

CTL IP Series

IP Series #2: Why are diagnostic claims so hard to get (in the US)?

2/17/2022

CTL CENTER FOR
TECHNOLOGY
LICENSING
AT CORNELL UNIVERSITY

CTL IP Series



Michael L. Goldman
Partner, Troutman
Pepper



Tate Tischner
Counsel, Troutman
Pepper



Brian Kelly
Director, Licensing, CTL

CTL CENTER FOR
TECHNOLOGY
LICENSING
AT CORNELL UNIVERSITY

Diagnostic Test IP

Brian Kelly, Mike Goldman, & Tate Tischner

February 17, 2022

These materials and commentary are intended for educational purposes only. No portion may be construed as rendering legal advice for specific cases, or as creating an attorney-client relationship between the audience and the author. The opinions expressed herein are solely those of the authors.

Why is this important?

The United States In-vitro Diagnostics Market Size was worth US\$ 26.9 Billion in 2020 and is projected to be worth US\$ 35.3 Billion by 2026

The in-vitro diagnostics industry has seen a huge spurt in demand due to the Covid-19 Pandemic.

Patients Benefit from Diagnostics:

- 70% of medical decisions by physicians rely on diagnostic assay results*

Patients Benefit from Companion Diagnostics:

- Quicker FDA Approval of New (more effective) Pharmaceuticals

Everyone Benefits from Jobs:

- Diagnostics Companies, Hospitals, USPTO, FDA and Universities

*Steve Burrill, Burrill & Co. Venture Capital, EMBO Rep. Oct., 2007; 8(10): 903-906

The Challenges

Obtaining patent protection for diagnostic technologies and methods is challenging.

When drafting method claims that cover a diagnostic testing method, two problems arise:

- First, the subject matter will include patent-ineligible elements because the method measures a natural phenomenon.
- Second, the divided responsibilities of the company and the laboratory might mean that neither party performs all the elements of the method claim, allowing the parties to potentially evade infringement liability.

35 U.S.C. § 101

“Whoever invents or discovers any new and useful **process, machine, manufacture, or composition of matter**, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.”

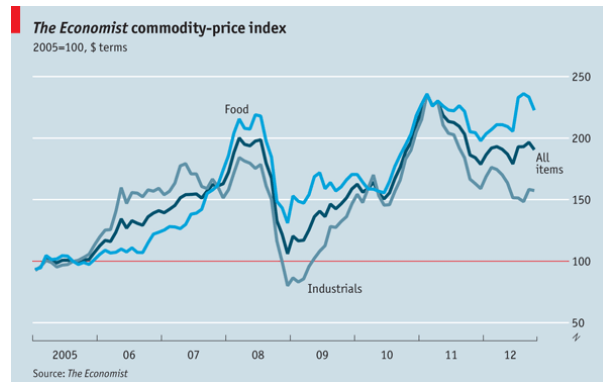
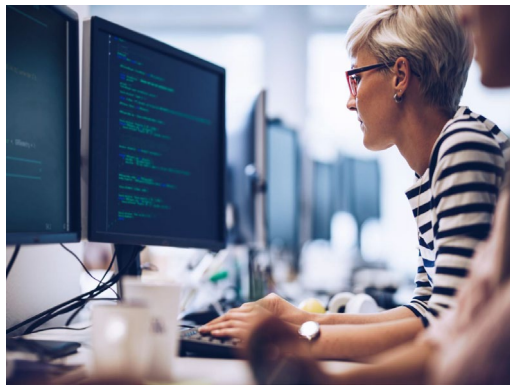
- Interpreted by courts to *exclude* “laws of nature, natural phenomena, and abstract ideas”—naturally occurring phenomena, mental processes, and mathematical algorithms.

