '650 in view of De Luca and Olson**
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. **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 '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 sample of the stool. Lapidus '650 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 '650 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 '650 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 '650 in view of De Luca and Olson**
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. **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 '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 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 '650 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 '650 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 '650 in view of De Luca and Olson.

7. Ahlquist in view of De Luca and Olson Renders Claim 3 Obvious

'781 Patent, Claim 3, Preamble	Ahlquist in view of De Luca and Olson
3. A method of processing a fecal sample, 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.

Assuming, without conceding, that the preamble of claim 3 is a limitation, Ahlquist discloses this limitation because Ahlquist discloses a stool (a fecal sample) collected by a patient into a plastic bucket that is transported to the Mayo Clinic for analysis. Furthermore, as discussed *supra*, Ahlquist 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	Ahlquist 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;	**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 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 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*, Ahlquist 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 Ahlquist 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	Ahlquist 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;	**Ahlquist** discloses for occult blood testing that "[t]he manufacturer that developed the Hemoccult and HemoccultSensa cards, without rehydration, trained technicians on-site at the Mayo Clinic. As recommended by the manufacturer, the technicians added the catalyst solution to cards stored at ambient temperature within 48 to 72 hours of collection. We defined a spreading (enlarging) blue color in 60 seconds in any window of the cards as a positive result and any other result as negative." Ex. 1004 at page 5, at heading 'Occult Blood Testing.' Alquist discloses that it "We compared fecal blood results from 3 stools per patient with stool DNA on 1 stool. Experienced technicians performed stool DNA and occult blood testing in separate central laboratories without knowledge of clinical findings or the results of other tests." *Id.* at page 3, at heading 'Design.' Further, Ahlquist discloses that "[d]etection sensitivities for the 290 screen-relevant neoplasms found among all 3764 evaluable participants were 10% (95% CI, 7% to 13%) with Hemoccult and 18% (CI, 13% to 22%) with HemoccultSensa (P <

	0.001). Based on all 3474 participants without screenrelevant neoplasia, the Hemoccult specificity of 98% (CI, 98% to 99%) was slightly higher than that of HemoccultSensa (97% [CI, 96% to 97%]) (P < 0.001). Hemoccult and HemoccultSensa positivity rates for the 39 patients with colorectal cancer or high-grade dysplasia were 33% (CI, 19% to 48%) and 44% (CI, 28% to 59%), respectively (*P* = 0.100). For the 251 patients with adenomas 1 cm or larger, the positivity rates were 6% (CI, 3% to 9%) versus 14% (CI, 9% to 18%) (*P* = 0.001)." *Id.* at pages 6-y, under heading 'Occult Blood Testing: Hemoccult versus HemoccultSensa.' **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].

Ahlquist discloses testing the removed portion of the fecal sample for an amount of a blood protein present in the removed portion. As discussed *supra*, Ahlquist discloses that 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. Further, Ahlquist discloses that occult blood testing was performed on the Hemoccult and HemoccultSensa cards. It is well known in the art that occult blood testing refers to analyzing for the presence of blood proteins such as hemoglobin. Ex. 1014 at paragraphs 119-120.

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 and as suggested by Ahlquist instead of the guaiac-based Hemoccult and HemoccultSensa tests of Ahlquist. *Id.* 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 Ahlquist 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.*

'781 Patent, Claim 3, Third Limitation	**Ahlquist in view of De Luca and Olson**
c) extracting nucleic acid from the remaining portion of the fecal sample; and	Ahlquist discloses that "[a]ll assays were polymerase chain reaction–based and were run at EXACT Sciences. Stool DNA test 1 was performed as described in Imperiale and colleagues' study (21). The marker panel for

	SDT-1 included 21 tumor-specific point mutations (3 on the Kras gene, 10 on the APC gene, and 8 on the p53 gene); the microsatellite-instability marker BAT-26; and long DNA, a marker for delayed apoptosis, which is characteristic of exfoliated neoplastic colonocytes (12). For SDT-2, sequence-specific DNA markers were detected by acrylamide gel electrophoresis, as described by Whitney and colleagues (24); the panel consisted of 3 tumor-specific markers broadly informative for both colorectal cancer and adenomas (25): K-ras mutations, scanning of APC mutator cluster regions, and methylation of the vimentin gene. We used methods described elsewhere to detect mutant Kras (12), APC scanning (25), and vimentin gene methylation (20) assays. We defined any positive component marker result according to the manufacturer's preestablished criteria as a positive test result. Ex. 1004, pages 4-5, at 'DNA testing' 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.

Ahlquist discloses extracting nucleic acid from the remaining portion of the fecal sample. As discussed *supra*, Ahlquist discloses that the patients collected stool and that rest of the stool in the plastic bucket (e.g., not including the smeared stool) corresponds to the 'remaining portion' of the fecal sample in independent claim 1.

Further, Ahlquist discloses that one or two "Stool DNA tests" were performed on stool via polymerase chain reaction and that sequence-specific DNA markers were detected. It is well known in the art that these tests include extracting nucleic acid. Ex. 1014 at paragraph 129.

Moreover, 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 and as suggested by Ahlquist in order to prevent degradation of nucleic acids. *Id.* 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 Ahlquist 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.*

'781 Patent, Claim 3, Fourth Limitation	**Ahlquist in view of De Luca and Olson**
d) testing the nucleic acid for an amount of a human nucleic acid.	**Ahlquist** discloses that "[a]ll assays were polymerase chain reaction–based and were run at EXACT Sciences. Stool DNA test 1 was performed as described in Imperiale and colleagues' study (21). The marker panel for SDT-1 included 21 tumor-specific point mutations (3 on the Kras gene, 10 on the APC gene, and 8 on the p53 gene); the microsatellite-instability marker BAT-26; and long DNA, a marker for delayed apoptosis, which is characteristic of exfoliated neoplastic

	colonocytes (12). For SDT-2, sequence-specific DNA markers were detected by acrylamide gel electrophoresis, as described by Whitney and colleagues (24); the panel consisted of 3 tumor-specific markers broadly informative for both colorectal cancer and adenomas (25): K-ras mutations, scanning of APC mutator cluster regions, and methylation of the vimentin gene. We used methods described elsewhere to detect mutant Kras (12), APC scanning (25), and vimentin gene methylation (20) assays. We defined any positive component marker result according to the manufacturer's preestablished criteria as a positive test result. Ex. 1004, pages 4-5, at 'DNA testing' 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.

Ahlquist discloses testing the nucleic acid for an amount of a human nucleic acid. In particular, Ahlquist discloses testing of nucleic acid via two stool DNA tests (i.e., SDT-1 and SDT-2) and corresponds the amount of identified nucleic acid with detection of neoplasm in the

human patients. Amongst others, Ahlquist discloses testing for human nucleic acids such as *K-ras*, *APC*, and *p53*.

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 Ahlquist 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. Ex. 1014 at paragraph 136.

In summary, Ahlquist 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 Ahlquist in view of De Luca and Olson.

8. O'Neill in view of De Luca and Olson Renders Claim 3 Obvious

'781 Patent, Claim 3, Preamble	O'Neill in view of De Luca and Olson
3. A method of processing a fecal sample, the method comprising:	**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.

Assuming, without conceding, that the preamble of claim 3 is a limitation, O'Neill discloses this limitation because O'Neill discloses a stool (a fecal sample) collected by a patient into a container that is transported to a clinic for analysis. Furthermore, as discussed *supra*, O'Neill 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	O'Neill 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;	**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]. **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 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*, O'Neill 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 O'Neill 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 paragraph 113.

'781 Patent, Claim 3, Second Limitation	**O'Neill 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;	**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 that "[e]xfoliated 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." *Id.* at page 1, lines 15-24.

	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].

O'Neill discloses testing the removed portion of cellular material from the fecal sample for various components, such as DNA, RNA, and proteins. It is well known in the art that testing such components from fecal samples could include occult blood testing, fecal immunochemical blood tests, and the like for evaluating colorectal cancer in patients. Ex. 1014 at paragraphs 121-122.

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 paragraphs 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 O'Neill 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 paragraphs 121-122.

'781 Patent, Claim 3, Third Limitation	**O'Neill in view of De Luca and Olson**
c) extracting nucleic acid from the remaining portion of the fecal sample; 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 that "[e]xfoliated 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." *Id.* at page 1, lines 15-24. Further, O'Neill discloses that "[t]he 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." *Id.* at page 16, lines 7-19. **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 that the patients collected stool in a container and that after removal of some cellular material, a large mass of stool remains in the container thus corresponding to the 'remaining portion' of the fecal sample in independent claim 1. O'Neill discloses testing DNA and RNA from cellular components of the fecal sample and discloses detailed examples of DNA analyses, such as fluorimetric DNA assay was performed with a TECAN™ Spectrafluor Plus using PicoGreen (Molecular Probes™) to yield the stool DNA index (SDNAI). It is well known in the art that these tests include extracting nucleic acid. Ex. 1014 at paragraph 130.

Moreover, 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 O'Neill 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 130.

'781 Patent, Claim 3, Fourth Limitation	O'Neill in view of De Luca and Olson
d) testing the nucleic acid for an amount of a human nucleic acid.	**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 that "[e]xfoliated 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." *Id.* at page 1, lines 15-24. Further, O'Neill discloses that "[t]he 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." *Id.* at page 16, lines 7-19. **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 testing DNA and RNA from cellular components of the fecal sample. It is well known in the art that these tests include testing the nucleic acid for an amount of a human nucleic acid. Ex. 1014 at paragraphs 137-138.

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 O'Neill 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.*

In summary, O'Neill 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 O'Neill in view of De Luca and Olson.

D. Dependent Claim 4

1. Lapidus '178 Anticipates Claim 4

'781 Patent, Claim 4	Lapidus '178
4. The method of claim 3, wherein testing the nucleic acid comprises determining expression from a human gene.	**Lapidus '178** describes "methods of the invention comprise detection of characteristics of such transformed cells, including, for example, mutations, proteins expressed uniquely or in altered amounts in transformed cells, and blood." Ex. 1002 at column 2, lines 59-63. Further, Lapidus '178 describes "DNA or RNA may be isolated from the homogenate using methods known

	in the art. Subsequent tests may be performed on the isolated DNA and RNA." *Id.* at column 9, lines 47-49.

Lapidus '178 describes testing the nucleic acid for determining expression from a human gene. Again, Lapidus '178 describes isolation of nucleic acids (e.g., DNA or RNA) and subsequent evaluation. It is well known in the art that testing of RNA is a definition of measuring expression from a human gene. Ex. 1014 at paragraph 148. Thus, Lapidus '178 describes determination of expression of a human gene via testing of a nucleic acid.

Lapidus '178 therefore describes the additional limitations of claim 4 of the '781 Patent. Because the other limitations of claim 4 are anticipated for the reasons explained above for claims 1 and 3, claim 4 is also anticipated by Lapidus '178.

2. Lapidus '650 Anticipates Claim 4

'781 Patent, Claim 4	Lapidus '650
4. The method of claim 3, wherein testing the nucleic acid comprises determining expression from a human gene.	**Lapidus '650** describes "methods of the invention comprise detection of characteristics of such transformed cells, including, for example, mutations, proteins expressed uniquely or in altered amounts in transformed cells, and blood." Ex. 1003 at column 2, lines 50-54. Further, Lapidus '650 describes "DNA or RNA may be isolated from the homogenate using methods known in the art. Subsequent tests may be performed on the isolated DNA and RNA." *Id.* at column 8, lines 22-25.

Lapidus '650 describes testing the nucleic acid for determining expression from a human gene. Again, Lapidus '650 describes isolation of nucleic acids (e.g., DNA or RNA) and subsequent evaluation. It is well known in the art that testing of RNA is a definition of

measuring expression from a human gene. Ex. 1014 at paragraph 148. Thus, Lapidus '650 describes determination of expression of a human gene via testing of a nucleic acid.

Lapidus '650 therefore describes the additional limitations of claim 4 of the '781 Patent. Because the other limitations of claim 4 are anticipated for the reasons explained above for claims 1 and 3, claim 4 is also anticipated by Lapidus '650.

3. Lapidus '178 Renders Claim 4 Obvious

'781 Patent, Claim 4	Lapidus '178
4. The method of claim 3, wherein testing the nucleic acid comprises determining expression from a human gene.	**Lapidus '178** discloses "methods of the invention comprise detection of characteristics of such transformed cells, including, for example, mutations, proteins expressed uniquely or in altered amounts in transformed cells, and blood." Ex. 1002 at column 2, lines 59-63. Further, Lapidus '178 discloses "DNA or RNA may be isolated from the homogenate using methods known in the art. Subsequent tests may be performed on the isolated DNA and RNA." *Id.* at column 9, lines 47-49.

In the alternative to the assertion that Lapidus '178 anticipates claim 4, Lapidus '178 further renders claim 4 obvious.

Lapidus '178 discloses testing the nucleic acid for determining expression from a human gene. Again, Lapidus '178 discloses isolation of nucleic acids (e.g., DNA or RNA) and subsequent evaluation. It is well known in the art that testing of RNA is a definition of measuring expression from a human gene. Ex. 1014 at paragraph 148. Thus, Lapidus '178 discloses determination of expression of a human gene via testing of a nucleic acid.

Lapidus '178 therefore discloses the additional limitations of claim 4 of the '781 Patent. Because the other limitations of claim 4 are obvious for the reasons explained above for claims 1 and 3, claim 4 is also obvious over Lapidus '178.

4. Lapidus '650 Renders Claim 4 Obvious

'781 Patent, Claim 4	Lapidus '650
4. The method of claim 3, wherein testing the nucleic acid comprises determining expression from a human gene.	**Lapidus '650** discloses "methods of the invention comprise detection of characteristics of such transformed cells, including, for example, mutations, proteins expressed uniquely or in altered amounts in transformed cells, and blood." Ex. 1003 at column 2, lines 50-54. Further, Lapidus '650 describes "DNA or RNA may be isolated from the homogenate using methods known in the art. Subsequent tests may be performed on the isolated DNA and RNA." *Id.* at column 8, lines 22-25.

In the alternative to the assertion that Lapidus '650 anticipates claim 4, Lapidus '650 further renders claim 4 obvious.

Lapidus '650 discloses testing the nucleic acid for determining expression from a human gene. Again, Lapidus '650 discloses isolation of nucleic acids (e.g., DNA or RNA) and subsequent evaluation. It is well known in the art that testing of RNA is a definition of measuring expression from a human gene. Ex. 1014 at paragraph 148. Thus, Lapidus '650 discloses determination of expression of a human gene via testing of a nucleic acid.

Lapidus '650 therefore discloses the additional limitations of claim 4 of the '781 Patent. Because the other limitations of claim 4 are obvious for the reasons explained above for claims 1 and 3, claim 4 is also obvious over Lapidus '650.

