US District Court Civil Docket

U.S. District - North Carolina Middle (Ncmd)

1:12cv1173

Esoterix Genetic Laboratories, Llc et al v. Life Technologies Corporation, et al

This case was retrieved from the court on Tuesday, June 18, 2013

Date Filed:	**10/31/2012**	**Class Code:**	**OPEN**
Assigned To:	**Judge CATHERINE C. EAGLES**	**Closed:**	**No**
Referred To:	**Magistrate Judge Joi Elizabeth Peake**	**Statute:**	**28:1338**
Nature of suit:	**Patent (830)**	**Jury Demand:**	**Both**
Cause:	**Patent Infringement**	**Demand Amount:**	**$0**
Lead Docket:	**None**	**NOS Description:**	**Patent**
Other Docket:	**1:12cv00411**		
Jurisdiction:	**Federal Question**		

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Date	#	Proceeding Text	Source
10/31/2012	1	COMPLAINT for Patent Infringement against LIFE TECHNOLOGIES CORPORATION, APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., (Filing fee $350 receipt number 0418-1203651), filed by ESOTERIX GENETIC LABORATORIES, LLC, THE JOHNS HOPKINS UNIVERSITY. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3) (GARDNER, JOHN) (Entered: 10/31/2012)	
10/31/2012	2	Corporate Disclosure Statement by ESOTERIX GENETIC LABORATORIES, LLC identifying Corporate Parent LABORATORY CORPORATION OF AMERICA HOLDINGS for ESOTERIX GENETIC LABORATORIES, LLC. (GARDNER, JOHN) (Main Document 2 replaced on 11/1/2012 with correct PDF form) (Garland, Leah) (Entered: 10/31/2012)	
10/31/2012	3	Corporate Disclosure Statement by THE JOHNS HOPKINS UNIVERSITY. (GARDNER, JOHN) (Main Document 3 replaced on 11/1/2012 with corrected PDF image) (Garland, Leah) (Entered: 10/31/2012)	
11/01/2012	5	Summons Issued as to LIFE TECHNOLOGIES CORPORATION, APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC. (Attachments: # 1 Summons for Applied Biosystems, LLC, # 2 Summons for Ion Torrent Systems, INC.) (Garland, Leah) (Entered: 11/01/2012)	
11/01/2012	6	Notice of Right to Consent. Counsel shall serve the attached form on all parties. (Garland, Leah) (Entered: 11/01/2012)	
11/01/2012		CASE REFERRED to Mediation pursuant to Local Rule 83.9b of the Rules of Practice and Procedure of this Court. Please go to our website under Attorney Information for a list of mediators which must be served on all parties. (Garland, Leah) (Entered: 11/01/2012)	
11/01/2012		CASE REFERRED to Standing Order 30. (Garland, Leah) (Entered: 11/01/2012)	
11/01/2012	7	NOTICE of Appearance by attorney MATIAS FERRARIO on behalf of Plaintiff ESOTERIX GENETIC LABORATORIES, LLC (FERRARIO, MATIAS) (Entered: 11/01/2012)	
11/01/2012	8	NOTICE of Appearance by attorney LESLIE THOMAS GRAB on behalf of Plaintiff ESOTERIX GENETIC LABORATORIES, LLC (GRAB, LESLIE) (Entered: 11/01/2012)	
11/05/2012	9	NOTICE of Appearance by attorney PAUL K. SUN, JR on behalf of Plaintiff THE JOHNS HOPKINS UNIVERSITY (SUN, PAUL) (Entered: 11/05/2012)	
11/08/2012	10	SUMMONS Returned Executed by ESOTERIX GENETIC LABORATORIES, LLC as to LIFE TECHNOLOGIES CORPORATION served on 11/2/2012, answer due 11/23/2012. (GARDNER, JOHN) (Entered: 11/08/2012)	
11/08/2012	11	SUMMONS Returned Executed by ESOTERIX GENETIC LABORATORIES, LLC as to APPLIED BIOSYSTEMS, LLC served on 11/2/2012, answer due 11/23/2012. (GARDNER, JOHN) (Entered: 11/08/2012)	
11/08/2012	12	SUMMONS Returned Executed by ESOTERIX GENETIC LABORATORIES, LLC as to ION TORRENT SYSTEMS, INC. served on 11/2/2012, answer due 11/23/2012. (GARDNER, JOHN) (Entered: 11/08/2012)	
11/12/2012	13	Consent MOTION for Extension of Time to File Answer by APPLIED BIOSYSTEMS, LLC, ESOTERIX GENETIC LABORATORIES, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION, THE JOHNS HOPKINS UNIVERSITY. (Attachments: # 1 Text of Proposed Order)(FERRARIO, MATIAS) (Entered: 11/12/2012)	
11/14/2012		Motions Referred: RE: 13 Consent MOTION for Extension of Time to File Answer , to MAG/JUDGE JOI ELIZABETH PEAKE (Garrett, Kim) (Entered: 11/14/2012)	
11/20/2012	14	ORDER signed by MAG/JUDGE JOI ELIZABETH PEAKE on 11/20/2012; that Plaintiffs' Agreed Motion Extending Time of Defendants Life Technologies Corporation, Applied	

		Biosystems, LLC and ION Torrent Systems Inc. to Respond to Complaint [Doc. # 13] is GRANTED, and Defendants have to and including January 10, 2013, within which to file an Answer or other responsive pleading to Plaintiffs' Complaint. Answer due by 1/10/2013. (Sheets, Jamie) (Entered: 11/20/2012)
01/10/2013	15	NOTICE of Appearance by attorney ALLISON O. VAN LANINGHAM on behalf of Defendants APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION (VAN LANINGHAM, ALLISON) (Entered: 01/10/2013)
01/10/2013	16	NOTICE of Appearance by attorney STEPHEN MCDANIEL RUSSELL, JR on behalf of Defendants APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION (RUSSELL, STEPHEN) (Entered: 01/10/2013)
01/10/2013	17	NOTICE by APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION OF SPECIAL APPEARANCE OF KATHERINE NOLAN-STEVAUX (VAN LANINGHAM, ALLISON) (Entered: 01/10/2013)
01/10/2013	18	MOTION TO DISMISS FOR FAILURE TO STATE A CLAIM by APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION. Responses due by 2/4/2013 (VAN LANINGHAM, ALLISON) (Entered: 01/10/2013)
01/10/2013	19	BRIEF re 18 MOTION TO DISMISS FOR FAILURE TO STATE A CLAIM by Defendants APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION filed by APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION. (VAN LANINGHAM, ALLISON) (Entered: 01/10/2013)
01/10/2013	20	Corporate Disclosure Statement by LIFE TECHNOLOGIES CORPORATION. (VAN LANINGHAM, ALLISON) (Entered: 01/10/2013)
01/10/2013	21	Corporate Disclosure Statement by APPLIED BIOSYSTEMS, LLC. (VAN LANINGHAM, ALLISON) (Entered: 01/10/2013)
01/10/2013	22	Corporate Disclosure Statement by ION TORRENT SYSTEMS, INC. (VAN LANINGHAM, ALLISON) (Entered: 01/10/2013)
01/11/2013	23	NOTICE of Appearance by attorney KATRINA M. QUICKER on behalf of Plaintiff THE JOHNS HOPKINS UNIVERSITY (QUICKER, KATRINA) (Entered: 01/11/2013)
01/29/2013	24	Consent MOTION for Extension of Time to File Response/Reply by ESOTERIX GENETIC LABORATORIES, LLC, THE JOHNS HOPKINS UNIVERSITY. (Attachments: # 1 Text of Proposed Order)(FERRARIO, MATIAS) (Entered: 01/29/2013)
01/30/2013		Motions Referred: RE: 24 Consent MOTION for Extension of Time to File Response/Reply , to MAG/JUDGE JOI ELIZABETH PEAKE (Garrett, Kim) (Entered: 01/30/2013)
01/31/2013	25	ORDER signed by MAG/JUDGE JOI ELIZABETH PEAKE on 1/31/2013; that Plaintiffs' Agreed Motion Extending Time of Plaintiffs Esoterix Genetic Laboratories LLC and the Johns Hopkins University to Respond to Defendants' Motion to Dismiss [Doc. # 24] is GRANTED, and Plaintiffs have to and including February 18, 2013, within which to respond to Defendants' Motion to Dismiss for Failure to State a Plausible Claim. Responses due by 2/18/2013. (Sheets, Jamie) (Entered: 01/31/2013)
02/11/2013	26	Notice to Parties RE: SO30. Responses due by 3/11/2013 (Winchester, Robin) (Entered: 02/11/2013)
02/19/2013	27	RESPONSE filed by Plaintiffs ESOTERIX GENETIC LABORATORIES, LLC, THE JOHNS HOPKINS UNIVERSITY re 18 MOTION TO DISMISS FOR FAILURE TO STATE A CLAIM filed by LIFE TECHNOLOGIES CORPORATION, ION TORRENT SYSTEMS, INC., APPLIED BIOSYSTEMS, LLC. Replies due by 3/8/2013. (FERRARIO, MATIAS) Modified on 2/20/2013 to remove duplicate text. (Sheets, Jamie) (Entered: 02/19/2013)
03/08/2013	28	REPLY, filed by Defendants ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION, to Response to 18 MOTION TO DISMISS FOR FAILURE TO STATE A CLAIM by all Defendants filed by ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION. (VAN LANINGHAM, ALLISON) (Entered: 03/08/2013)
03/11/2013		Motions Referred: RE: 18 MOTION TO DISMISS FOR FAILURE TO STATE A CLAIM , to MAG/JUDGE JOI ELIZABETH PEAKE (Garrett, Kim) (Entered: 03/11/2013)
03/12/2013		Motions Submitted: 18 MOTION TO DISMISS FOR FAILURE TO STATE A CLAIM to JUDGE CATHERINE C. EAGLES. (Sanders, Marlene) (Entered: 03/12/2013)
03/15/2013		Case Reassigned to JUDGE CATHERINE C. EAGLES. UNASSIGNED no longer assigned to the case. (Powell, Gloria) (Entered: 03/15/2013)

