

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,
Petitioner,

v.

EXACT SCIENCES CORPORATION,
Patent Owner.

Case No: IPR2024-01330
U.S. Patent 11,970,746

PATENT OWNER'S DEMONSTRATIVES



Geneoscopy, Inc. v. Exact Sciences Corp.

IPR2024-01330

U.S. Patent No. 11,970,746

Patent Owner Exact Sciences' Demonstratives

Hearing: November 20, 2025

Summary Of Disputed Issues

Geneoscopy Has Failed To Meet Its Burden

- No motivation to combine Kanaoka frozen samples to arrive at RNA claims
- No reasonable expectation of success using RNA of Kanaoka without freezing
- No motivation to require at-home separation of the fecal sample
- No motivation for at-home test for two classes of biomarkers
- Objective indicia support finding non-obviousness

Reasonable Expectation Of Success Would Require Data

Finding of no reasonable expectation of success is proper where there is no data or data of limited weight.

Novartis Pharms. Corp. v. W.-Ward Pharms. Int'l Ltd., 923 F.3d 1051, 1061 (Fed. Cir. 2019); Sur-Reply at 18

It is at all times Petitioner's burden to show reasonable expectation of success, a burden that is not met by unresolved uncertainty and unpredictability.

Eli Lilly and Co. v. Teva Pharma. Intn'l GmbH, 8 F.4th 1331, 1348 (Fed. Cir. 2021); Sur-Reply at 18

For Motivation, Benefits Lost And Gained Must Be Considered

“But immediately after the sentence quoted by HPC, Winner continues: ‘[T]he benefits, *both lost and gained*, should be weighed against one another’ 202 F.3d at 1349 n.8 (emphasis added). That is consistent with the longstanding principle that the prior art must be considered for all its teachings, not selectively.”

Henny Penny Corp. v. Frymaster LLC, 938 F.3d 1324, 1332 (Fed. Cir. 2019); POR at 2; Sur-Reply at 5

“In fact, the prior art could contain one reference suggesting a combination and others critiquing or otherwise discouraging the same. Even a single reference can include both types of statements, and we have held that it is error to fail to consider the entirety of the art.”

Arctic Cat Inc. v. Bombardier Recreational Prods., Inc., 876 F.3d 1350, 1360 (Fed. Cir. 2017); POR at 27, Sur-Reply at 5

No Motivation Or Reasonable Expectation For Combining RNA

- Kanaoka – Petitioner's only RNA reference:
 - Taught difficulties of using RNA
 - Laboratory, not at-home, collection
 - Samples immediately frozen in liquid nitrogen
- Nechvatal – Petitioner's only reference for purported reasonable expectation:
 - Focused on bacterial DNA
 - No RNA testing/contains no RNA data
- Geneoscopy's reasonable expectation arguments: unsupported and inconsistent with other arguments

No Motivation For At-Home Separation

- POSA would not have been motivated to use separate buffers
- POSA would have understood the same buffer—e.g. Tris-EDTA—could both:
 - Stabilize nucleic acids from stool sample
 - Prevent denaturation of hemoglobin in stool
- Olson and Shuber used Tris-EDTA to stabilize nucleic acids
- Tsuji taught Tris-EDTA to prevent hemoglobin denaturation
- On balance, a POSA would have used a single buffer over separation
- Geneoscopy has redesigned its own test to use a single buffer

Geneoscopy Improperly Discounts Disadvantages Of Separation

Known disadvantages of separation	Speculative disadvantage of single buffer
More costly and more complex than using single buffer in single container. POR at 24, 35-36; EX2044 ¶¶ 119-128, 152-156 More patient interaction with stool sample/less patient acceptability. POR at 24, 34-35; Sur-Reply at 4; EX1006 at 116-117; EX2044 at ¶¶ 127-128,152 Vilkin iFOBT samples required objectionable at-home refrigeration. POR at 33-34; EX1005 at 2520, 2524; EX2044 at ¶¶ 147-151	Alleged need for optimization of a well-known, prior art buffer that had been reported to stabilize both nucleic acids and proteins in stool. Reply at 3-5; POR at 22-23; Sur-Reply at 3-5; EX2044 at ¶¶ 119-128

POSA Would Not Have Combined References To Arrive At Claims

ENTIRETY OF THE ART:

- Lenhard's sensitivity was worse than single marker tests
- Combined results in Lenhard neither statistically significant nor representative of target population
- No expectation to improve detection of advanced adenomas
- Petitioner's proposed combinations would:
 - Be more complex and costly than test for single class of markers
 - Require undesirable at-home patient stool interaction
 - Reduce specificity →
 - Unnecessary colonoscopies
 - Decreased patient trust and acceptance

Strong Objective Indicia Show Geneoscopy's Hindsight Bias

- **No dispute that:**
 - Claim 3 describes Cologuard's fundamental workflow
 - Cologuard is a commercial success
 - Others failed in attempting to develop a non-invasive CRC screening test that has sufficient diagnostic accuracy and is acceptable to patients
 - Cologuard met the long-felt but unmet need for such a CRC screening test
 - Industry has praised Cologuard
- **Geneoscopy's only argument—lack of nexus—fails**
 - Cologuard success results directly from claimed invention
 - No evidence the 60 other patents are relevant to Cologuard success
 - No evidence marketing is the nexus to Cologuard success

No Motivation Or Reasonable Expectation Of Success To Add Kanaoka's RNA To The Proposed Combinations

Grounds

Ground	Challenged Claims
I. Lenhard, Vilkin, and Itzkowitz	3-4, 14-19
II. Lenhard, Vilkin, Itzkowitz, and Kanaoka	12 and 13
III. Shuber and Vilkin	3-4, 14-19
IV. Shuber, Vilkin, and Kanaoka	12 and 13
VI. Inbar, Vilkin, and Shuber	3-4, 14-19
VII. Inbar, Vilkin, Shuber, and Kanaoka	12 and 13

Pet. at 12; Institution Decision at 2

Claims 12 And 13 Require Measuring Amount Of Human RNA

4. The method of claim 3, wherein testing the nucleic acid comprises determining expression from a human gene.

EX1001 at 47:17-18; Sur-Reply at 18

12. The method of claim 4, wherein determining expression from the human gene comprises measuring an amount of RNA expressed from the human gene.

13. The method of claim 12, wherein measuring an amount of RNA expressed from the human gene comprises reverse transcriptase polymerase chain reaction (RT-PCR).

EX1001 at 48:6-11; Sur-Reply at 18

Kanaoka: RNA Difficult To Extract And More Unstable Than DNA

Kanaoka

[0009] However, the method making use of RNA described above could not have the sensitivity exceeding that of the fecal occult blood test method, because it was impossible to extract RNA easily and efficiently from a small amount of feces.

EX1007 ¶ 9; POR at 15

[0011] However, since RNA is more unstable compared with DNA and is always subjected to a danger of decomposition by RNA digesting enzymes (RNases) which are ubiquitous in all the biological samples and very stable, strict control to avoid contamination of RNases is necessary in the RT-PCR method, during and after purification processes of RNA.

EX1007 ¶ 11; POR at 15

Kanaoka: Method Requires Immediately Freezing Sample

Kanaoka

(57)

ABSTRACT

* * *

existing fecal occult blood test. More specifically speaking, a method of detecting a tumor marker for diagnosing colon cancer which comprises collecting biological sample which is immediately frozen using liquid nitrogen in some cases,

EX1007 at Abstract; POR at 15-16; EX2044 ¶¶ 99,180

[0057] As soon as possible after sampling feces, the feces were separated into 5 ml tubes about 1 g each, were frozen using liquid nitrogen, and were stored at -80°C . Also, for

EX1007 at 57; POR at 16, 47-48; EX2044 ¶ 99

Geneoscopy Falls Short Of Its Burden

- Known difficulties using RNA undermine both:
 - Motivation to combine, and
 - Reasonable expectation of success
- No data on RNA to support expectation of success without freezing
- Single conclusory sentence in Petition fails to support expectation of success argument

Nechvatal: Pure Supposition, *No Data* Re RNA Preservation

Nechvatal

only DNA but also RNA for analysis. In addition to *Bacteroides*, the primary bacterial group analyzed in the 10 VA patient samples, preliminary testing showed that DNA (Table 2) as well as RNA (data not shown) of multiple other bacterial groups were PCR detectable. Furthermore, human genomic DNA, pre-

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to the bacterial constituents of the same human subject. In conclusion, this study suggests that preserving fecal samples at room temperature for a duration of 5 days, in a medium suitable for DNA and RNA analysis is feasible. With development of a

EX1024 at 131; POR at 50; Sur-Reply at 18

No reasonable expectation of success for cancer treatment without supporting data.

Novartis Pharms. Corp. v. W.-Ward Pharms. Int'l Ltd., 923 F.3d 1051, 1061 (Fed. Cir. 2019)

It is “at all times” Petitioner’s burden to show reasonable expectation of success.

Eli Lilly and Co. v. Teva Pharma. Intn’l GmbH, 8 F.4th 1331, 1348 (Fed. Cir. 2021)

Dr. Whitney's Inconsistency: Suitability For RNA In Stool

Dr. Whitney's IPR Opinion: POSA would use RNAlater buffer despite lack of any data

it, as Kanaoka illustrates. As of the Priority Date, a known alternative to freezing a sample using liquid nitrogen would be to stabilize the fecal RNA with a buffer, such as the then-commercially available RNAlater buffer.⁷⁶ Indeed, Kanaoka

EX1086 ¶ 60; Reply at 19

Dr. Whitney's District Court Opinion: extensive effort required for buffer capable of stabilization in stool

(RNases), or proteins (proteases), destabilize sample integrity. Stabilization of biomolecules in fecal samples is significantly more challenging than in most other biological sources. Extensive scientific effort has therefore been required to develop buffer solutions capable of stabilizing biomolecules in stool samples.

EX2052 ¶52; Sur-Reply at 18-19

Dr. Whitney's Inconsistency: Suitability For RNA In Stool

Dr. Whitney's IPR Opinion: Nechvatal provides reasonable expectation for RNA stabilization without any RNA data

successful combination of a COX-2 RNA assay with an iFOBT.³⁰³ A person of skill in the art would reasonably expect to be able to preserve the fecal RNA in the sample without freezing because by the Priority Date it had been reported that “preserving fecal samples at room temperature for a duration of 5 days, in a medium *suitable for DNA and RNA analysis is feasible*.”³⁰⁴

EX1002 ¶ 223; Pet. at 36; Sur-Reply at 19

Dr. Whitney's District Court Opinion: different biomarkers require validated specialized stabilization conditions

53. Optimal conditions to stabilize a sample depend on the type of biomarker to be recovered (e.g., cells, proteins, DNA, or RNA). The stability of each type of

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convenient, at-home sample collection. As a result, specialized stabilization conditions often need to be developed and clinically validated to prove their effectiveness for preserving a given biomarker from a given sample type under applicable conditions (e.g., for DNA or protein, from stool, for shipment to a laboratory via a traditional courier).