Diagnostic Test IP – Background and Law

Historically Limited to Computer Software

➤ *Bilski v. Kappos* 561 U.S. 593 (2010)

- A business method patent rejected for being an “abstract idea”
- The rejected claim related to a method of how buyers and sellers of commodities in the energy market can protect, or hedge, against the risk of price changes



Moved Into Biological Methods

➤ ***Mayo Collaborative Servs. v. Prometheus Laboratories, Inc.*, 566 U.S. 66 (2012)**

➤ Diagnostic claims deemed ineligible for patenting – effectively claim a law of nature

1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder comprising:

(a) administering a drug providing a 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and

(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder, wherein the level of 6-thioguanine less than about 230 pmol per 8×10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and

wherein the level of 6-thioguanine greater than about 400 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Biological Methods Post-Mayo

➤ *Ariosa v. Sequenom* (Fed. Cir. 2015) - **ineligible**

1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises

amplifying a paternally inherited nucleic acid from the serum or plasma sample and

detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.



25. A method for performing a prenatal diagnosis on a maternal blood sample, which method comprises

obtaining a non-cellular fraction of the blood sample

amplifying a paternally inherited nucleic acid from the non-cellular fraction

and performing nucleic acid analysis on the amplified nucleic acid to detect paternally inherited fetal nucleic acid.

Biological Methods Post-Mayo

➤ *Vanda Pharmaceuticals v. West-Ward Pharmaceuticals (Fed. Cir. 2018)* – **eligible**

A method for treating a patient with iloperidone, wherein the patient is suffering from schizophrenia, the method comprising the steps of:

determining whether the patient is a CYP2D6 poor metabolizer by:

- obtaining or having obtained a biological sample from the patient;

- and

- performing or having performed a genotyping assay on the biological sample to determine if the patient has a CYP2D6 poor metabolizer genotype; and

if the patient has a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount of 12 mg/day or less, and

if the patient does not have a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount that is greater than 12 mg/day, up to 24 mg/day,

wherein a risk of QTc prolongation for a patient having a CYP2D6 poor metabolizer genotype is lower following the internal administration of 12 mg/day or less than it would be if the iloperidone were administered in an amount of greater than 12 mg/day, up to 24 mg/day.



Biological Methods Post-Mayo

➤ *Endo Pharmaceuticals v. Teva Pharmaceuticals* (Fed. Cir. 2019) – **eligible**

1. A method of treating pain in a renally impaired patient, comprising the steps of:

a. providing a solid oral controlled release dosage form, comprising:

- i. about 5 mg to about 80 mg of oxymorphone or a pharmaceutically acceptable salt thereof as the sole active ingredient; and
- ii. a controlled release matrix;



b. measuring a creatinine clearance rate of the patient and determining it to be

- (a) less than about 30 ml/min,
- (b) about 30 mL/min to about 50 mL/min,
- (c) about 51 mL/min to about 80 mL/min, or
- (d) above about 80 mL/min; and

c. orally administering to said patient, in dependence on which creatinine clearance rate is found, a lower dosage of the dosage form to provide pain relief;

wherein after said administration to said patient, the average AUC of oxymorphone over a 12-hour period is less than about 21 ng ·hr/mL.

Diagnostic Test IP – Examples from Cornell's Patent Portfolio (Lyden)

U.S. Patent Application Serial No. 15/517,697 to Lyden et al.

“Methods for Prognosing and Preventing Metastatic Liver Disease”

1. A method of identifying a subject having or at risk of developing metastatic liver disease, said method comprising:

measuring, in a sample isolated from the subject, exosomal levels of one or more markers of metastatic liver disease selected from the group consisting of Annexin A1 (ANXA1), CD44, CD47, cadherin 1 (CDH1), filamin A (FLNA), high mobility group box 1 (HMGB1), integrin β 3 (ITGB3), lectin galactoside-binding soluble 1 (LGALS1), lectin galactoside-binding soluble 3 (LGALS3), macrophage migration inhibitory factor (MIF), matrix metalloproteinase 14 (MMP14), plasminogen activator urokinase receptor (PLAUR), prostaglandin-endoperoxide synthase 2 (PTGS2), and ras-related C3 botulinum toxin substrate 1 (RAC1);

comparing the measured exosomal levels of the one or more markers of metastatic liver disease to exosomal levels of the one or more markers of metastatic liver disease in a control sample; and

identifying the subject as having or at risk of developing liver metastases when said subject has increased exosomal levels of the one or more markers of metastatic liver disease relative to control levels of the one or more markers of metastatic liver disease.