03/19/2013	29	NOTICE of Hearing: Motion Hearing set for 4/23/2013 02:00 PM in Greensboro Courtroom #1 before JUDGE CATHERINE C. EAGLES. (Sanders, Marlene) (Entered: 03/19/2013)
03/19/2013	30	NOTICE by APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION OF SPECIAL APPEARANCE OF ANNE S. TOKER (RUSSELL, STEPHEN) (Entered: 03/19/2013)
03/19/2013	31	NOTICE by APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION OF SPECIAL APPEARANCE OF PETER J. ARMENIO (RUSSELL, STEPHEN) (Entered: 03/19/2013)
03/21/2013	32	NOTICE of Appearance by attorney ALLISON O. VAN LANINGHAM on behalf of Defendants APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION (VAN LANINGHAM, ALLISON) (Entered: 03/21/2013)
04/10/2013	33	NOTICE OF CANCELLATION of Motion Hearing set for 4/23/2013 at 2:00 PM in Greensboro Courtroom #1 before JUDGE CATHERINE C. EAGLES. (Sanders, Marlene) (Entered: 04/10/2013)
04/19/2013	34	Suggestion of Subsequently Decided Authority re 18 MOTION TO DISMISS FOR FAILURE TO STATE A CLAIM by Defendants APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION. (Attachments: # 1 Exhibit A)(VAN LANINGHAM, ALLISON) (Entered: 04/19/2013)
04/19/2013	35	WITHDRAWAL of Motion by Defendants APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION re 18 MOTION TO DISMISS FOR FAILURE TO STATE A CLAIM filed by LIFE TECHNOLOGIES CORPORATION, ION TORRENT SYSTEMS, INC., APPLIED BIOSYSTEMS, LLC (VAN LANINGHAM, ALLISON) (Entered: 04/19/2013)
05/01/2013	36	NOTICE of Initial Pretrial Conference Hearing set for 6/7/2013 at 11:00 AM in Greensboro Courtroom #3 before JUDGE CATHERINE C. EAGLES. (Sanders, Marlene) (Entered: 05/01/2013)
05/03/2013	37	ANSWER to 1 Complaint, with Jury Demand, Counterclaim against THE JOHNS HOPKINS UNIVERISTY, ESOTERIX GENETIC LABORATORIES, LLC, by APPLIED BIOSYSTEMS, LLC, LIFE TECHNOLOGIES CORPORATION, ION TORRENT SYSTEMS, INC. (VAN LANINGHAM, ALLISON) Modified on 5/6/2013 to add countercliam parties. (Sheets, Jamie) (Entered: 05/03/2013)
05/22/2013	38	NOTICE by ESOTERIX GENETIC LABORATORIES, LLC of Special Appearance of Susan A. Cahoon (FERRARIO, MATIAS) (Entered: 05/22/2013)
05/28/2013	39	RESPONSE re 37 Answer to Complaint, Counterclaim,, Esoterix Genetic Laboratories, LLC's Answer to Defendants Counterclaims by ESOTERIX GENETIC LABORATORIES, LLC. (FERRARIO, MATIAS) Modified on 5/29/2013 to remove reply deadline. (Sheets, Jamie) (Entered: 05/28/2013)
05/28/2013	40	RESPONSE re 37 Answer to Complaint, Counterclaim, The Johns Hopkins University's Answer to Defendants' Counterclaims filed by THE JOHNS HOPKINS UNIVERSITY. (SUN, PAUL) Modified on 5/29/2013 to remove reply deadline. (Sheets, Jamie) (Entered: 05/28/2013)
05/28/2013	41	Rule 26(f) Report (Individual). Responses due by 6/21/2013 by ESOTERIX GENETIC LABORATORIES, LLC, THE JOHNS HOPKINS UNIVERSITY. (Attachments: # 1 Exhibit 1 - Proposed Rule 26(f) Schedule of Pre-Markman Hearing Dates, # 2 Exhibit 2 - Competing Proposed Rule 26(f) Schedules of Post-Markman Hearing Dates)(FERRARIO, MATIAS) (Entered: 05/28/2013)
05/28/2013	42	Rule 26(f) Report (Individual). Responses due by 6/21/2013 by APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION. (Attachments: # 1 Exhibit 1 - Proposed Case Management Schedule Through The Markman Claim Construction Hearing, # 2 Exhibit 2 - Competing Proposed Case Management Schedules For Post-Markman Claim Construction Hearing Dates)(VAN LANINGHAM, ALLISON) (Entered: 05/28/2013)
05/29/2013		Motions Submitted: 41 Rule 26(f) Report (Individual), 42 Rule 26(f) Report (Individual). to JUDGE CATHERINE C. EAGLES. (Sanders, Marlene) (Entered: 05/29/2013)
06/07/2013		Minute Entry for proceedings held before JUDGE CATHERINE C. EAGLES: Initial Pretrial Conference held on 6/7/2013. Attorneys Susan Cahoon, Matias Ferrario and Paul Sun present for plaintiffs and Attorneys Allison Van Laningham and Peter Armenio present for defendants. Written Scheduling Order forthcoming, the parties may proceed as to the matters agreed upon in the Rule 26(f) reports. (Court Reporter Lori Russell.) (Sanders,

Marlene) (Entered: 06/07/2013)

06/11/2013	43	SCHEDULING ORDER signed by JUDGE CATHERINE C. EAGLES on 06/11/2013, the Court adopts the Rule 26(f) Reports as to subjects on which the parties agree, as reflected in Documents 41 and 42 . The Court agrees with the plaintiff that fact discovery should not be barred until after the Markman claim construction hearing and may instead proceed upon filing of this order. The Court will also grant the defendants request that discovery be held open for 90 days following the Courts entry of a claim construction order. This will allow each party flexibility in deciding whether to conduct none, some, or all of their fact discovery before or after the claim construction hearing.The Court enters the following Scheduling Order, and includes recently elapsed deadlines as set out herein. Parties agree that mediation should be conducted late in the discovery period, after the Claim Construction briefing and order. Parties agrree to select a mediator 60 days before the close of all discovery. Parties agree that Plaintiff should be allowed to join additional parties or amend pleadings without leave up until the Plaintiff's final contentions are due. Parties agree that Life should be be allowed to join additional parties or amend pleadings without leave up until the date Defendnat's final contentions are due. Parties do not consent to a magistrate judge. A jury trial has been demanded. (Taylor, Abby) (Entered: 06/11/2013)
06/17/2013	44	MOTION to Stay Pending Reexamination of Patents-In-Suit by APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION. Responses due by 7/11/2013 (VAN LANINGHAM, ALLISON) (Entered: 06/17/2013)
06/17/2013	45	BRIEF re 44 MOTION to Stay Pending Reexamination of Patents-In-Suit by Defendants APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION filed by APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION. (Attachments: # 1 Exhibit 1 - USPTO Acknowledgement Receipts, # 2 Exhibit 2 - USPTO Ex Parte Reexamination Filing Data, # 3 Exhibit 3 - Sealy Tech, LLC v. Simmons Bedding Co.)(VAN LANINGHAM, ALLISON) (Entered: 06/17/2013)
06/17/2013	46	DECLARATION filed by Defendants APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION re 44 MOTION to Stay Pending Reexamination of Patents-In-Suit (Declaration of Rosy Lee) filed by APPLIED BIOSYSTEMS, LLC, ION TORRENT SYSTEMS, INC., LIFE TECHNOLOGIES CORPORATION. (VAN LANINGHAM, ALLISON) (Entered: 06/17/2013)

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617368 (12) 7915015 March 29, 2011

UNITED STATES PATENT AND TRADEMARK OFFICE GRANTED PATENT

7915015

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March 29, 2011

Digital amplification

INVENTOR: Vogelstein, Bert - Baltimore, Maryland, United States of America (US), United States of America () ; Kinzler, Kenneth W. - Baltimore, Maryland, United States of America (US), United States of America ()

APPL-NO: 617368 (12)

FILED-DATE: November 12, 2009

GRANTED-DATE: March 29, 2011

CORE TERMS: sequence, amplification, sample, mutation, probe, mutant, template, ratio, prime, molecule, digital, allele, assay, genetic, fluorescence, cell, gene, primer, amplified, analyzed, diluted, transcript, detection, detect, experiment, stool, loop, sequencing, molecular, fraction

ENGLISH-ABST:

The identification of pre-defined mutations expected to be present in a minor fraction of a cell population is important for a variety of basic research and clinical applications. The exponential, analog nature of the polymerase chain reaction is transformed into a linear, digital signal suitable for this purpose. Single molecules can be isolated by dilution and individually amplified; each product is then separately analyzed for the presence of pre-defined mutations. The process provides a reliable and quantitative measure of the proportion of variant sequences within a DNA sample.

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1. Instrument Business Outlook, October 31, 2012, Pg. 1(3), 323857056, 1733 words, Litigation round up: more settlements.

   CORE TERMS: patent, IBO, Illumina, prejudice, infringement, dismissed, District Court, Esoterix, stipulated, judgment, defendant, Biosciences, plaintiff's, genetic, patent infringement, Genomics, Helicos, dismissal, motion, probes, Affymetrix, Panagene, Ion, non-infringement, counterclaims, complaint, summary, Nucleic Acid, Bio-Synthesis, eBioscience

   ... The John Applied **7,915,015** ...

2. News Bites - Central and Eastern Europe, April 23, 2012 Monday, STOCK, 1375 words, Europejski Fundusz Hipoteczny drops to three-month low, for a 2-day fall of 16.4% on firm volume

   CORE TERMS: PLN, groszy, WIG, quartile, bearish, signal, Poland, volatility, indicator, relative, rank, Trailing, EFH, EMA, 1-month, versus, book value, capital loss, Hipoteczny, Europejski, Fundusz, Polish, Bottom, Beta, PLN1,000, resistance, suggesting, invested, advance, halted

   ... time) and was untraded once (20% of the time). The volume was 1.3 times average trading of **7,915,015** shares. The value of PLN1,000 invested a week ago is PLN920 [vs PLN963 ...

3. News Bites Asian Markets : South Korea, September 24, 2011 Saturday, 1207 words, Weekly: Tong Yang Major hits year-low

   CORE TERMS: KRX, relative, KRW1,250.0, VWP, concrete, rank, South Korean, A001520, capitalisation, 3-month, indicator, strength, trailing, bearish, capital loss, Signals, KRW1,000, buysellsignals, resistance, invested, trend, pdf, South Korea's, price change, high low, single occasion, Southkorea, Yang, Tong, KRW2,265.0

   ... time) and was unchanged twice (8% of the time). The volume was 0.8 times average trading of **7,915,015** shares. The value of KRW1,000 invested five weeks ago is KRW701 [vs KRW980 ...

4. Targeted News Service, March 31, 2011 Thursday 2:03 PM EST, , 5117 words, U.S. Patents Awarded to Inventors in Maryland (March 31), Targeted News Service Targeted News Service, Alexandria, VA.

CORE TERMS: patent, assigned, ISD, method, co-inventors, Trademark Office, http, nph-Parser, Panigrahi, Satyaban, Hemanta, Contify, Sect1, Sect2, Rath, HITOFF, PTO2, PTXT, ASST, collaboration, published, full-text, abstract, netacgi, patft, uspto, html, gov, co1, polypeptide

... Va., March 30 -- Johns Hopkins University, Baltimore, has been assigned a patent **(7,915,015)** developed by Bert Vogelstein, Baltimore, and Kenneth W. Kinzler, Baltimore, for ...

5. Targeted News Service, March 30, 2011 Wednesday 8:42 PM EST, , 249 words, Johns Hopkins University Assigned Patent for Digital Amplification, Targeted News Service, Alexandria, Va.

CORE TERMS: patent, Myron, ISD, pre-defined, mutations, cell

... Va., March 30 -- Johns Hopkins University, Baltimore, has been assigned a patent **(7,915,015)** developed by Bert Vogelstein, Baltimore, and Kenneth W. Kinzler, Baltimore, for ...

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Patent Assignment Abstract of Title

Total Assignments: 1

Application #: 09613826 **Filing Dt:** 07/11/2000 **Patent #:** 6440706 **Issue Dt:** 08/27/2002

PCT #: NONE **Publication #:** NONE **Pub Dt:**

Inventors: Bert Vogelstein, Kenneth W. Kinzler

Title: DIGITAL AMPLIFICATION

Assignment: 1

Reel/Frame: 011372 / 0414 **Received:** 01/02/2001 **Recorded:** 12/15/2000 **Mailed:** 03/08/2001 **Pages:** 2

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: VOGELSTEIN, BERT **Exec Dt:** 11/28/2000

KINZLER, KENNETH W. **Exec Dt:** 11/28/2000

Assignee: JOHNS HOPKINS UNIVERSITY, THE
111 MARKET PLACE, SUITE 906
BALTIMORE, MARYLAND 21202

Correspondent: BANNER & WITCOFF, LTD.
SARAH A. KAGAN
1001 G STREET, N.W., SUITE 1100
WASHINGTON, D.C. 20001-4597

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90/012,896	06/17/2013	7915015

CONFIRMATION NO. 8361

LIFE TECHNOLOGIES CORPORATION
ATTN: IP DEPARTMENT
5791 VAN ALLEN WAY
CARLSBAD, CA 92008

REEXAMINATION REQUEST NOTICE

OC000000062089823

Date Mailed: 06/20/2013

NOTICE OF REEXAMINATION REQUEST FILING DATE

(Third Party Requester)

Requester is hereby notified that the filing date of the request for reexamination is 06/17/2013, the date that the filing requirements of 37 CFR § 1.510 were received.