EX2052 ¶53; Sur-Reply at 18-19

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successful combination of a COX-2 RNA assay with an iFOBT.³⁰³ A person of skill in the art would reasonably expect to be able to preserve the fecal RNA in the sample without freezing because by the Priority Date it had been reported that “preserving fecal samples at room temperature for a duration of 5 days, in a medium *suitable for DNA and RNA analysis is feasible*.”³⁰⁴

EX1002 ¶ 223; Pet. at 36; Sur-Reply at 19

Dr. Whitney's District Court Opinion: Dr. Whitney's own DNA buffer *not expected* to work with RNA

stool samples. The optimized buffer we developed was never intended to stabilize RNA, and I would not expect it to do so effectively given RNA's increased susceptibility to degradation compared to DNA.

EX2052 ¶54; Sur-Reply at 18-19

Dr. Whitney's Inconsistency: Suitability For RNA In Stool

Dr. Whitney's IPR Opinion: Nechvatal provides reasonable expectation for RNA stabilization without any RNA data

successful combination of a COX-2 RNA assay with an iFOBT.³⁰³ A person of skill in the art would reasonably expect to be able to preserve the fecal RNA in the sample without freezing because by the Priority Date it had been reported that “preserving fecal samples at room temperature for a duration of 5 days, in a medium *suitable for DNA and RNA analysis is feasible*.”³⁰⁴

EX1002 ¶ 223; Pet. at 36; Sur-Reply at 19

Dr. Whitney's District Court Opinion: preserving RNA in fecal samples “particularly challenging”

to achieve sufficient stabilization. RNA is a fragile biomolecule, exhibiting reduced stability compared to DNA primarily due to its single-stranded structure and susceptibility to hydrolytic cleavage. Additionally, RNA nucleases are abundant in biological samples, including fecal matter, and can rapidly degrade RNA if not properly inhibited. Furthermore, the complex and diverse microbiome environment in fecal samples may contribute to a high level of RNase activity, making RNA stabilization in such samples particularly challenging. Therefore, it is generally recognized that additional precautions must be taken for isolating RNA and running RNA-based testing protocols compared to DNA-based testing. Accordingly, RNA stabilization buffers need

EX2052 ¶55; Sur-Reply at 18-19

Dr. Whitney's Inconsistency: Suitability For RNA In Stool

Dr. Whitney's IPR Opinion: Nechvatal provides reasonable expectation for RNA stabilization without any RNA data

successful combination of a COX-2 RNA assay with an iFOBT.³⁰³ A person of skill in the art would reasonably expect to be able to preserve the fecal RNA in the sample without freezing because by the Priority Date it had been reported that “preserving fecal samples at room temperature for a duration of 5 days, in a medium *suitable for DNA and RNA analysis is feasible*.”³⁰⁴

EX1002 ¶ 223; Pet. at 36; Sur-Reply at 19

Dr. Whitney's District Court Opinion: Stabilizing RNA requires buffers that differ from DNA stabilizing buffers

1. Different Stabilization Buffers are Required for DNA and RNA

* * *

protocols compared to DNA-based testing. Accordingly, RNA stabilization buffers need to be specifically formulated to address the unique challenges posed by RNA's fragility and susceptibility to degradation by RNases, and thus differ in composition from DNA stabilizing buffers.

EX2052 ¶55; Sur-Reply at 18-19

Dr. Whitney's Inconsistent Position: Requirement For Data

Dr. Whitney's IPR Opinion: Nechvatal provides reasonable expectation for RNA stabilization without any RNA data

successful combination of a COX-2 RNA assay with an iFOBT.³⁰³ A person of skill in the art would reasonably expect to be able to preserve the fecal RNA in the sample without freezing because by the Priority Date it had been reported that “preserving fecal samples at room temperature for a duration of 5 days, in a medium *suitable for DNA and RNA analysis is feasible*.”³⁰⁴

EX1002 ¶ 223; Sur-Reply at 19

Dr. Whitney's Testimony: POSA would require data for reasonable expectation of success

- Q. And, in your opinion, would the person of ordinary skill in the art required -- require data for the specific buffer, in combination with the specific analyte, to have that predictability?
- A. I -- I think that a person of skill in the art would typically rely on data. The data would not necessarily need to come from that particular - - it wouldn't need to come from that particular person. You know, person of -- skilled in the art would typically be expected and be able to interpret published data and, in some cases, be able to convince themselves that there's -- based on experiments that other people have done, that there is a reasonable expectation that there would be a successful outcome to -- to trying something.
- If -- if that data did not already exist in -- in the literature, then that person may want to design experiments to test it themselves and generate their own data.

EX2057 at 18:24-19:18 (Whitney 09/26/25 Dep. Tr.) (objection omitted);
Sur-Reply at 19

Nechvatal Does Not Satisfy Dr. Whitney's Own Data Requirement

Dr. Whitney's IPR Opinion: Nechvatal provides reasonable expectation for RNA stabilization without any RNA data

successful combination of a COX-2 RNA assay with an iFOBT.³⁰³ A person of skill in the art would reasonably expect to be able to preserve the fecal RNA in the sample without freezing because by the Priority Date it had been reported that “preserving fecal samples at room temperature for a duration of 5 days, in a medium *suitable for DNA and RNA analysis is feasible*.”³⁰⁴

EX1002 ¶ 223; Sur-Reply at 19
See also EX2044 at ¶ 189; POR at 49

Dr. Whitney's Testimony: data required regarding buffer's stabilization ability

Q. So it is your opinion that it would be imperative that there be some data concerning the ability of a buffer to stabilize the analyte of interest; correct?

A. Yes, if one were relying on those analytes for detection of cancer.

EX2057 at 17:14-19 (Whitney 09/26/25 Dep. Tr.);
Sur-Reply at 19

Geneoscopy Failed To Meet Its Burden To Show Motivation For At-Home Sample Separation

Geneoscopy's Incorrect Standard For Motivation

Geneoscopy's Improper Focus:

- Whether separating sample was feasible

Decades before the Priority Date, scientists and clinicians recognized that testing different biomarkers could be facilitated by instructing patients to separate their fecal sample into portions stabilized in separate containers prior to shipment to a diagnostic laboratory. EX1002 ¶¶68-70, 72, 83-88. Such a process is illustrated in the below figure, from a 1985 laboratory manual, adapted from a 1949 publication. EX1002 ¶84; EX1010 p.12.

Pet. at 6

Law Requires:

- Whether separating sample was desirable

“Trade-offs often concern what is feasible, not what is, on balance, desirable.
Motivation to combine requires the latter.”

Winner Intern. Royalty Corp. v. Wang, 202 F.3d 1340, 1349
(Fed. Cir. 2000)

Sur-Reply at 2

Patient Acceptance Is Critical

Itzkowitz

Inherent in the success of any screening test is patient acceptance. Our preliminary experience with the new fecal DNA

EX1006 at 116; POR at 14, 58

Geneoscopy Ignores Key Characteristics Of CRC Screening

Hoepffner

CRC a lucrative health goal. An ideal screening test must be non-invasive, acceptable to patients, simple, have high sensitivity and specificity, inexpensive, cost-effective, easy to implement across a large population and should be effective in reducing morbidity and mortality from CRC in the screened population.⁶

EX1023 at 146; POR at 3; Sur-Reply at 5-6

Dr. Whitney Agrees – Patient Acceptance Is Critical

Q. Do you agree the first step for any test being successful is that the patient's will use it; correct?

A. In order -- yeah, I -- in this context for the sake of trying to get people to use at-home tests, that, in order to be able to assess their colorectal cancer risk, it is important that they use the test.

EX2057 at 42:11-19 (objection omitted) (Whitney 09/26/25 Dep. Tr.);
Sur-Reply at 1

Vilkin: Collect Three Stool Samples, Refrigerate At Home

Vilkin

name and date on the tube. The examinee is requested to prepare three consecutive daily samples during the week before colonoscopy examination. Samples are double-closed in zip-lock bags and kept in the refrigerator until returned to the developing laboratory where they are also kept at 4°C until development.

EX1005 at 2520, POR at 13-14,26; EX2044 ¶¶ 82-84

At-Home Interaction With Stool Was Undesirable

Vilkin

temperatures, even when homes are air-conditioned. The double zip-lock bags we provided answered some of the screeners' hesitancy about keeping the prepared test transiently in their home refrigerator. This packaging could be further improved.

EX1005 at 2524, POR at 14, 34

Itkowitz

Inherent in the success of any screening test is patient acceptance. Our preliminary experience with the new fecal DNA test in which patients add stabilization buffer to stool confirms a very high degree of patient satisfaction. These findings support results from the previous multicenter study in which subjects preferred fecal DNA testing to both the fecal occult blood test and colonoscopy.¹⁶

EX1006 at 116-117; POR at 14

Hoepffner

CRC a lucrative health goal. An ideal screening test must be non-invasive, acceptable to patients, simple, have high sensitivity and specificity, inexpensive, cost-effective, easy to implement across a large population and should be effective in reducing morbidity and mortality from CRC in the screened population.⁶

EX1023 at 146; POR at 27

Geneoscopy: At Home Separation The *Most Undesirable Step*

Q. And is it your understanding that that modified method for collecting samples no longer requires patients to separate their sample into multiple containers at home?

A. For -- for this -- **for the specific application of the ColoSense test for colorectal cancer screening, my understanding was that the announcement was related to what you described; is that, the at-home separation of a sample was not required**; that a single buffer could be used to stabilize analytes used in the test.

EX2057:31:7-18 (objection omitted) (Whitney 09/26/25 Dep. Tr.);
Sur-Reply at 4

Q. Do you see in that same paragraph the last sentence that states (as read):

"By eliminating the most confusing and undesirable step, we believe ColoSense will drive higher adherence and better outcomes"?

A. I see that, yes.

Q. That is also attributed to Dr. Erica Barnell?

A. It would appear so, yes.

EX2057:40:8-18 (objections omitted) (Whitney 09/26/25 Dep. Tr.);
Sur-Reply at 4

POSA Would Separate Sample *Only* If Different Buffers Were Needed

Melvin

A single solution is not available for preserving all of the diagnostic forms (helminth eggs and larvae and protozoan cysts and trophozoites) and for providing material that can be both concentrated and permanently stained. Therefore, more than one preservative solution may be needed to permit reliable diagnoses.

EX1010 at 59; POR at 23

Inbar

At times a variety of different entities have to be assayed in the pasty material. This is the case, for example, in stool, where it is generally desired to assay both bacteria and parasites, which as noted above, require different media. A system for assaying a plurality of entities, which require different media, comprises at least two containers, each holding a different preservation medium, each suitable for different entities. The containers in

EX1009 at 4:12-18;POR at 19, 46

Known Tris-EDTA Buffers Would Stabilize Both Analytes

Tris-EDTA Buffer Prevented Hemoglobin Denaturation

Tsuji

Tris-EDTA Buffer Stabilized Nucleic Acids

Olson

The experiments also included an addition of stabilization buffer to stool aliquots. Stabilization buffer consisted of 0.5 mol/L Tris, 0.15 mol/L EDTA, and 10 mmol/L NaCl (pH 9.0). In

EX1022 at 184; POR at 22-23; EX2044 ¶ 120

Shuber

In some embodiments, the buffer in the stabilization solution is 0.5 mM to 25 mM Tris, e.g., 5 mM to 15 mM Tris, 8 mM to 13 mM Tris or about 10 mM Tris. However, other buffers and/or concentrations may be used.