- Original claim **rejected** under 35 U.S.C. § 101
 - The correlation is a natural phenomenon
 - Mental process of comparing is an abstract idea.

Diagnostic Test IP – Examples from Cornell's Patent Portfolio (Lyden)

U.S. Patent Application Serial No. 15/517,697 to Lyden et al.

“Methods for Prognosing and Preventing Metastatic Liver Disease”

Claim amended:

- Added more “active” steps

Was **not** successful in overcoming the § 101 rejection

- Correlation of biomarkers is a “natural phenomenon”

Claim 1 (as amended):

1. (Currently Amended) A method of ~~identifying a subject having or at risk of developing metastatic liver disease, said method~~ comprising:
selecting a subject having a pancreatic lesion;
obtaining, from the selected subject, a sample containing exosomes;
isolating exosomes from said sample; and
detecting, in said isolated exosomes, expression ~~measuring, in a sample isolated from the subject, exosomal~~ levels of one or more markers of metastatic liver disease selected from the group consisting of Annexin A1 (ANXA1), CD44, CD47, cadherin 1 (CDH1), filamin A (FLNA), high mobility group box 1 (HMGB1), integrin β 3 (ITGB3), lectin galactoside-binding soluble 1 (LGALS1), lectin galactoside-binding soluble 3 (LGALS3), macrophage migration inhibitory factor (MIF), matrix metalloproteinase 14 (MMP14), plasminogen activator urokinase receptor (PLAUR), prostaglandin-endoperoxide synthase 2 (PTGS2), and ras-related C3 botulinum toxin substrate 1 (RAC1) to phenotype said pancreatic lesion;
~~comparing the measured exosomal levels of the one or more markers of metastatic liver disease to exosomal levels of the one or more markers of metastatic liver disease in a control sample; and~~
~~identifying the subject as having or at risk of developing liver metastases when said subject has increased exosomal levels of the one or more markers of metastatic liver disease relative to control levels of the one or more markers of metastatic liver disease.~~

Diagnostic Test IP – Examples from Cornell's Patent Portfolio (Lyden)

U.S. Patent Application Serial No. 15/517,697 to Lyden et al.

“Methods for Prognosing and Preventing Metastatic Liver Disease”

Claim 1 (as further amended):

Further claim amendments:

- “detecting” proteins rather than “markers”

The amended method was **allowed**

1. (Currently Amended) A method comprising:
selecting a subject having a pancreatic lesion;
obtaining, from the selected subject, a sample containing exosomes;
isolating exosomes from said sample; and
detecting, in said isolated exosomes, expression levels of one or more proteins
markers of metastatic liver disease selected from the group consisting of Annexin A1 (ANXA1),
CD44, CD47, cadherin 1 (CDH1), filamin A (FLNA), high mobility group box 1 (HMGB1), integrin
β3 (ITGB3), lectin galactoside-binding soluble 1 (LGALS1), lectin galactoside-binding soluble 3
(LGALS3), macrophage migration inhibitory factor (MIF), matrix metalloproteinase 14 (MMP14),
plasminogen activator urokinase receptor (PLAUR), prostaglandin-endoperoxide synthase 2
(PTGS2), and ras-related C3 botulinum toxin substrate 1 (RAC1) to phenotype said pancreatic lesion.

Diagnostic Test IP – Examples from Cornell's Patent Portfolio (Barany)

U.S. Patent Application Serial No. 12/520,386 to Barany et al.

“Use of Lecithin:Retinol Acyl Transferase Gene Promoter Methylation in Evaluating the Cancer State of a Subject”

1. A method of evaluating the cancer state of a subject comprising;
isolating a sample of DNA from a subject, and
determining a first methylation level of the lecithin:retinol acyl transferase gene promoter nucleotide sequence, or of the region upstream of the lecithin:retinol acyl transferase gene promoter nucleotide sequence, in the DNA sample wherein the detection of a methylated lecithin:retinol acyl transferase gene promoter nucleotide sequence, or region upstream thereof, within the sample permits the evaluation of the cancer state of the subject.