A decision on the request for reexamination will be mailed within three months from the filing date of the request for reexamination. (See 37 CFR 1.515(a)).

A copy of the Notice is being sent to the person identified by the requester as the patent owner. Further patent owner correspondence will be the latest attorney or agent of record in the patent file. (See 37 CFR 1.33). Any paper filed should include a reference to the present request for reexamination (by Reexamination Control Number).

cc: Patent Owner
11332
Banner & Witcoff, Ltd.
Attorneys for client 001107
1100 13th Street N.W.
Suite 1200
Washington, DC 20005-4051

/rbell/

Legal Instruments Examiner
Central Reexamination Unit 571-272-7705; FAX No. 571-273-9900

REEXAM CONTROL NUMBER	FILING OR 371 (c) DATE	PATENT NUMBER
90/012,896	06/17/2013	7915015

CONFIRMATION NO. 8361

REEXAM ASSIGNMENT NOTICE

OC000000062089824

11332
Banner & Witcoff, Ltd.
Attorneys for client 001107
1100 13th Street N.W.
Suite 1200
Washington, DC 20005-4051

Date Mailed: 06/20/2013

NOTICE OF ASSIGNMENT OF REEXAMINATION REQUEST

The above-identified request for reexamination has been assigned to Art Unit 3991. All future correspondence to the proceeding should be identified by the control number listed above and directed to the assigned Art Unit.

A copy of this Notice is being sent to the latest attorney or agent of record in the patent file or to all owners of record. (See 37 CFR 1.33(c)). If the addressee is not, or does not represent, the current owner, he or she is required to forward all communications regarding this proceeding to the current owner(s). An attorney or agent receiving this communication who does not represent the current owner(s) may wish to seek to withdraw pursuant to 37 CFR 1.36 in order to avoid receiving future communications. If the address of the current owner(s) is unknown, this communication should be returned within the request to withdraw pursuant to Section 1.36.

NOTICE OF USPTO EX PARTE REEXAMINATION PATENT OWNER STATEMENT WAIVER PROGRAM

The USPTO has implemented a pilot program where, after a reexamination proceeding has been granted a filing date and before the examiner begins his or her review, the patent owner may orally waive the right to file a patent owner's statement. See *"Pilot Program for Waiver of Patent Owner's Statement in Ex Parte Reexamination Proceedings,"* 75 FR 47269 (August 5, 2010). One goal of the pilot program is to reduce the pendency of reexamination proceedings and improve the efficiency of the reexamination process.

Ordinarily when ex parte reexamination is ordered, the USPTO must wait until after the receipt of the patent owner's statement and the third party requester's reply, or after the expiration of the time period for filing the statement and reply (a period that can be as long as 5 to 6 months), before mailing a first determination of patentability. The USPTO's first determination of patentability is usually a first Office action on the merits or a Notice of Intent to Issue Reexamination Certificate (NIRC).

Under the pilot program, the patent owner's oral waiver allows the USPTO to act on the first determination of patentability immediately after determining that reexamination will be ordered, and in a suitable case issue the reexamination order and the first determination of patentability (which could be a NIRC if the claims under reexamination are confirmed) at the same time.

Benefits to the Patent Owner for participating in this pilot program include reduction in pendency.

To participate in this pilot program, Patent Owners may contact the USPTO's Central Reexamination Unit (CRU) at 571-272-7705. The USPTO will make the oral waiver of record in the reexamination file in an interview summary and a copy will be mailed to the patent owner and any third party requester.

cc: Third Party Requester(if any)
LIFE TECHNOLOGIES CORPORATION
ATTN: IP DEPARTMENT
5791 VAN ALLEN WAY
CARLSBAD, CA 92008

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Legal Instruments Examiner
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/012,896	06/17/2013	7915015	LT00831 REX 3	8361

11332 7590 08/22/2013
Banner & Witcoff, Ltd.
Attorneys for client 001107
1100 13th Street N.W.
Suite 1200
Washington, DC 20005-4051

EXAMINER	
CAMPELL, BRUCE R	
ART UNIT	**PAPER NUMBER**
3991	

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

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EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

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PATENT NO. *7915015*.

ART UNIT *3991*.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Request for Ex Parte Reexamination

A request for *ex parte* reexamination of claims 1-18 of U.S. Patent 7,915,015 was filed on June 17, 2013 by a third party requester.

Decision on Request

A substantial new question of patentability (SNQ) affecting claims 1-18 of U.S. Patent 7,915,015 is raised by the request for ex parte reexamination.

Scope of the Claims

In reexamination, patent claims are construed broadly. In re Yamamoto, 740 F.2d 1569, 1571, 222 USPQ 934, 936 (Fed. Cir. 1984) (claims given "their broadest reasonable interpretation consistent with the specification"). The independent claims subject to reexamination read as follows:

1. A method for determining an allelic imbalance in a biological sample, comprising the steps of:

amplifying template molecules within a set comprising a plurality of assay samples to form a population of amplified molecules in each of the assay samples of the set, wherein the template molecules are obtained from the biological sample;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker, wherein between 0.1 and 0.9 of the assay samples yield an amplification product;

comparing the first number to the second number to ascertain an allelic imbalance in the biological sample; and

identifying an allelic imbalance in the biological sample.

8. A method for determining an allelic imbalance in a biological sample, comprising the steps of:

distributing nucleic acid template molecules from a biological sample to form a set comprising a plurality of assay samples;

amplifying the template molecules within the assay samples to form a population of amplified molecules in the assay samples of the set;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker;

comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance between the first allelic form and the second allelic form in the biological sample.

Claim Interpretation

The “biological sample” can either be comprised of cells, tissues, bodily fluids, etc. or cell free. See col. 7, lines 10-14. In either case, nucleic acids are distributed throughout the sample. Therefore any process in which the sample is diluted is considered "distributing nucleic acid template molecules from a biological sample." An “assay sample” is a portion of the biological sample. "Allelic imbalance" is not defined in the specification. The term is used in the art to refer to situations in which one allele (of a pair) is expressed at a lower level than the other due to gene silencing, imprinting, mutations in regulatory sequences, etc., as well as situations in which one allele is duplicated or deleted from the genome. The claims encompass both possibilities, since the specification discloses amplification of both genomic DNA and cDNA produced by reverse transcription.

Documents Submitted by Requester

Bischoff et al., "Single cell analysis demonstrating somatic mosaicism involving 11p in a patient with paternal isodisomy and Beckwith-Wiedemann syndrome", Human Molecular Genetics, Vol. 4, No. 3, 1995, 395-399

Li *et al.,* "Amplification and analysis of DNA sequences in single human sperm and diploid cells." Nature 335(6189):414-7 (1988)

Kalinina *et al.,* "Nanoliter scale PCR with TaqMan detection," *Nucl. Acids. Res.* vol 25, 1999-2004 (1997)

Ruano et al., "Direct haplotyping of chromosomal segments from multiple heterozygotes via allele-specific PCR amplification", Nucleic Acids Research, Vol. 17, No. 20, 10/25/1989, 8392

Review of the ‘015 patent file shows that Li was cited in an information disclosure statement but not applied in any rejection. None of the other references were considered during prosecution.

Requester’s Proposed SNQs

Requester proposes 4 SNQs (summarized in Request, pp. 10-14).

1. Requester considers claims 1, 4, 5, 7-11, 16 and 17 unpatentable over **Bischoff** (proposed SNQ 1).

Bischoff discloses a study which demonstrated somatic mosaicism (i.e. the somatic cells of an individual are not all genetically identical) in a patient with Beckwith-Wiedemann syndrome (BWS). The study focused on a segment of chromosome 11 between the 11p15.5 and 11p13 regions. It was found that the patient had two populations of cells. One population of cells contained a maternally inherited copy of chromosome 11 and a paternally inherited copy, as expected. The other population of cells displayed partial paternal isodisomy, i.e. the segment of interest on the maternal chromosome was actually derived from the paternal chromosome. (Abstract. See Fig. 3 for diagrammatic explanation of how this can occur.) This situation is “allelic imbalance” because genes in the affected cells do not show the expected 1:1 ratio of maternal and paternal alleles.

In a preliminary experiment, Bischoff isolated genomic DNA from blood samples obtained from the patient and both parents and subjected it to PCR using primers designed to amplify 6 markers from the 11p region, 4 markers from the 11q region and one from the 21q region (chromosome 21). The markers comprise dinucleotide repeats and there are as many 4 different alleles known

for each marker. Results are shown in Fig. 1 and Table 1. For example, marker HRAS was uninformative because both parents had the same genotype. Marker DHS922 was informative; the mother had alleles 1 and 3, while the father had the alleles 2 and 3. The patient had allele 1 from the mother and allele 2 from the father, but the probe for allele 2 produced a much stronger signal. This was interpreted as evidence for mosaic paternal disomy, i.e. some cells contain alleles 1 and 2 while other cells contain 2 copies of the (paternal) allele 2. A total of 4 markers for the 11p region were informative and all suggested mosaic paternal disomy. Only one marker from the 11q region proved informative, and it indicated normal biparental disomy (i.e. one allele from each parent). The marker from chromosome 21 also indicated normal biparental disomy.

Bischoff then produced a set of "assay samples" by isolating 6 individual lymphocytes from a "biological sample" of the patient's blood ("distributing" step). The cells were lysed and genomic DNA was subjected to primer extension preamplification (PEP), which amplifies essentially the entire genome by extension of a complete set of random oligonucleotide primers. Following PEP, the DNA from each cell was subjected to PCR using the primer sets previously shown to amplify informative alleles ("amplifying" step). Results are shown in Fig. 2 and Table 2. Cells 1, 5 and 6 were found to show paternal isodisomy and cells 2, 3 and 4 showed normal biparental disomy ("analyzing" step). It is arbitrary which allele is considered the selected sequence and which the reference sequence. For example, marker HBB showed that all 6 cells contained allele 1 from the paternal chromosome, but only 3 cells contained allele 2 from the maternal chromosome, thereby demonstrating an allelic imbalance ("comparing" step). Bischoff also amplified the informative markers from the 11q and 21q regions, which both showed normal biparental disomy. Comparison of the frequency of the informative maternal allele with the frequency of the 4 possible reference sequences from these sites also demonstrates allelic imbalance.

A reasonable examiner would consider the disclosure of Bischoff important in determining whether claims 1, 4, 5, 7-11, 16 and 17 are patentable. Accordingly, Bischoff raises a SNQ regarding claims 1, 4, 5, 7-11, 16 and 17.

2. Requester considers claims 2, 3, 6, 12-15 and 18 unpatentable over **Bischoff** in combination with one or more of **Kalinina**, **Li** and **Ruano** (proposed SNQs 2-4).

Bischoff is discussed above.

Kalinina discloses a method for PCR amplification and detection using TaqMan probes. Samples diluted to contain approximately 1 template molecule are subjected to TaqMan PCR in sealed capillary tubes containing a few nanoliters of reactants, then presence of PCR product is determined by measuring the probe fluorescence (entire document, see especially p. 2000). The method is considered especially useful for assays meant to determine the presence or absence of PCR product (i.e. not quantitative analysis; p. 2004, last paragraph).