5. Lapidus '178 in view of De Luca and Olson Renders Claim 4 Obvious

'781 Patent, Claim 4	Lapidus '178 in view of De Luca and Olson
4. The method of claim 3, wherein testing the nucleic acid comprises determining expression from a human gene.	**Lapidus '178** discloses "methods of the invention comprise detection of characteristics of such transformed cells, including, for example, mutations, proteins expressed uniquely or in altered amounts in transformed cells, and blood." Ex. 1002 at column 2, lines 59-63. Further, Lapidus '178 discloses "DNA or RNA may be isolated from the homogenate using methods known in the art. Subsequent tests may be performed on the isolated DNA and RNA." *Id.* at column 9, lines 47-49. **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 '178 in view of De Luca and Olson disclose the limitations of claim 3. As discussed *supra*, Lapidus '178 discloses isolation of nucleic acids (e.g., DNA or RNA) and subsequent evaluation. It is well known in the art that testing of RNA is a definition of measuring expression from a human gene. Ex. 1014 at paragraph 148. Similarly, Olson also discloses testing the nucleic acid for human DNA. It is well known in the art that these tests include testing the nucleic acid comprises determining expression from a human gene. *Id.*

Lapidus '178 in view of De Luca and Olson therefore discloses the additional limitations of claim 4 of the '781 Patent. Because the other limitations of claim 4 are obvious for the reasons explained above for claim 3, claim 4 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 4 Obvious

'781 Patent, Claim 4	Lapidus '650 in view of De Luca and Olson
4. The method of claim 3, wherein testing the nucleic acid comprises determining expression from a human gene.	**Lapidus '650** discloses "methods of the invention comprise detection of characteristics of such transformed cells, including, for example, mutations, proteins expressed uniquely or in altered amounts in transformed cells, and blood." Ex. 1003 at column 2, lines 50-54. Further, Lapidus '650 describes "DNA or RNA may be isolated from the homogenate using methods known in the art. Subsequent tests may be performed on the isolated DNA and RNA." *Id.* at column 8, lines 22-25. **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 the limitations of claim 3. As discussed *supra*, Lapidus '650 discloses isolation of nucleic acids (e.g., DNA or RNA) and subsequent evaluation. It is well known in the art that testing of RNA is a definition of measuring expression from a human gene. Ex. 1014 at paragraph 148. Similarly, Olson also discloses testing the nucleic acid for human DNA. It is well known in the art that these tests include testing the nucleic acid comprises determining expression from a human gene. *Id.*

Lapidus '650 in view of De Luca and Olson therefore discloses the additional limitations of claim 4 of the '781 Patent. Because the other limitations of claim 4 are obvious for the reasons explained above for claim 3, claim 4 is also obvious over Lapidus '650 in view of De Luca and Olson.

7. Ahlquist in view of De Luca and Olson Renders Claim 4 Obvious

'781 Patent, Claim 4	Ahlquist in view of De Luca and Olson
4. The method of claim 3, wherein testing the nucleic acid comprises determining expression from a human gene.	**Ahlquist** discloses that "[a]ll assays were polymerase chain reaction–based and were run at EXACT Sciences. Stool DNA test 1 was performed as described in Imperiale and colleagues' study (21). The marker panel for SDT-1 included 21 tumor-specific point mutations (3 on the Kras gene, 10 on the APC gene, and 8 on the p53 gene); the microsatellite-instability marker BAT-26; and long DNA, a marker for delayed apoptosis, which is characteristic of exfoliated neoplastic colonocytes (12). For SDT-2, sequence-specific DNA markers were detected by acrylamide gel electrophoresis, as described by Whitney and colleagues (24); the panel consisted of 3 tumor-specific markers broadly informative for both colorectal cancer and adenomas (25): K-ras mutations, scanning of APC mutator cluster regions, and methylation of the vimentin gene. We used methods described elsewhere to detect mutant Kras (12), APC scanning (25), and vimentin gene methylation (20) assays. We defined any positive component marker result according to the manufacturer's preestablished criteria as a positive test result. Ex. 1004, pages 4-5, at 'DNA testing' heading. Further, Ahlquist discloses "we examined SDT-2 (which targets

	a potentially more informative marker panel) in a more limited manner. Stool DNA test 2 had significantly better neoplasm detection rates than did the fecal blood tests or SDT-1. We accounted for the higher detection rates of SDT-2 by better detection of advanced adenomas, a finding of particular importance for cancer prevention." *Id.* at page 9, first full paragraph.

As discussed *supra*, Ahlquist in view of De Luca and Olson disclose the limitations of claim 3. Further, Ahlquist discloses testing the nucleic acid comprises determining expression from a human gene. In particular, Ahlquist discloses testing of nucleic acid via two stool DNA tests (i.e., SDT-1 and SDT-2) that identify human genes such as the Kras gene, the APC gene, and the p53 gene. Determining expression of these cancer-causing genes is evident given the identification of neoplasms in the patients and correlation to the human genes. Ex. 1014 at paragraphs 151 and 153.

Ahlquist in view of De Luca and Olson therefore discloses the additional limitations of claim 4 of the '781 Patent. Because the other limitations of claim 4 are obvious for the reasons explained above for claim 3, claim 4 is also obvious over Ahlquist in view of De Luca and Olson.

8. O'Neill in view of De Luca and Olson Renders Claim 4 Obvious

'781 Patent, Claim 4	O'Neill in view of De Luca and Olson
4. The method of claim 3, wherein testing the nucleic acid comprises determining expression from a human gene.	**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 that "[e]xfoliated 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." *Id.* at page 1, lines 15-24. **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 in view of De Luca and Olson disclose the limitations of claim 3. As discussed *supra*, O'Neill discloses testing DNA and RNA from cellular components of the fecal sample including "procedures for qualitative and/or quantitative analysis of, for example, DNA alterations, gene expression and enzyme activity." Similarly, Olson also discloses testing the nucleic acid for human DNA. It is well known in the art that these tests include testing the nucleic acid comprises determining expression from a human gene. Ex. 1014 at paragraphs 152-153.

O'Neill in view of De Luca and Olson therefore discloses the additional limitations of claim 4 of the '781 Patent. Because the other limitations of claim 4 are obvious for the reasons explained above for claim 3, claim 4 is also obvious over O'Neill in view of De Luca and Olson.

E. Dependent Claim 5

1. Lapidus '178 in view of De Luca, Olson, and Leung Renders Claim 5 Obvious

'781 Patent, Claim 5	Lapidus '178 in view of De Luca, Olson, and Leung
5. The method of claim 4, wherein determining expression from the human gene comprises testing the nucleic acid for the	**Leung** discloses "detecting aberrantly methylated DNA … in feces of patients with

presence of human DNA having an epigenetic modification.	colorectal cancer or polyps." Ex. 1008 at p. 1070, Abstract (Background).

As discussed *supra*, Lapidus '178 in view of De Luca and Olson disclose the limitations of claim 4.

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." '781 patent at column 12, lines 35-39. Furthermore, the '781 patent states that "[i]n specific embodiments, the epigenetic modification is methylation." *Id.* at column 12, line 46-47.

As discussed *supra,* Lapidus '178 and Olson discloses testing DNA and/or RNA from portions of a fecal sample. However, Lapidus '178/De Luca/Olson does not specifically disclose testing the nucleic acid for the presence of human DNA having an epigenetic modification.

Leung also discloses evaluation of human DNA from feces, including the detection of methylated DNA for utilization in colorectal cancer evaluations of the patients. Thus, Leung teaches that before the time of filing, it was routine in the art to detect an epigenetic modification (methylation) of DNA in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect an epigenetic modification of DNA in feces as disclosed in claim 5. Ex. 1014 at paragraphs 164-165. A skilled person would have a reasonable expectation of success to detect an epigenetic modification of DNA because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 5. Because the other limitations of claim 5 are obvious for the reasons explained above for claim 4, claim 5 is also obvious over Lapidus '178 in view of De Luca, Olson, and Leung.

2. Lapidus '650 in view of De Luca, Olson, and Leung Renders Claim 5 Obvious

'781 Patent, Claim 5	Lapidus '650 in view of De Luca, Olson, and Leung
5. The method of claim 4, wherein determining expression from the human gene comprises testing the nucleic acid for the presence of human DNA having an epigenetic modification.	**Leung** discloses "detecting aberrantly methylated DNA … in feces of patients with colorectal cancer or polyps." Ex. 1008 at p. 1070, Abstract (Background).

As discussed *supra*, Lapidus '650 in view of De Luca and Olson disclose the limitations of claim 4.

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." '781 patent at column 12, lines 35-39. Furthermore, the '781 patent states that "[i]n specific embodiments, the epigenetic modification is methylation." *Id.* at column 12, line 46-47.

As discussed *supra,* Lapidus '650 and Olson discloses testing DNA and/or RNA from portions of a fecal sample. However, Lapidus '650/De Luca/Olson does not specifically disclose testing the nucleic acid for the presence of human DNA having an epigenetic modification.

Leung also discloses evaluation of human DNA from feces, including the detection of methylated DNA for utilization in colorectal cancer evaluations of the patients. Thus, Leung teaches that before the time of filing, it was routine in the art to detect an epigenetic modification (methylation) of DNA in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect an epigenetic modification of DNA in feces as disclosed in claim 5. Ex. 1014 at paragraphs 164-165. A skilled person would have a reasonable expectation of success to detect an epigenetic modification of DNA because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 5. Because the other limitations of claim 5 are obvious for the reasons explained above for claim 4, claim 5 is also obvious over Lapidus '650 in view of De Luca, Olson, and Leung.

3. Ahlquist in view of De Luca and Olson Renders Claim 5 Obvious

'781 Patent, Claim 5	Ahlquist in view of De Luca and Olson
5. The method of claim 4, wherein determining expression from the human gene comprises testing the nucleic acid for the presence of human DNA having an epigenetic modification.	**Ahlquist** discloses for evaluation of the second stool DNA test (SDT-1), "sequence-specific DNA markers were detected by acrylamide gel electrophoresis, as described by Whitney and colleagues (24); the panel consisted of 3 tumor-specific markers broadly informative for both colorectal cancer and adenomas (25): K-ras mutations, scanning of APC mutator cluster regions, and methylation of the vimentin gene. We used methods described elsewhere to detect mutant Kras (12), APC scanning (25), and vimentin gene methylation (20) assays." Ex. 1004, page 4 at 'DNA Testing' heading.

As discussed *supra*, Ahlquist in view of De Luca and Olson disclose the limitations of claim 4.

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." '781 patent at column 12, lines 35-39. Furthermore, the '781 patent states that "[i]n specific embodiments, the epigenetic modification is methylation." *Id.* at column 12, line 46-47.

Ahlquist teaches determining expression from a human gene, wherein the nucleic acid is tested for the presence of human DNA having an epigenetic modification. In particular, Ahlquist discloses that assays for "methylation of the vimentin gene" were undertaken. A person of ordinary skill in the art would recognize that the vimentin gene is a human gene and that

Geneoscopy Exhibit 1021, Page 203

evaluation of its methylation would meet the definition of testing for an epigenetic modification as defined by the '781 patent. Ex. 1014 at paragraphs 163 and 165.

Ahlquist in view of De Luca and Olson therefore discloses the additional limitations of claim 5 of the '781 Patent. Because the other limitations of claim 5 are obvious for the reasons explained above for claim 4, claim 5 is also obvious over Ahlquist in view of De Luca and Olson.

4. O'Neill in view of De Luca, Olson, and Leung Renders Claim 5 Obvious

'781 Patent, Claim 5	**O'Neill in view of De Luca, Olson, and Leung**
5. The method of claim 4, wherein determining expression from the human gene comprises testing the nucleic acid for the presence of human DNA having an epigenetic modification.	**Leung** discloses "detecting aberrantly methylated DNA … in feces of patients with colorectal cancer or polyps." Ex. 1008 at p. 1070, Abstract (Background).

As discussed *supra*, O'Neill in view of De Luca and Olson disclose the limitations of claim 4.

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." '781 patent at column 12, lines 35-39. Furthermore, the '781 patent states that "[i]n specific embodiments, the epigenetic modification is methylation." *Id.* at column 12, line 46-47.

As discussed *supra,* O'Neill and Olson discloses testing DNA and/or RNA from portions of a fecal sample. However, O'Neill/De Luca/Olson does not specifically disclose testing the nucleic acid for the presence of human DNA having an epigenetic modification.

Leung also discloses evaluation of human DNA from feces, including the detection of methylated DNA for utilization in colorectal cancer evaluations of the patients. Thus, Leung teaches that before the time of filing, it was routine in the art to detect an epigenetic modification (methylation) of DNA in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect an epigenetic modification of DNA in feces as

disclosed in claim 5. Ex. 1014 at paragraphs 164-165. A skilled person would have a reasonable expectation of success to detect an epigenetic modification of DNA because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 5. Because the other limitations of claim 5 are obvious for the reasons explained above for claim 4, claim 5 is also obvious over O'Neill in view of De Luca, Olson, and Leung.

F. Dependent Claim 6

1. Lapidus '178 in view of De Luca, Olson, and Leung Renders Claim 6 Obvious

'781 Patent, Claim 6	Lapidus '178 in view of De Luca, Olson, and Leung
6. The method of claim 5, wherein testing the nucleic acid for the presence of human DNA having an epigenetic modification comprises measuring an amount of a methylated human DNA.	**Leung** discloses "detecting aberrantly methylated DNA … in feces of patients with colorectal cancer or polyps." Ex. 1008 at p. 1070, Abstract (Background).

As discussed *supra*, Lapidus '178 in view of De Luca, Olson, and Leung disclose the limitations of claim 5. Leung also discloses evaluation of human DNA from feces, including the detection of methylated DNA for utilization in colorectal cancer evaluations of the patients. Thus, Leung teaches that before the time of filing, it was routine in the art to measure an amount of a methylated human DNA in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to measure an amount of a methylated human DNA in feces as disclosed in claim 6. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to measure an amount of a methylated human DNA because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 6. Because the other limitations of claim 6 are obvious for the reasons explained above for claim 5, claim 6 is also obvious over Lapidus '178 in view of De Luca, Olson, and Leung.

Geneoscopy Exhibit 1021, Page 205

2. Lapidus '650 in view of De Luca, Olson, and Leung Renders Claim 6 Obvious

'781 Patent, Claim 6	Lapidus '650 in view of De Luca, Olson, and Leung
6. The method of claim 5, wherein testing the nucleic acid for the presence of human DNA having an epigenetic modification comprises measuring an amount of a methylated human DNA.	**Leung** discloses "detecting aberrantly methylated DNA … in feces of patients with colorectal cancer or polyps." Ex. 1008 at p. 1070, Abstract (Background).

As discussed *supra*, Lapidus '650 in view of De Luca, Olson, and Leung disclose the limitations of claim 5. Leung also discloses evaluation of human DNA from feces, including the detection of methylated DNA for utilization in colorectal cancer evaluations of the patients. Thus, Leung teaches that before the time of filing, it was routine in the art to measure an amount of a methylated human DNA in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to measure an amount of a methylated human DNA in feces as disclosed in claim 6. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to measure an amount of a methylated human DNA because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 6. Because the other limitations of claim 6 are obvious for the reasons explained above for claim 5, claim 6 is also obvious over Lapidus '650 in view of De Luca, Olson, and Leung.