2. A method of evaluating the cancer state of a subject according to claim 1 further comprising:
comparing the first methylation level of the lecithin:retinol acyl transferase gene promoter nucleotide sequence, or region upstream thereof, to a second methylation level of a lecithin:retinol acyl transferase gene promoter nucleotide sequence, or region upstream thereof, in a reference DNA sample, wherein a difference between the first and second methylation levels permits evaluation of the cancer state of the subject.

Original claims rejected under 35 U.S.C. § 101

➤ Alleged to recite nothing more than a law of nature

Diagnostic Test IP – Examples from Cornell's Patent Portfolio (Barany)

U.S. Patent Application Serial No. 12/520,386 to Barany et al.

“Use of Lecithin:Retinol Acyl Transferase Gene Promoter Methylation in Evaluating the Cancer State of a Subject”

Claim amended:

- Argued that administering step is a transformative step

1. (Currently Amended) A method of evaluating the cancer state of
prognosing colorectal cancer in a subject comprising;
isolating a colorectal cancer sample of DNA from a from the subject; ~~and~~
determining a first methylation level of the lecithin:retinol acyl transferase gene
promoter nucleotide sequence in the isolated sample from the subject; ~~or of the region upstream~~
~~of the lecithin:retinol acyl transferase gene promoter nucleotide sequence, in the DNA sample~~
~~wherein the detection of a methylated lecithin:retinol acyl transferase gene promoter nucleotide~~
~~sequence, or region upstream thereof, within the sample permits the evaluation of the cancer state~~
~~of the subject~~
providing a second methylation level of the lecithin:retinol acyl transferase gene
promoter nucleotide sequence, said second methylation level being from either (1) a colorectal
cancer sample obtained from the subject at a time before said determining, or (2) one or more
reference samples of colorectal cancer obtained from early stage colorectal tumors;
comparing the first methylation level of the lecithin:retinol acyl transferase gene
promoter nucleotide sequence with the second methylation level of the lecithin:retinol acyl
transferase gene promoter nucleotide sequence, wherein a decrease in the first methylation level
compared to the second methylation level, indicates an unfavorable colorectal cancer prognosis;
and
administering a pharmaceutical composition comprising a lecithin:retinol acyl
transferase inhibitor to the subject when said comparing indicates an unfavorable colorectal cancer
prognosis.

Diagnostic Test IP – Examples from Cornell's Patent Portfolio (Barany)

U.S. Patent Application Serial No. 12/520,386 to Barany et al.

“Use of Lecithin:Retinol Acyl Transferase Gene Promoter Methylation in Evaluating the Cancer State of a Subject”

Also added new claim 57

57. (New) A method of prognosing colorectal cancer in a subject, said method comprising:

- isolating a colorectal cancer sample from a subject;
- contacting the isolated sample from the subject with reagents suitable to detect a first methylation level of the lecithin:retinol acyl transferase gene promoter nucleotide sequence in the sample;
- providing a second methylation level of the lecithin:retinol acyl transferase gene promoter nucleotide sequence, said second methylation level from either (1) a colorectal cancer sample obtained from the subject at a time before said contacting, or (2) one or more reference samples of colorectal cancer obtained from early stage colorectal tumors; and
- comparing the first methylation level of the lecithin:retinol acyl transferase gene promoter nucleotide sequence detected in the sample from the subject with the second methylation level of a lecithin:retinol acyl transferase gene promoter nucleotide sequence, wherein (i) a decrease in the first methylation level of the lecithin:retinol acyl transferase gene promoter nucleotide sequence in the sample compared to the second methylation level indicates an unfavorable colorectal cancer prognosis for the subject, and (ii) an increase or no change in the first methylation level of the lecithin:retinol acyl transferase gene promoter nucleotide sequence in the sample compared to the second methylation level indicates a favorable colorectal cancer prognosis for the subject.

Diagnostic Test IP – Examples from Cornell's Patent Portfolio (Barany)

U.S. Patent Application Serial No. 12/520,386 to Barany et al.