Li discloses a method in which a ratio of genetic sequences (β-globin) was obtained from a tissue culture flask containing co-cultured cells (the biological sample) of an individual homozygous for the β^S allele ("selected genetic sequence," which causes sickle cell anemia) and another individual homozygous for the β^A allele (normal, "reference genetic sequence"). The nucleic acid template molecules, contained within the cultured cells, were diluted by isolating single cells from the culture. Thirty seven single cells (assay samples) were lysed, and the released DNA was subjected to polymerase chain reaction (PCR) to amplify the portion of the globin gene containing the sickle cell mutation. Amplified DNA was hybridized with allele specific probes. It was found that 19 of the samples contained the normal allele, 12 contained the sickle cell allele, and 6

samples did not hybridize with either probe. These numerical values were "compared," which inherently ascertains a ratio between the two values (19:12). See pp. 414-415, Fig. 1.

In another experiment (p. 415, Fig. 2), the biological sample was semen obtained from a subject heterozygous for a polymorphism in the LDLr gene. Eighty individual sperm cells were lysed and the DNA subjected to PCR followed by hybridization with allele specific probes. A total of 55% of sperm cells ("assay samples") gave a hybridization signal. It was found that 22 assay samples contained one allele and 21 samples contained the other, a ratio of 22:21. Either allele can be considered the "selected genetic sequence" or the "reference genetic sequence."

Ruano discloses a method for haplotyping chromosomal segments from heterozygotes wherein allele-specific PCR primers are used to amplify sample DNA in separate reactions. This ensures that the amplification product is homogenous.

A reasonable examiner would consider the disclosure of Bischoff important in determining whether claims 2, 3, 6, 12-15 and 18 are patentable, particularly in combination with Kalinina, Li or Ruano. Accordingly, Bischoff in combination with Kalinina, Li or Ruano raises a SNQ regarding claims 2, 3, 6, 12-15 and 18.

Conclusion

In view of the analysis above, the request for reexamination is **GRANTED**. Claims 1-18 of US Patent 7,915,015 will be reexamined.

Duty to Disclose

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 7,915,015 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Waiver of Right to File Patent Owner Statement

In a reexamination proceeding, Patent Owner may waive the right under 37 C.F.R. 1.530 to file a Patent Owner Statement. The waiver document must contain a statement that Patent Owner waives the right under 37 C.F.R. 1.530 to file a Patent Owner Statement and proof of service in the manner provided by 37 C.F.R. 1.248, if the request for reexamination was made by a third party requester (see 37 C.F.R 1.550(f)).

Amendment in Reexamination Proceedings

Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c).

Service of Papers

After the filing of a request for reexamination by a third party requester, any document filed by either the patent owner or the third party requester must be served on the other party (or parties where two or more third party requester proceedings are merged) in the reexamination proceeding in the manner provided in 37 CFR 1.248. See 37 CFR 1.550(f).

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRUCE CAMPELL whose telephone number is 571-272-0974. The examiner can normally be reached on Monday - Thursday from 8:00 to 5:00. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Jones, can be reached on 571-272-1535. The fax phone number for the organization where this application or proceeding is assigned is 571-273-9900.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this ex parte reexamination proceeding should be directed:

By EFS: Registered users may submit via the electronic filing system EFS-Web at

https://efs.uspto.gov/efile/myportal/efs-registered

By Mail to: Mail Stop *Ex Parte* Reexam
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Commissioner for Patents
United States Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

By FAX to: (571) 273-9900
Central Reexamination Unit

By hand: Customer Service Window
Randolph Building
401 Dulany Street

Alexandria, VA 22314

/Bruce Campell/
Patent Reexamination Specialist
Central Reexamination Unit 3991

Conferee:

/Padmashri Ponnaluri/
Patent Reexamination Specialist
CRU-3991

/Deborah D Jones/
Supervisory Patent Examiner, Art Unit 3991

Order Granting / Denying Request For Ex Parte Reexamination	**Control No.** 90/012,896	**Patent Under Reexamination** 7915015
	Examiner BRUCE CAMPELL	**Art Unit** 3991

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

The request for *ex parte* reexamination filed *17 June 2013* has been considered and a determination has been made. An identification of the claims, the references relied upon, and the rationale supporting the determination are attached.

Attachments: a)☒ PTO-892, b)☒ PTO/SB/08, c)☐ Other: ______

1. ☒ The request for *ex parte* reexamination is GRANTED.

RESPONSE TIMES ARE SET AS FOLLOWS:

For Patent Owner's Statement (Optional): TWO MONTHS from the mailing date of this communication (37 CFR 1.530 (b)). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).**

For Requester's Reply (optional): TWO MONTHS from the **date of service** of any timely filed Patent Owner's Statement (37 CFR 1.535). **NO EXTENSION OF THIS TIME PERIOD IS PERMITTED.** If Patent Owner does not file a timely statement under 37 CFR 1.530(b), then no reply by requester is permitted.

2. ☐ The request for *ex parte* reexamination is DENIED.

This decision is not appealable (35 U.S.C. 303(c)). Requester may seek review by petition to the Commissioner under 37 CFR 1.181 within ONE MONTH from the mailing date of this communication (37 CFR 1.515(c)). **EXTENSION OF TIME TO FILE SUCH A PETITION UNDER 37 CFR 1.181 ARE AVAILABLE ONLY BY PETITION TO SUSPEND OR WAIVE THE REGULATIONS UNDER 37 CFR 1.183.**

In due course, a refund under 37 CFR 1.26 (c) will be made to requester:

a) ☐ by Treasury check or,

b) ☐ by credit to Deposit Account No. ______, or

c) ☐ by credit to a credit card account, unless otherwise notified (35 U.S.C. 303(c)).

/Bruce Campell/
Patent Reexamination Specialist
Central Reexamination Unit 3991

cc:Requester (if third party requester)

Notice of References Cited	Application/Control No. 90/012,896	Applicant(s)/Patent Under Reexamination 7915015	
	Examiner BRUCE CAMPELL	Art Unit 3991	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
*	U	Li et al., "Amplification and analysis of DNA sequences in single human sperm and diploid cells."Nature 335(6189):414-7 (1988)
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

U.S. Patent and Trademark Office
PTO-892 (Rev. 01-2001) **Notice of References Cited** Part of Paper No. 20130801

Search Notes	Application/Control No. 90012896	Applicant(s)/Patent Under Reexamination 7915015
	Examiner BRUCE CAMPELL	Art Unit 3991

CPC- SEARCHED

Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED

Symbol	Date	Examiner

US CLASSIFICATION SEARCHED

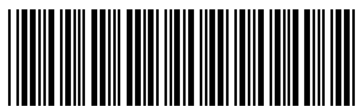
Class	Subclass	Date	Examiner

SEARCH NOTES

Search Notes	Date	Examiner
reviewed file history of 12/617,368	8/1/13	/BC/

INTERFERENCE SEARCH

US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

Reexamination 	**Application/Control No.** 90012896	**Applicant(s)/Patent Under Reexamination** 7915015
	Certificate Date	**Certificate Number** C1

Requester Correspondence Address:	☐ **Patent Owner**	☒ **Third Party**
LIFE TECHNOLOGIES CORPORATION ATTN: IP DEPARTMENT 5791 VAN ALLEN WAY CARLSBAD, CA 92008		

LITIGATION REVIEW ☒	/BC/ (examiner initials)	06/18/2013 (date)
Case Name		Director Initials
Esoterix Genetic Laboratories v Life Technolgies Corporation		
US District NC MIddle 1:12cv1173		

COPENDING OFFICE PROCEEDINGS	
TYPE OF PROCEEDING	**NUMBER**
1. none	

EXHIBIT 2

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Field

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)					
				Application Number	Unknown
				Filing Date	June 17, 2013
				First Named Inventor	Bert Vogelstein
				Art Unit	Unknown
				Examiner Name	
Sheet	1	of	1	**Docket Number**	LT00831 REX 3

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS

Examiner Initial*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
/B.C./	C1	BISCHOFF, FARIDEH et al., "Single cell analysis demonstrating somatic mosaicism involving 11p in a patient with paternal isodisomy and Beckwith-Wiedemann syndrome", Human Molecular Genetics, Vol. 4, No. 3, 1995, 395-399	
/B.C./	C2	KALININA, OLGA et al., "Nanoliter Scale PCR with TaqMan Detection", Nucleic Acids Research, Vol. 25, No. 10, 1997, 1999-2004	
/B.C./	C3	RUANO, GUALBERTO et al., "Direct haplotyping of chromosonal segments from multiple heterozygotes via allele-specific PCR amplification", Nucleic Acids Research, Vol. 17, No. 20, 10/25/1989, 8392	

EXAMINER SIGNATURE

Examiner Signature	/Bruce Campell/	Date Considered	08/12/2013

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

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter the office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.
[4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/012,896	06/17/2013	7915015	LT00831 REX 3	8361

11332 7590 11/27/2013

Banner & Witcoff, Ltd.
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EXAMINER	
CAMPELL, BRUCE R	

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
11/27/2013	PAPER

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

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

PTOL-90A (Rev. 04/07)

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LIFE TECHNOLOGIES CORPORATION

ATTN: IP DEPARTMENT

5791 VAN ALLEN WAY

CARLSBAD, CA 92008

EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. *90/012,896*.

PATENT NO. *7915015*.

ART UNIT *3991*.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Office Action in Ex Parte Reexamination	Control No. 90/012,896	Patent Under Reexamination 7915015
	Examiner BRUCE CAMPELL	Art Unit 3991

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

a☐ Responsive to the communication(s) filed on ____ .   b☐ This action is made FINAL.
c☒ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire _2_ month(s) from the mailing date of this letter.
Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).**
If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Information Disclosure Statement, PTO/SB/08.
3. ☐ Interview Summary, PTO-474.
4. ☐ ____.

Part II SUMMARY OF ACTION

1a. ☒ Claims _1-18_ are subject to reexamination.
1b. ☐ Claims ____ are not subject to reexamination.
2. ☐ Claims ____ have been canceled in the present reexamination proceeding.
3. ☐ Claims ____ are patentable and/or confirmed.
4. ☒ Claims _1-18_ are rejected.
5. ☐ Claims ____ are objected to.
6. ☐ The drawings, filed on ____ are acceptable.
7. ☐ The proposed drawing correction, filed on ____ has been (7a)☐ approved (7b)☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).

   a)☐ All b)☐ Some* c)☐ None of the certified copies have

   1☐ been received.

   2☐ not been received.

   3☐ been filed in Application No. ____ .

   4☐ been filed in reexamination Control No. ____.

   5☐ been received by the International Bureau in PCT application No. ____.

   * See the attached detailed Office action for a list of the certified copies not received.

9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.

10. ☐ Other: ____

cc: Requester (if third party requester)

Ex Parte Reexamination

Detailed Non-Final Office Action

This is a reexamination of U.S. Patent 7,915,015, issued March 29, 2011. A Request pursuant to 37 CFR 1.510 for ex parte reexamination of claims 1-18 of U.S. Patent 7,915,015 was filed on June 17, 2013 by a third party requester. An Order granting the request was mailed August 22, 2013.

Patent Owner Statement

No patent owner statement has been received.

Status of the Claims

Claims 1-18 of U.S. Patent 7,915,015 are subject to reexamination.