In some embodiments, the chelating agent in the stabilization solution is 0.01 to 2.5 mM EDTA, e.g., 0.75-1.25 mM EDTA, or 1mM EDTA. However, other chelating agents and/or concentrations may be used.

In some embodiments, the salt in the stabilization solution is 75 mM to 225 mM NaCl, e.g., 100 mM to 175 mM NaCl, or 150 mM NaCl. However, other salts (e.g., KCl etc.) and/or concentrations may be used.

EX1008 at 3:25-33; POR at 23; EX2044 ¶¶ 107, 121

[0008]

[Problems to be Solved by the Invention] The present invention has been made to solve the above-mentioned shortcomings of the conventional technology, and its purpose is to provide a method for detecting human hemoglobin accurately and with high sensitivity while preventing the denaturation of human hemoglobin present in a test liquid containing feces when left unattended, and a buffer solution for dissolving feces to be used therein.

* * *

[0010] In the method of the present invention, as a liquid for dissolving human hemoglobin or feces containing human hemoglobin as a test subject, for example, a phosphate buffer, a glycine buffer, a Tris-HCl buffer, a borate buffer, or the like is used as the base liquid. The pH of the buffer should be in the range of 6 to 9, preferably 6.5 to 8.5. It is preferable to add salt to the buffer solution at a concentration close to that of physiological salt. Moreover, to inhibit the denaturation of the

* * *

[0011] In the method of the present invention, a chelating agent is added to the above buffer solution to suppress the denaturation of human hemoglobin. The chelating agents used in the present invention may include ethylenediamine tetraacetic acid (hereinafter referred to as EDTA), trans-1,2-

EX1049 [0008], [0010], [0011]; POR at 23; Sur-Reply at 3; EX2044 ¶ 123

Known Tris-EDTA Buffers Would Prevent Hb Denaturation

Tsuji taught using a chelating agent—such as EDTA—to prevent denaturation of hemoglobin

(21) Application number Japanese Patent Application H3-292163

(22) Date of application October 11, 1991

(71) Applicant 000003964
Nitto Denko Corporation
1-1-2 Shimohozumi, Ibaraki City, Osaka
Prefecture

(72) Inventor Takashi Tsuji
c/o Nitto Denko Corporation
1-1-2 Shimohozumi, Ibaraki City, Osaka
Prefecture

(57) [Abstract]

[Objective] To provide a method for detecting human hemoglobin accurately and sensitively, while preventing the denaturation of human hemoglobin present in a test liquid containing feces when left unattended, and a buffer solution for dissolving feces to be used therein.

[Constitution] A chelating agent is added to a buffer for dissolving stool, and human hemoglobin is detected using an anti-human hemoglobin antibody.

Ex 2049 [Abstract]; POR at 22; Sur-Reply at 3; EX2044 ¶ 123

Grow taught use of “known” buffers

United States Patent [19]

Grow et al.

[54] **FECAL SAMPLE IMMUNOASSAY METHOD
TESTING FOR HEMOGLOBIN**

[22] Filed: **Sep. 23, 1991**

For hemoglobin immunoassays, a buffer solution having a pH of from 7.0 to 8.0 is desirable. Any conventional buffering agents can be used to prepare the test buffer solution, if they do not interfere with the later assay procedure and assay reagents. One example of a suitable

EX1041 at 5:34-38; Sur-Reply at 3-4

Known Tris-EDTA Buffers Would Stabilize Both Analytes

Dr. Backman's Declaration:

122. Tris, EDTA, and NaCl were all common components of buffer solutions by 2009. A POSA in 2009 would have expected that a Tris/EDTA buffer, such as those described in Olson and Shuber, would prevent denaturation or degradation of blood protein in stool. This is because, if two molecules are degraded by similar processes and, therefore, are preserved by similar processes (e.g., both require the same pH), a POSA would expect that the same buffer could be used to preserve both. This is the case with nucleic acids and proteins such as hemoglobin. DNA and proteins may be degraded enzymatically or

EX2044 ¶122; POR at 22

Known Tris-EDTA Buffers Would Stabilize Both Analytes

Dr. Backman's Declaration:

maintaining stable, neutral pH, Tris inhibits these enzymes. For these reasons, Tris and EDTA work synergistically to preserve both nucleic acids and proteins including hemoglobin. Importantly, the two most detrimental processes to both DNA and proteins—enzymatic digestion and denaturation/aggregation—depend on the same conditions—non-neutral pH and divalent cations—and both conditions are inhibited by Tris/EDTA.

EX2044 ¶122; POR at 22

No Evidence For Dr. Whitney's Opinions Re Vilkin Buffer

Dr. Whitney' Opinion About "Other Buffers"

sample collection and laboratory analysis, without freezing.⁸⁴ For example, certain buffers prevent degradation of DNA, and are therefore used when long DNA, mutated DNA, or methylated DNA is used as a biomarker.⁸⁵ Other buffers stabilize blood proteins and are therefore used when blood proteins are used as a biomarker.⁸⁶

EX1002 ¶ 75; POR at 21-22

Vilkin does not disclose components of unidentified "Hb stabilizing buffer"

the serrations (Fig. 1). The tip is then put in a closed amount of Hb stabilizing buffer. Each sample tube has a unique bar

EX1005 at 2520; POR at 22

No Evidence Two Buffers (Rather Than One) Were Needed

Q. Let me ask again.

Is it -- in your opinion, would it be impossible to form a buffer that would stabilize both nucleic acids and proteins?

A. Again, my opinions are formed by reviewing data which illustrates to me what is possible. I have not viewed data, in my recollection, that would allow me to answer that question.

EX2020 (Whitney 10/10/24 Dep. Tr.) at 148:14-22 (objection omitted); POR at 22

Dr. Whitney Does Not Dispute That A Single Buffer Could Work

Q. Is it your opinion that there was no buffer as of 2009 that would have stabilized both DNA and hemoglobin in a stool sample?

A. No, I'm not sure that I'm saying that -- well, maybe I am saying that.

I -- what I am saying is that in order to be able to run both a hemoglobin-based test as well as a DNA-based test for use in colorectal cancer screening from fecal samples, that it's imperative that both of those analytes are properly preserved. I believe that there very well may have been buffers that were available and perhaps have been described as potentially providing some stabilization, but not necessarily optimized buffer solutions that could be used for both of those analytes.

EX2057 (Whitney 09/26/25 Dep. Tr.) at 14:16-15:8; Sur-Reply at 4

Dr. Whitney Does Not Dispute That A Single Buffer Could Work

Q. So, in your opinion, there may have been buffers that could have stabilized both nucleic acid and hemoglobin in stool in 2009; correct?

A. What I'm saying is that I'm allowing for the realm of possibilities, but I'm also saying that in order for a test to be effective as a screening test, it's imperative that both of those types of analytes are properly preserved. I'm not aware of any data that shows that there is a single buffer that could stabilize both of those types of analytes in a way that's been demonstrated to be useful in colorectal cancer screening.

EX2057 at 15:9-20 (Whitney 09/26/25 Dep. Tr.); Sur-Reply at 4

Dr. Whitney's Inconsistent Position: Different Buffer Requirement

Dr. Whitney's RNA Opinion: Buffer Tested For Only DNA Likely To Work For RNA

successful combination of a COX-2 RNA assay with an iFOBT.³⁰³ A person of skill in the art would reasonably expect to be able to preserve the fecal RNA in the sample without freezing because by the Priority Date it had been reported that “preserving fecal samples at room temperature for a duration of 5 days, in a medium *suitable for DNA and RNA analysis is feasible*.”³⁰⁴

EX1002 ¶ 223; Sur-Reply at 19

Dr. Whitney's Conflicting Opinion: Buffers “Unlikely” To Be Optimized For Different Analytes

acknowledged in his deposition.⁹⁷ Indeed, using such an optimized buffer is critical to the reliability of at-home fecal diagnostic tests. As I explained in my Opening

* * *

DNA-stabilizing buffer.⁹⁹ A POSA would understand that a buffer optimized for one biomarker type (e.g. DNA) is unlikely to be optimized for another biomarker type (e.g. protein). Indeed, at his deposition, Dr. Backman acknowledged that the

EX1086 ¶ 68; Sur-Reply at 19

Art As A Whole Would Not Motivate POSA To Combine References

Benefits Lost And Gained Must Be Considered

“But immediately after the sentence quoted by HPC, Winner continues: ‘[T]he benefits, *both lost and gained*, should be weighed against one another’ 202 F.3d at 1349 n.8 (emphasis added). That is consistent with the longstanding principle that the prior art must be considered for all its teachings, not selectively.”

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“In fact, the prior art could contain one reference suggesting a combination and others critiquing or otherwise discouraging the same. Even a single reference can include both types of statements, and *we* have held that it is error to fail to consider the entirety of the art.”

Arctic Cat Inc. v. Bombardier Recreational Prods., Inc., 876 F.3d 1350, 1360 (Fed. Cir. 2017); POR at 27; Sur-Reply at 5

Geneoscopy Ignores Implications Of The Art As A Whole

- Based on combinations of references, POSA would have expected:
 - Combining different marker classes would:
 - **increase** complexity/cost including for different containers and buffers
 - **not increase** adenoma sensitivity
 - **decrease** specificity
 - Requiring patients to manipulate and refrigerate stool multiple times would **decrease** patient acceptance
- POSA would have weighed negative results of combination against Lenhard's statistically insignificant data re CRC sensitivity
- Geneoscopy ignores how a POSA would view collective teachings (with statistically insignificant data) in combination

Each Reference Achieves Reported Results With Different Methodology

Lenhard

rectal tumors before stool sampling. Samples were received within 10 hours after defecation at the laboratory, aliquoted, and stored at -80°C .

EX1004 at 143; POR at 9

Vilkin

name and date on the tube. The examinee is requested to prepare three consecutive daily samples during the week before colonoscopy examination. Samples are double-closed in zip-lock bags and kept in the refrigerator until returned to the developing laboratory where they are also kept at 4°C until development.

EX1005 at 2520; POR at 13

Itzkowitz

ning the presurgical bowel preparation. Subjects were given detailed instructions and a special stool collection kit that is mounted on the toilet bowl. Immediately after defecation, subjects added 250 mL of a DNA-stabilizing buffer⁷ to a stool specimen of at least 50 g. Only 10 patients provided less than

EX1006 at 112; POR at 26

Kanaoka

[0057] As soon as possible after sampling feces, the feces were separated into 5 ml tubes about 1 g each, were frozen using liquid nitrogen, and were stored at -80°C . Also, for

EX1007 at [57]; POR at 16

Shuber

In any of the aspects of the invention described herein, including the examples, a sample (e.g., a stool sample) may be directly deposited into a container (e.g., a sealable container) that already contains stabilization solution. The amount of solution may be

EX1008 at 29:7-19; POR at 17

Inbar

A system for collecting, storing and transporting of specimens of a pasty material, e.g. stool is provided. The system comprises at least one container holding a preservation medium for preserving a chemical entity or living matter to be assayed in a specimen, the container being sealed by a pierceable membrane having a closure arrangement for sealing the container after the membrane is pierced. The system further comprises a sampling device having a handle and at least one elongated specimen collecting member detachably attached thereto, the collecting member being adapted to be received within the container and having the pasty material retaining portion and a piercing tip for piercing the membrane at a lowermost end thereof remote from said handle, for piercing said film. Also provided is a stool collecting device for easy collecting of excreted stool.