“Use of Lecithin:Retinol Acyl Transferase Gene Promoter Methylation in Evaluating the Cancer State of a Subject”

Both claims 1 and 57 again rejected under § 101

Claims amended further:

1. (Currently Amended) A method of ~~prognosing colorectal cancer in a~~ subject comprising[:];

- isolating a colorectal cancer sample from ~~the a human~~ subject;
- determining in the isolated sample from the subject a first methylation level of the lecithin:retinol acyl transferase gene promoter having a nucleotide sequence corresponding to the nucleotide sequence of SEQ ID NO: 1 in the isolated sample from the subject;
- providing a second methylation level of the lecithin:retinol acyl transferase gene promoter having a nucleotide sequence corresponding to the nucleotide sequence of SEQ ID NO: 1, said second methylation level being from either (1) a colorectal ~~cancer~~ sample obtained from the subject at a time before said determining, or (2) one or more reference samples of ~~colorectal cancer~~ obtained from early stage colorectal tumors or benign colorectal tissue;
- comparing the first methylation level of the lecithin:retinol acyl transferase gene promoter nucleotide sequence with the second methylation level of the lecithin:retinol acyl transferase gene promoter nucleotide sequence, ~~wherein a decrease in the first methylation level compared to the second methylation level, indicates an unfavorable colorectal cancer prognosis;~~
- and
- detecting a decrease in the first methylation level compared to the second methylation level; and
- administering a pharmaceutical composition comprising a lecithin:retinol acyl transferase inhibitor to the subject ~~when said comparing indicates an unfavorable colorectal cancer prognosis based on said detecting.~~

Diagnostic Test IP – Examples from Cornell's Patent Portfolio (Barany)

U.S. Patent Application Serial No. 12/520,386 to Barany et al.

“Use of Lecithin:Retinol Acyl Transferase Gene Promoter Methylation in Evaluating the Cancer State of a Subject”

57. (Currently Amended) A method of ~~prognosing colorectal cancer in a subject, said method~~ comprising:

isolating a colorectal cancer sample from a human subject;

contacting the isolated sample from the subject with reagents suitable to detect a first methylation level of ~~the~~ a lecithin:retinol acyl transferase gene promoter having a nucleotide sequence corresponding to the nucleotide sequence of SEQ ID NO: 1 in the sample wherein said methylation level is determined based on methylation status of at least one or more nucleotides corresponding to nucleotides 114, 172, 222, 242, 263, and 279 of SEQ ID NO:1;

providing a second methylation level of the lecithin:retinol acyl transferase gene promoter having a nucleotide sequence corresponding to the nucleotide sequence of SEQ ID NO: 1, said second methylation level from either (1) a colorectal ~~cancer~~ sample obtained from the subject at a time before said contacting, or (2) one or more reference samples ~~of colorectal cancer~~ obtained from early stage colorectal tumors or benign colorectal tissue wherein said methylation level is determined based on methylation status of at least one or more nucleotides corresponding to nucleotides 114, 172, 222, 242, 263, and 279 of SEQ ID NO:1; and

comparing the first methylation level of the lecithin:retinol acyl transferase gene promoter nucleotide sequence detected in the sample from the subject with the second methylation level of [[a]] the lecithin:retinol acyl transferase gene promoter nucleotide sequence; and

detecting a decrease in the first methylation level compared to the second methylation level - wherein (i) a decrease in the first methylation level of the lecithin:retinol acyl transferase gene promoter nucleotide sequence in the sample compared to the second methylation level indicates an unfavorable colorectal cancer prognosis for the subject, and (ii) an increase or no change in the first methylation level of the lecithin:retinol acyl transferase gene promoter nucleotide sequence in the sample compared to the second methylation level indicates a favorable colorectal cancer prognosis for the subject.

The claims were **rejected** a third time under § 101

Additional amendments resulted in **allowance** of claim 1 (claim 57 was deleted)

Diagnostic Test IP – Examples from Cornell's Patent Portfolio (Barany)

U.S. Patent Application Serial No. 12/520,386 to Barany et al.