Scope of the Claims

In reexamination, patent claims are construed broadly. In re Yamamoto, 740 F.2d 1569, 1571, 222 USPQ 934, 936 (Fed. Cir. 1984) (claims given "their broadest reasonable interpretation consistent with the specification"). The independent claims subject to reexamination read as follows:

1. A method for determining an allelic imbalance in a biological sample, comprising the steps of:

amplifying template molecules within a set comprising a plurality of assay samples to form a population of amplified molecules in each of the assay samples of the set, wherein the template molecules are obtained from the biological sample;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker, wherein between 0.1 and 0.9 of the assay samples yield an amplification product;

comparing the first number to the second number to ascertain an allelic imbalance in the biological sample; and

identifying an allelic imbalance in the biological sample.

8. A method for determining an allelic imbalance in a biological sample, comprising the steps of:

distributing nucleic acid template molecules from a biological sample to form a set comprising a plurality of assay samples;

amplifying the template molecules within the assay samples to form a population of amplified molecules in the assay samples of the set;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker;

comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance between the first allelic form and the second allelic form in the biological sample.

Claim Interpretation

The “biological sample” can either be comprised of cells, tissues, bodily fluids, etc. or cell free. See col. 7, lines 10-14. In either case, nucleic acids are distributed throughout the sample. Therefore any process in which the sample is diluted is considered "distributing nucleic acid template molecules from a biological sample.” An “assay sample” is a portion of the biological sample. "Allelic imbalance" is not defined in the specification. The term is used in the art to refer to situations in which one allele (of a pair) is expressed at a lower level than the other due to gene silencing, imprinting, mutations in regulatory sequences, etc., as well as situations in which one allele is duplicated or deleted from the genome. The claims encompass both possibilities, since the specification discloses amplification of both genomic DNA and cDNA produced by reverse transcription.

Documents Submitted by Requester

Bischoff et al., "Single cell analysis demonstrating somatic mosaicism involving 11p in a patient with paternal isodisomy and Beckwith-Wiedemann syndrome", Human Molecular Genetics, Vol. 4, No. 3, 1995, 395-399

Li *et al.,* "Amplification and analysis of DNA sequences in single human sperm and diploid cells."Nature 335(6189):414-7 (1988)

Kalinina *et al.,* "Nanoliter scale PCR with TaqMan detection," *Nucl. Acids. Res.* vol 25, 1999-2004 (1997)

Ruano et al., "Direct haplotyping of chromosomal segments from multiple heterozygotes via allele-specific PCR amplification", Nucleic Acids Research, Vol. 17, No. 20, 10/25/1989, 8392

Documents Cited by Examiner

U.S. Patent 5,928,907, issued July 27, 1999 to Woudenberg et al.

Jeffreys *et al.,* "Amplification of human minisatellites by the polymerase chain reaction: towards DNA fingerprinting of single cells." *Nucl. Acids. Res.,* vol 16, no. 23, pages 10953-10971 (1988)

Claim Rejections – 35 U.S.C. §§ 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to

a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 5, 7-11, 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Bischoff.

Bischoff discloses a study which demonstrated somatic mosaicism (i.e. the somatic cells of an individual are not all genetically identical) in a patient with Beckwith-Wiedemann syndrome (BWS). The study focused on a segment of chromosome 11 between the 11p15.5 and 11p13 regions. It was found that the patient had two populations of cells. One population of cells contained a maternally inherited copy of chromosome 11 and a paternally inherited copy, as expected. The other population of cells displayed partial paternal isodisomy, i.e. the segment of interest on the maternal chromosome was actually derived from the paternal chromosome. (Abstract. See Fig. 3 for diagrammatic explanation of how this can occur.) This situation is “allelic imbalance” because genes on the affected cells do not show the expected 1:1 ratio of maternal and paternal alleles. The procedure used by Bischoff meets the limitations of the claims as follows.

In a preliminary experiment, Bischoff isolated genomic DNA from blood samples obtained from the patient and both parents and subjected it to PCR using primers designed to amplify 6 markers from the 11p region, 4 markers from the 11q region and one from the 21q region (chromosome 21). The markers comprise dinucleotide repeats and there are as many as 4 alleles for each marker. Results are shown in Fig. 1 and Table 1. For example, marker HRAS was uninformative because both parents had the same genotype. Marker DHS922 was informative; the mother had alleles 1 and 3, while the father had the alleles 2 and 3. The patient had allele 1 from the mother and allele 2 from the father, but the probe for allele 2 produced a much stronger signal. This was interpreted as evidence for mosaic paternal disomy, i.e. some cells contain alleles 1 and 2 while other cells contain 2 copies of the (paternal) allele 2. A total of 4 markers for the 11p region were informative and all suggested mosaic paternal disomy. Only one marker from the 11q region proved informative, and it indicated normal biparental

disomy (i.e. one allele from each parent). The marker from chromosome 21 also indicated normal biparental disomy.

Bischoff then produced a set of “assay samples” by isolating 6 individual lymphocytes from a “biological sample” of the patient’s blood (“distributing” step). The cells were lysed and genomic DNA was subjected to primer extension preamplification (PEP), which amplifies essentially the entire genome by extension of a complete set of random oligonucleotide primers. Following PEP, the DNA from each cell was subjected to PCR using the primer sets previously shown to amplify informative alleles (“amplifying” step). Results are shown in Fig. 2 and Table 2. Cells 1, 5 and 6 were found to show paternal isodisomy and cells 2, 3 and 4 showed normal biparental disomy (“analyzing” step). It is arbitrary which allele is considered the first form and which the second form. For example, marker HBB showed that all 6 cells contained allele 1 from the paternal chromosome, but only 3 cells contained allele 2 from the maternal chromosome, thereby demonstrating an allelic imbalance (“comparing” step). Therefore claim 8 is anticipated.

With regard to the limitation “between 0.1 and 0.9 of the assay samples yield an amplification product,” claims 4 and 5 explicitly allow this limitation to refer to the number of samples in which either the first or second allele is amplified. Since 50% (0.5) of the samples contained amplified maternal HBB sequence, and the maternal sequence can be considered either the first or second allele, this result meets the limitations of claims 1, 4, 5, 10, 11, 16 and 17.

With regard to claims 7 and 9, the biological sample was from blood.

Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bischoff.

Bischoff is described above. Bischoff does not disclose a method wherein at least 500 or 1,000 assay samples are produced from the biological sample. This modification would have been obvious to the skilled artisan, however, because it is readily apparent that assaying a larger number of samples (cells) would provide a more

accurate (statistically) determination of the number of cells containing the allelic imbalance (or any given allele of interest). Moreover, in cases where an allelic imbalance (or a particular allele) is associated with a disease state (e.g. cancer), it would be obvious to assay a large number of cells before and after therapy in order to assess the efficacy of the therapy employed, or to assay a large number of cells from surrounding tissues to search for possible metastatic cells. Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 2, 3, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bischoff as applied to claim 1 and further in view of Woudenberg.

Bischoff is relied upon as described above. Bischoff does not disclose a method wherein DNA is amplified by real-time PCR using a dual labeled fluorogenic probe.

Woudenberg describes a method and apparatus for real time PCR with detection by a dual labelled fluorogenic probe. See entire document, especially claim 12; col. 7, line 47 - col. 8, line 61; col. 9, line 61 - col. 10, line 67.

It would have been obvious to one of ordinary skill in the art to modify the method of Bischoff amplifying DNA using real time PCR with detection by a dual labelled fluorogenic probe as taught by Woudenberg. One would have been motivated to do this in order to obtain the benefits noted by Woudenberg, i.e. more accurate quantitation of template nucleic acids, less sample handling, reduced reagent use, etc. (col. 3, lines 31-41). Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 6 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bischoff as applied to claim 1 and furhter in view of Jeffreys.

Bischoff is relied upon as described above. Bischoff does not disclose a method wherein the amplified DNA sequences in the assay samples are homogenous.

Jeffreys discloses methods for amplification of human minisatellite DNA for the purpose of producing DNA fingerprints of individuals. In one method, a biological sample is split into multiple assay samples by isolating single cells, then analyzed in much the same way as in Bischoff (pp. 10955-10956). In an alternative method, isolated (cell free) DNA was diluted into multiple assay samples, each containing 6 pg DNA. This amount was estimated to be equivalent to the amount of DNA in a single cell. It was concluded that single DNA molecules could be faithfully amplified (pp. 10960-10962). In the experiment shown in Fig. 4, each assay sample was subjected to PCR with 4 sets of primers (in a single reaction), the primers designed to amplify two alleles for each of 2 minisatellites. Successful amplification was obtained, with a mean failure rate of 63% per allele per reaction, equating to an estimated 0.46 successful amplification events per 6 pg sample (because statistically one would not expect the template sequence to be present in every sample; p. 10961). Of the 16 samples shown in Fig. 4, 3 were a+/b+ (positive for both markers a and b), 5 were a-/b- (negative for both markers), 8 were a-/b+ and 0 were a+/b-. Therefore the proportion of samples homogenous for marker b was 0.5 (8/16) or, if doubly negative samples are excluded, 0.73 (8/11). Similar results were obtained for markers c and d; 2 samples were c+/d+, 8 were c-/d-, 4 were c+/d- and 2 were c-/d+.

It would have been obvious to one of ordinary skill in the art to modify the method of Bischoff by obtaining DNA from a cell free sample, then diluting it into multiple assay samples which each contain approximately as much DNA as a single cell, as taught by Jeffreys. Jeffreys shows that some assay samples will contain a single copy of the marker in question, some will contain more than one, and others will not contain any copies, as expected with a random distribution of genomic DNA in each sample. If genomic DNA from the patient studied by Bischoff were analyzed in this manner (diluting DNA into a plurality of assay samples, each containing approximately one copy of an informative marker sequence), the result would be that, of the samples testing positive for a single allele, more than 50% would be positive for the paternal allele. This

result (allelic imbalance, i.e not a 1:1 ratio of maternal:paternal alleles) would indicate paternal isodisomy in some of the patient's cells. (If half the cells in the patient's blood had the paternal isodisomic genotype, as in the small sample reported by Bischoff, the expected ratio would be 1 maternal allele : 3 paternal alleles.) One would have been motivated to analyze DNA from a cell free biological sample as taught by Jeffreys in order to eliminate the labor intensive process of isolating single cells. Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Documents Not Relied Upon

Kalinina is cited in the Request as disclosing real time PCR. While Kalinina does disclose PCR with product detection using dual labeled fluorogenic probes, the procedure could take as long as several hours (p. 2003, col. 2) and is therefore not considered to be a "real time" process.

Li is cited in the Request as suggesting the use of 500 or more assay samples. However, Li makes this suggestion in the context of mapping genetic markers in sperm cells. The method envisioned by Li is not analogous to that of Bischoff because sperm cells are haploid, not diploid (so disomy would only occur rarely, if at all), and also because there does not appear to be any reason why mapping genetic markers would involve determining which allele of a marker is present as required by the claims.

Ruano is cited in the Request for its disclosure of a method wherein allele-specific PCR primers are used to amplify sample DNA in separate reactions. This does ensure a homogenous amplification product, of course, but it is not the process envisioned in the '015 patent. The '015 patent obtains homogenous amplification by diluting the assay samples until they contain a single template molecule available for amplification (col. 4, lines 7-14).

Conclusion

Claims 1-18 are rejected.

Extensions of Time

Extensions of time under 37 CFR 1.136(a) will not be permitted in these proceedings because the provisions of 37 CFR 1.136 apply only to "an applicant" and not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that reexamination proceedings "will be conducted with special dispatch" (37 CFR 1.550(a)). Extension of time in *ex parte* reexamination proceedings are provided for in 37 CFR 1.550(c).

Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c).

In order to ensure full consideration of any amendments, affidavits or declarations, or other documents as evidence of patentability, such documents must be submitted in response to this Office action. Submissions after the next Office action, which is intended to be a final action, will be governed by the requirements of 37 CFR 1.116, after final rejection and 37 CFR 41.33 after appeal, which will be strictly enforced.