3. Ahlquist in view of De Luca and Olson Renders Claim 6 Obvious

'781 Patent, Claim 6	Ahlquist in view of De Luca and Olson
6. The method of claim 5, wherein testing the nucleic acid for the presence of human DNA having an epigenetic modification comprises	**Ahlquist** discloses for evaluation of the second stool DNA test (SDT-1), "sequence-specific DNA markers were detected by acrylamide gel electrophoresis, as described

measuring an amount of a methylated human DNA.	by Whitney and colleagues (24); the panel consisted of 3 tumor-specific markers broadly informative for both colorectal cancer and adenomas (25): K-ras mutations, scanning of APC mutator cluster regions, and methylation of the vimentin gene. We used methods described elsewhere to detect mutant Kras (12), APC scanning (25), and vimentin gene methylation (20) assays." Ex. 1004, page 4 at 'DNA Testing' heading.

As discussed *supra*, Ahlquist in view of De Luca and Olson disclose the limitations of claim 5. Further, Ahlquist teaches determining expression from a human gene, wherein the nucleic acid is tested for the presence of human DNA having an epigenetic modification by measuring an amount of a methylated human DNA. In particular, Ahlquist discloses that assays for "methylation of the vimentin gene" were undertaken. A person skilled in the art would recognize that the vimentin gene is a human gene and that such assays would evaluate the amount of its methylation. Ex. 1014 at paragraph 172.

Ahlquist in view of De Luca and Olson therefore discloses the additional limitations of claim 6 of the '781 Patent. Because the other limitations of claim 6 are obvious for the reasons explained above for claim 5, claim 6 is also obvious over Ahlquist in view of De Luca and Olson.

4. O'Neill in view of De Luca, Olson, and Leung Renders Claim 6 Obvious

'781 Patent, Claim 6	**O'Neill in view of De Luca, Olson, and Leung**
6. The method of claim 5, wherein testing the nucleic acid for the presence of human DNA having an epigenetic modification comprises measuring an amount of a methylated human DNA.	**Leung** discloses "detecting aberrantly methylated DNA … in feces of patients with colorectal cancer or polyps." Ex. 1008 at p. 1070, Abstract (Background).

As discussed *supra*, O'Neill in view of De Luca, Olson, and Leung disclose the limitations of claim 5. Leung also discloses evaluation of human DNA from feces, including the detection of methylated DNA for utilization in colorectal cancer evaluations of the patients. Thus, Leung teaches that before the time of filing, it was routine in the art to measure an amount of a methylated human DNA in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to measure an amount of a methylated human DNA in feces as disclosed in claim 6. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to measure an amount of a methylated human DNA because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 6. Because the other limitations of claim 6 are obvious for the reasons explained above for claim 5, claim 6 is also obvious over O'Neill in view of De Luca, Olson, and Leung.

G. Dependent Claim 7

1. Lapidus '178 in view of De Luca, Olson, and Leung Renders Claim 7 Obvious

'781 Patent, Claim 7	Lapidus '178 in view of De Luca, Olson, and Leung
7. The method of claim 5, wherein the epigenetic modification comprises aberrant methylation.	**Leung** discloses "detecting aberrantly methylated DNA … in feces of patients with colorectal cancer or polyps." Ex. 1008 at p. 1070, Abstract (Background).

As discussed *supra*, Lapidus '178 in view of De Luca, Olson, and Leung disclose the limitations of claim 6. Leung also discloses evaluation of human DNA from feces, including the detection of aberrantly methylated DNA for utilization in colorectal cancer evaluations of the patients. Thus, Leung teaches that before the time of filing, it was routine in the art to detect aberrantly methylated DNA in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect aberrantly methylated DNA in feces as disclosed in claim 7. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a

reasonable expectation of success to detect aberrantly methylated DNA because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 7. Because the other limitations of claim 7 are obvious for the reasons explained above for claim 5, claim 7 is also obvious over Lapidus '178 in view of De Luca, Olson, and Leung.

2. Lapidus '650 in view of De Luca, Olson, and Leung Renders Claim 7 Obvious

'781 Patent, Claim 7	Lapidus '650 in view of De Luca, Olson, and Leung
7. The method of claim 5, wherein the epigenetic modification comprises aberrant methylation.	**Leung** discloses "detecting aberrantly methylated DNA … in feces of patients with colorectal cancer or polyps." Ex. 1008 at p. 1070, Abstract (Background).

As discussed *supra*, Lapidus '650 in view of De Luca, Olson, and Leung disclose the limitations of claim 6. Leung also discloses evaluation of human DNA from feces, including the detection of aberrantly methylated DNA for utilization in colorectal cancer evaluations of the patients. Thus, Leung teaches that before the time of filing, it was routine in the art to detect aberrantly methylated DNA in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect aberrantly methylated DNA in feces as disclosed in claim 7. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to detect aberrantly methylated DNA because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 7. Because the other limitations of claim 7 are obvious for the reasons explained above for claim 5, claim 7 is also obvious over Lapidus '650 in view of De Luca, Olson, and Leung.

3. Ahlquist in view of De Luca, Olson, and Leung Renders Claim 7 Obvious

'781 Patent, Claim 7	Ahlquist in view of De Luca, Olson, and Leung
7. The method of claim 5, wherein the epigenetic modification comprises aberrant methylation.	**Leung** discloses "detecting aberrantly methylated DNA … in feces of patients with colorectal cancer or polyps." Ex. 1008 at p. 1070, Abstract (Background).

As discussed *supra*, Ahlquist in view of De Luca and Olson disclose the limitations of claim 6. As discussed *supra,* Ahlquist discloses determining expression from a human gene, wherein the nucleic acid is tested for the presence of human DNA having an epigenetic modification. However, Ahlquist/De Luca/Olson does not specifically disclose testing for aberrant methylation.

Leung also discloses evaluation of human DNA from feces, including the detection of aberrantly methylated DNA for utilization in colorectal cancer evaluations of the patients. Thus, Leung teaches that before the time of filing, it was routine in the art to detect aberrantly methylated DNA in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect aberrantly methylated DNA in feces as disclosed in claim 7. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to detect aberrantly methylated DNA because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 7. Because the other limitations of claim 7 are obvious for the reasons explained above for claim 5, claim 7 is also obvious over Ahlquist in view of De Luca, Olson, and Leung.

4. O'Neill in view of De Luca, Olson, and Leung Renders Claim 7 Obvious

'781 Patent, Claim 7	O'Neill in view of De Luca, Olson, and Leung
7. The method of claim 5, wherein the epigenetic modification comprises aberrant methylation.	**Leung** discloses "detecting aberrantly methylated DNA … in feces of patients with colorectal cancer or polyps." Ex. 1008 at p. 1070, Abstract (Background).

As discussed *supra*, O'Neill in view of De Luca, Olson, and Leung disclose the limitations of claim 6. Leung also discloses evaluation of human DNA from feces, including the detection of aberrantly methylated DNA for utilization in colorectal cancer evaluations of the patients. Thus, Leung teaches that before the time of filing, it was routine in the art to detect aberrantly methylated DNA in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect aberrantly methylated DNA in feces as disclosed in claim 7. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to detect aberrantly methylated DNA because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 7. Because the other limitations of claim 7 are obvious for the reasons explained above for claim 5, claim 7 is also obvious over O'Neill in view of De Luca, Olson, and Leung.

H. Dependent Claim 8

1. Lapidus '178 in view of De Luca, Olson, and Leung Renders Claim 8 Obvious

'781 Patent, Claim 8	Lapidus '178 in view of De Luca, Olson, and Leung
8. The method of claim 7, wherein the aberrant methylation comprises hypermethylation.	**Leung** discloses that "[f]ecal samples were collected prior to colonoscopy from 20 patients with colorectal cancer, 30 patients

	with colorectal polyps, and 30 subjects with normal colonic examination. Presence of hypermethylated DNA in 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1) in stool was analyzed by methylation-specific PCR. Ex. 1008 at p. 1070, Abstract (Methods).

As discussed *supra*, Lapidus '178 in view of De Luca, Olson, and Leung disclose the limitations of claim 7. Further, Leung also discloses evaluation of human DNA from feces, including the detection of hypermethylation of DNA for utilization in colorectal cancer evaluations of the patients. Thus, Leung teaches that before the time of filing, it was routine in the art to detect hypermethylation of DNA in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect hypermethylation of DNA in feces as disclosed in claim 8. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to detect hypermethylation of DNA because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 8. Because the other limitations of claim 8 are obvious for the reasons explained above for claim 7, claim 8 is also obvious over Lapidus '178 in view of De Luca, Olson, and Leung.

2. Lapidus '650 in view of De Luca, Olson, and Leung Renders Claim 8 Obvious

'781 Patent, Claim 8	**Lapidus '650 in view of De Luca, Olson, and Leung**
8. The method of claim 7, wherein the aberrant methylation comprises hypermethylation.	**Leung** discloses that "[f]ecal samples were collected prior to colonoscopy from 20 patients with colorectal cancer, 30 patients with colorectal polyps, and 30 subjects with normal colonic examination. Presence of

	hypermethylated DNA in 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1) in stool was analyzed by methylation-specific PCR. Ex. 1008 at p. 1070, Abstract (Methods).

As discussed *supra*, Lapidus '650 in view of De Luca, Olson, and Leung disclose the limitations of claim 7. Further, Leung also discloses evaluation of human DNA from feces, including the detection of hypermethylation of DNA for utilization in colorectal cancer evaluations of the patients. Thus, Leung teaches that before the time of filing, it was routine in the art to detect hypermethylation of DNA in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect hypermethylation of DNA in feces as disclosed in claim 8. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to detect hypermethylation of DNA because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 8. Because the other limitations of claim 8 are obvious for the reasons explained above for claim 7, claim 8 is also obvious over Lapidus '650 in view of De Luca, Olson, and Leung.

3. Ahlquist in view of De Luca, Olson, and Leung Renders Claim 8 Obvious

'781 Patent, Claim 8	**Ahlquist in view of De Luca, Olson, and Leung**
8. The method of claim 7, wherein the aberrant methylation comprises hypermethylation.	**Leung** discloses that "[f]ecal samples were collected prior to colonoscopy from 20 patients with colorectal cancer, 30 patients with colorectal polyps, and 30 subjects with normal colonic examination. Presence of hypermethylated DNA in 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF,

	MGMT, and GSTP1) in stool was analyzed by methylation-specific PCR. Ex. 1008 at p. 1070, Abstract (Methods).

As discussed *supra*, Ahlquist in view of De Luca, Olson, and Leung disclose the limitations of claim 7. Further, Leung also discloses evaluation of human DNA from feces, including the detection of hypermethylation of DNA for utilization in colorectal cancer evaluations of the patients. Thus, Leung teaches that before the time of filing, it was routine in the art to detect hypermethylation of DNA in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect hypermethylation of DNA in feces as disclosed in claim 8. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to detect hypermethylation of DNA because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 8. Because the other limitations of claim 8 are obvious for the reasons explained above for claim 7, claim 8 is also obvious over Ahlquist in view of De Luca, Olson, and Leung.

4. O'Neill in view of De Luca, Olson, and Leung Renders Claim 8 Obvious

'781 Patent, Claim 8	**O'Neill in view of De Luca, Olson, and Leung**
8. The method of claim 7, wherein the aberrant methylation comprises hypermethylation.	**Leung** discloses that "[f]ecal samples were collected prior to colonoscopy from 20 patients with colorectal cancer, 30 patients with colorectal polyps, and 30 subjects with normal colonic examination. Presence of hypermethylated DNA in 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1) in stool was analyzed by methylation-specific PCR. Ex. 1008 at p. 1070, Abstract (Methods).

As discussed *supra*, O'Neill in view of De Luca, Olson, and Leung disclose the limitations of claim 7. Further, Leung also discloses evaluation of human DNA from feces, including the detection of hypermethylation of DNA for utilization in colorectal cancer evaluations of the patients. Thus, Leung teaches that before the time of filing, it was routine in the art to detect hypermethylation of DNA in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect hypermethylation of DNA in feces as disclosed in claim 8. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to detect hypermethylation of DNA because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 8. Because the other limitations of claim 8 are obvious for the reasons explained above for claim 7, claim 8 is also obvious over O'Neill in view of De Luca, Olson, and Leung.

I. Dependent Claim 9

1. Lapidus '178 in view of De Luca, Olson, and Leung Renders Claim 9 Obvious

'781 Patent, Claim 9	Lapidus '178 in view of De Luca, Olson, and Leung
9. The method of claim 5, wherein the human DNA having an epigenetic modification comprises a gene and/or a promoter region of a gene.	**Leung** discloses that "[f]ecal samples were collected prior to colonoscopy from 20 patients with colorectal cancer, 30 patients with colorectal polyps, and 30 subjects with normal colonic examination. Presence of hypermethylated DNA in 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1) in stool was analyzed by methylation-specific PCR. Ex. 1008 at p. 1070, Abstract (Methods).

As discussed *supra*, Lapidus '178 in view of De Luca, Olson, and Leung disclose the limitations of claim 5.

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." '781 patent at column 12, lines 35-39. Furthermore, the '781 patent states that "[i]n specific embodiments, the epigenetic modification is methylation." *Id.* at column 12, line 46-47.

As discussed *supra,* Lapidus '178 and Olson discloses testing DNA and/or RNA from portions of a fecal sample. However, Lapidus '178/De Luca/Olson does not specifically disclose a human DNA having an epigenetic modification that comprises a gene and/or a promoter region of a gene.

Leung also discloses evaluation of human DNA from feces, including the detection of methylated DNA for utilization in colorectal cancer evaluations of the patients. For instance, Leung teaches analysis in stool by methylation-specific PCR for the presence of hypermethylated DNA in 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1). Thus, Leung teaches that before the time of filing, it was routine in the art to detect human DNA having an epigenetic modification that comprises a gene and/or a promoter region of a gene in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect human DNA having an epigenetic modification that comprises a gene and/or a promoter region of a gene as disclosed in claim 5. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to detect human DNA having an epigenetic modification that comprises a gene and/or a promoter region of a gene because Leung teaches that this evaluation is routine in the art. *Id.*

Lapidus '178 in view of De Luca, Olson, and Leung therefore discloses the additional limitations of claim 9 of the '781 Patent. Because the other limitations of claim 9 are obvious for the reasons explained above for claim 5, claim 9 is also obvious over Lapidus '178 in view of De Luca, Olson, and Leung.

2. Lapidus '650 in view of De Luca, Olson, and Leung Renders Claim 9 Obvious

'781 Patent, Claim 9	Lapidus '650 in view of De Luca, Olson, and Leung
9. The method of claim 5, wherein the human DNA having an epigenetic modification comprises a gene and/or a promoter region of a gene.	**Leung** discloses that "[f]ecal samples were collected prior to colonoscopy from 20 patients with colorectal cancer, 30 patients with colorectal polyps, and 30 subjects with normal colonic examination. Presence of hypermethylated DNA in 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1) in stool was analyzed by methylation-specific PCR. Ex. 1008 at p. 1070, Abstract (Methods).

As discussed *supra*, Lapidus '650 in view of De Luca, Olson, and Leung disclose the limitations of claim 5.

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." '781 patent at column 12, lines 35-39. Furthermore, the '781 patent states that "[i]n specific embodiments, the epigenetic modification is methylation." *Id.* at column 12, line 46-47.