EX1009 at 1; POR at 8

Lenhard's Results From Non-Representative Population

Q. And so the 26 cancers, again, is a little more than one-third of the complete sample set; right?

A. Yes, I -- just barely.

Q. So would you agree that one-third positive cancer diagnoses is not representative of the prevalence of CRC in the general population?

A. The prevalence of CRC in an average risk asymptomatic population is probably closer to 1 percent.

EX2057 at 72:10-19 (Whitney 09/26/25 Dep. Tr.); Sur-Reply at 7

POSA Would Not Be Motivated By Lenhard's 65% Sensitivity

Table 4. Positivity Rates of the Fecal DNA Assay, FOBT, and Combination of the Tests

	HIC1		FOBT		Combined	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
All cancers	11/26 (42)	23%–63%	9/26 (35)	17%–56%	17/26 (65)	44%–83%
Localized cancers	4/6 (67)	22%–96%	2/6 (33)	4%–77%	6/6 (100)	12%–188% ^a
Advanced cancers	5/20 (25)	9%–49%	7/20 (35)	15%–59%	11/20 (55)	32%–77%
Rectum and sigmoid colon	5/13 (39)	14%–68%	5/13 (39)	14%–68%	9/13 (69)	39%–91%
From descending colon to cecum	6/13 (46)	19%–75%	4/13 (31)	14%–68%	8/13 (62)	39%–91%
Asymptomatic cases	4/10 (40)	12%–74%	3/10 (30)	7%–65%	6/10 (60)	26%–88%
Symptomatic cases	7/16 (44)	20%–70%	6/16 (38)	15%–65%	11/16 (69)	41%–89%
Adenomas	4/13 (31)	9%–61%	1/13 (8)	.2%–36%	4/13 (31)	9%–61%

^aEstimated by normal approximation of Poisson distribution.

EX1004 at 146; POR at 9-10; Sur-Reply at 6; EX2044 ¶¶ 64-66

- Tested non-representative subjects with known, mostly advanced CRCs
- More than one third still missed (false negatives)

Confidence Intervals Undermine A Benefit From Combination

Lenhard small sample size with overlapping confidence intervals:

Table 4. Positivity Rates of the Fecal DNA Assay, FOBT, and Combination of the Tests

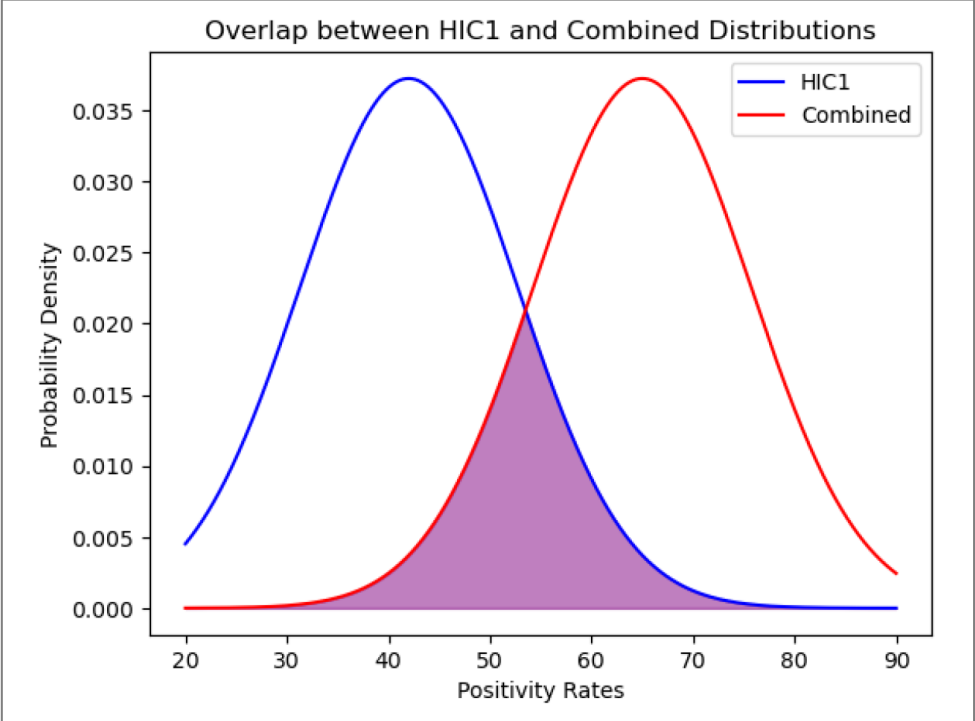
	HIC1		FOBT		Combined	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
All cancers	11/26 (42)	23%–63%	9/26 (35)	17%–56%	17/26 (65)	44%–83%
Localized cancers	4/6 (67)	22%–96%	2/6 (33)	4%–77%	6/6 (100)	12%–188% ^a
Advanced cancers	5/20 (25)	9%–49%	7/20 (35)	15%–59%	11/20 (55)	32%–77%
Rectum and sigmoid colon	5/13 (39)	14%–68%	5/13 (39)	14%–68%	9/13 (69)	39%–91%
From descending colon to cecum	6/13 (46)	19%–75%	4/13 (31)	14%–68%	8/13 (62)	39%–91%
Asymptomatic cases	4/10 (40)	12%–74%	3/10 (30)	7%–65%	6/10 (60)	26%–88%
Symptomatic cases	7/16 (44)	20%–70%	6/16 (38)	15%–65%	11/16 (69)	41%–89%
Adenomas	4/13 (31)	9%–61%	1/13 (8)	.2%–36%	4/13 (31)	9%–61%

^aEstimated by normal approximation of Poisson distribution.

EX1004 at 146; POR at 10-11; Sur-Reply at 6; EX2044 ¶¶ 64-66

- No P value reported for comparison
- No statistical significance shown

Wide overlapping confidence intervals indicate combination not an improvement, even for CRC



EX2044 ¶ 66; Sur-Reply at 6

A POSA Would Not Be Motivated By Multi-Sample iFOBT

Vilkin

At present, we will continue with collecting three annual fecal tests, as we have confirmed the additive clinical value of repeated occult blood testing in this high-risk population. This is in contrast to the annual 2-day, average-risk population I-FOBT collection, as routinely used in Japan, United States, and Australia and 1-day biennial testing as performed in Italy (11, 12, 16–18).

EX1005 at 2524; POR at 34

Nakama

In conclusion, our findings suggest that the immunochemical fecal occult blood test is effective for the diagnosis of colorectal cancer, and that the 2-day fecal collection method is the most desirable in immunochemical occult blood testing as a means of screening for colorectal cancer.

EX2047 at 231; POR at 34; Sur-Reply at 12; EX2044 ¶149

No Reason for POSA To Choose Vilkin iFOBT Over gFOBT

Levin

Based on data from these 6 studies, it appears that there are no clear patterns of superior performance in overall test performance between a high-sensitivity guaiac-based test (Hemoccult SENSA) and a variety of FIT.

EX1013 at 1576; POR at 42-43

2008 Guidelines Did Not Suggest gFOBT Over iFOBT (FIT)

Levin

AGA INSTITUTE

The following article contains new recommendations for colorectal cancer screening, the first set we have published since 2003 (Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. Gastroenterology 2003;124:544–560.) The current recommendations have emerged through the participation of multiple national societies, taking into consideration newly emerging technologies. Please note the US Multi-Society Task Force (USMTF) represents the American Gastroenterological Association (AGA) Institute, the American Society for Gastrointestinal Endoscopy, and the American College of Gastroenterology. Commissioned originally by the American Cancer Society, this compendium will be published concurrently in CA: A Cancer Journal for Clinicians and reprinted in the June issue of Radiology.

Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline From the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology

EX1013 at 1570

required. Another question worthy of consideration is whether or not including a sensitive gFOBT or FIT at the time of testing would improve sensitivity without adversely affecting specificity. In a recent retrospective anal-

EX1013 at 1578; POR at 42; Sur-Reply at 15

Itzkowitz: Two DNA Markers Only, Reduces Assay Complexity

Itzkowitz

cost effectiveness.²⁴ Our results suggest that with only 2 markers (vimentin+DY) providing a sensitivity of 88%, the assay complexity can be reduced significantly, thereby decreasing cost and facilitating the development of an assay kit that could be managed by local clinical laboratories. At the present time, fecal

EX1006 at 117; POR at 15, 30

- Itzkowitz teaches benefit of only two DNA markers, not combining different classes of markers with different collection processes and different buffers

Itzkowitz: Prefer Small Number Of Markers From Same Class

Itzkowitz

ated with older age. **Conclusions:** An improved fecal DNA test that incorporates only 2 markers shows much higher sensitivity for CRC. The new assay is easier to perform and should be less costly, thereby facilitating its use for noninvasive CRC screening.

EX1006 at 111; POR at 15; Sur-Reply at 9-10

cost effectiveness.²⁴ Our results suggest that with only 2 markers (vimentin+DY) providing a sensitivity of 88%, the assay complexity can be reduced significantly, thereby decreasing cost and facilitating the development of an assay kit that could be managed by local clinical laboratories. At the present time, fecal

EX1006 at 117; POR at 15, 30

Shuber: Main Obviousness Reference Grounds III-IV

Shuber

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
1 December 2005 (01.12.2005)

PCT

(10) International Publication Number
WO 2005/113769 A1

(71) Applicant (*for all designated States except US*): **EXACT SCIENCES CORPORATION** [US/US]; 100 Campus Drive, Marlborough, MA 01752 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **SHUBER, Anthony, P.** [US/US]; 6 Parker Road, Mendon, MA 01756 (US).
WHITNEY, Duncan, H. [US/US]; 20 Read Road, Sudbury, MA 01776 (US).

EX1008; POR at 16-17

Shuber: Up To 98% Sensitivity For Adenomas

Shuber

adenomas. Therefore, detecting adenomas is particularly useful for identifying early signs or risks of colorectal cancer (e.g., cancerous and precancerous lesions or growths in the colon).

EX1008 at 13:7-8; POR at 17

In one embodiment, a combination of all of the above loci may be used to detect adenomas with a greater than 95% sensitivity (e.g., greater than 98% sensitivity).