Duty to Disclose

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving U.S. Patent No. 7,915,015 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRUCE CAMPELL whose telephone number is (571)272-0154. The examiner can normally be reached on Monday - Thursday from 8:00 to 5:00. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Jones, can be reached on 571-272-1535. The fax phone number for the organization where this proceeding is assigned is 571-273-9900.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this ex parte reexamination proceeding should be directed:

By EFS: Registered users may submit via the electronic filing system EFS-Web at

https://efs.uspto.gov/efile/myportal/efs-registered

By Mail to: Mail Stop *Ex Parte* Reexam
Central Reexamination Unit
Commissioner for Patents
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Alexandria, VA 22313-1450

By FAX to: (571) 273-9900
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/Bruce Campell/
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Central Reexamination Unit 3991

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Patent Reexamination Specialist
Central Reexamination Unit 3991

/Deborah D Jones/
Supervisory Patent Examiner,
Art Unit 3991

Notice of References Cited	Application/Control No. 90/012,896	Applicant(s)/Patent Under Reexamination 7915015	
	Examiner BRUCE CAMPELL	Art Unit 3991	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,928,907	07-1999	Woudenberg et al.	435/91.2
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Jeffreys et al., "Amplification of human minisatellites by the polymerase chain reaction: towards DNA fingerprinting of single cells." Nucl. Acids. Res., vol 16, no. 23, pages 10953-10971 (1988)
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No. 90012896	Applicant(s)/Patent Under Reexamination 7915015
	Examiner BRUCE CAMPELL	Art Unit 3991

CPC- SEARCHED

Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED

Symbol	Date	Examiner

US CLASSIFICATION SEARCHED

Class	Subclass	Date	Examiner

SEARCH NOTES

Search Notes	Date	Examiner
reviewed file history of 12/617,368	8/1/13	/BC/

INTERFERENCE SEARCH

US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

Reexamination	Application/Control No. 90012896	Applicant(s)/Patent Under Reexamination 7915015
	Certificate Date	**Certificate Number** C1

Requester Correspondence Address:	☐ **Patent Owner**	☒ **Third Party**

LIFE TECHNOLOGIES CORPORATION
ATTN: IP DEPARTMENT
5791 VAN ALLEN WAY
CARLSBAD, CA 92008

LITIGATION REVIEW ☒	/BC/ (examiner initials)	06/18/2013 (date)
Case Name		Director Initials
Esoterix Genetic Laboratories v Life Technolgies Corporation		
US District NC MIddle 1:12cv1173		

COPENDING OFFICE PROCEEDINGS	
TYPE OF PROCEEDING	**NUMBER**
1. none	

PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(**Not for submission under 37 CFR 1.99)**

Application Number	90012896
Filing Date	2013-06-17
First Named Inventor	
Art Unit	3991
Examiner Name	Bruce R. Campell
Attorney Docket Number	001107.00988

U.S.PATENTS

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	90012896
	Filing Date	2013-06-17
	First Named Inventor	
	Art Unit	3991
	Examiner Name	Bruce R. Campell
	Attorney Docket Number	001107.00988

	1	Supplemental Joint Claim Construction Statement filed in Civil Action No. 12-cv-1173-CCE-JEP on October 28, 2013 (filed with exhibits A, B, and C)	☐
	2	Defendants' Responsive Claim Construction Brief filed in Case No. 1:12-CV-1173 on November 26, 2013	☐
	3	Deposition of David Sherman, Ph.D., dated October 17, 2013	☐
	4	Supplemental Joint Claim Construction Statement Exhibit C filed in Civil Action No. 12-cv-1173-CCE-JEP on October 28, 2013 (filed with Supplemental Joint Claim Construction Statement filed in Civil Action No. 12-cv-1173-CCE-JEP on October 28, 2013)	☐
	5	Plaintiffs' Responsive Claim Construction Brief filed in filed in Civil Action No. 12-cv-1173-CCE-JEP on November 26, 2013	☐
	6	Plaintiffs' Proposed Construction of Disputed Terms, Supporting Evidence, and Rebuttal Evidence Exhibit B, filed in filed in Civil Action No. 12-cv-1173-CCE-JEP on October 28, 2013 (filed with Supplemental Joint Claim Construction Statement filed in Civil Action No. 12-cv-1173-CCE-JEP on October 28, 2013)	☐
	7	Declaration of David H. Sherman in Support of Esoterix Genetic Laboratories' Claim Construction Brief filed in Civil Action Nos. 12-cv-411-CCE-JEP and 12-cv-1173-CCE-JEP, executed September 27, 2013	☐
	8	Defendants' Opening Claim Construction Brief filed in Case No. 1:12-CV-1173 on November 5, 2013	☐
	9	Exhibit A filed in Civil Action No. 12-cv-1173-CCE-JEP on October 28, 2013 (filed with Supplemental Joint Claim Construction Statement filed in Civil Action No. 12-cv-1173-CCE-JEP on October 28, 2013)	☐
	10	Plaintiffs' Opening Claim Construction Brief filed in Civil Action No. 12-cv-1173-CCE-JEP on November 5, 2013	☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		90012896
	Filing Date		2013-06-17
	First Named Inventor		
	Art Unit		3991
	Examiner Name	Bruce R. Campell	
	Attorney Docket Number		001107.00988

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	
*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.			
[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.			

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	90012896
	Filing Date	2013-06-17
	First Named Inventor	
	Art Unit	3991
	Examiner Name	Bruce R. Campell
	Attorney Docket Number	001107.00988

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

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

☐ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Sarah A. Kagan/	Date (YYYY-MM-DD)	2014-01-27
Name/Print	Sarah A. Kagan	Registration Number	32141

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

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

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

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

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF NORTH CAROLINA
GREENSBORO DIVISION

Esoterix Genetic Laboratories, LLC, Plaintiff, vs. Life Technologies Corporation, Applied Biosystems, LLC, and Ion Torrent Systems, Inc., Defendants.	))))))))))	Civil Action No. 12-cv-411-CCE-JEP
Esoterix Genetic Laboratories, LLC and The Johns Hopkins University, Plaintiffs, vs. Life Technologies Corporation, Applied Biosystems, LLC, and Ion Torrent Systems, Inc., Defendants.	))))))))))	Civil Action No. 12-cv-1173-CCE-JEP

DECLARATION OF DAVID H. SHERMAN IN SUPPORT OF ESOTERIX GENETIC LABORATORIES' CLAIM CONSTRUCTION BRIEF

I, David H. Sherman, declare:

1. I am the Associate Dean for Research and Graduate Education, College of Pharmacy at the University of Michigan, Ann Arbor. I am also the Hans W. Vahlteich Professor in the Department of Medicinal Chemistry. I have been retained as an expert

consultant by Esoterix Genetic Laboratories ("EGL") in connection with the two above-captioned matters.

I. QUALIFICATIONS

2. I have a Bachelor of Arts in Chemistry from the University of California, Santa Cruz.

3. I hold a Ph.D. in Organic Chemistry from Columbia University. I also completed my postdoctoral work at Yale University and the Massachusetts Institute of Technology, where I was awarded the Myron A. Bantrell Postdoctoral Fellowship in Molecular Biology.

4. I am a named inventor of eleven United States Patents and over twenty United States Patent Applications.

5. I was a research scientist at Biogen Research Corporation from 1984 – 1987. While at Biogen, I worked on the molecular immunology of T cell immune responses in relation to the mouse and human major histocompatibility complex.

6. I worked at the John Innes Institute as a research scientist from 1987 – 1990. My work at the John Innes Institute focused on bacterial genetics, molecular biology and biochemistry of polyketide biosynthesis in *Streptomyces* bacteria.

7. I was a Professor at the University of Minnesota in the Department of Microbiology and BioTechnology Institute from 1990 – 2003. I also served as the Director of the UMN-NIGMS Biotechnology training program.

8. I founded Acera Biosciences, Inc. in 1999 and remained with the company as the Chief Technical Consultant until 2007. Acera Biosciences focused on drug discovery and development from new chemical entities to fight infectious agents and cancer.

9. A true and correct copy of my curriculum vitae, which includes a list of my honors, papers that I have published, patents on which I am named as an inventor, and the committees and boards on which I serve, is attached to this declaration as Exhibit 1.

II. BASES FOR OPINION

10. I submit this declaration in support of EGL's claim construction brief.

11. In forming the facts and opinions set forth in this declaration, I relied upon my education, background, and experience in the field of biotechnology. I have also reviewed U.S. Patent Nos. 5,670,325 ("the '325 patent"); 6,440,706 ("the '706 patent"); 7,824,889 ("the '889 patent"); and 7,915,015 ("the '015 patent") and their associated file histories.

12. I understand that claims 1-5, 7-9, 11, 18-22, 32, 33, 36 and 37 of the '325 patent have been asserted by EGL against certain products sold by Life Technologies Corporation, Applied Biosystems, LLC and Ion Torrent Systems, Inc. (collectively, "Defendants").

13. I also understand that claims 1-3, 6-12, 15-16, 19-32, 38-44, 47-48, and 51-64 of the '607 patent have been asserted by EGL and The Johns Hopkins University ("JHU") against certain products sold by Defendants.

14. I understand that claims 1-2 and 4-22 of the '889 patent have been asserted by EGL and JHU against certain products sold by Defendants.

15. I understand that claims 1-2, 4-14, and 16-18 of the '015 patent have been asserted by EGL and JHU against certain products sold by Defendants.

16. The purpose of my declaration is to assist the Court in understanding the invention described and claimed in the '325 patent as well as in the '607 patent, the '889 patent, and the '015 patent (collectively, "the Vogelstein patents"), their wide-ranging applicability to the identification of mutations within cells, and the state of the art at the time of the invention.

17. I understand that the parties disagree about the meaning of some claim terms used in the patent. I also understand that the purpose of my declaration is to assist

the Court in understanding some of the claim terms and phrases used in the patent application.

18. I am not a lawyer nor do I have any sort of legal training. Nonetheless, as a scientist working in the field of molecular biology, through my previous work as an expert consultant and witness in other patent litigation matters, and as an inventor of numerous patents and patent applications, I am generally familiar with the process of applying for patents with the United States Patent and Trademark Office ("Patent Office").

19. I understand that the Court reads the claims of the patent from the viewpoint of "one of ordinary skill in the art." I understand that this person is someone with the requisite training and education, but is not most expert, in the relevant field of the invention. The '325 patent is directed to methods for the detection of nucleic acid sequences in a biological sample. The Vogelstein patents are directed to digital PCR based methods for determining the ratio of genetic sequences in a biological sample. In my opinion, one of ordinary skill in the art of the patent would have training in molecular biology techniques, such as PCR and related laboratory procedures. This definition would include, for example, a person with a bachelor degree in biological or chemical sciences and at least three years of experience in a laboratory or a person with a master's degree in biochemical sciences and at least one year of laboratory experience. I

understand that Defendants contend that one of ordinary skill in the art would be someone with a Ph.D. in Molecular Biology.

20. I also understand that the relevant date for defining the claim terms is the earliest filing date of the patent specification, *i.e.*, August 14, 1996 for the '325 patent and June 25, 1998 for the Vogelstein patents. My opinions are directed to what one of ordinary skill in the art would have known or understood on or prior to that date.

21. In addition to the opinions and subject matter identified in this declaration, I reserve the right to offer testimony or a declaration in response or rebuttal to any expert opinions offered by Defendants in support of its proposed claim constructions.

