

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Janelle J. Bruinsma	Confirmation No.: 9571
Serial No.: 14/145,082	Group No.: 1637
Filed: 12/31/2013	Examiner: Aaron Priest
Entitled: ISOLATION OF NUCLEIC ACID	

**AMENDMENT UNDER 37 C.F.R. §1.116 AFTER
FINAL OFFICE ACTION MAILED JULY 6, 2015
AND
REQUEST FOR AFTER-FINAL CONSIDERATION UNDER AFCP 2.0**

VIA EFS WEB

Commissioner for Patents
P.O. Box 1450
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CERTIFICATE OF EFS WEB TRANSMISSION UNDER 37 C.F.R. § 1.8	
I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being transmitted to the United States Patent and Trademark Office transmitted via the Office electronic filing system in accordance with 37 C.F.R. §1.6(a)(4).	
Dated: <u>July 31, 2015</u>	By: <u>/Mary Ann D. Brow/</u> Mary Ann D. Brow, Reg. No. 42,363

This communication is an After Final Amendment under 37 C.F.R. §1.116, responsive to the Final Office Communication mailed July 6, 2015, with a response due on or before October 6, 2015, and is filed with a Request for After-Final Consideration under AFCP 2.0. Applicants respectfully request entry of this amendment.

The Commissioner is hereby authorized to charge any fees during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 that may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-4302, referencing Attorney Docket No.: EXCT-31920/US-3/CON. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

Amendments to the Claims are reflected in the Listing of Claims beginning on page 2.

Remarks begin on page 5.

AMENDMENTS TO THE CLAIMS:

This listing of the claims will replace all prior listings and versions of claims in the application:

1. (currently amended) A system for isolating a target human DNA from a human stool sample, the system comprising:
 - a) a volume of stool homogenization solution suitable for processing a human stool sample having a mass of at least 4 grams;
 - b) an inhibitor-adsorbing composition comprising insoluble polyvinylpyrrolidone particles;
 - c) a spin filter, comprising
 - i) a hollow body;
 - ii) a bottom end; and
 - iii) an open top end opposite the bottom end,

wherein the hollow body of said spin filter is made from a porous filtering material;

 - d) guanidine thiocyanate; and
 - e) ~~a magnetic target-specific capture particle comprising a covalently-attached oligonucleotide that is complementary to at least a portion of a target human DNA selected from the group consisting of *vimentin*, *NDRG4*, *BMP3*, *TFPI2* and *beta-actin*.~~ a plurality of different magnetic target-specific capture particles, wherein different target-specific capture particles comprise covalently-attached oligonucleotides complementary to at least a portion of different target human DNAs, and wherein said different target human DNAs comprise *NDRG4*, *BMP3*, and *KRAS*.
2. (original) The system of claim 1, further comprising a magnet.
- 3-4. (cancelled)

5. (previously presented) The system of claim 1 wherein said polyvinylpolypyrrolidone is in a premeasured form.
6. (previously presented) The system of claim 3 wherein said polyvinylpolypyrrolidone is provided as a capsule or pressed tablet comprising a premeasured amount of polyvinylpolypyrrolidone.
7. (cancelled)
8. (previously presented) The system of claim 1, further comprising an elution solution and/or a wash solution.
- 9-12. (cancelled)
13. (previously presented) The system of claim 1, further comprising a sample container configured to hold said stool sample.
14. (original) The system of claim 1 further comprising a vessel in which to hold isolated target human DNA.
15. (original) The system of claim 1, further comprising a shipping container.
16. (original) The system of claim 1, further comprising a control reagent.
17. (original) The system of claim 16, wherein said control comprises a nucleic acid.
- 18-23. (cancelled)
24. (currently amended) The system of claim 1, wherein said covalently-attached oligonucleotide comprises a sequence selected from the group consisting of SEQ ID NOS: 4-52-3 and 6-7.

25. (previously presented) The system of claim 1, further comprising a magnetic target-specific capture particle comprising an oligonucleotide that is complementary to at least a portion of a human reference DNA.
26. (currently amended) The system of claim 1, ~~comprising a plurality of different magnetic target-specific capture particles, wherein different target-specific capture particles comprise covalently attached oligonucleotides complementary to at least a portion of different target human DNAs, and wherein said different target human DNAs comprise a plurality of target human DNAs selected from the group consisting of~~ further comprises *vimentin, NDRG4, BMP3, TFPI2, or beta-actin, and KRAS.*
27. (previously presented) The system of claim 26, wherein said covalently-attached oligonucleotides comprise sequences selected from the group consisting of SEQ ID NOS:1-7.
28. (currently amended) The system of claim ~~26~~25, wherein said ~~plurality of different target human DNAs comprises~~ *vimentin, NDRG4, BMP3, TFPI2,* human reference DNA is *beta-actin, and KRAS.*
29. (currently amended) The system of claim 28, wherein said covalently-attached oligonucleotides comprise the ~~sequences of SEQ ID NOS:1-7~~sequence of SEQ ID NO:5.