EX1008 at 14:15-16; POR at 17

Additional References Fail To Show Art-Recognized Strategy

- Geneoscopy's other references do not describe an at-home test, and provide no evidence any potential benefit gained from combination would outweigh benefits lost:
 - Nishikawa (2002): **one sentence** speculating (without data) that testing for *K-ras* mutation could be combined with FOBT or other methods
 - Kutzner (2005): retrospective study of frozen samples
 - Speculates whether DNA and gFOBT (non-quantitative) should be used together
 - States its data do not allow conclusions on that approach
 - Levin (2008 Guidelines): queries “whether **or not**” combining DNA with gFOBT or iFOBT would “improve sensitivity **without adversely affecting specificity**”

POR at 40-43; EX2044 (Backman Declaration), ¶¶ 168-171; Sur-Reply at 15

Inbar: Geneoscopy's Additional Reference Grounds VI-VII

Inbar

(30) Priority Data:
116824

19 January 1996 (19.01.96)

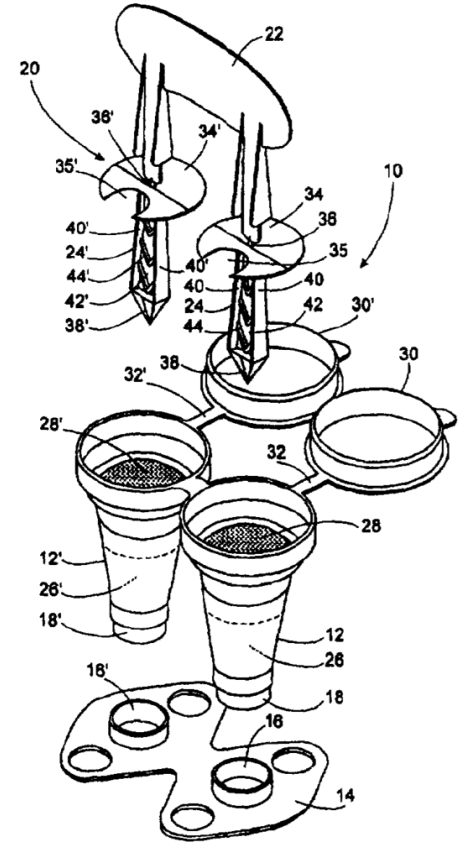
IL

(72) Inventor; and
(75) Inventor/Applicant (*for US only*): INBAR, Michael [IL/IL];
Neot Achva 10, 79800 D.N. Shikmim (IL).

(54) Title: COLLECTION AND TRANSPORTATION OF A PASTY MATERIAL SAMPLE

(57) Abstract

A system for collecting, storing and transporting of specimens of a pasty material, e.g. stool is provided. The system comprises at least one container holding a preservation medium for preserving a chemical entity or living matter to be assayed in a specimen, the container being sealed by a pierceable membrane having a closure arrangement for sealing the container after the membrane is pierced. The system further comprises a sampling device having a handle and at least one elongated specimen collecting member detachably thereto, the collecting member being adapted to be received within the container and having the pasty material retaining portion and a piercing tip for piercing the membrane at a lowermost end thereof remote from said handle, for piercing said film. Also provided is a stool collecting device for easy collecting of excreted stool.



EX1009, POR at 18-19

No Motivation To Combine Inbar With Shuber And Vilkin

Inbar:

- Does not mention at-home collection
- Does not mention nucleic acids (DNA or RNA)
- Has only limited reference to “cryptic blood”
- Does not disclose solution that prevents denaturation or degradation of blood protein

EX1009; POR at 18-19, 45-46; EX2044 ¶¶113-115, 117

Inbar: Separate Only When Required

Inbar

At times a variety of different entities have to be assayed in the pasty material. This is the case, for example, in stool, where it is generally desired to assay both bacteria and parasites, which as noted above, require different media. A system for assaying a plurality of entities, which require different media, comprises at least two containers, each holding a different preservation medium, each suitable for different entities. The containers in

EX1009 at 4:12-18; POR at 19, 46

Failure To Improve Advanced Adenoma Detection Weighed Against Combination

POSA Would Know Goal Of Screening = Early Detection

Lenhard

a time period of usually more than 10 years.³ Detection of early disease and precancerous adenomatous lesions leads to a decrease of CRC-related mortality.⁴⁻⁷ There-

EX1004 at 142; POR at 11, 29

Levin

It is the strong opinion of this expert panel that *colon cancer prevention* should be the primary goal of CRC screening. Tests that are designed to detect both early

EX1013 at 1573; Sur-Reply at 9

POSA Would Know Goal Of Screening = Early Detection

Shuber

adenomas. Therefore, detecting adenomas is particularly useful for identifying early signs or risks of colorectal cancer (e.g., cancerous and precancerous lesions or growths in the colon).

EX1008 at 13:7-8; POR at 17

Vilkin

specificity of 95.3% (1). This means that in this group of high-risk and symptomatic patients, all cases of cancer and most advanced adenomas would be detected and a negative test would provide a very high degree of certainty that there was no clinically significant colorectal neoplasia at this round of screening.

EX1005 at 2524; POR at 30

Lenhard: gFOBT Did Not Improve Early Detection

Lenhard

Table 2. Clinicopathologic Data and HIC1 Methylation Status of Patients With Adenomatous Polyps

No.	Sex	Age (y)	Diagnosis	HIC1 methylation	FOBT
27	M	72	Tubular adenoma, ascending colon, 3 cm	+	—
28	F	63	Tubulovillous adenoma, ascending colon, hepatic flexure, sigmoid colon, 1–1.5 cm	—	—
29	M	63	Tubulovillous adenoma, ascending colon, 2 cm	—	—
30	M	76	Tubulovillous adenoma, ascending and transverse colon, 1, 3, 4 cm	+	+
31	M	83	Tubulovillous adenoma, transverse colon, 3 cm	—	—
32	F	65	Tubulovillous adenoma, sigmoid colon, 1.5 cm	—	—
33	M	72	Tubulovillous adenoma, ascending colon, 1 cm	—	—
34	F	60	Tubular adenoma, sigmoid colon, 1.5 cm	—	—
35	M	69	Tubular adenoma, 1.5 cm, ascending colon	—	—
36	M	70	Tubulovillous adenoma, sigmoid colon, 1 cm	—	—
37	M	64	Tubulovillous adenoma, rectum, 1 cm	—	—
38	M	72	Adenoma, cecum, 2 cm	+	—
39	F	63	Tubulovillous adenoma, sigmoid colon, 2 cm	+	—

M, male; F, female.

EX1004 at 144; POR at 11; EX2044 ¶71

Shuber: Disclosed 95/98%+ Sens For Adenomas Using DNA

Shuber

adenomas. Therefore, detecting adenomas is particularly useful for identifying early signs or risks of colorectal cancer (e.g., cancerous and precancerous lesions or growths in the colon).

EX1008 at 13:7-8; POR at 17

In one embodiment, a combination of all of the above loci may be used to detect adenomas with a greater than 95% sensitivity (e.g., greater than 98% sensitivity).

EX1008 at 14:15-16; POR at 17

Decreased Specificity Weighed Against Combination

Petitioner's References Emphasize Need For High Specificity

Lenhard

at 77%. Therefore, identification of both sensitive and highly specific methylation markers is required before MSP can be evaluated as a stool-based screening procedure for CRC in prospective studies.

uation will compromise specificity severely. In addition, low specificity of a test results in a low positive predictive value and consecutively in high rates of unnecessarily performed colonoscopies.

EX1004 at 143, 148; POR at 11-12

Levin

required. Another question worthy of consideration is whether or not including a sensitive gFOBT or FIT at the time of testing would improve sensitivity without adversely affecting specificity. In a recent retrospective anal-

EX1013 at 1578; POR at 42-43

Vilkin

The clinical evaluation demonstrated a high sensitivity of 76.5% for all significant colorectal neoplasia and acceptable specificity of 95.3%.

EX1005 at 2523; POR at 12

Nishikawa

tions is low among cancers as a whole. However, the technique is highly specific, noninvasive, and cost-effective, and should provide a more sensitive and specific tool for mass screening of colorectal cancer than is currently available, especially if used in combination with fecal occult blood testing and other methods for detecting genetic abnormalities.

EX1011 at 112; POR at 40

Young

rate. FITs provide for an improved sensitivity/specificity ratio; in other words, they can achieve better sensitivity without an unacceptable deterioration in specificity.

EX1020 at 28; POR at 3

Lenhard: Decreasing Specificity Is Undesirable

Lenhard

tations. This shows that methylation markers as well as genetic markers need to be selected carefully to achieve both high sensitivity and specificity. Choosing sensitive markers that already are positive in a premalignant situation will compromise specificity severely. In addition, low specificity of a test results in a low positive predictive value and consecutively in high rates of unnecessarily performed colonoscopies.

EX1004 at 148; POR at 32

Geneoscopy's Expert: High Specificity Is Desirable

not have the disease being tested for). Having a high specificity is desirable in fecal CRC tests, because patients who wrongly test positive are often subjected to an unnecessary medical procedures and potentially unnecessary treatment.

EX1002 (Whitney Dec.) ¶ 30; POR at 4

Lenhard: Combining DNA With Protein Decreases Specificity

Lenhard

Table 3. HIC1 Methylation Status of Healthy Controls and Patients With Nonneoplastic Disease

No.	Sex	Age	Diagnosis	HIC1 methylation	FOBT
40	F	61	Normal	—	+
41	F	61	Normal	—	—
42	F	73	Normal	—	—
43	M	63	Normal	—	—
44	M	47	Normal	—	—
45	F	41	Normal	—	—
46	M	53	Normal	—	—
47	F	59	Normal	—	+
48	F	73	Normal	—	—
49	M	36	Normal	—	—
50	M	71	Normal	—	—
51	F	65	Normal	—	—
52	F	60	Normal	—	—
53	F	66	Normal	—	—
54	M	80	Normal	—	—
55	M	70	Normal	—	—
56	F	27	Normal	—	—
57	F	57	Normal	—	—
58	M	55	Normal	—	ND
59	M	23	Normal	—	—
60	F	73	Normal	—	—
61	F	79	Normal	—	—
62	M	68	Normal	—	—
63	F	78	Normal	—	—
64	F	38	Normal	—	—
65	F	62	Normal	—	—
66	M	76	Normal	—	—
67	F	61	Normal	—	—
68	M	23	Normal	NA	—
69	M	74	Normal	—	—
70	M	60	Normal	—	—
71	F	49	Normal	—	—
72	M	59	Hyperplastic polyp	—	—
73	F	66	Hyperplastic polyp	—	—
74	F	67	Hyperplastic polyp	—	—
75	F	65	Hyperplastic polyp	—	—
76	F	58	Hyperplastic polyp	NA	—
77	F	76	Hyperplastic polyp	—	—
78	F	54	Hyperplastic polyp	—	—
79	F	76	Hyperplastic polyp	—	—
80	F	60	Hyperplastic polyp	—	—
81	M	47	Ulcerative colitis	+	+
82	M	64	Ulcerative colitis	—	+
83	M	27	Ulcerative colitis	—	—
84	M	67	Ulcerative colitis	—	+
85	M	53	Ulcerative colitis	—	—
86	M	51	Ulcerative colitis	—	—
87	F	44	Crohn's disease	—	—
88	M	30	Crohn's disease	—	—
89	M	37	Crohn's disease	—	—

F, female; M, male; ND, not determined; NA, no amplification.