As discussed *supra,* Lapidus '650 and Olson discloses testing DNA and/or RNA from portions of a fecal sample. However, Lapidus '650/De Luca/Olson does not specifically disclose a human DNA having an epigenetic modification that comprises a gene and/or a promoter region of a gene.

Leung also discloses evaluation of human DNA from feces, including the detection of methylated DNA for utilization in colorectal cancer evaluations of the patients. For instance, Leung teaches analysis in stool by methylation-specific PCR for the presence of hypermethylated DNA in 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1).

Thus, Leung teaches that before the time of filing, it was routine in the art to detect human DNA having an epigenetic modification that comprises a gene and/or a promoter region of a gene in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect human DNA having an epigenetic modification that comprises a gene and/or a promoter region of a gene as disclosed in claim 5. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to detect human DNA having an epigenetic modification that comprises a gene and/or a promoter region of a gene because Leung teaches that this evaluation is routine in the art. *Id.*

Lapidus '650 in view of De Luca, Olson, and Leung therefore discloses the additional limitations of claim 9 of the '781 Patent. Because the other limitations of claim 9 are obvious for the reasons explained above for claim 5, claim 9 is also obvious over Lapidus '650 in view of De Luca, Olson, and Leung.

3. Ahlquist in view of De Luca and Olson Renders Claim 9 Obvious

'781 Patent, Claim 9	Ahlquist in view of De Luca and Olson
9. The method of claim 5, wherein the human DNA having an epigenetic modification comprises a gene and/or a promoter region of a gene.	**Ahlquist** discloses for evaluation of the second stool DNA test (SDT-1), "sequence-specific DNA markers were detected by acrylamide gel electrophoresis, as described by Whitney and colleagues (24); the panel consisted of 3 tumor-specific markers broadly informative for both colorectal cancer and adenomas (25): K-ras mutations, scanning of APC mutator cluster regions, and methylation of the vimentin gene. We used methods described elsewhere to detect mutant Kras (12), APC scanning (25), and vimentin gene methylation (20) assays." Ex. 1004, page 4 at 'DNA Testing' heading.

As discussed *supra*, Ahlquist in view of De Luca and Olson disclose the limitations of claim 5.

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." '781 patent at column 12, lines 35-39. Furthermore, the '781 patent states that "[i]n specific embodiments, the epigenetic modification is methylation." *Id.* at column 12, line 46-47.

Ahlquist teaches determining expression from a human gene, wherein the nucleic acid is tested for the presence of human DNA having an epigenetic modification. In particular, Ahlquist discloses that assays for "methylation of the vimentin gene" were undertaken. A person skilled in the art would recognize that the vimentin gene is a human gene and that evaluation of its methylation would meet the definition of testing for an epigenetic modification comprises a gene. Ex. 1014 at paragraph 172.

Ahlquist in view of De Luca and Olson therefore discloses the additional limitations of claim 9 of the '781 Patent. Because the other limitations of claim 9 are obvious for the reasons explained above for claim 5, claim 9 is also obvious over Ahlquist in view of De Luca and Olson.

4. O'Neill in view of De Luca, Olson, and Leung Renders Claim 9 Obvious

'781 Patent, Claim 9	**O'Neill in view of De Luca, Olson, and Leung**
9. The method of claim 5, wherein the human DNA having an epigenetic modification comprises a gene and/or a promoter region of a gene.	**Leung** discloses that "[f]ecal samples were collected prior to colonoscopy from 20 patients with colorectal cancer, 30 patients with colorectal polyps, and 30 subjects with normal colonic examination. Presence of hypermethylated DNA in 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1) in stool was analyzed by methylation-specific PCR. Ex. 1008 at p. 1070, Abstract (Methods).

As discussed *supra*, O'Neill in view of De Luca, Olson, and Leung disclose the limitations of claim 5.

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." '781 patent at column 12, lines 35-39. Furthermore, the '781 patent states that "[i]n specific embodiments, the epigenetic modification is methylation." *Id.* at column 12, line 46-47.

As discussed *supra,* O'Neill and Olson discloses testing DNA and/or RNA from portions of a fecal sample. However, O'Neill/De Luca/Olson does not specifically disclose a human DNA having an epigenetic modification that comprises a gene and/or a promoter region of a gene.

Leung also discloses evaluation of human DNA from feces, including the detection of methylated DNA for utilization in colorectal cancer evaluations of the patients. For instance, Leung teaches analysis in stool by methylation-specific PCR for the presence of hypermethylated DNA in 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1). Thus, Leung teaches that before the time of filing, it was routine in the art to detect human DNA having an epigenetic modification that comprises a gene and/or a promoter region of a gene in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect human DNA having an epigenetic modification that comprises a gene and/or a promoter region of a gene as disclosed in claim 5. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to detect human DNA having an epigenetic modification that comprises a gene and/or a promoter region of a gene because Leung teaches that this evaluation is routine in the art. *Id.*

O'Neill in view of De Luca, Olson, and Leung therefore discloses the additional limitations of claim 9 of the '781 Patent. Because the other limitations of claim 9 are obvious for the reasons explained above for claim 5, claim 9 is also obvious over O'Neill in view of De Luca, Olson, and Leung.

J. Dependent Claim 10

1. Lapidus '178 in view of De Luca, Olson, and Leung Renders Claim 10 Obvious

'781 Patent, Claim 10	Lapidus '178 in view of De Luca, Olson, and Leung
10. The method of claim 9, wherein the gene is selected from the group consisting of PHACTR3, NDRG4, FOXE1, GATA4, GPNMB, TFP12, SOX17, SYNE1, LAMA, MMP2, OSMR, SFRP2, and CDO1.	**Leung** discloses that "[f]ecal samples were collected prior to colonoscopy from 20 patients with colorectal cancer, 30 patients with colorectal polyps, and 30 subjects with normal colonic examination. Presence of hypermethylated DNA in 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1) in stool was analyzed by methylation-specific PCR. Ex. 1008 at page 1070, Abstract (Methods).

As discussed *supra*, Lapidus '178 in view of De Luca, Olson, and Leung disclose the limitations of claim 9. Leung also discloses evaluation of human DNA from feces, including the detection of an epigenetic modification (hypermethylated DNA) in at least 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1). A person of ordinary skill in the art would understand that 'sFRP2' as taught by Leung and 'SFRP2' as stated in claim 10 are the same gene. Thus, Leung teaches that before the time of filing, it was routine in the art to detect epigenetic modification of the SFRP2 gene in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect epigenetic modification of the SFRP2 gene in feces as disclosed in claim 10. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to detect epigenetic modification of the SFRP2 gene because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 10. Because the other limitations of claim 10 are obvious for the reasons explained above for claim 9, claim 10 is also obvious over Lapidus '178 in view of De Luca, Olson, and Leung.

Geneoscopy Exhibit 1021, Page 221

2. Lapidus '650 in view of De Luca, Olson, and Leung Renders Claim 10 Obvious

'781 Patent, Claim 10	Lapidus '650 in view of De Luca, Olson, and Leung
10. The method of claim 9, wherein the gene is selected from the group consisting of PHACTR3, NDRG4, FOXE1, GATA4, GPNMB, TFP12, SOX17, SYNE1, LAMA, MMP2, OSMR, SFRP2, and CDO1.	**Leung** discloses that "[f]ecal samples were collected prior to colonoscopy from 20 patients with colorectal cancer, 30 patients with colorectal polyps, and 30 subjects with normal colonic examination. Presence of hypermethylated DNA in 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1) in stool was analyzed by methylation-specific PCR. Ex. 1008 at page 1070, Abstract (Methods).

As discussed *supra*, Lapidus '650 in view of De Luca, Olson, and Leung disclose the limitations of claim 9. Leung also discloses evaluation of human DNA from feces, including the detection of an epigenetic modification (hypermethylated DNA) in at least 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1). A person of ordinary skill in the art would understand that 'sFRP2' as taught by Leung and 'SFRP2' as stated in claim 10 are the same gene. Thus, Leung teaches that before the time of filing, it was routine in the art to detect epigenetic modification of the SFRP2 gene in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect epigenetic modification of the SFRP2 gene in feces as disclosed in claim 10. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to detect epigenetic modification of the SFRP2 gene because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 10. Because the other limitations of claim 10 are obvious for the reasons explained above for claim 9, claim 10 is also obvious over Lapidus '650 in view of De Luca, Olson, and Leung.

3. Ahlquist in view of De Luca, Olson, and Leung Renders Claim 10 Obvious

'781 Patent, Claim 10	Ahlquist in view of De Luca, Olson, and Leung
10. The method of claim 9, wherein the gene is selected from the group consisting of PHACTR3, NDRG4, FOXE1, GATA4, GPNMB, TFP12, SOX17, SYNE1, LAMA, MMP2, OSMR, SFRP2, and CDO1.	**Leung** discloses that "[f]ecal samples were collected prior to colonoscopy from 20 patients with colorectal cancer, 30 patients with colorectal polyps, and 30 subjects with normal colonic examination. Presence of hypermethylated DNA in 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1) in stool was analyzed by methylation-specific PCR. Ex. 1008 at page 1070, Abstract (Methods).

As discussed *supra*, Ahlquist in view of De Luca and Olson disclose the limitations of claim 9. As discussed *supra,* Ahlquist discloses determining expression from the human gene by testing for the presence of human DNA having an epigenetic modification. However, Ahlquist/De Luca/Olson does not specifically disclose testing for a gene listed in claim 10.

Leung also discloses evaluation of human DNA from feces, including the detection of an epigenetic modification (hypermethylated DNA) in at least 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1). A person of ordinary skill in the art would understand that 'sFRP2' as taught by Leung and 'SFRP2' as stated in claim 10 are the same gene. Thus, Leung teaches that before the time of filing, it was routine in the art to detect epigenetic modification of the SFRP2 gene in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect epigenetic modification of the SFRP2 gene in feces as disclosed in claim 10. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to detect epigenetic modification of the SFRP2 gene because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 10. Because the other limitations of claim 10 are obvious for the reasons explained above for claim 9, claim 10 is also obvious over Ahlquist in view of De Luca, Olson, and Leung.

4. O'Neill in view of De Luca, Olson, and Leung Renders Claim 10 Obvious

'781 Patent, Claim 10	O'Neill in view of De Luca, Olson, and Leung
10. The method of claim 9, wherein the gene is selected from the group consisting of PHACTR3, NDRG4, FOXE1, GATA4, GPNMB, TFP12, SOX17, SYNE1, LAMA, MMP2, OSMR, SFRP2, and CDO1.	**Leung** discloses that "[f]ecal samples were collected prior to colonoscopy from 20 patients with colorectal cancer, 30 patients with colorectal polyps, and 30 subjects with normal colonic examination. Presence of hypermethylated DNA in 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1) in stool was analyzed by methylation-specific PCR. Ex. 1008 at page 1070, Abstract (Methods).

As discussed *supra*, O'Neill in view of De Luca, Olson, and Leung disclose the limitations of claim 9. Leung also discloses evaluation of human DNA from feces, including the detection of an epigenetic modification (hypermethylated DNA) in at least 7 tumor-related genes (APC, ATM, hMLH1, sFRP2, HLTF, MGMT, and GSTP1). A person of ordinary skill in the art would understand that 'sFRP2' as taught by Leung and 'SFRP2' as stated in claim 10 are the same gene. Thus, Leung teaches that before the time of filing, it was routine in the art to detect epigenetic modification of the SFRP2 gene in feces. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to detect epigenetic modification of the SFRP2 gene in feces as disclosed in claim 10. Ex. 1014 at paragraphs 171 and 173. A skilled person would have a reasonable expectation of success to detect epigenetic modification of the SFRP2 gene because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 10. Because the other limitations of claim 10 are obvious for the reasons explained above for claim 9, claim 10 is also obvious over O'Neill in view of De Luca, Olson, and Leung.

K. Dependent Claim 11

1. Lapidus '178 in view of De Luca, Olson, and Leung Renders Claim 11 Obvious

'781 Patent, Claim 11	Lapidus '178 in view of De Luca, Olson, and Leung
11. The method of claim 5, wherein testing the nucleic acid for the presence of human DNA having an epigenetic modification comprises modifying the nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil.	**Leung** discloses that "[t]he presence of methylated DNA in stool was detected by methylation-specific PCR (MSP). Briefly, 2 μg of DNA was chemically modified to convert all unmethylated cytosine to uracil by the EZ DNA methylation kit (Zymo Research, Orange, CA). Ex. 1008 at page 1071, second column, first full paragraph.

As discussed *supra*, Lapidus '178 in view of De Luca, Olson, and Leung disclose the limitations of claim 5. Leung also discloses evaluation of human DNA from feces. Further, Leung teaches that methylated DNA in stool was detected by methylation-specific PCR that utilized the EZ DNA methylation kit from Zymo Research in which "2 μg of DNA was chemically modified to convert all unmethylated cytosine to uracil."

It is well known in the art that the EZ DNA methylation kit from Zymo Research utilizes bisulfate ions for modifying the nucleic acid with under conditions wherein unmethylated cytosine is converted to uracil. Ex. 1014 at paragraphs 171 and 173. Thus, Leung teaches that before the time of filing, it was routine in the art to modify nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil in order to test for epigenetic modifications. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to modify nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil in order to test for epigenetic modifications as

disclosed in claim 11. *Id.* A skilled person would have a reasonable expectation of success to modify nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil in order to test for epigenetic modifications because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 11. Because the other limitations of claim 11 are obvious for the reasons explained above for claim 5, claim 11 is also obvious over Lapidus '178 in view of De Luca, Olson, and Leung.

2. Lapidus '650 in view of De Luca, Olson, and Leung Renders Claim 11 Obvious

'781 Patent, Claim 11	Lapidus '650 in view of De Luca, Olson, and Leung
11. The method of claim 5, wherein testing the nucleic acid for the presence of human DNA having an epigenetic modification comprises modifying the nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil.	**Leung** discloses that "[t]he presence of methylated DNA in stool was detected by methylation-specific PCR (MSP). Briefly, 2 μg of DNA was chemically modified to convert all unmethylated cytosine to uracil by the EZ DNA methylation kit (Zymo Research, Orange, CA). Ex. 1008 at page 1071, second column, first full paragraph.

As discussed *supra*, Lapidus '650 in view of De Luca, Olson, and Leung disclose the limitations of claim 5. Leung also discloses evaluation of human DNA from feces. Further, Leung teaches that methylated DNA in stool was detected by methylation-specific PCR that utilized the EZ DNA methylation kit from Zymo Research in which "2 μg of DNA was chemically modified to convert all unmethylated cytosine to uracil."

It is well known in the art that the EZ DNA methylation kit from Zymo Research utilizes bisulfate ions for modifying the nucleic acid with under conditions wherein unmethylated cytosine is converted to uracil. Ex. 1014 at paragraphs 171 and 173. Thus, Leung teaches that before the time of filing, it was routine in the art to modify nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil in order to test for epigenetic

modifications. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to modify nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil in order to test for epigenetic modifications as disclosed in claim 11. *Id.* A skilled person would have a reasonable expectation of success to modify nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil in order to test for epigenetic modifications because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 11. Because the other limitations of claim 11 are obvious for the reasons explained above for claim 5, claim 11 is also obvious over Lapidus '650 in view of De Luca, Olson, and Leung.