REMARKS

Claims 1-2, 5-6, 8, 13-17 and 24-29 are pending and under examination in the present application. In the Office Action mailed July 6, 2015, the Examiner made the following objections and rejections:

Claims 1-2, 5, 8, 13-14, 16-17 and 24-29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over BAKER (US 2003/0173284, published 9/18/2003), in view of, SHUBER (US 2002/0164631, published 11/7/2002) and FOTEDAR et al. (Laboratory Diagnostic Techniques for Entamoeba Species, Clinical Microbiology Reviews, July 2007, p. 511-532; as evidenced by MORGAN et al. (Comparison of PCR and Microscopy for Detection of Cryptosporidium parvum in Human Fecal Specimens: Clinical Trial, J. Clin Micro, Apr. 1998, p. 995-998), in further view of VAN ENGELAND (WO 2008084219, published 7/17/2008), ZOU, et al. (Highly Methylated Genes in Colorectal Neoplasia: Implications for Screening, Cancer Epidemiol Biomarkers Prev 2007 Dec;16(12):2686-96.), NCBI ACCESSION NOs. X56134 (10/7/2008), AC009118 (3/18/2003), NM_006528 (5/2/2010), NG_007992 (5/7/2010), NM_001201 (3/5/2010) and NM_033360 (4/25/2010).

Claim 6 is rejected under 35 U.S.C. § 103(a) as being unpatentable over BAKER, in view of SHUBER and FOTEDAR (as evidenced by MORGAN), in further view of VAN ENGELAND, ZOU, NCBI ACCESSION NOs. X56134 (10/7/2008), AC009118 (3/18/2003), NM_006528 (5/2/2010), NG_007992 (5nt2010), NM_001201 (3/5/2010) and NM_033360 (4/25/2010), in further view of Qiagen (QIAamp DNA Stool Mini Kit Handbook, 8/2001).

Claim 15 is rejected under 35 U.S.C. § 103(a) as being unpatentable over BAKER, in view of SHUBER and FOTEDAR (as evidenced by MORGAN), in further view of VAN ENGELAND, ZOU, NCBI ACCESSION NOs. X56134 (10/7/2008), AC009118 (3/18/2003), NM_006528 (5/2/2010), NG_007992 (5nt2010), NM_001201 (3/5/2010) and NM_033360 (4/25/2010), in further view of STEPHAN (US 2010/0293130, published 11/18/2010, effective filing date 11/30/2006).

Applicants note with appreciation that the Examiner has suggested amendment to include all of the genes shown in the multi-marker stool test of Example 7. However, for the reasons discussed below, for business reasons and to advance prosecution, and reserving the right to prosecute the original or similar claims in one or more future applications, Applicants herein

amend Claim 1 to recite “. . . a plurality of different magnetic target-specific capture particles, wherein different target-specific capture particles comprise covalently-attached oligonucleotides complementary to at least a portion of different target human DNAs, and wherein said different target human DNAs comprise *NDRG4*, *BMP3*, and *KRAS*”.

The claims are not obvious

The Examiner asserts that all of vimentin, *NDRG4*, *BMP3*, *TFPI2*, and *KRAS* were known colorectal cancer markers, and beta-actin was a familiar control gene at the time of the invention, and that a skilled artisan at the time of the invention would have had an interest in all of the above genes in order to detect colorectal cancer.

Applicants respectfully submit that the cited art does not teach or suggest selection of the particular combination of ‘genes of interest’ recited in the claims as amended, nor the particular combination of reagents used to assemble a sufficiently successful stool DNA assay for the detection of colorectal cancer. In contrast, Applicants have now shown that the particular combination of target human DNAs and system components for capturing them provide an the basis for an assay that has received regulatory approval. Specifically, the system components of instant claim 1 as amended are included in Applicants’ product, the “Cologuard®” colorectal cancer screening test, which is the first stool DNA screening test for colorectal cancer to receive FDA approval. The cited art does not teach or suggest the *particular* combination of *NDRG4*, *BMP3* and *KRAS* target human DNAs, or the collected set of system components to perform the steps to isolate these particular target human DNAs from human stool samples.

Provided herewith are the following documents:

1. FDA Press Release “FDA approves first non-invasive DNA screening test for colorectal cancer.” August 8, 2014; announcing approval of the “Cologuard®” stool DNA test product;
2. A set of instructions for the commercial assay entitled “Cologuard® sDNA-based Colorectal Cancer Screening Test Instructions for Use” (“Instructions”) (a draft version of which is also available for download on the World Wide Web at fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/

MedicalDevicesAdvisoryCommittee/MolecularandClinicalGeneticsPanel/UCM390231.pdf), providing a complete description of the FDA-approved screening test.

As stated in the second paragraph of the “Principles of the Procedure” beginning on page 8, the target human DNAs are NDRG4, BMP3, KRAS, and a reference gene (beta actin, ACTB):

In the processing procedure for DNA testing, the stool sample is mixed with buffer in the Container using the Sample Mixer. An aliquot of the buffered stool sample is centrifuged to pellet solids and generate supernatant. The assay procedure begins with treatment of the supernatant with an Inhibitor Removal Tablet to remove inhibitors that may affect the detection of the DNA biomarkers. Treated supernatant is then combined with denaturing reagents and incubated with target-specific magnetic particles using the Capture Incubator instrument to capture sequences for *NDRG4*, *BMP3*, *KRAS*, and *ACTB* (reference gene).