Q. And then there are four more false positives in the FOBT column; is that right?

A. That's correct.

Q. So the combination, therefore, reduced the specificity with more false positives; is that right?

A. That would seem to be the case, yes.

EX2020 (Whitney 10/10/24 Dep. Tr.) at 54:19-55:1

EX1004, Table 3;
POR at 11-12

Petitioner Incorrectly Assumes POSA Would Sacrifice Specificity

Levin

AGA INSTITUTE

The following article contains new recommendations for colorectal cancer screening, the first set we have published since 2003 (Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. Gastroenterology 2003;124:544–560.) The current recommendations have emerged through the participation of multiple national societies, taking into consideration newly emerging technologies. Please note the US Multi-Society Task Force (USMTF) represents the American Gastroenterological Association (AGA) Institute, the American Society for Gastrointestinal Endoscopy, and the American College of Gastroenterology. Commissioned originally by the American Cancer Society, this compendium will be published concurrently in CA: A Cancer Journal for Clinicians and reprinted in the June issue of Radiology.

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EX1013 at 1570

required. Another question worthy of consideration is whether or not including a sensitive gFOBT or FIT at the time of testing would improve sensitivity without adversely affecting specificity. In a recent retrospective anal-

EX1013 at 1578; POR at 42; Sur-Reply at 15

Kutzner Does Not Provide Motivation to Combine

- Levin (2008) shows that Kutzner (2005) at most raised question of whether one benefit could be gained without losing another

Levin

AGA INSTITUTE

The following article contains new recommendations for colorectal cancer screening, the first set we have published since 2003 (Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. Gastroenterology 2003;124:544–560.) The current recommendations have emerged through the participation of multiple national societies, taking into consideration newly emerging technologies. Please note the US Multi-Society Task Force (USMTF) represents the American Gastroenterological Association (AGA) Institute, the American Society for Gastrointestinal Endoscopy, and the American College of Gastroenterology. Commissioned originally by the American Cancer Society, this compendium will be published concurrently in CA: A Cancer Journal for Clinicians and reprinted in the June issue of Radiology.

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EX1013 at 1570

required. Another question worthy of consideration is whether or not including a sensitive gFOBT or FIT at the time of testing would improve sensitivity without adversely affecting specificity. In a recent retrospective analysis of stool samples from patients with CRC and donor controls, combined results from a standard gFOBT and a panel of DNA markers (APC, BAT26, and L-DNA) resulted in a combined sensitivity for cancer of 93% and specificity of 89%.⁷⁶

76. Kutzner N, Hoffmann I, Linke C, et al. Noninvasive detection of colorectal tumours by the combined application of molecular diagnosis and the faecal occult blood test. Cancer Lett 2005; 229:33–41.

EX1013 at 1578; POR at 42; Sur-Reply at 15

Kutzner: Speculative Potential Benefit Would Be Discounted

Kutzner

alone. Regarding the low cost and the little technical expense of the FOBT, we suggest that MD and FOBT should complement rather than replace each other. The sensitivity of the combined application of MD and FOBT is in the range reported for invasive methods. This leads to the question whether both methods should be used together in broad diagnostic screening programs. We are aware that our retrospective data do not allow any conclusion on the potential of this approach in diagnostic screening.

EX1012 at 40; POR at 41-42

Kanaoka – Combined Results Reduced Specificity

Kanaoka

[0065] COX-2 was detected in 27 cases among the 30 colon cancer cases (caeca: 2/2, ascending colon: 3/5, descending colon: 1/1, sigmoid colon: 7/7, rectum: 12/13; early cancer: 2/3, advanced cancer: 25/27), but was not detected in any of 22 cases in the control group (sensitivity: 90%, specificity: 100%).

[0066] In the immunological fecal occult blood test, 23 among 28 colon cancer cases and 3 among 22 control cases were positive (sensitivity: 82.1%, specificity: 86.3%).

EX1007 at ¶¶ 65-66; POR at 16, 47-48; EX2044 ¶¶183-184

No Improvements Gained From Combination

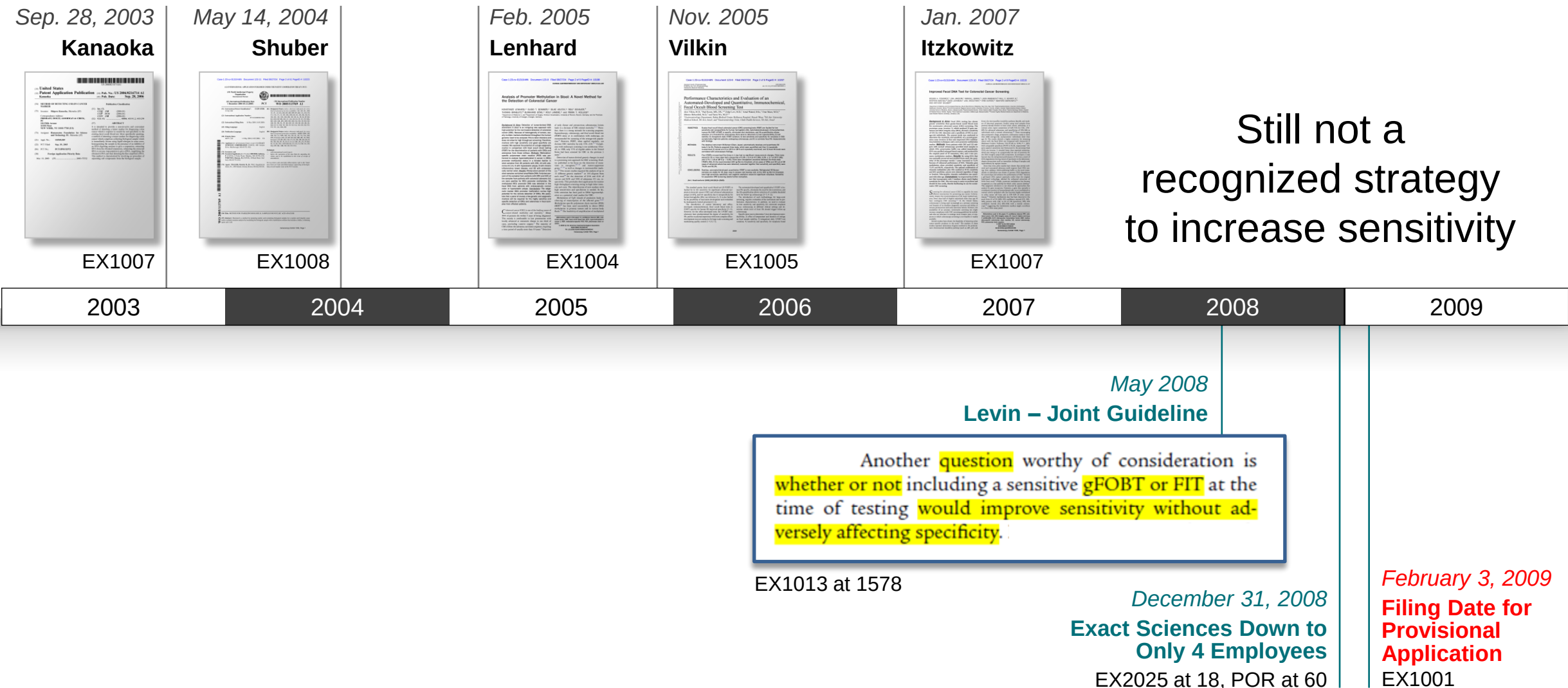
Benefit Purportedly Gained	Benefit Not Actually Gained
Potential for increased sensitivity for CRC	Lenhard specificity was low, not statistically significant, and based on subjects with known, mostly advanced, cancers EX1004 143, 146; POR at 10-11, 29; Sur-Reply at 6-7, EX2044 ¶¶64-70 No expectation of improvement in detection of advanced adenomas – i.e., preventing cancer. EX1004 at 142, 147; POR at 11, 29; EX2044 ¶ 62

Drawbacks Outweighed Any Arguable Benefits Gained

Benefit Purportedly Gained	Drawbacks From Combination
Potential for increased sensitivity for CRC	More costly and more complex than test for single marker class. POR at 35-36; Sur-Reply at 13-14; EX2044 at ¶¶152-156 More patient interaction with stool sample/less patient acceptability than Itzkowitz alone. POR at 33-35; Sur-Reply at 2-4; EX1006 at 116-117; EX2044 at ¶152 Vilkin samples required objectionable at-home refrigeration. POR at 33-34; Sur-Reply at 12-13; EX1005 at 2520, 2524; EX2044 at ¶¶147-151 Reduced specificity – more false positives leads to more unnecessary colonoscopies. POR at 4-5, 11-12, 32, 43, 48; EX1004 at 145; Sur-Reply at 9-11; EX2044 at ¶¶139-146; see <i>also</i> EX1007 at [0065][0066]

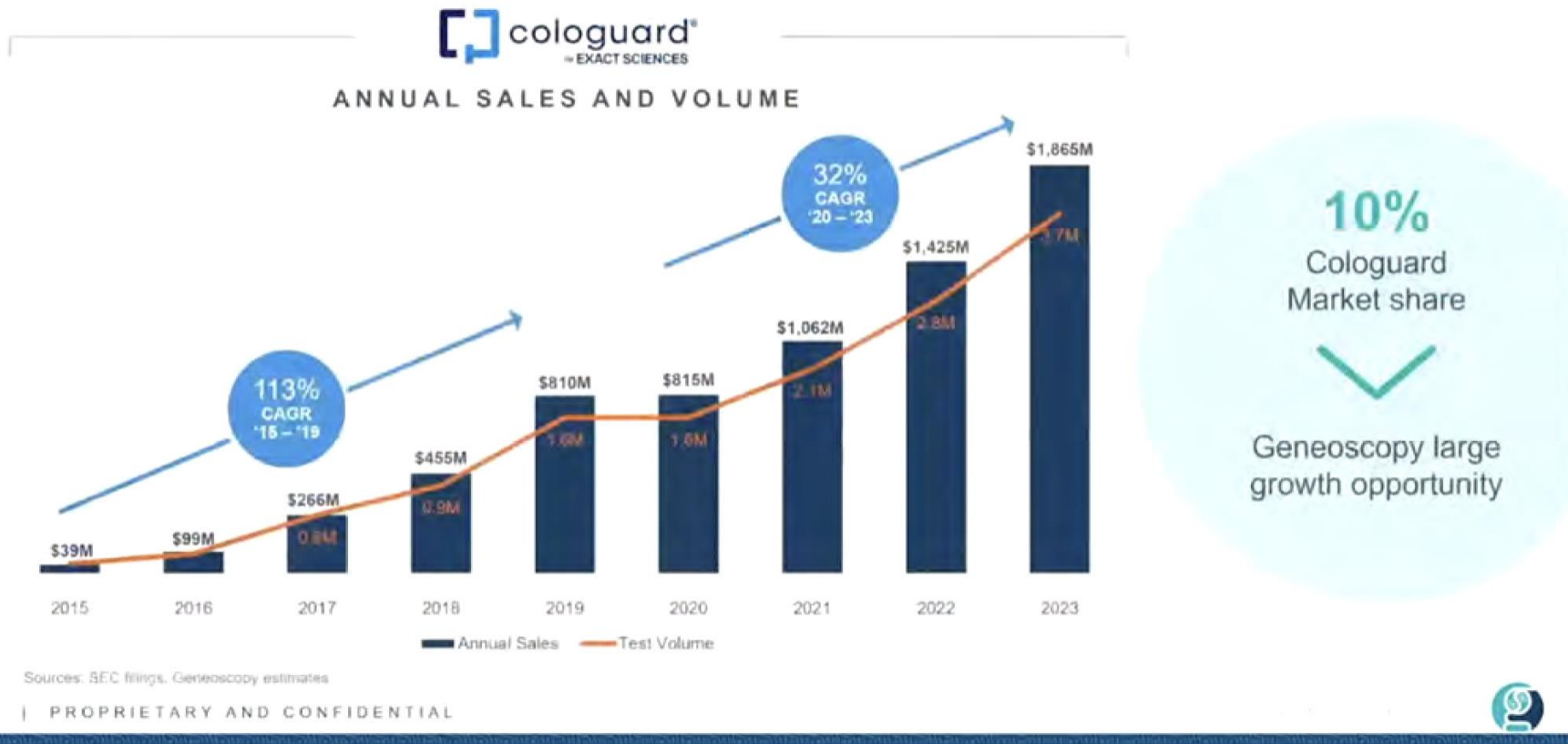
Objective Indicia Of Non-Obviousness Show Geneoscopy Relies On Hindsight