3. Ahlquist in view of De Luca, Olson, and Leung Renders Claim 11 Obvious

'781 Patent, Claim 11	Ahlquist in view of De Luca, Olson, and Leung
11. The method of claim 5, wherein testing the nucleic acid for the presence of human DNA having an epigenetic modification comprises modifying the nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil.	**Leung** discloses that "[t]he presence of methylated DNA in stool was detected by methylation-specific PCR (MSP). Briefly, 2 μg of DNA was chemically modified to convert all unmethylated cytosine to uracil by the EZ DNA methylation kit (Zymo Research, Orange, CA). Ex. 1008 at page 1071, second column, first full paragraph.

As discussed *supra*, Ahlquist in view of De Luca and Olson disclose the limitations of claim 5. As discussed *supra,* Ahlquist discloses determining expression from the human gene by testing for the presence of human DNA having an epigenetic modification. However, Ahlquist/De Luca/Olson does not specifically disclose modifying the nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil.

Leung also discloses evaluation of human DNA from feces. Further, Leung teaches that methylated DNA in stool was detected by methylation-specific PCR that utilized the EZ DNA

methylation kit from Zymo Research in which "2 µg of DNA was chemically modified to convert all unmethylated cytosine to uracil."

It is well known in the art that the EZ DNA methylation kit from Zymo Research utilizes bisulfate ions for modifying the nucleic acid with under conditions wherein unmethylated cytosine is converted to uracil. Ex. 1014 at paragraphs 171 and 173. Thus, Leung teaches that before the time of filing, it was routine in the art to modify nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil in order to test for epigenetic modifications. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to modify nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil in order to test for epigenetic modifications as disclosed in claim 11. *Id.* A skilled person would have a reasonable expectation of success to modify nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil in order to test for epigenetic modifications because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 11. Because the other limitations of claim 11 are obvious for the reasons explained above for claim 5, claim 11 is also obvious over Ahlquist in view of De Luca, Olson, and Leung.

4. O'Neill in view of De Luca, Olson, and Leung Renders Claim 11 Obvious

'781 Patent, Claim 11	O'Neill in view of De Luca, Olson, and Leung
11. The method of claim 5, wherein testing the nucleic acid for the presence of human DNA having an epigenetic modification comprises modifying the nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil.	**Leung** discloses that "[t]he presence of methylated DNA in stool was detected by methylation-specific PCR (MSP). Briefly, 2 µg of DNA was chemically modified to convert all unmethylated cytosine to uracil by the EZ DNA methylation kit (Zymo Research, Orange, CA). Ex. 1008 at page 1071, second column, first full paragraph.

As discussed *supra*, O'Neill in view of De Luca, Olson, and Leung disclose the limitations of claim 5. Leung also discloses evaluation of human DNA from feces. Further, Leung teaches that methylated DNA in stool was detected by methylation-specific PCR that utilized the EZ DNA methylation kit from Zymo Research in which "2 μg of DNA was chemically modified to convert all unmethylated cytosine to uracil."

It is well known in the art that the EZ DNA methylation kit from Zymo Research utilizes bisulfate ions for modifying the nucleic acid with under conditions wherein unmethylated cytosine is converted to uracil. Ex. 1014 at paragraphs 171 and 173. Thus, Leung teaches that before the time of filing, it was routine in the art to modify nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil in order to test for epigenetic modifications. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to modify nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil in order to test for epigenetic modifications as disclosed in claim 11. *Id.* A skilled person would have a reasonable expectation of success to modify nucleic acid with bisulfate ions under conditions wherein unmethylated cytosine is converted to uracil in order to test for epigenetic modifications because Leung teaches that this evaluation is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 11. Because the other limitations of claim 11 are obvious for the reasons explained above for claim 5, claim 11 is also obvious over O'Neill in view of De Luca, Olson, and Leung.

L. Dependent Claim 12

1. Lapidus '178 Anticipates Claim 12

'781 Patent, Claim 12	Lapidus '178
12. The method of claim 4, wherein determining expression from the human gene comprises measuring an amount of RNA expressed from the gene.	**Lapidus '178** describes "DNA or RNA may be isolated from the homogenate using methods known in the art. Subsequent tests may be performed on the isolated DNA and RNA." Ex. 1002 at column 9, lines 47-49. Furthermore, Lapidus '178 describes that "[n]on-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 58 – column 7, line 2.

Lapidus '178 describes determining expression from the human gene comprises measuring an amount of RNA expressed from the gene. In particular, Lapidus '178 describes that RNA can be isolated according to methods known in the art and that testing may be performed on the isolated RNA. One of ordinary skill in the art would understand that RNA expression from a particular gene, especially one utilized for the possible detection of colon cancer, could be an assay included in such evaluations.

As discussed *supra,* Lapidus '178 expressly incorporates by reference dozens of assays on nucleic acids, including those described in U.S. Pat. Nos. 5,137,806, 5,348,855, 5,512,441, 5,272,057, 5,380,645, 5,527,676, 5,330,892, 5,352,775, and 5,532,108. For instance, U.S. Patent No. 5,527,676 (Ex. 1013; incorporated by reference into Lapidus '178 at column 6, lines 63-64) provides a teaching that relatively little expression of p53 mRNA was observed compared to other tumors. This low level of expression of p53 was specific in that c-myc, histone H3, and phosphoglycerate kinase mRNAs were expressed in these four tumors at levels similar to those seen in other colorectal tumors and at least as high as in non-neoplastic colonic mucosa. A

person of ordinary skill in the art understands that such assay involves determining expression from a human gene by measuring an amount of RNA expressed from the gene extraction of nucleic acid in order to perform the assay. Ex. 1014 at paragraph 179. Thus, Lapidus '178 describes assays for determining expression from human gene comprising measuring an amount of RNA expressed from the gene.

Lapidus '178 therefore describes the additional limitations of claim 12 of the '781 Patent. Because the other limitations of claim 12 are anticipated for the reasons explained above for claims 1, 3, and 4, claim 12 is also anticipated by Lapidus '178.

2. Lapidus '650 Anticipates Claim 12

'781 Patent, Claim 12	Lapidus '650
12. The method of claim 4, wherein determining expression from the human gene comprises measuring an amount of RNA expressed from the gene.	**Lapidus '650** describes "DNA or RNA may be isolated from the homogenate using methods known in the art. Subsequent tests may be performed on the isolated DNA and RNA." Ex. 1003 at column 8, lines 22-25. Furthermore, Lapidus '650 describes that "[n]on-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 15-28.

Lapidus '650 describes determining expression from the human gene comprises measuring an amount of RNA expressed from the gene. In particular, Lapidus '650 describes that RNA can be isolated according to methods known in the art and that testing may be performed on the isolated RNA. One of ordinary skill in the art would understand that RNA expression from a particular gene, especially one utilized for the possible detection of colon cancer, could be an assay included in such evaluations.

As discussed *supra,* Lapidus '650 expressly incorporates by reference dozens of assays on nucleic acids, including those described in U.S. Pat. Nos. 5,137,806, 5,348,855, 5,512,441, 5,272,057, 5,380,645, 5,527,676, 5,330,892, 5,352,775, and 5,532,108. For instance, U.S. Patent No. 5,527,676 (Ex. 1013; incorporated by reference into Lapidus '650 at column 6, lines 15-26) provides a teaching that relatively little expression of p53 mRNA was observed compared to other tumors. This low level of expression of p53 was specific in that c-myc, histone H3, and phosphoglycerate kinase mRNAs were expressed in these four tumors at levels similar to those seen in other colorectal tumors and at least as high as in non-neoplastic colonic mucosa. A person of ordinary skill in the art understands that such assay involves determining expression from a human gene by measuring an amount of RNA expressed from the gene extraction of nucleic acid in order to perform the assay. Ex. 1014 at paragraph 179. Thus, Lapidus '650 describes assays for determining expression from human gene comprising measuring an amount of RNA expressed from the gene.

Lapidus '650 therefore describes the additional limitations of claim 12 of the '781 Patent. Because the other limitations of claim 12 are anticipated for the reasons explained above for claims 1, 3, and 4, claim 12 is also anticipated by Lapidus '650.

3. Lapidus '178 Renders Claim 12 Obvious

'781 Patent, Claim 12	Lapidus '178
12. The method of claim 4, wherein determining expression from the human gene comprises measuring an amount of RNA expressed from the gene.	**Lapidus '178** discloses "DNA or RNA may be isolated from the homogenate using methods known in the art. Subsequent tests may be performed on the isolated DNA and RNA." Ex. 1002 at column 9, lines 47-49. Furthermore, Lapidus '178 discloses that "[n]on-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 58 – column 7, line 2.

In the alternative to the assertion that Lapidus '178 anticipates claim 12, Lapidus '178 further renders claim 12 obvious.

Lapidus '178 discloses determining expression from the human gene comprises measuring an amount of RNA expressed from the gene. In particular, Lapidus '178 discloses that RNA can be isolated according to methods known in the art and that testing may be

performed on the isolated RNA. One of ordinary skill in the art would understand that RNA expression from a particular gene, especially one utilized for the possible detection of colon cancer, could be an assay included in such evaluations. Ex. 1014 at paragraphs 179-180.

As discussed *supra,* Lapidus '178 expressly incorporates by reference dozens of assays on nucleic acids, including those described in U.S. Pat. Nos. 5,137,806, 5,348,855, 5,512,441, 5,272,057, 5,380,645, 5,527,676, 5,330,892, 5,352,775, and 5,532,108. For instance, U.S. Patent No. 5,527,676 (Ex. 1013; incorporated by reference into Lapidus '178 at column 6, lines 63-64) provides a teaching that relatively little expression of p53 mRNA was observed compared to other tumors. This low level of expression of p53 was specific in that c-myc, histone H3, and phosphoglycerate kinase mRNAs were expressed in these four tumors at levels similar to those seen in other colorectal tumors and at least as high as in non-neoplastic colonic mucosa. A person of ordinary skill in the art understands that such assay involves determining expression from a human gene by measuring an amount of RNA expressed from the gene extraction of nucleic acid in order to perform the assay. Ex. 1014 at paragraph 179. Thus, Lapidus '178 discloses assays for determining expression from human gene comprising measuring an amount of RNA expressed from the gene.

Lapidus '178 therefore describes the additional limitations of claim 12 of the '781 Patent. Because the other limitations of claim 12 are obvious for the reasons explained above for claims 1, 3, and 4, claim 12 is obvious over Lapidus '178.

4. Lapidus '650 Renders Claim 12 Obvious

'781 Patent, Claim 12	Lapidus '650
12. The method of claim 4, wherein determining expression from the human gene comprises measuring an amount of RNA expressed from the gene.	**Lapidus '650** describes "DNA or RNA may be isolated from the homogenate using methods known in the art. Subsequent tests may be performed on the isolated DNA and RNA." Ex. 1003 at column 8, lines 22-25. Furthermore, Lapidus '650 describes that "[n]on-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 15-28.

In the alternative to the assertion that Lapidus '650 anticipates claim 12, Lapidus '650 further renders claim 12 obvious.

Lapidus '650 discloses determining expression from the human gene comprises measuring an amount of RNA expressed from the gene. In particular, Lapidus '650 discloses that RNA can be isolated according to methods known in the art and that testing may be performed on the isolated RNA. One of ordinary skill in the art would understand that RNA expression from a particular gene, especially one utilized for the possible detection of colon cancer, could be an assay included in such evaluations. Ex. 1014 at paragraphs 179-180.

As discussed *supra,* Lapidus '650 expressly incorporates by reference dozens of assays on nucleic acids, including those described in U.S. Pat. Nos. 5,137,806, 5,348,855, 5,512,441, 5,272,057, 5,380,645, 5,527,676, 5,330,892, 5,352,775, and 5,532,108. For instance, U.S. Patent No. 5,527,676 (Ex. 1013; incorporated by reference into Lapidus '650 at column 6, lines 15-26) provides a teaching that relatively little expression of p53 mRNA was observed compared to

other tumors. This low level of expression of p53 was specific in that c-myc, histone H3, and phosphoglycerate kinase mRNAs were expressed in these four tumors at levels similar to those seen in other colorectal tumors and at least as high as in non-neoplastic colonic mucosa. A person of ordinary skill in the art understands that such assay involves determining expression from a human gene by measuring an amount of RNA expressed from the gene extraction of nucleic acid in order to perform the assay. Ex. 1014 at paragraph 179. Thus, Lapidus '650 discloses assays for determining expression from human gene comprising measuring an amount of RNA expressed from the gene.

Lapidus '650 therefore describes the additional limitations of claim 12 of the '781 Patent. Because the other limitations of claim 12 are obvious for the reasons explained above for claims 1, 3, and 4, claim 12 is obvious over Lapidus '650.

5. Lapidus '178 in view of De Luca, Olson, and Leung Renders Claim 12 Obvious

'781 Patent, Claim 12	Lapidus '178 in view of De Luca, Olson, and Leung
12. The method of claim 4, wherein determining expression from the human gene comprises measuring an amount of RNA expressed from the gene.	**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." Ex. 1002 at column 9, line 62 – column 10, line 6. **Leung** discloses that "COX-2 expression in stool samples was detected by RT-PCR. Messenger RNA was extracted from stool samples by the QIAamp Viral Mini Spin Kit

	(Qiagen)." Ex. 1008 at page 1071, second column, second full paragraph.

As discussed *supra*, Lapidus '178 in view of De Luca and Olson disclose the limitations of claim 4. As discussed *supra,* Lapidus '178 and Olson discloses testing human DNA and/or RNA from portions of a fecal sample. Lapidus '178 discloses determining expression from the human gene comprises measuring an amount of RNA expressed from the gene. In particular, Lapidus '178 discloses that RNA can be isolated according to methods known in the art and that testing may be performed on the isolated RNA. One of ordinary skill in the art would understand that RNA expression from a particular gene, especially one utilized for the possible detection of colon cancer, could be an assay included in such evaluations. Ex. 1014 at paragraph 179.

Even if Lapidus '178 is determined to not specifically disclose determining expression from the human gene comprises measuring an amount of RNA expressed from the gene, Leung removes this deficiency.

Leung also discloses evaluation of nucleic acid from feces. Further, Leung teaches that mRNA was evaluated from stool to determine expression of cyclooxygenase-2 (COX-2). Thus, Leung teaches that before the time of filing, it was routine in the art to test RNA from stool to determine expression from the COX-2 gene. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to determine expression from the human gene comprises measuring an amount of RNA expressed from the gene as disclosed in claim 12. Ex. 1014 at paragraph 181. A skilled person would have a reasonable expectation of success to determine expression from the human gene comprises measuring an amount of RNA expressed from the gene because Leung teaches that this testing is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 12. Because the other limitations of claim 12 are obvious for the reasons explained above for claim 4, claim 12 is also obvious over Lapidus '178 in view of De Luca, Olson, and Leung.