(Instructions for Use, page 8)

This document further shows that the FDA-approved test comprises the system components recited in the instant claims as amended: stool homogenization buffer, PVPP inhibitor adsorbant, spin filter and guanidine thiocyanate (see Instructions, page 11, items 200204, 200151, 200138, and 200121, respectively), and magnetic target-specific capture particles for capturing NDRG4, BMP3 and KRAS target human DNAs (“Capture Beads”, Instructions, page 9, item 200150).

3. Thomas F. Imperiale, M.D., et al., “Multitarget Stool DNA Testing for Colorectal-Cancer Screening”, New England Journal of Medicine 370(14):1287 (2014).

This document reports on the clinical trial of the Cologuard® test. Page 6 of the Appendix, “Supplemental Figure Legend” for Figure S1 shows that the method used in the study comprised use of system components according to instant claim 1 as amended:

100 ng Hb / ml buffer. The hemoglobin component of the multi-target sDNA test was analyzed by a separate immunochemical assay. The buffered residual stool sample was normalized with additional buffer to a 1 gm:5 ml stool:buffer ratio and homogenized. Homogenates were aliquoted 42 ml/tube and frozen at -80°C until analyzed. Aliquots were thawed at room temperature, centrifuged and the supernatant was treated with polyvinylpyrrolidone to remove PCR inhibitors and spin filtered to clarify. Sequence specific DNA biomarker targets were isolated directly from the clarified supernatant using a magnetic bead based oligonucleotide hybrid capture method. The captured DNA was split and one portion was subjected to the bisulfite reaction for the identification of aberrantly methylated *MDR34* and *BRP3* and the other portion was used to determine the presence of any of seven *K-ras* point mutations. The test does not distinguish the specific mutation. Using quantitative real-time target and signal

(Imperiale, et al., Supplementary Appendix, page 6)

The data published by Imperiale show that:

- Sensitivity of the Cologuard assay in detecting patients with colorectal cancer was 92% versus 74% for FIT (fecal immunochemical test) ;
- Sensitivity in detecting patients with colorectal cancers in Stages I-III —those determined by the American Joint Committee on Cancer to be associated with an increased rate of being cured—was 93% for Cologuard versus 73 % for FIT;
- Sensitivity for patients with advanced pre-cancerous lesions was 42% for Cologuard versus 24% for FIT;
- Cologuard detected 69% of patients with polyps with high-grade dysplasia versus 46% for FIT;
- Cologuard achieved a specificity of 87% versus FIT specificity of 95%.

(Imperiale, page 1293, col 1 and Table 1).

Long felt need and the failure of others

As evidenced by the art cited by the Examiner, isolation of human DNA from stool samples for use in colorectal cancer screening has long been a goal in this field (see, *e.g.*, SHUBER as cited above, published in 2002; ZOU and VAN ENGELAND, published in 2007 and 2008, respectively), and different combinations of markers to detect colorectal cancer in stool samples have been tried (see, *e.g.*, ZOU and VAN ENGELAND).

VAN ENGELAND provides a detailed summary of the state of the art of isolating DNA from stool samples in 2008, and highlights that these methods are unsatisfactory:

The initial DNA isolation techniques typically recovered DNA from 10g to 4g stool and more conveniently purified the human DNA component using streptavidin-bound magnetic beads (Dong et al., 2001; Ahlquist et al., 2000). Further improvements in recovery of target human DNA from stool comprised an electrophoresis-driven separation of target DNA sequences, using oligonucleotide capture probes immobilized in an acrylamide gel (Whitney et al., 2004). Later, when DNA integrity proved to be a suitable marker it was also important to prevent degradation during sample handling. Improved results were obtained with stool samples frozen as quickly as possible after collection. Alternatively, stabilization buffer was added to the stool samples before further transport (Olson et al., 2005). A recent improvement involves the use of an MBD column to extract methylated human DNA in a high background of fecal bacterial DNA (Zou et al., 2007). However, despite these advances, current tools for cancer detection in faecal samples are still unsatisfactory.

(VAN ENGELAND, page 6, line 21 to page 7, line 7, emphasis added)

The references cited in making the rejection, including SHUBER, ZOU, and VAN ENGELAND, demonstrate that there has been a long-felt need for a way to screen for colorectal cancers based on stool DNA testing. However, even in possession of the methods and markers disclosed in the art cited by the Examiner, as stated by VAN ENGELAND, other workers in the field have failed. In contrast, Applicants have been able to meet this need and succeed where others had failed by using a particular combination of markers and methods for extracting the marker DNA, as described in the instant application. The embodiments as claimed herein addressed this long-felt need and succeeded where others had failed, as evidenced by first-ever FDA approval for the product containing these components.

Accordingly, it is respectfully submitted that the claims are not obvious and the rejection is overcome, and Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all objections and rejections have been addressed, and Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 662-1277.

Dated: July 31, 2015

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