Common Sense: If Claims Were Obvious, Why Did It Take So Long?



No Dispute – Cologuard Is A Commercial Success

Noninvasive screening tests have seen rapid growth, but opportunities remain for further market expansion



EX2021 at 11; POR at 7

No Dispute – Cologuard Met A Long-Felt Need

Form 10-K 2023

More than 55% of Americans between the ages of 45 and 85 who are at average risk for colorectal cancer are not up-to-date with screening according to the American Cancer Society's ("ACS") colorectal cancer screening guidelines. We believe our Cologuard test helps more people get screened for colorectal cancer. Internal studies have shown that approximately 40% of surveyed Cologuard users were previously unscreened for colorectal cancer.

Miller-Wilson

EX2029 at 5; POR at 61

disparities. The number of people screened with the mt-sDNA test further increased in 2019, with 1.7 million patients successfully screened using mt-sDNA testing [8].

EX2037 at 2472; POR at 61

Kisiel

FIT adherence. A recent study of cross-sectional adherence in a large, national sample (n = 368,494) of Medicare beneficiaries reported an mt-sDNA test completion rate of 71%.⁵⁵ This rate exceeds by 58% the modeled FIT screening adherence rate of 45%,⁵⁴ and is well above the proposed cost-effectiveness threshold from Naber and colleagues.⁵³

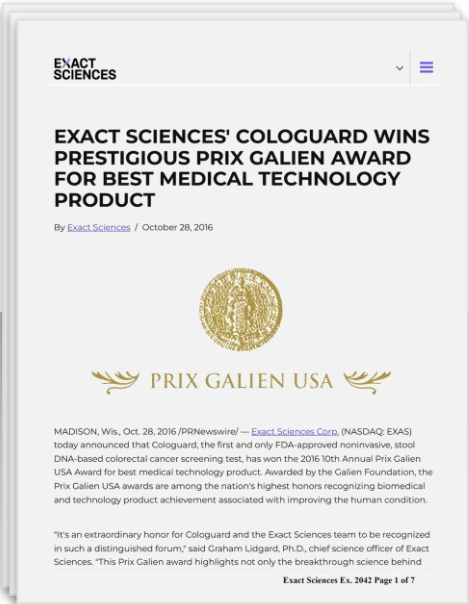
EX2038 at 562; POR at 61

Eckmann

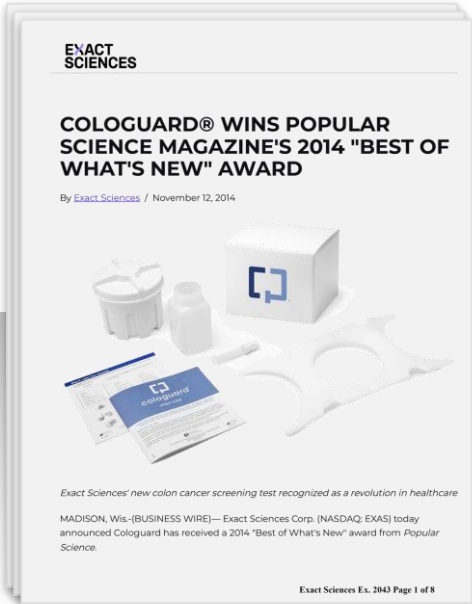
overdue [44]. While there may be many reasons for patients to go without screening, these findings suggest that MT-sDNA is attracting previously non-adherent patients, a critical outcome in the ongoing long-term fight to reduce CRC-attributable mortality.

EX2039 at 112; POR at 61

No Dispute – Cologuard Is Subject Of Praise And Awards



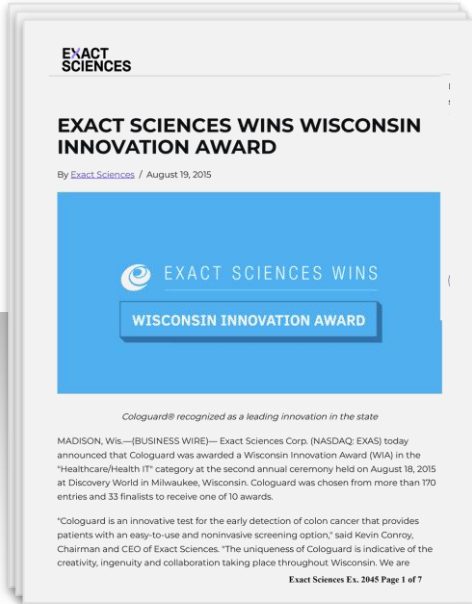
EX2031



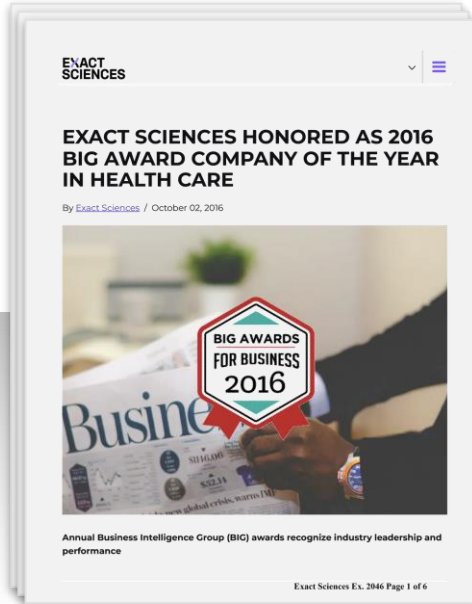
EX2032



EX2033



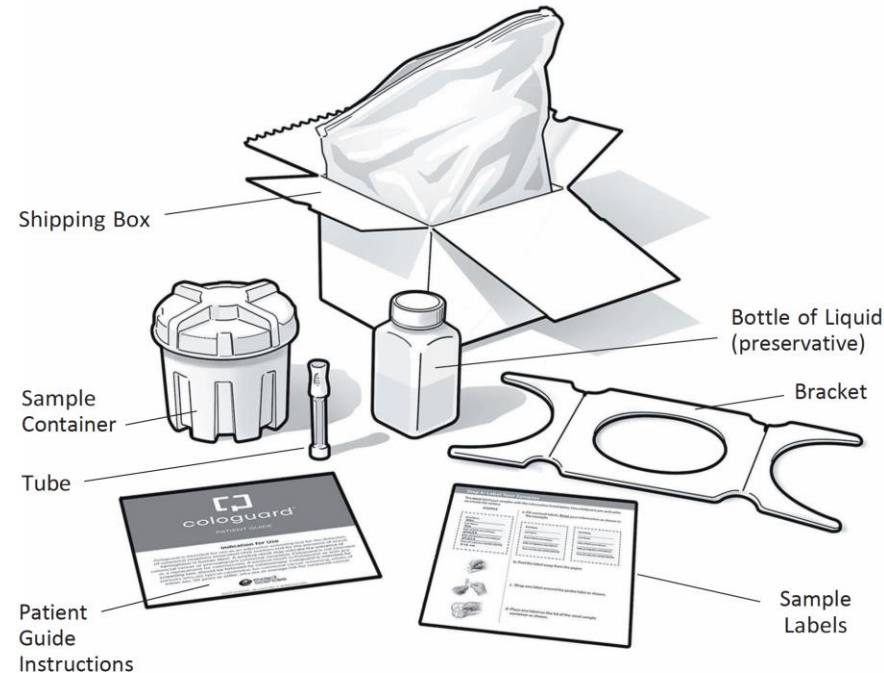
EX2034



EX2035

Common Sense Belies Petitioner's Denial Of Copying

What Is Inside the Cologuard Collection Kit



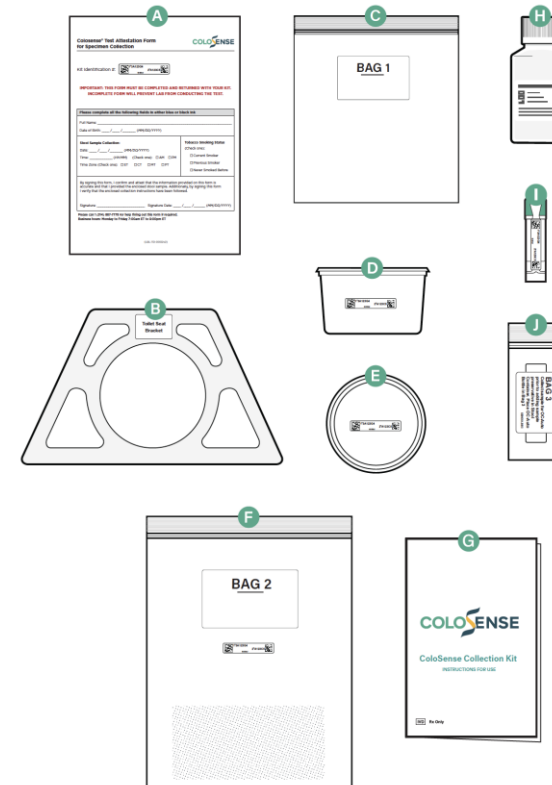
- The bottle of liquid contains a preservative (less than 10% EDTA in Tris buffered solution).
- The tube contains a 10% albumin in Tris buffered detergent solution with an antimicrobial agent.