6. Lapidus '650 in view of De Luca, Olson, and Leung Renders Claim 12 Obvious

'781 Patent, Claim 12	Lapidus '650 in view of De Luca, Olson, and Leung
12. The method of claim 4, wherein determining expression from the human gene comprises measuring an amount of RNA expressed from the gene.	**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. **Leung** discloses that "COX-2 expression in stool samples was detected by RT-PCR. Messenger RNA was extracted from stool samples by the QIAamp Viral Mini Spin Kit (Qiagen)." Ex. 1008 at page 1071, second column, second full paragraph.

As discussed *supra*, Lapidus '650 in view of De Luca and Olson disclose the limitations of claim 4. As discussed *supra,* Lapidus '650 and Olson discloses testing human DNA and/or RNA from portions of a fecal sample. Lapidus '650 discloses determining expression from the human gene comprises measuring an amount of RNA expressed from the gene. In particular, Lapidus '650 discloses that RNA can be isolated according to methods known in the art and that testing may be performed on the isolated RNA. One of ordinary skill in the art would understand that RNA expression from a particular gene, especially one utilized for the possible detection of colon cancer, could be an assay included in such evaluations. Ex. 1014 at paragraph 179.

Even if Lapidus '650 is determined to not specifically disclose determining expression from the human gene comprises measuring an amount of RNA expressed from the gene, Leung removes this deficiency.

Leung also discloses evaluation of nucleic acid from feces. Further, Leung teaches that mRNA was evaluated from stool to determine expression of cyclooxygenase-2 (COX-2). Thus, Leung teaches that before the time of filing, it was routine in the art to test RNA from stool to determine expression from the COX-2 gene. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to determine expression from the human gene comprises measuring an amount of RNA expressed from the gene as disclosed in claim 12. Ex. 1014 at paragraph 181. A skilled person would have a reasonable expectation of success to determine expression from the human gene comprises measuring an amount of RNA expressed from the gene because Leung teaches that this testing is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 12. Because the other limitations of claim 12 are obvious for the reasons explained above for claim 4, claim 12 is also obvious over Lapidus '650 in view of De Luca, Olson, and Leung.

7. Ahlquist in view of De Luca, Olson, and Leung Renders Claim 12 Obvious

'781 Patent, Claim 12	Ahlquist in view of De Luca, Olson, and Leung
12. The method of claim 4, wherein determining expression from the human gene comprises measuring an amount of RNA expressed from the gene.	**Leung** discloses that "COX-2 expression in stool samples was detected by RT-PCR. Messenger RNA was extracted from stool samples by the QIAamp Viral Mini Spin Kit (Qiagen)." Ex. 1008 at page 1071, second column, second full paragraph.

As discussed *supra*, Ahlquist in view of De Luca and Olson disclose the limitations of claim 4. As discussed *supra,* Ahlquist discloses testing the nucleic acid comprises determining expression from a human gene. However, Ahlquist/De Luca/Olson does not specifically disclose determining expression from the human gene comprising measuring an amount of RNA expressed from the gene.

Leung also discloses evaluation of nucleic acid from feces. Further, Leung teaches that mRNA was evaluated from stool to determine expression of cyclooxygenase-2 (COX-2). Thus,

Geneoscopy Exhibit 1021, Page 239

Leung teaches that before the time of filing, it was routine in the art to test RNA from stool to determine expression from the COX-2 gene. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to determine expression from the human gene comprises measuring an amount of RNA expressed from the gene as disclosed in claim 12. Ex. 1014 at paragraph 181. A skilled person would have a reasonable expectation of success to determine expression from the human gene comprises measuring an amount of RNA expressed from the gene because Leung teaches that this testing is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 12. Because the other limitations of claim 12 are obvious for the reasons explained above for claim 4, claim 12 is also obvious over Ahlquist in view of De Luca, Olson, and Leung.

8. O'Neill in view of De Luca, Olson, and Leung Renders Claim 12 Obvious

'781 Patent, Claim 12	O'Neill in view of De Luca, Olson, and Leung
12. The method of claim 4, wherein determining expression from the human gene comprises measuring an amount of RNA expressed from the gene.	**Leung** discloses that "COX-2 expression in stool samples was detected by RT-PCR. Messenger RNA was extracted from stool samples by the QIAamp Viral Mini Spin Kit (Qiagen)." Ex. 1008 at page 1071, second column, second full paragraph.

As discussed *supra*, O'Neill in view of De Luca and Olson disclose the limitations of claim 4. As discussed *supra,* O'Neill and Olson discloses testing human DNA and/or RNA from portions of a fecal sample. However, O'Neill/De Luca/Olson does not specifically disclose determining expression from the human gene comprising measuring an amount of RNA expressed from the gene.

Leung also discloses evaluation of nucleic acid from feces. Further, Leung teaches that mRNA was evaluated from stool to determine expression of cyclooxygenase-2 (COX-2). Thus, Leung teaches that before the time of filing, it was routine in the art to test RNA from stool to determine expression from the COX-2 gene. As such, a person of ordinary skill in the art would

be motivated to utilize the teachings of Leung to determine expression from the human gene comprises measuring an amount of RNA expressed from the gene as disclosed in claim 12. Ex. 1014 at paragraph 181. A skilled person would have a reasonable expectation of success to determine expression from the human gene comprises measuring an amount of RNA expressed from the gene because Leung teaches that this testing is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 12. Because the other limitations of claim 12 are obvious for the reasons explained above for claim 4, claim 12 is also obvious over O'Neill in view of De Luca, Olson, and Leung.

M. Dependent Claim 13

1. Lapidus '178 in view of De Luca, Olson, and Leung Renders Claim 13 Obvious

'781 Patent, Claim 13	Lapidus '178 in view of De Luca, Olson, and Leung
13. The method of claim 12, wherein measuring an amount of RNA expressed from the gene comprises reverse transcriptase polymerase chain reaction (RT-PCR).	**Leung** discloses that "COX-2 expression in stool samples was detected by RT-PCR. Messenger RNA was extracted from stool samples by the QIAamp Viral Mini Spin Kit (Qiagen)." Ex. 1008 at page 1071, second column, second full paragraph.

As discussed *supra*, Lapidus '178 in view of De Luca, Olson, and Leung disclose the limitations of claim 12. Leung discloses evaluation of nucleic acid from feces. Further, Leung teaches that mRNA was evaluated from stool to determine expression of cyclooxygenase-2 (COX-2) via reverse transcriptase polymerase chain reaction (RT-PCR). Thus, Leung teaches that before the time of filing, it was routine in the art to measure an amount of RNA expressed from a gene using RT-PCR. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to measure an amount of RNA expressed from a gene using RT-PCR as disclosed in claim 13. Ex. 1014 at paragraph 191. A skilled person would have a reasonable expectation of success to measure an amount of RNA expressed from a gene using RT-PCR because Leung teaches that this testing is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 13. Because the other limitations of claim 13 are obvious for the reasons explained above for claim 12, claim 13 is also obvious over Lapidus '178 in view of De Luca, Olson, and Leung.

2. Lapidus '650 in view of De Luca, Olson, and Leung Renders Claim 13 Obvious

'781 Patent, Claim 13	Lapidus '650 in view of De Luca, Olson, and Leung
13. The method of claim 12, wherein measuring an amount of RNA expressed from the gene comprises reverse transcriptase polymerase chain reaction (RT-PCR).	**Leung** discloses that "COX-2 expression in stool samples was detected by RT-PCR. Messenger RNA was extracted from stool samples by the QIAamp Viral Mini Spin Kit (Qiagen)." Ex. 1008 at page 1071, second column, second full paragraph.

As discussed *supra*, Lapidus '650 in view of De Luca, Olson, and Leung disclose the limitations of claim 12. Leung discloses evaluation of nucleic acid from feces. Further, Leung teaches that mRNA was evaluated from stool to determine expression of cyclooxygenase-2 (COX-2) via reverse transcriptase polymerase chain reaction (RT-PCR). Thus, Leung teaches that before the time of filing, it was routine in the art to measure an amount of RNA expressed from a gene using RT-PCR. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to measure an amount of RNA expressed from a gene using RT-PCR as disclosed in claim 13. Ex. 1014 at paragraph 191. A skilled person would have a reasonable expectation of success to measure an amount of RNA expressed from a gene using RT-PCR because Leung teaches that this testing is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 13. Because the other limitations of claim 13 are obvious for the reasons explained above for claim 12, claim 13 is also obvious over Lapidus '650 in view of De Luca, Olson, and Leung.

Geneoscopy Exhibit 1021, Page 242

3. Ahlquist in view of De Luca, Olson, and Leung Renders Claim 13 Obvious

'781 Patent, Claim 13	Ahlquist in view of De Luca, Olson, and Leung
13. The method of claim 12, wherein measuring an amount of RNA expressed from the gene comprises reverse transcriptase polymerase chain reaction (RT-PCR).	**Leung** discloses that "COX-2 expression in stool samples was detected by RT-PCR. Messenger RNA was extracted from stool samples by the QIAamp Viral Mini Spin Kit (Qiagen)." Ex. 1008 at page 1071, second column, second full paragraph.

As discussed *supra*, Ahlquist in view of De Luca, Olson, and Leung disclose the limitations of claim 12. Leung discloses evaluation of nucleic acid from feces. Further, Leung teaches that mRNA was evaluated from stool to determine expression of cyclooxygenase-2 (COX-2) via reverse transcriptase polymerase chain reaction (RT-PCR). Thus, Leung teaches that before the time of filing, it was routine in the art to measure an amount of RNA expressed from a gene using RT-PCR. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to measure an amount of RNA expressed from a gene using RT-PCR as disclosed in claim 13. Ex. 1014 at paragraph 191. A skilled person would have a reasonable expectation of success to measure an amount of RNA expressed from a gene using RT-PCR because Leung teaches that this testing is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 13. Because the other limitations of claim 13 are obvious for the reasons explained above for claim 12, claim 13 is also obvious over Ahlquist in view of De Luca, Olson, and Leung.

4. O'Neill in view of De Luca, Olson, and Leung Renders Claim 13 Obvious

'781 Patent, Claim 13	O'Neill in view of De Luca, Olson, and Leung
13. The method of claim 12, wherein measuring an amount of RNA expressed from	**Leung** discloses that "COX-2 expression in stool samples was detected by RT-PCR.

the gene comprises reverse transcriptase polymerase chain reaction (RT-PCR).	Messenger RNA was extracted from stool samples by the QIAamp Viral Mini Spin Kit (Qiagen)." Ex. 1008 at page 1071, second column, second full paragraph.

As discussed *supra*, O'Neill in view of De Luca, Olson, and Leung disclose the limitations of claim 12. Leung discloses evaluation of nucleic acid from feces. Further, Leung teaches that mRNA was evaluated from stool to determine expression of cyclooxygenase-2 (COX-2) via reverse transcriptase polymerase chain reaction (RT-PCR). Thus, Leung teaches that before the time of filing, it was routine in the art to measure an amount of RNA expressed from a gene using RT-PCR. As such, a person of ordinary skill in the art would be motivated to utilize the teachings of Leung to measure an amount of RNA expressed from a gene using RT-PCR as disclosed in claim 13. Ex. 1014 at paragraph 191. A skilled person would have a reasonable expectation of success to measure an amount of RNA expressed from a gene using RT-PCR because Leung teaches that this testing is routine in the art. *Id.*

Leung therefore teaches the additional limitation of claim 13. Because the other limitations of claim 13 are obvious for the reasons explained above for claim 12, claim 13 is also obvious over O'Neill in view of De Luca, Olson, and Leung.

N. Dependent Claim 14

1. Lapidus '178 in view of De Luca and Olson Renders Claim 14 Obvious

'781 Patent, Claim 14	Lapidus '178 in view of De Luca, Olson, and Leung
14. The method of claim 3, wherein testing for an amount of a blood protein in the removed portion comprises testing for a concentration of hemoglobin 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].

As discussed *supra*, 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 197.

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 hemoglobin by utilizing the fecal immunochemical blood tests taught by De Luca. *Id.* at paragraph 201. To this end, De Luca also discloses testing a removed portion of the fecal sample for hemoglobin, 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 201.

Because the other limitations of claim 14 would have been obvious for the reasons explained above for claim 3, claim 14 also would have been obvious to a person of ordinary skill in the art in view of Lapidus '178 in view of De Luca and Olson.

2. Lapidus '650 in view of De Luca and Olson Renders Claim 14 Obvious

'781 Patent, Claim 14	Lapidus '650 in view of De Luca, Olson, and Leung
14. The method of claim 3, wherein testing for an amount of a blood protein in the removed portion comprises testing for a concentration of hemoglobin in the removed portion.	**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". Ex. 1003 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' 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. 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 197.

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 hemoglobin by utilizing the fecal immunochemical blood tests taught by De Luca. *Id.* at paragraph 201. To this end, De Luca also discloses testing a removed portion of the fecal sample for hemoglobin, albeit with the more effective fecal immunochemical blood tests. Therefore, one skilled in the art would recognize that Lapidus '650 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 201.

Because the other limitations of claim 14 would have been obvious for the reasons explained above for claim 3, claim 14 also would have been obvious to a person of ordinary skill in the art in view of Lapidus '650 in view of De Luca and Olson.

3. Ahlquist in view of De Luca and Olson Renders Claim 14 Obvious

'781 Patent, Claim 14	Ahlquist in view of De Luca and Olson
14. The method of claim 3, wherein testing for an amount of a blood protein in the removed portion comprises testing for a concentration of hemoglobin in the removed portion.	**Ahlquist** discloses for occult blood testing that "[t]he manufacturer that developed the Hemoccult and HemoccultSensa cards, without rehydration, trained technicians on-site at the Mayo Clinic. As recommended by the manufacturer, the technicians added the catalyst solution to cards stored at ambient temperature within 48 to 72 hours of collection. We defined a spreading (enlarging) blue color in 60 seconds in any window of the cards as a positive result and any other result as negative." Ex. 1004 at page 5, at heading 'Occult Blood Testing.' Ahlquist discloses that "[d]etection sensitivities for the 290 screen-relevant neoplasms found among all 3764 evaluable participants were 10% (95% CI, 7% to 13%) with Hemoccult and 18% (CI, 13% to 22%) with HemoccultSensa ($P < 0.001$). Based on all 3474 participants without screenrelevant neoplasia, the Hemoccult specificity of 98% (CI, 98% to 99%) was slightly higher than that of HemoccultSensa (97% [CI, 96% to 97%]) ($P < 0.001$). Hemoccult and

	HemoccultSensa positivity rates for the 39 patients with colorectal cancer or high-grade dysplasia were 33% (CI, 19% to 48%) and 44% (CI, 28% to 59%), respectively (P = 0.100). For the 251 patients with adenomas 1 cm or larger, the positivity rates were 6% (CI, 3% to 9%) versus 14% (CI, 9% to 18%) (P = 0.001)." *Id.* at pages 6-y, under heading 'Occult Blood Testing: Hemoccult versus HemoccultSensa.' **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].