III. EXHIBITS

22. Attached hereto as Exhibit 2 is a true and correct copy of U.S. Patent No. 5,670,325, dated September 23, 1997.

23. Attached hereto as Exhibit 3 is a true and correct copy of U.S. Patent No. 6,440,706, dated August 27, 2002.

24. Attached hereto as Exhibit 4 is a true and correct copy of U.S. Patent No. 7,824,889, dated November 2, 2010.

25. Attached hereto as Exhibit 5 is a true and correct copy of U.S. Patent No. 7,915,015, dated March 29, 2011.

IV. BACKGROUND INFORMATION

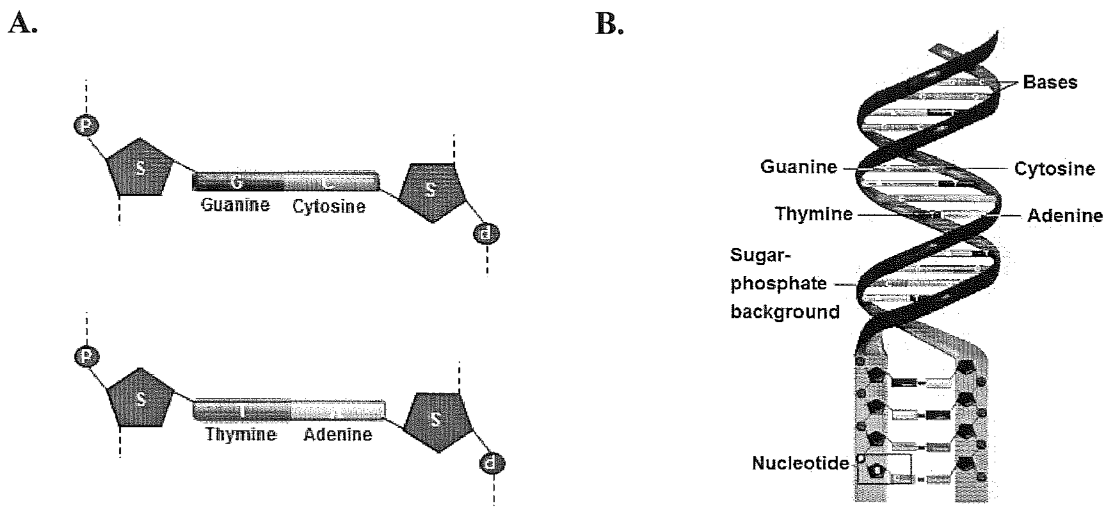
26. DNA, or deoxyribonucleic acid, is the hereditary material in all humans and in almost all other organisms. The information in DNA is stored as a code made up of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T). Human DNA consists of about 3 billion bases, and more than 99 percent of those bases are the same in all people. The order, or sequence, of these bases determines the information available for the building, maintaining and function of an organism, similar to the way in which letters of the alphabet appear in a certain order to form words and sentences.

27. DNA bases pair up with each other – A with T and C with G – to form units called base pairs. See **Figure 1A**. Each base is also attached to a sugar molecule (S) and a phosphate molecule (P). Together, a base, sugar, and phosphate are called a nucleotide. Nucleotides are arranged in two long strands that form a spiral structure called a double helix. The double helix forms because the nucleotides in one stranded pair with nucleotides in the second strand. This ability for two strands of nucleotides to pair with each other (an interaction also referred to as binding or hybridizing) is referred to complementarity. In other words, the sequence of one strand is complementary to the sequence of the other strand. The identity and order of nucleotides in a given region of DNA is referred to as a genetic sequence or nucleic acid sequence. The structure of the double helix is somewhat like a ladder, with base pairs forming the ladder's rungs and the

sugar and phosphate molecules forming the vertical sides of the ladder. **Figure 1B** below illustrates the structure of a double helix DNA.

Figure 1. DNA Structure.

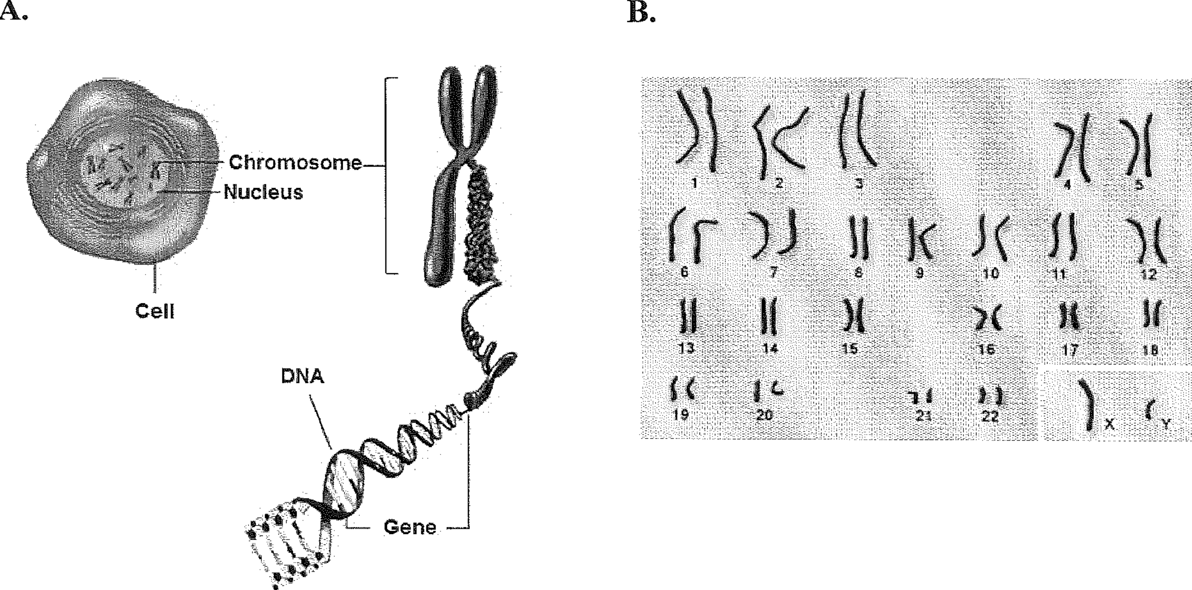
A. **B.**



28. DNA in cells of the body exists as long double-stranded helices that are packaged tightly into structures called chromosomes. In cells, chromosomes are located in a region called the nucleus. Every cell in your body, except for eggs, sperm, and red blood cells contains a full set of chromosomes. **Figure 2A** illustrates how the double helix DNA is tightly wound into chromosomes and shows the location of the chromosomes within the nucleus of the cell. There are 24 types of chromosomes in humans: 22 autosome chromosomes and 2 sex chromosomes (X and Y). Each of these types of chromosomes contains a distinct set of genes. A person has two copies of each

type of chromosome – one inherited from each of the person's biological parents.[1] A full complement of human chromosomes is shown in **Figure 2B**.

Figure 2. DNA in cells exists in the form of chromosomes.



29. Specific regions of nucleotides on each chromosome form functional units called genes. Gene sequences vary widely in length and are often thousands of nucleotides long. Gene sequences provide the information received for the cell to construct a protein molecule. Proteins are the structural components of cells and tissues and enzymes that perform biochemical reactions.

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[1] The X and Y sex chromosomes are the only chromosomes in which a chromosome pair may not contain two of the same type of chromosome. For the sex chromosomes, a male receive an X chromosome inherited from his mother and a Y chromosome inherited from his father, while a female inherits an X chromosome from each parent.

30. Chromosomes, and the genes on them, have a particular sequence of nucleotides that is generally considered normal. In the context of genes, the normal sequence is commonly referred to as the wild-type sequence. However, there are also many positions in the sequence of a chromosome or gene that may vary from person to person. For example, a particular nucleotide in a gene may be a T in some people and a G in other people. A region that is variable is called a polymorphic locus. Where the variation is at a single nucleotide position and the variant sequence has a certain degree of prevalence in people, the variant sequences at the nucleotide position are referred to as single nucleotide polymorphisms (SNPs).

31. However, some variations in the sequence of a chromosome cause deleterious effects. These types of variations are called mutations. For example, mutations may cause a change in how much protein is made from a gene (referred to as gene expression). Mutations may also cause a defective protein to be made from the gene. In both cases, the mutation can impact cellular function and often underlies disease and its severity. Mutations typically arise when there is an error in the cell processes that allow cells to grow and divide.

32. There are several different kinds of mutations. The simplest form of mutation is a change in the sequence at a single nucleotide position, which is called a point mutation. The difference between point mutations and SNPs are that point

mutations are generally sequence variations that are not very prevalent in people (*i.e.*, they are rare). Another type of mutation is called a deletion, which refers to when part of the sequence of a chromosome is missing. Conversely, an insertion mutation occurs when the normal sequence of a chromosome is interrupted by the aberrant insertion of some number of nucleotides. Sometimes regions of a chromosome, including portions of genes or entire genes, get repeated. These types of mutations are called gene duplication mutations or gene amplification mutations. Another type of mutation is where a sequence from one chromosome gets added onto the sequence of a different chromosome. These mutations are called translocation mutations, and they can also result in deletion mutations or amplification mutations.

33. Because a person inherits a copy of each chromosome from each of their parents, and each chromosome contains genes, a person inherits two copies of each gene – one copy from each parent. The copy of a gene, or a genetic region, present on a chromosome is called an allele. As such, each person has two alleles for each gene or genetic region – one allele inherited from their mother (maternal allele) and one allele inherited from their father (paternal allele). The terms allele is also used to refer to the sequences that may be present at a polymorphic locus.

34. The genes comprising alleles on each of the chromosomes inherited from the mother and the father may be the same (*i.e.*, have the same nucleotide sequence) or

they may be different (*i.e.*, one or more of the nucleic acid sequences may contain a polymorphism). When a person has two identical copies of the sequence, the person is said to be homozygous for a particular allele. When the person has inherited different copies of the sequence, the person is said to be heterozygous for that particular allele.

35. It is important to note that DNA can also exist in various contexts outside of cells. For example, DNA can be extracted from a biological sample and manipulated through various techniques to generate shorter pieces of DNA than exist in nature. Alternatively, DNA can by synthesized chemically in a laboratory. Relatively short pieces (*e.g.*, ~6-60 nucleotides long) of DNA are referred to an oligonucleotides. Longer pieces of DNA are referred to as polynucleotides (*e.g.*, ~60-1000s nucleotides long). However, the length of the DNA at which point one uses the term polynucleotides versus oligonucleotide is relatively undefined. Oligonucleotides and polynucleotides can exist as single-stranded molecules or double-stranded molecules.

V. THE '325 PATENT

A. EXPLANATION OF INVENTION

36. I have read and reviewed the Declaration of Stanley N. Lapidus. I agree with his testimony in the Background and '325 Patent sections of the declaration. If called to testify on the points raised in those sections, I will do so. I also reserve the right

to testify on basic molecular biology topics that are relevant and fundamental to the principles of the '325 patent.

B. CLAIM CONSTRUCTION

37. I understand that the parties have proposed definitions for certain claim terms that are at issue in the claims of the '325 patent. My understanding is that the parties have disagreed with respect to the definitions of certain claim terms.

38. I understand that the Defendants contend that the methods of the '325 patent do not contemplate PCR as an enrichment or sample preparation step. It is my opinion that Defendants' position is unequivocally incorrect.

39. I understand Defendants' position is based on certain statements contained in the patent concerning PCR. The patent discusses various limitations of PCR as it was used in prior methods as an endpoint for detection as well as the use of PCR to amplify and detect various mutant nucleic acids in a heterogeneous biological sample.

40. As Mr. Lapidus explains in his Declaration at paragraph 65, gel-based detection methods lacked the sensitivity necessary to elucidate differences between two nucleic acids that may be present in similar amounts in a biological sample.