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EX1076 at 8; POR at 53-54

ColoSense Collection Kit Contents



EX2040 at 34; POR at 63-64

Geneoscopy's Arguments On Objective Indicia Fail

- Geneoscopy does not dispute objective indicia of non-obviousness:
 - Cologuard's commercial success
 - Failure of others
 - Long-felt but unmet need
 - Industry Praise for Cologuard
- Geneoscopy ***only argues lack of nexus***

Geneoscopy Ignores Proper Framework For Nexus

We presume a nexus “when the patentee shows that the asserted objective evidence is tied to a specific product and that product ‘embodies the claimed features, and is coextensive with them.’ ”

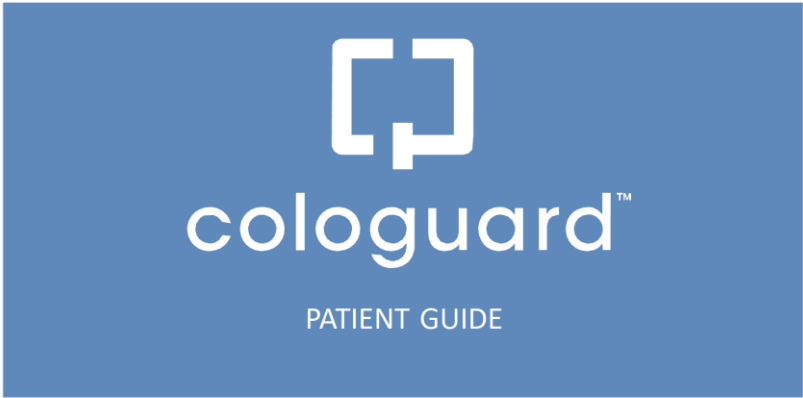
* * *

“The coextensive requirement does not require a patentee to prove perfect correspondence between the product and a patent claim.”

Quanergy Sys. Inc. v. Velodyne Lidar USA, Inc., 24 F.4th 1406, 1417 (Fed. Cir. 2022) (citations omitted);
POR at 52; Sur-Reply at 20

'746 Patent Covers Cologuard Workflow

Cologuard Patient Guide



The cover of the Cologuard Patient Guide features the Cologuard logo, which consists of a stylized 'C' made of two interlocking squares. Below the logo, the word 'cologuard' is written in a lowercase, sans-serif font, followed by a trademark symbol. Underneath that, 'PATIENT GUIDE' is written in a smaller, all-caps, sans-serif font.

Indication for Use

Cologuard is intended for the qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer (CRC) or advanced adenoma (AA) and should be followed by diagnostic colonoscopy. Cologuard is indicated to screen adults of either sex, 50 years or older, who are at typical average-risk for CRC. Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high risk individuals.



exact sciences



IVD

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Exact Sciences
Madison WI USA

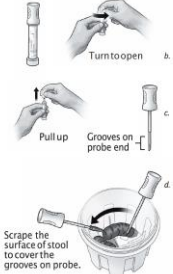
LBL-0207rev3

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EX1076 (Cologuard Patient Guide);
EX2044 ¶¶200-210; POR at 53-54

Step 4: Scrape the Stool Sample

You must scrape the stool sample with the probe to get another small sample for the Cologuard test.



The diagram shows a person's hands using a probe to scrape a stool sample from a container. The probe is held at an angle, and the tip is shown scraping the surface of the stool. The resulting sample is shown in a small container.

- Lift the tube out of the box.
- Turn the white tube cap and unscrew it.
- Pull the probe from the tube.
 - You may have to pull hard.
- Scrape the surface of your stool sample until the end of the probe has stool on it.
 - Your stool sample may look different from the stool sample pictured.

Scrape the surface of stool to cover the grooves on probe.

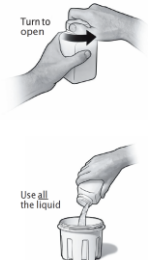
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Step 5: Prepare Stool Sample Container for Shipping

The stool sample must have a preservative poured into it to make sure the lab can test it. Then, the container must be closed tightly for shipping.



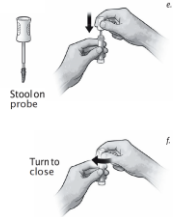
The diagram shows a person's hands pouring liquid from a bottle into a container. The bottle is held upside down, and the liquid is being poured into the container. The container is then shown with the lid being closed.

- Lift the bottle of liquid preservative out of the box.
- Hold the bottle and turn the cap to unscrew it.
 - Do **not** drink the liquid.
 - If the liquid from the bottle touches your skin or eyes, wash with water.
- Pour **all** the liquid in the bottle into the container with the stool.
 - The empty bottle and cap can be recycled or thrown in the trash.

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The diagram shows a person's hands turning the cap of the tube to close it. The cap is being turned clockwise.

- Place the probe back into the open end of the tube.
- Turn the cap to close.
- Set the tube down.

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The diagram shows a person's hands turning the lid of the container to seal it. The lid is being turned clockwise. A 'Correct!' label is shown next to the sealed container, and a 'Wrong!' label is shown next to a container with a gap in the seal.

- Hold the stool sample container on a hard, flat surface.
- Place the lid on top of the container.
 - Make sure the lid is straight so it will close tightly.
- Turn the lid to tighten until it does not tighten anymore.

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'746 Patent Covers Cologuard Workflow

Cologuard Physician's Brochure

Assay Technology

The patient stool samples are processed at the laboratory to isolate the DNA for testing. Amplification and detection of methylated target DNA (NDRG4, BMP3), KRAS point mutations, and ACTB (a reference gene for quantitative estimation of the total amount of human DNA in each sample) is performed using the Quantitative Allele-specific Real-time Target and Signal Amplification (QuARTS™) technology. Multi-plexed QuARTS reactions are processed using a real-time cyclor with each marker (NDRG4, BMP3, KRAS, and ACTB) monitored separately through independent fluorescent detection channels. The hemoglobin stool sample is prepared and analyzed in a quantitative Enzyme-Linked Immunosorbent Assay (ELISA) that determines the concentration of hemoglobin in the sample.

EX1080 at 4; POR at 54; EX2044 ¶210-213;
see also POR at 52-58

'278 Patent File History Not Relevant To Nexus

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:

EX1029 at 8-9; POR at 55-56; Sur-Reply at 24

- Comments concern need for DNA isolation methods
- Do not address need for convenient at-home CRC screening, and do not attribute success of Cologuard to the '278 subject matter

Petitioner's Cursory Arguments Regarding Other Patents

- **Patents related to general use of stool in CCR screening:** *e.g.*, U.S. Pat. Nos. 5,741,650, 5,952,178, 6,303,304, 6,586,177.
- **Patents related to containers for collecting and storing stool samples:** *e.g.*, U.S. Pat. Nos. 9,211,112, 9,750,482, 10,265,054, 10,486,158, 10,702,250, 10,894,256.
- **Patents related to DNA stabilizing buffer:** *e.g.*, U.S. Pat. Nos. 6,551,777, 8,722,330.
- **Patents related to DNA isolation methods:** *e.g.*, U.S. Pat. Nos. 6,268,136, 6,406,857, 8,993,341, 8,999,176, 9,000,146, 9,057,098, 9,163,278, 9,169,511, 9,657,330, 9,631,228, 9,845,491, 9,856,515, 10,047,390, 10,822,639.
- **Patents related to DNA markers:** *e.g.*, U.S. Pat. Nos. 8,673,555, 8,969,046, 9,121,070, 9,127,318, 9,163,278, 9,169,511, 9,399,800, 9,783,856, 9,803,249, 9,845,491, 10,435,753.
- **Patents related to methods of preparing DNA for methylation analysis:** *e.g.*, U.S. Pat. Nos. 9,315,853, 10,144,953, 10,704,083.
- **Patents related to methods of testing for methylated DNA:** *e.g.*, U.S. Pat. Nos. 8,916,344, 9,637,792, 10,519,510, 10,590,489, 10,808,286.
- **Patents related to methods of detecting DNA mutations:** *e.g.*, U.S. Pat. Nos. 8,361,720, 8,715,937, 9,024,006, 9,121,071, 9,212,392, 9,290,797, 9,376,721, 10,000,817, 10,106,844, 10,590,489.
- **Patents related to control molecules used with DNA assays:** *e.g.*, U.S. Pat. Nos. 9,212,392, 10,106,844, 10,138,524, 10,253,358, 10,889,867.

EX1002 ¶ 344; POR at 54-55

Geneoscopy Ignores Proper Framework For Nexus

It is “unsound” to require that “presumption of nexus does not apply if any unclaimed feature materially affects the functioning of the product that is alleged to be coextensive” as “**virtually every innovative product inevitably has some unclaimed feature that materially affects its functionality.**”

Teva Pharms. Int'l GmbH v. Eli Lilly & Co., 8 F.4th 1349, 1361 (Fed. Cir. 2021)) POR at 52; Sur-Reply at 20

No Evidence Other Cited Patents Are Relevant

Q. So you don't have an opinion as to whether or not those 60 patents are the reason for patient uptake or accuracy of the test?

A. I have an opinion on patient uptake of Cologuard, but I don't have -- I'm not asserting that there is a direct connection between the patient uptake and those 60 patents, either in my declaration or here.

EX2051 (Whitney 1/9/25 Dep. Tr.) at 61:18-62:3; POR at 55

Q. Are you aware of whether any of those 60 patents you reference in Paragraph 9 of your second declaration are expired?

A. I know that some of the patents that we reference were expired. I don't recall which ones or how many.

EX2051 (Whitney 1/9/25 Dep. Tr.) at 59:6-12; Sur-Reply at 21

Evidence Shows Marketing Is Not The Reason For Success

To be clear, Conroy and Exact have not relied solely - or even primarily - on DTC tactics to turn Cologuard into a powerhouse. Their playbook has included more traditional elements, including innovation, discipline, and grit, that have led to Cologuard achieving adoption by more than 10 million patients over the past decade. “Getting into the clinical guidelines required

EX1091 at 7; Sur-Reply at 25

Efficacy Data Was Critical To Commercial Success

Q. And what is your opinion about that, not about the FDA, but about whether the medical community would prescribe Cologuard if there was not data to support its use?

A. I see. I see what you're getting at. I believe that the -- let me think about the way I want to answer this. **I believe there must be evidence that provides some convincing aspect of utility of a test in order for people to prescribe it.**

EX2051 (Whitney 1/9/25 Dep. Tr.) at 143:3-14; Sur-Reply at 25

Cologuard's Success Is Due To The Merits Of The Invention

With respect to the objective indicia of nonobviousness, while there is evidence that marketing and financing played a role in the success of Hybritech's kits, as they do with any product, it is clear to us on the entire record that the commercial success here was due to the merits of the claimed invention. It cannot be argued on this record that Hybritech's success would have been as great and as prolonged as admittedly it has been if that success were not due to the merits of the invention. The evidence is that these kits compete successfully with numerous others for the trust of persons who have to make fast, accurate, and safe diagnoses. This is not the kind of merchandise that can be sold by advertising hyperbole.

Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1382 (Fed. Cir. 1986); Sur-Reply at 25

THANK YOU

CERTIFICATE OF SERVICE

The undersigned certifies that the foregoing Patent Owner Exact Science's Demonstratives were served via email on the following counsel of record for the Petitioner:

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Date: November 17, 2025

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