As discussed *supra*, Ahlquist in view of De Luca and Olson disclose the limitations of claim 3. Further, Ahlquist discloses testing the removed portion of the fecal sample for a concentration of hemoglobin in the removed portion. As discussed *supra*, Ahlquist discloses that 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. Further, Ahlquist discloses that occult blood testing was performed on the Hemoccult and HemoccultSensa cards. It is well known in the art that occult blood testing refers to analyzing for the presence of blood proteins such as hemoglobin. Ex. 1014 at paragraph 199.

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 and as suggested by Ahlquist instead of the guaiac-based Hemoccult and HemoccultSensa tests of Ahlquist. Ex. 1014 at paragraph 201. To this end, De Luca also discloses testing a removed portion of the fecal sample for hemoglobin, albeit with the more effective fecal immunochemical blood tests.

Because the other limitations of claim 14 would have been obvious for the reasons explained above for claim 3, claim 14 also would have been obvious to a person of ordinary skill in the art in view of Ahlquist in view of De Luca and Olson.

4. O'Neill in view of De Luca and Olson Renders Claim 14 Obvious

'781 Patent, Claim 14	O'Neill in view of De Luca, and Olson
14. The method of claim 3, wherein testing for an amount of a blood protein in the removed portion comprises testing for a concentration of hemoglobin in the removed portion.	**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 that "[e]xfoliated 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." *Id.* at page 1, lines 15-24. **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].

As discussed *supra*, O'Neill in view of De Luca and Olson disclose the limitations of claim 3. O'Neill discloses testing the removed portion of cellular material from the fecal sample for various components, such as DNA, RNA, and proteins. It is well known in the art that testing such components from fecal samples could include analysis of hemoglobin via occult blood testing, fecal immunochemical blood tests, and the like for evaluating colorectal cancer in patients. Ex. 1014 at paragraphs 198 and 200-201.

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 hemoglobin by utilizing the fecal immunochemical blood tests taught by De Luca. Ex. 1014 at paragraph 201. To this end, De Luca also discloses testing a removed portion of the fecal sample for hemoglobin, albeit with the more effective fecal immunochemical blood tests. Therefore, one skilled in the art would recognize that O'Neill 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.*

Because the other limitations of claim 14 would have been obvious for the reasons explained above for claim 3, claim 14 also would have been obvious to a person of ordinary skill in the art in view of O'Neill in view of De Luca and Olson.

O. Dependent Claim 15

1. Lapidus '178 in view of De Luca and Olson Renders Claim 15 Obvious

'781 Patent, Claim 15	Lapidus '178 in view of De Luca and Olson
15. The method of claim 14, wherein testing for the concentration of hemoglobin comprises immunochemical detection of hemoglobin.	**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].

As discussed *supra*, Lapidus '178 in view of De Luca and Olson disclose the limitations of claim 14. Lapidus '178 discloses testing the removed portion of cellular material from the fecal sample for various components, such as DNA, RNA, and proteins. It is well known in the art that testing such components from fecal samples could include analysis of hemoglobin via occult blood testing, fecal immunochemical blood tests, and the like for evaluating colorectal cancer in patients. Ex. 1014 at paragraph 207.

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 hemoglobin by utilizing the fecal immunochemical blood tests taught by De Luca. *Id.* at paragraphs 208 and 211. To this end, De

Luca also discloses testing a removed portion of the fecal sample for hemoglobin, 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.*

Because the other limitations of claim 15 would have been obvious for the reasons explained above for claim 14, claim 15 also would have been obvious to a person of ordinary skill in the art in view of Lapidus '178 in view of De Luca and Olson.

2. Lapidus '650 in view of De Luca and Olson Renders Claim 15 Obvious

'781 Patent, Claim 15	Lapidus '650 in view of De Luca and Olson
15. The method of claim 14, wherein testing for the concentration of hemoglobin comprises immunochemical detection of hemoglobin.	**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].

As discussed *supra*, Lapidus '650 in view of De Luca and Olson disclose the limitations of claim 14. Lapidus '650 discloses testing the removed portion of cellular material from the fecal sample for various components, such as DNA, RNA, and proteins. It is well known in the art that testing such components from fecal samples could include analysis of hemoglobin via occult blood testing, fecal immunochemical blood tests, and the like for evaluating colorectal cancer in patients. Ex. 1014 at paragraph 207.

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 hemoglobin by utilizing the fecal immunochemical blood tests taught by De Luca. *Id.* at paragraphs 208 and 211. To this end, De Luca also discloses testing a removed portion of the fecal sample for hemoglobin, albeit with the more effective fecal immunochemical blood tests. Therefore, one skilled in the art would recognize that Lapidus '650 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.*

Because the other limitations of claim 15 would have been obvious for the reasons explained above for claim 14, claim 15 also would have been obvious to a person of ordinary skill in the art in view of Lapidus '650 in view of De Luca and Olson.

3. Ahlquist in view of De Luca and Olson Renders Claim 15 Obvious

'781 Patent, Claim 15	Ahlquist in view of De Luca and Olson
15. The method of claim 14, wherein testing for the concentration of hemoglobin comprises immunochemical detection of hemoglobin.	**Ahlquist** discloses for occult blood testing that "[t]he manufacturer that developed the Hemoccult and HemoccultSensa cards, without rehydration, trained technicians on-site at the Mayo Clinic. As recommended by the manufacturer, the technicians added the

	catalyst solution to cards stored at ambient temperature within 48 to 72 hours of collection. We defined a spreading (enlarging) blue color in 60 seconds in any window of the cards as a positive result and any other result as negative." Ex. 1004 at page 5, at heading 'Occult Blood Testing.' Ahlquist discloses that "[d]etection sensitivities for the 290 screen-relevant neoplasms found among all 3764 evaluable participants were 10% (95% CI, 7% to 13%) with Hemoccult and 18% (CI, 13% to 22%) with HemoccultSensa ($P < 0.001$). Based on all 3474 participants without screenrelevant neoplasia, the Hemoccult specificity of 98% (CI, 98% to 99%) was slightly higher than that of HemoccultSensa (97% [CI, 96% to 97%]) ($P < 0.001$). Hemoccult and HemoccultSensa positivity rates for the 39 patients with colorectal cancer or high-grade dysplasia were 33% (CI, 19% to 48%) and 44% (CI, 28% to 59%), respectively ($P = 0.100$). For the 251 patients with adenomas 1 cm or larger, the positivity rates were 6% (CI, 3% to 9%) versus 14% (CI, 9% to 18%) ($P = 0.001$)." *Id.* at pages 6-y, under heading 'Occult Blood Testing: Hemoccult versus HemoccultSensa.' **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].

As discussed *supra*, Ahlquist in view of De Luca and Olson disclose the limitations of claim 14. Further, Ahlquist discloses testing the removed portion of the fecal sample for a concentration of hemoglobin in the removed portion. As discussed *supra*, Ahlquist discloses that 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. Further, Ahlquist discloses that occult blood testing was performed on the Hemoccult and HemoccultSensa cards. It is well known in the art that occult blood testing refers to analyzing for the presence of blood proteins such as hemoglobin. Ex. 1014 at paragraph 209.

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 and as suggested by Ahlquist instead of the guaiac-based Hemoccult and HemoccultSensa tests of Ahlquist. *Id.* at paragraphs 208-209 and 211.

Because the other limitations of claim 15 would have been obvious for the reasons explained above for claim 14, claim 15 also would have been obvious to a person of ordinary skill in the art in view of Ahlquist in view of De Luca and Olson.

4. O'Neill in view of De Luca and Olson Renders Claim 15 Obvious

'781 Patent, Claim 15	O'Neill in view of De Luca and Olson
15. The method of claim 14, wherein testing for the concentration of hemoglobin comprises immunochemical detection of hemoglobin.	**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 that "[e]xfoliated 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." *Id.* at page 1, lines 15-24.

	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].

As discussed *supra*, O'Neill in view of De Luca and Olson disclose the limitations of claim 14. O'Neill discloses testing the removed portion of cellular material from the fecal sample for various components, such as DNA, RNA, and proteins. It is well known in the art that testing such components from fecal samples could include analysis of hemoglobin via occult blood testing, fecal immunochemical blood tests, and the like for evaluating colorectal cancer in patients. Ex. 1014 at paragraph 210.

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 hemoglobin by utilizing the fecal immunochemical blood tests taught by De Luca. *Id.* at paragraphs 208 and 211. To this end, De Luca also discloses testing a removed portion of the fecal sample for hemoglobin, albeit with the more effective fecal immunochemical blood tests. Therefore, one skilled in the art would recognize that O'Neill 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 211.

Because the other limitations of claim 15 would have been obvious for the reasons explained above for claim 14, claim 15 also would have been obvious to a person of ordinary skill in the art in view of O'Neill in view of De Luca and Olson.

P. Dependent Claim 16

1. Lapidus '178 in view of De Luca, Olson, and Hoepffner Renders Claim 16 Obvious

'781 Patent, Claim 16	Lapidus '178 in view of De Luca, Olson, and Hoepffner
16. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 5 ng/ml.	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, Lapidus '178 in view of De Luca and Olson disclose the limitations of claim 14. In particular, Lapidus '178 and De Luca teach the evaluation of fecal samples includes testing the removed portion of the fecal sample for the presence of blood by evaluating proteins such as hemoglobin. However, Lapidus '178/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based

tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is greater than or equal to10 ng/ml.

Since Lapidus '178 and De Luca teach evaluation of proteins such as hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result. Ex. 1014 at paragraph 219.

Moreover, a person of ordinary skill in the art would have been motivated to further improve the sensitivity of the hemoglobin detection tests by reducing the amount of identified hemoglobin that indicates a positive test. For instance, based on the teachings of Hoepffner, a skilled artisan would want to reduce the amount of identified hemoglobin that indicates a positive test to as low as possible (e.g., from 10 mg/mL to a value of "at least 5 ng/ml"). Such motivation exists because a skilled artisan would desire to improve disease diagnosis in patients with blood/hemoglobin in their stools. Ex. 1014 at paragraph 219.

Because the other limitations of claim 16 would have been obvious for the reasons explained above for claim 14, claim 16 also would have been obvious to a person of ordinary skill in the art in view of Lapidus '178 in view of De Luca, Olson, and Hoepffner.

2. Lapidus '650 in view of De Luca, Olson, and Hoepffner Renders Claim 16 Obvious

'781 Patent, Claim 16	Lapidus '650 in view of De Luca, Olson, and Hoepffner
16. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 5 ng/ml.	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, Lapidus '650 in view of De Luca and Olson disclose the limitations of claim 14. In particular, Lapidus '650 and De Luca teach the evaluation of fecal samples includes testing the removed portion of the fecal sample for the presence of blood by evaluating proteins such as hemoglobin. However, Lapidus '650/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is greater than or equal to10 ng/ml.

Since Lapidus '650 and De Luca teach evaluation of proteins such as hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result. Ex. 1014 at paragraph 219.

Moreover, a person of ordinary skill in the art would have been motivated to further improve the sensitivity of the hemoglobin detection tests by reducing the amount of identified hemoglobin that indicates a positive test. For instance, based on the teachings of Hoepffner, a skilled artisan would want to reduce the amount of identified hemoglobin that indicates a positive test to as low as possible (e.g., from 10 mg/mL to a value of "at least 5 ng/ml"). Such motivation exists because a skilled artisan would desire to improve disease diagnosis in patients with blood/hemoglobin in their stools. Ex. 1014 at paragraph 219.

Because the other limitations of claim 16 would have been obvious for the reasons explained above for claim 14, claim 16 also would have been obvious to a person of ordinary skill in the art in view of Lapidus '650 in view of De Luca, Olson, and Hoepffner.

3. Ahlquist in view of De Luca, Olson, and Hoepffner Renders Claim 16 Obvious

'781 Patent, Claim 16	Ahlquist in view of De Luca, Olson, and Hoepffner
16. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 5 ng/ml.	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, Ahlquist in view of De Luca and Olson disclose the limitations of claim 14. In particular, Ahlquist and De Luca teach the evaluation of fecal samples discloses testing the removed portion of the fecal sample for the presence of blood by evaluating hemoglobin. However, Ahlquist/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since Ahlquist and De Luca teach evaluation of hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result. Ex. 1014 at paragraph 219.

Moreover, a person of ordinary skill in the art would have been motivated to further improve the sensitivity of the hemoglobin detection tests by reducing the amount of identified hemoglobin that indicates a positive test. For instance, based on the teachings of Hoepffner, a skilled artisan would want to reduce the amount of identified hemoglobin that indicates a

positive test to as low as possible (e.g., from 10 mg/mL to a value of "at least 5 ng/ml"). Such motivation exists because a skilled artisan would desire to improve disease diagnosis in patients with blood/hemoglobin in their stools. Ex. 1014 at paragraph 219.

Because the other limitations of claim 16 would have been obvious for the reasons explained above for claim 14, claim 16 also would have been obvious to a person of ordinary skill in the art in view of Ahlquist in view of De Luca, Olson, and Hoepffner.

4. O'Neill in view of De Luca, Olson, and Hoepffner Renders Claim 16 Obvious

'781 Patent, Claim 16	O'Neill in view of De Luca, Olson, and Hoepffner
16. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 5 ng/ml.	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, O'Neill in view of De Luca and Olson disclose the limitations of claim 14. In particular, O'Neill and De Luca teach the evaluation of fecal samples includes testing the removed portion of the fecal sample for the presence of blood by evaluating proteins such as hemoglobin. However, O'Neill/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since O'Neill and De Luca teach evaluation of proteins such as hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result. Ex. 1014 at paragraph 219.

Moreover, a person of ordinary skill in the art would have been motivated to further improve the sensitivity of the hemoglobin detection tests by reducing the amount of identified hemoglobin that indicates a positive test. For instance, based on the teachings of Hoepffner, a skilled artisan would want to reduce the amount of identified hemoglobin that indicates a positive test to as low as possible (e.g., from 10 mg/mL to a value of "at least 5 ng/ml"). Such motivation exists because a skilled artisan would desire to improve disease diagnosis in patients with blood/hemoglobin in their stools. Ex. 1014 at paragraph 219.

Because the other limitations of claim 16 would have been obvious for the reasons explained above for claim 14, claim 16 also would have been obvious to a person of ordinary skill in the art in view of O'Neill in view of De Luca, Olson, and Hoepffner.

Q. Dependent Claim 17

1. Lapidus '178 in view of De Luca, Olson, and Hoepffner Renders Claim 17 Obvious

'781 Patent, Claim 17	Lapidus '178 in view of De Luca, Olson, and Hoepffner
17. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 10 ng/ml.	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, Lapidus '178 in view of De Luca and Olson disclose the limitations of claim 14. In particular, Lapidus '178 and De Luca teach the evaluation of fecal samples includes testing the removed portion of the fecal sample for the presence of blood by evaluating

proteins such as hemoglobin. However, Lapidus '178/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since Lapidus '178 and De Luca teach evaluation of proteins such as hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result, wherein the concentration is greater than or equal to 10 ng/ml. Ex. 1014 at paragraph 219.

Because the other limitations of claim 17 would have been obvious for the reasons explained above for claim 14, claim 17 also would have been obvious to a person of ordinary skill in the art in view of Lapidus '178 in view of De Luca, Olson, and Hoepffner.