“Use of Lecithin:Retinol Acyl Transferase Gene Promoter Methylation in Evaluating the Cancer State of a Subject”

1. (Currently Amended) A method comprising:

isolating providing a colorectal cancer sample from a human subject;

determining in the ~~isolated~~ provided sample from the subject a first methylation

level of lecithin:retinol acyl transferase gene promoter having a nucleotide sequence corresponding to the nucleotide sequence of SEQ ID NO: 1;

providing a second methylation level of the lecithin:retinol acyl transferase gene promoter having a nucleotide sequence corresponding to the nucleotide sequence of SEQ ID NO: 1, said second methylation level being from either (1) a colorectal sample obtained from the subject at a time before said determining, or (2) one or more reference samples obtained from early stage colorectal tumors or benign colorectal tissue;

comparing the first methylation level of the lecithin:retinol acyl transferase gene promoter nucleotide sequence with the second methylation level of the lecithin:retinol acyl transferase gene promoter nucleotide sequence

detecting a decrease in the first methylation level compared to the second methylation level; and

administering a pharmaceutical composition comprising a lecithin:retinol acyl transferase inhibitor to the subject based on said detecting.

Allowed Claim

Diagnostic Test IP – Examples from Cornell's Patent Portfolio (Barany)

Claim 1 of U.S. Patent No. 11,209,424

- An example of the type of coverage we are routinely able to get on Francis Barany's technology where steps of manipulating nucleic acids is involved.

(12) United States Patent Barany et al.	(10) Patent No.: US 11,209,424 B2 (45) Date of Patent: Dec. 28, 2021
(54) METHOD FOR RELATIVE QUANTIFICATION OF NUCLEIC ACID SEQUENCE, EXPRESSION, OR COPY CHANGES, USING COMBINED NUCLEASE, LIGATION, AND POLYMERASE REACTIONS	(58) Field of Classification Search CPC G01N 33/5308; C12Q 1/6813; C12Q 1/6806; C12Q 2521/501; C12Q 2533/107; C12Q 1/6851 See application file for complete search history.
(71) Applicant: Cornell University , Ithaca, NY (US)	(56) References Cited
(72) Inventors: Francis Barany , New York, NY (US); Eugene Spier , Los Altos, CA (US); Alain Mir , Redwood City, CA (US)	U.S. PATENT DOCUMENTS 5,573,907 A 11/1996 Carrino et al. 5,854,033 A 12/1998 Lizardi (Continued)
(73) Assignee: CORNELL UNIVERSITY , Ithaca, NY (US)	FOREIGN PATENT DOCUMENTS
(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 95 days.	WO 2004/053105 A2 6/2004 WO 2010/0105074 9/2010 WO 2011/0063388 5/2011
(21) Appl. No.: 16/422,538	OTHER PUBLICATIONS
(22) Filed: May 24, 2019	Haaqi, "Direct Ligation of PCR Products for Cloning and Sequencing," <i>Nucleic Acids Research</i> 20(23):6427 (1992).
(65) Prior Publication Data	(Continued)
US 2019/0346430 A1 Nov. 14, 2019	<i>Primary Examiner</i> — Joseph G. Dauner
Related U.S. Application Data	(74) <i>Attorney, Agent, or Firm</i> — Troutman Pepper Hamilton Sanders LLP (Rochester)
(62) Division of application No. 15/425,516, filed on Feb. 6, 2017, now Pat. No. 10,338,062, which is a division (Continued)	ABSTRACT
(51) Int. Cl. C12Q 1/6806 (2018.01) C12Q 1/6813 (2018.01) (Continued)	The present invention is directed to methods for identifying the presence of one or more target nucleotide sequences in a sample that involve a ligation and/or polymerase reaction. In some embodiments, the ligation products formed in the ligation process of the present invention are subsequently amplified using a polymerase chain reaction. The ligated product sequences or extension products thereof are detected, and the presence of one or more target nucleotide sequences in the sample is identified based on the detection.
(52) U.S. Cl. CPC G01N 33/5308 (2013.01); C12Q 1/6806 (2013.01); C12Q 1/6813 (2013.01);	