2. Lapidus '650 in view of De Luca, Olson, and Hoepffner Renders Claim 17 Obvious

'781 Patent, Claim 17	Lapidus '650 in view of De Luca, Olson, and Hoepffner
17. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 10 ng/ml.	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, Lapidus '650 in view of De Luca and Olson disclose the limitations of claim 14. In particular, Lapidus '650 and De Luca teach the evaluation of fecal samples includes testing the removed portion of the fecal sample for the presence of blood by evaluating proteins such as hemoglobin. However, Lapidus '650/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since Lapidus '650 and De Luca teach evaluation of proteins such as hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result, wherein the concentration is greater than or equal to 10 ng/ml. Ex. 1014 at paragraph 219.

Because the other limitations of claim 17 would have been obvious for the reasons explained above for claim 14, claim 17 also would have been obvious to a person of ordinary skill in the art in view of Lapidus '650 in view of De Luca, Olson, and Hoepffner.

3. Ahlquist in view of De Luca, Olson, and Hoepffner Renders Claim 17 Obvious

'781 Patent, Claim 17	Ahlquist in view of De Luca, Olson, and Hoepffner
17. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 10 ng/ml.	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, Ahlquist in view of De Luca and Olson disclose the limitations of claim 14. In particular, Ahlquist and De Luca teach the evaluation of fecal samples discloses testing the removed portion of the fecal sample for the presence of blood by evaluating hemoglobin. However, Ahlquist/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since Ahlquist and De Luca teach evaluation of hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result, wherein the concentration is greater than or equal to 10 ng/ml. Ex. 1014 at paragraph 219.

Because the other limitations of claim 17 would have been obvious for the reasons explained above for claim 14, claim 17 also would have been obvious to a person of ordinary skill in the art in view of Ahlquist in view of De Luca, Olson, and Hoepffner.

4. O'Neill in view of De Luca, Olson, and Hoepffner Renders Claim 17 Obvious

'781 Patent, Claim 17	O'Neill in view of De Luca, Olson, and Hoepffner
17. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 10 ng/ml.	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, O'Neill in view of De Luca and Olson disclose the limitations of claim 14. In particular, O'Neill and De Luca teach the evaluation of fecal samples includes testing the removed portion of the fecal sample for the presence of blood by evaluating proteins such as hemoglobin. However, O'Neill/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since O'Neill and De Luca teach evaluation of proteins such as hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result, wherein the concentration is greater than or equal to 10 ng/ml. Ex. 1014 at paragraph 219.

Because the other limitations of claim 17 would have been obvious for the reasons explained above for claim 14, claim 17 also would have been obvious to a person of ordinary skill in the art in view of O'Neill in view of De Luca, Olson, and Hoepffner.

R. Dependent Claim 18

1. Lapidus '178 in view of De Luca, Olson, and Hoepffner Renders Claim 18 Obvious

'781 Patent, Claim 18	Lapidus '178 in view of De Luca, Olson, and Hoepffner
18. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin	**Hoepffner** discloses that "the sensitivity of [various] 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

detected in the removed portion is at least 20 ng/ml.	***<10 ng/mL***) respectively." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, Lapidus '178 in view of De Luca and Olson disclose the limitations of claim 14. In particular, Lapidus '178 and De Luca teach the evaluation of fecal samples includes testing the removed portion of the fecal sample for the presence of blood by evaluating proteins such as hemoglobin. However, Lapidus '178/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since Lapidus '178 and De Luca teach evaluation of proteins such as hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result, wherein the concentration is greater than or equal to 10 ng/ml. Ex. 1014 at paragraph 219.

2. Lapidus '650 in view of De Luca, Olson, and Hoepffner Renders Claim 18 Obvious

'781 Patent, Claim 18	**Lapidus '650 in view of De Luca, Olson, and Hoepffner**
18. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148,

Geneoscopy Exhibit 1021, Page 274

detected in the removed portion is at least 20 ng/ml.	second column, first full paragraph (emphasis added).

As discussed *supra*, Lapidus '650 in view of De Luca and Olson disclose the limitations of claim 14. In particular, Lapidus '650 and De Luca teach the evaluation of fecal samples includes testing the removed portion of the fecal sample for the presence of blood by evaluating proteins such as hemoglobin. However, Lapidus '650/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since Lapidus '650 and De Luca teach evaluation of proteins such as hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result, wherein the concentration is greater than or equal to 10 ng/ml. Ex. 1014 at paragraph 219.

3. Ahlquist in view of De Luca, Olson, and Hoepffner Renders Claim 18 Obvious

'781 Patent, Claim 18	**Ahlquist in view of De Luca, Olson, and Hoepffner**
18. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 20 ng/ml.	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148,

	second column, first full paragraph (emphasis added).

As discussed *supra*, Ahlquist in view of De Luca and Olson disclose the limitations of claim 14. In particular, Ahlquist and De Luca teach the evaluation of fecal samples discloses testing the removed portion of the fecal sample for the presence of blood by evaluating hemoglobin. However, Ahlquist/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since Ahlquist and De Luca teach evaluation of hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result, wherein the concentration is greater than or equal to 10 ng/ml. Ex. 1014 at paragraph 219.

Because the other limitations of claim 18 would have been obvious for the reasons explained above for claim 14, claim 18 also would have been obvious to a person of ordinary skill in the art in view of Ahlquist in view of De Luca, Olson, and Hoepffner.

4. O'Neill in view of De Luca, Olson, and Hoepffner Renders Claim 18 Obvious

'781 Patent, Claim 18	O'Neill in view of De Luca, Olson, and Hoepffner
18. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148,

detected in the removed portion is at least 20 ng/ml.	second column, first full paragraph (emphasis added).

As discussed *supra*, O'Neill in view of De Luca and Olson disclose the limitations of claim 14. In particular, O'Neill and De Luca teach the evaluation of fecal samples includes testing the removed portion of the fecal sample for the presence of blood by evaluating proteins such as hemoglobin. However, O'Neill/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since O'Neill and De Luca teach evaluation of proteins such as hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result, wherein the concentration is greater than or equal to 10 ng/ml. Ex. 1014 at paragraph 219.

Because the other limitations of claim 18 would have been obvious for the reasons explained above for claim 14, claim 18 also would have been obvious to a person of ordinary skill in the art in view of O'Neill in view of De Luca, Olson, and Hoepffner.

S. Dependent Claim 19

1. Lapidus '178 in view of De Luca, Olson, and Hoepffner Renders Claim 19 Obvious

'781 Patent, Claim 19	Lapidus '178 in view of De Luca, Olson, and Hoepffner
19. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood	**Hoepffner** discloses that "the sensitivity of [various] tests to detect faecal Hb was 37.0%, 74.0% and 77.7% for the Guaiac-based test,

when the concentration of hemoglobin detected in the removed portion is at least 50 ng/ml.	the bedside IFOBT and the ELISA (cut-off ***<10 ng/mL***) respectively." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, Lapidus '178 in view of De Luca and Olson disclose the limitations of claim 14. In particular, Lapidus '178 and De Luca teach the evaluation of fecal samples includes testing the removed portion of the fecal sample for the presence of blood by evaluating proteins such as hemoglobin. However, Lapidus '178/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since Lapidus '178 and De Luca teach evaluation of proteins such as hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result, wherein the concentration is greater than or equal to 10 ng/ml. Ex. 1014 at paragraph 219.

Because the other limitations of claim 19 would have been obvious for the reasons explained above for claim 14, claim 19 also would have been obvious to a person of ordinary skill in the art in view of Lapidus '178 in view of De Luca, Olson, and Hoepffner.

2. Lapidus '650 in view of De Luca, Olson, and Hoepffner Renders Claim 19 Obvious

'781 Patent, Claim 19	Lapidus '650 in view of De Luca, Olson, and Hoepffner
19. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 50 ng/ml.	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, Lapidus '650 in view of De Luca and Olson disclose the limitations of claim 14. In particular, Lapidus '650 and De Luca teach the evaluation of fecal samples includes testing the removed portion of the fecal sample for the presence of blood by evaluating proteins such as hemoglobin. However, Lapidus '650/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since Lapidus '650 and De Luca teach evaluation of proteins such as hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result, wherein the concentration is greater than or equal to 10 ng/ml. Ex. 1014 at paragraph 219.

Because the other limitations of claim 19 would have been obvious for the reasons explained above for claim 14, claim 19 also would have been obvious to a person of ordinary skill in the art in view of Lapidus '650 in view of De Luca, Olson, and Hoepffner.

3. Ahlquist in view of De Luca, Olson, and Hoepffner Renders Claim 19 Obvious

'781 Patent, Claim 19	Ahlquist in view of De Luca, Olson, and Hoepffner
19. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 50 ng/ml.	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, Ahlquist in view of De Luca and Olson disclose the limitations of claim 14. In particular, Ahlquist and De Luca teach the evaluation of fecal samples discloses testing the removed portion of the fecal sample for the presence of blood by evaluating hemoglobin. However, Ahlquist/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since Ahlquist and De Luca teach evaluation of hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result, wherein the concentration is greater than or equal to 10 ng/ml. Ex. 1014 at paragraph 219.

Because the other limitations of claim 19 would have been obvious for the reasons explained above for claim 14, claim 19 also would have been obvious to a person of ordinary skill in the art in view of Ahlquist in view of De Luca, Olson, and Hoepffner.

4. O'Neill in view of De Luca, Olson, and Hoepffner Renders Claim 19 Obvious

'781 Patent, Claim 19	O'Neill in view of De Luca, Olson, and Hoepffner
19. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 50 ng/ml.	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, O'Neill in view of De Luca and Olson disclose the limitations of claim 14. In particular, O'Neill and De Luca teach the evaluation of fecal samples includes testing the removed portion of the fecal sample for the presence of blood by evaluating proteins such as hemoglobin. However, O'Neill/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since O'Neill and De Luca teach evaluation of proteins such as hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result, wherein the concentration is greater than or equal to 10 ng/ml. Ex. 1014 at paragraph 219.

Because the other limitations of claim 19 would have been obvious for the reasons explained above for claim 14, claim 19 also would have been obvious to a person of ordinary skill in the art in view of O'Neill in view of De Luca, Olson, and Hoepffner.

T. Dependent Claim 20

1. Lapidus '178 in view of De Luca, Olson, and Hoepffner Renders Claim 20 Obvious

'781 Patent, Claim 20	Lapidus '178 in view of De Luca, Olson, and Hoepffner
20. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 200 ng/ml.	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, Lapidus '178 in view of De Luca and Olson disclose the limitations of claim 14. In particular, Lapidus '178 and De Luca teach the evaluation of fecal samples includes proteins such as hemoglobin the removed portion of the fecal sample for the presence of blood by evaluating hemoglobin. However, Lapidus '178/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of proteins such as hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since Lapidus '178 and De Luca teach evaluation of hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult

Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result, wherein the concentration is greater than or equal to 10 ng/ml. Ex. 1014 at paragraph 219.

Because the other limitations of claim 20 would have been obvious for the reasons explained above for claim 14, claim 20 also would have been obvious to a person of ordinary skill in the art in view of Lapidus '178 in view of De Luca, Olson, and Hoepffner.

2. Lapidus '650 in view of De Luca, Olson, and Hoepffner Renders Claim 20 Obvious

'781 Patent, Claim 20	Lapidus '650 in view of De Luca, Olson, and Hoepffner
20. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 200 ng/ml.	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, Lapidus '650 in view of De Luca and Olson disclose the limitations of claim 14. In particular, Lapidus '650 and De Luca teach the evaluation of fecal samples includes proteins such as hemoglobin the removed portion of the fecal sample for the presence of blood by evaluating hemoglobin. However, Lapidus '650/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of proteins such as hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since Lapidus '650 and De Luca teach evaluation of hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result, wherein the concentration is greater than or equal to 10 ng/ml. Ex. 1014 at paragraph 219.

Because the other limitations of claim 20 would have been obvious for the reasons explained above for claim 14, claim 20 also would have been obvious to a person of ordinary skill in the art in view of Lapidus '650 in view of De Luca, Olson, and Hoepffner.

3. Ahlquist in view of De Luca, Olson, and Hoepffner Renders Claim 20 Obvious

'781 Patent, Claim 20	Ahlquist in view of De Luca, Olson, and Hoepffner
20. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 200 ng/ml.	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, Ahlquist in view of De Luca and Olson disclose the limitations of claim 14. In particular, Ahlquist and De Luca teach the evaluation of fecal samples discloses testing the removed portion of the fecal sample for the presence of blood by evaluating hemoglobin. However, Ahlquist/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader. Hoepffner discloses

that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since Ahlquist and De Luca teach evaluation of hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result, wherein the concentration is greater than or equal to 10 ng/ml. Ex. 1014 at paragraph 219.

Because the other limitations of claim 20 would have been obvious for the reasons explained above for claim 14, claim 20 also would have been obvious to a person of ordinary skill in the art in view of Ahlquist in view of De Luca, Olson, and Hoepffner.

4. O'Neill in view of De Luca, Olson, and Hoepffner Renders Claim 20 Obvious

'781 Patent, Claim 20	O'Neill in view of De Luca, Olson, and Hoepffner
20. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 200 ng/ml.	**Hoepffner** discloses that "the sensitivity of [various] 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." Ex. 1009, p. 148, second column, first full paragraph (emphasis added).

As discussed *supra*, O'Neill in view of De Luca and Olson disclose the limitations of claim 14. In particular, O'Neill and De Luca teach the evaluation of fecal samples includes proteins such as hemoglobin the removed portion of the fecal sample for the presence of blood by evaluating hemoglobin. However, O'Neill/De Luca do not teach a concentration of hemoglobin that is associated with a positive result.

Hoepffner removes this deficiency. Hoepffner analyzes concentration of proteins such as hemoglobin in fecal samples obtained from human patients via various methodologies such as guaiac-based tests, bedside-based immunochemical faecal occult blood tests (IFOBTs), and laboratory-based IFOBTs that use an enzyme linked immunosorbent assay (ELISA) reader.

Hoepffner discloses that the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at 10 ng/ml.

Since O'Neill and De Luca teach evaluation of hemoglobin to determine a positive blood protein test, a person of ordinary skill in the art would have been motivated to consult Hoepffner to determine a particular concentration of hemoglobin corresponding to a positive result, wherein the concentration is greater than or equal to 10 ng/ml. Ex. 1014 at paragraph 219.

Because the other limitations of claim 20 would have been obvious for the reasons explained above for claim 14, claim 20 also would have been obvious to a person of ordinary skill in the art in view of O'Neill in view of De Luca, Olson, and Hoepffner.

VIII. CONCLUSION

For at least the reasons set forth above it is respectfully submitted that the prior art cited in this Request present substantial new questions of patentability with respect to claims 1-20 of the '781 Patent. Accordingly, it is earnestly requested that the Office declare a reexamination proceeding of claims 1-20 of the '781 Patent and reject them under at least one of the grounds of rejection set forth above.

In the event there are any unresolved issues that may readily be handled by telephone the Examiner or other Office personnel are kindly invited to contact Requester's undersigned attorney by telephone at (317) 231-6410 so that such issues may be resolved as expeditiously as possible.

Respectfully submitted,
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