Diagnostic Test IP – Examples from Cornell's Patent Portfolio (Barany)

1. A method for identifying a presence of one or more target nucleotide sequences in a sample comprising:

- providing a sample potentially containing the one or more target nucleotide sequences;

- forming primary products in a reaction process, said reaction process comprising a ligation and/or polymerase reaction, wherein each primary product comprises, in a 5' to 3' orientation, a 5' primer-specific portion, a first portion of a zip-code portion, a first tag portion, a target-specific portion, a second tag portion, a second portion of the zip-code portion, and a 3' primer-specific portion, wherein the first and second portions of the zip-code portion of a primary product, when adjacently positioned, form a full-length zip-code, and wherein the first and second tag portions of a primary product are complementary to each other;

- providing one or more oligonucleotide primer sets, each set comprising (a) a first oligonucleotide primer comprising the same nucleotide sequence as the 5' primer-specific portion of the primary product, (b) a second oligonucleotide primer comprising a nucleotide sequence that is complementary to the 3' primer-specific portion of the primary product, and (c) a capture oligonucleotide complementary to a portion of the first zip-code portion and a portion of the second zip-code portion, wherein the capture oligonucleotide comprises a quencher molecule and a detectable label;

- blending the primary products, the one or more oligonucleotide primer sets, and a DNA polymerase to form one or more polymerase chain reaction mixtures;

- subjecting the one or more polymerase chain reaction mixtures to one or more polymerase chain reaction cycles thereby forming primary extension products, wherein during the one or more polymerase reaction cycles, said primary extension products are subject to conditions effective for (i) the first and second tag portions of a particular primary extension product to hybridize to each other to form hairpinned extension products with adjacently positioned first and second zip-code portions and (ii) the capture oligonucleotide to hybridize to complementary adjacently positioned first and second zip-code portions of the hairpinned extension products;

- cleaving the quencher molecule or the detectable label from the hybridized capture oligonucleotides;

- detecting the detectable label after said cleaving; and

- identifying the presence of the one or more target nucleotide sequences in the sample based on said detecting.

Diagnostic Test IP – Practical Considerations from Cornell Disclosures

When developing a molecular diagnostic for a disease state that **involves specific critical reagents** ensure that the reagents do not simply read on naturally occurring counterparts (e.g., genomic DNA or fragments thereof, polypeptides, peptides, RNA transcripts, antibodies, cells etc.). To avoid this hurdle, consider:

- Introducing mutations in the nucleic acid or amino acid sequences of reagents
- Altering linkages or backbones in nucleic acid or amino acid reagents to yield molecules that are structurally distinct
- Conjugating the naturally occurring diagnostic reagent with another chemical moiety
- Transfecting a host cell with a non-endogenous naturally occurring protein or nucleic acid from a distinct species/genus to yield a cell-based construct with a distinct function/property compared with an untransfected host cell.

When you are developing a molecular diagnostic for a disease state that **does NOT involve specific critical reagents**, consider incorporating a novel detection methodology or sample preparation step

Diagnostic Test IP – Practical Considerations from Cornell Disclosures

Many diagnostic methods do not require novel reagents so consider adding an administration step to the diagnostic methods.

Adding an administration step to diagnostic claims can also be a problem because a testing clinic may perform the diagnosis and a doctor or hospital may do the administration – leading to a “two-actor” problem.

- The solution: turn the diagnostic claims into medical treatment claims.
- “A method comprising administering X to a subject having cancer cells that express Y”

The details of the diagnostic methods (detecting Y) can also be included in the independent or dependent claims.

35 U.S.C. § 101: Practical Tips (How to avoid problems)

- Avoid combination of trivial positive manipulative steps and purely mental steps in method claims
- Include unique reagents that do not occur in nature in method claims
- Include steps that involve non-trivial positive manipulative steps in method claims
- Include steps that involve sample preparation in method claims
- Claim alternatives to pure diagnostic method claims that can meaningfully protect invention, e.g., kits, methods of treatment, devices

Thank you!

Brian Kelly, Mike Goldman, & Tate Tischner

February 17, 2022