41. Similarly, Mr. Lapidus and Mr. Shuber discuss the limitations of using PCR as a method to identify mutated or deleted DNA sequences in a heterogeneous sample

(paragraph 67 of Mr. Lapidus' Declaration and paragraph 28 of Mr. Shuber's Declaration).

42. I agree with the testimony of Mr. Lapidus and Mr. Shuber on these points and believe that one of ordinary skill in the art would understand these issues in reading the teachings of the '325 patent.

43. In my opinion, the '325 patent does not exclude the use of PCR, but merely discusses its limitations in certain contexts, as discussed above. However, these limitations of PCR and the patent's recognition of such limitations does not mean that one of skill in the art would have been dissuaded from using PCR as an enrichment tool on the biological sample when employing methods of the invention.

44. Specifically, at the time of the invention of the subject matter of the '325 patent, PCR was commonly used as an enrichment step to increase the signal to noise ratio for various analytical techniques. The '325 patent contemplates this use of PCR as an enrichment step for sample preparation and discusses such "indirect" detection methods. (*See, e.g.*, Col. 5, ll. 31-34.)

45. Further, as was discussed in Mr. Lapidus' Declaration at paragraph 71, at the time of the invention, PCR was a useful tool to enrich samples for relatively small amounts of starting materials to enable reliable detection of the desired target sequences. Therefore, in my opinion, one of skill in the art would have understood that PCR was an

acceptable enrichment tool to prepare samples for detection using the enumerative methods claimed in the '325 patent.

46. I also understand that the Defendants contend that claim 1 of the '325 patent requires that the first wild-type polynucleotide be different from the second wild-type polynucleotide (*i.e.*, in a different part of the genome). With respect to claim 18, I understand that the Defendants also contend that the wild-type target allele must be different (from another part of the genome) from the reference allele. Defendants' contention is incorrect and is contradicted by the disclosure in the specification of the '325 patent. (See, *e.g.*, Col. 3, ll. 25-31; Col. 3, ll. 44-50; Col. 3, ll. 54-56; Col. 3, ll. 60-61; Col. 5, ll. 24-25; Col. 6, ll. 1-10; Col. 7, ll. 66 – Col. 8, ll. 6; Col. 8, ll. 24-33; Col. 10, ll. 33-40; Col. 11, ll. 57-60; Col. 15, ll. 27-29; Col. 17, ll. 46-50; Col. 18, ll. 11-13; Col. 18, ll. 24-27; Col. 18, ll. 30-33; Col. 18, ll. 52-60; Col. 19, ll. 4-18; Col. 20, ll. 17-29).

47. Based upon my understanding of the disclosure of the '325 patent, the first and second wild-type polynucleotides of claim 1 and the wild-type and reference alleles of claim 18 may, in fact, be from different parts of the genome.

48. However, this comparison between two polynucleotides is not the only embodiment disclosed in the '325 patent. The '325 patent also contemplates that the two polynucleotides to be compared may be from the same region on two different chromosomes. For example, the first polynucleotide may be on one allele and the second

polynucleotide may be from the other allele at the same location. A difference in the amounts of the two alleles would indicate a mutation or deletion. (See, *e.g.*, Abstract; Col. 4, ll. 38-41; Col. 17, ll. 39 – Col. 18, ll. 2, Col. 18, ll. 11-33, Col. 18, ll. 47-60; Col. 23, ll. 30-49; Col. 26, ll. 45-58).

49. Another embodiment disclosed in the '325 patent contemplates the comparison of the same allele over time. The '325 patent refers to this method as the "fingerprint method." (*See*, *e.g.*, Col. 18, ll. 24-34; Col. 20, ll. 17-29.) In the fingerprint method, the same region is analyzed at one time point and then analyzed again at a later time point. The measurements from the two time points are compared to determine if any changes in the region have occurred.

50. An alternative embodiment disclosed in the '325 patent includes the comparison of two different regions on the same chromosome. For example, the first region would be a region that one would expect to be stable (unchanged) and the second region on the same chromosome would be one that is suspected of being mutated. A difference between the two regions would indicate that mutation or deletion had occurred. (See, *e.g.*, Col. 7, ll. 57 – Col. 8, ll. 6).

51. In my opinion, any reading of the claims that would require that the two polynucleotides to be analyzed must be in different parts of the genome or on different chromosomes is incorrect and is not supported by the disclosure of the '325 patent.

52. I understand that Defendants contend that a biological sample comprises a single heterogeneous cellular sample. This assertion is incorrect and is contradicted by the specification. The '325 patent contemplates that a biological sample may be cellular, or it may comprise DNA that is not contained within cells in the biological sample. Other examples are also provided in the specification of the '325 patent. (See, *e.g.*, Col. 2, ll. 31-35, Co. 3, ll. 13-16, Col. 4, ll. 37-41, Col. 5, ll. 15-21, Col. 5, ll. 40-43, Col. 8, ll. 9-11, Col. 8, ll. 21-24, Col. 17. Ll. 46-52, Col. 18, ll. 23-33, Col. 18, ll. 52-60, Col. 19, ll. 19-20, Col. 20, ll. 17-29, Col. 23, ll. 50-55).

53. With respect to claim 32, I understand that Defendants contend that the identity and origin of the nucleotide sequence in the maternal allele and the paternal allele must be known prior to conducting the method claimed in the '325 patent. This contention is incorrect. Claim 32 simply requires the detection of an amount of a maternal allele and a paternal allele at a polymorphic locus. By definition, the identity of the two nucleotides at the polymorphic locus will be different. It is not necessary to know the origin of the sequence of the allele, only that the allele at that locus is polymorphic. (See, *e.g.*, Col. 17, ll. 39 – Col. 18, ll. 2, Col. 18, ll. 11-33, Col. 18, ll. 47-60).

54. I understand that Defendants contend that the methods of the '325 patent must be performed on samples that were not previously known to contain a mutation.

Defendants are incorrect. As is described in the specification, the inventors contemplated that the method could be used to detect the progression of disease over time. In at least these cases, the user would know or suspect that the mutation was present in the sample prior to running the analysis – and would then be able to determine whether the disease had progressed since the last time the analysis was performed. (*See*, *e.g.*, Col. 18, ll. 29-33.)

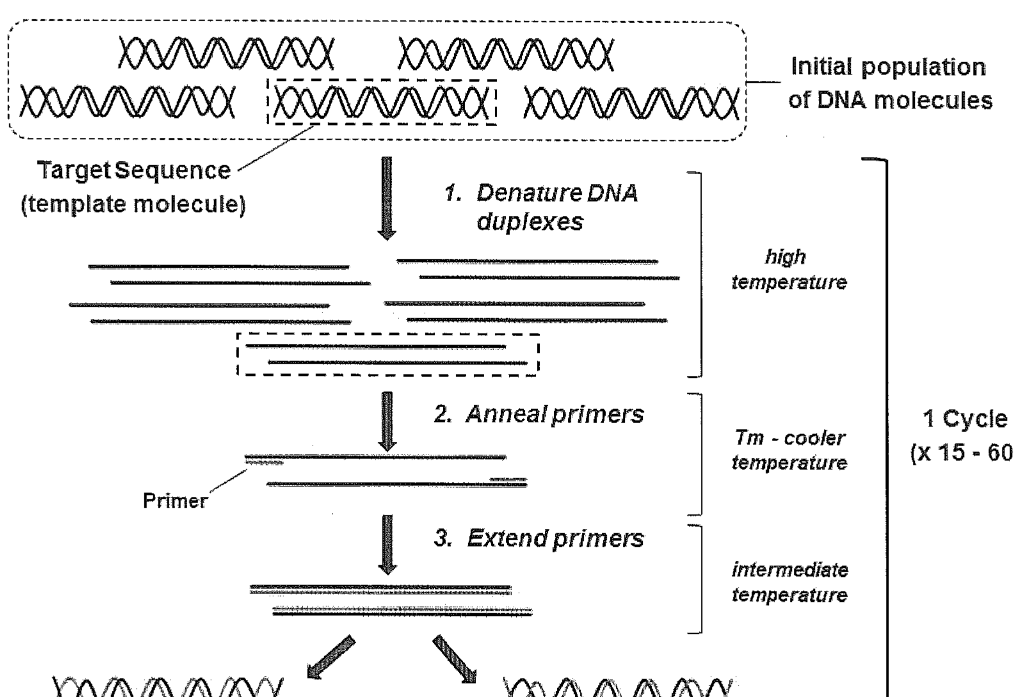
55. With respect to the term "oligonucleotide probe," I understand that Defendants contend that the probe must be "detectably labeled." This limitation is not present in the claims and is not supported by the specification. For example, the '325 patent contemplates that probes may be used that bind to the target DNA sequence of interest adjacent to a polymorphic site (in such circumstances, the probes are essentially acting as a primer). The probes/primers may then be extended using a DNA polymerase and the incorporation of nucleotides determined. The probes described above are not labeled in any way. At the time of the invention, the nucleotides to be incorporated were differentially labeled and methods were used to measure the incorporation of these labeled nucleotides into the probe/primer. (*See, e.g.*, Col. 18, ll. 34-60).

VI. THE VOGELSTEIN PATENTS

A. EXPLANATION OF INVENTION

56. To understand the inventions of the Patents in Suit, a brief description of a prior art procedure will be informative. A well-known technique for analyzing genetic sequences is called the polymerase chain reaction (PCR). PCR is a method of generating a large number of copies of a target DNA sequence. This process of generating multiple copies is called amplification. DNA containing the target sequence of interest is combined with certain reagents and is subjected to a series of different temperatures (typically a denaturing temperature, an annealing temperature, and an extending temperature) with each series of temperatures constituting a cycle. See **Figure 3**. The number of cycles in PCR can vary, but typical assays use roughly 15-60 cycles. Each cycle exponentially generates more copies of the target genetic sequence. During a first cycle of PCR, the target genetic sequence is copied (*e.g.*, 1 copy is made into 2 copies). During the next cycle of PCR, the two copies of target genetic sequence are each copied again (*e.g.*, 2 copies are made into 4 copies). Iterative cycles increase the amount of DNA copies from 4 to 8, to 16, to 32, etc. Thus, after 20 cycles, one can go from a single copy of a target genetic sequence to over 500,000 copies.

Figure 3. Polymerase chain reaction (PCR).



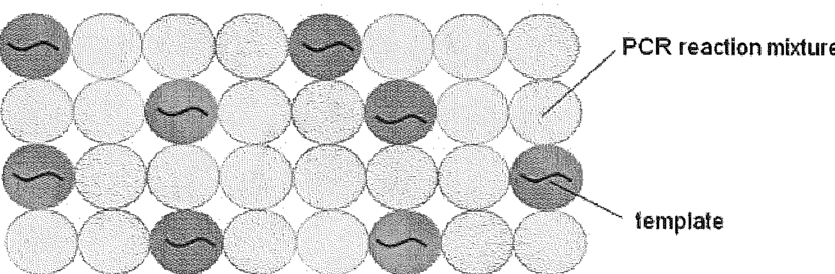
57. As shown in **Figure 3**, short single-stranded DNA oligonucleotides, referred to as primers, are designed to hybridize (bind) to regions of genetic sequence flanking the target genetic sequence. The primers bind to the genetic sequences in the starting sample of DNA through the base pair interactions described above (*i.e.*, complementarity). In a single-plex PCR, only one target sequence is amplified using a single pair of primers. In a multi-plex PCR, more than one target sequence is amplified using a pair of primers for each of the target sequences. In the first step of a PCR cycle, high temperatures are used to denature (or melt) the duplex DNA so the two strands of nucleotides that form the duplex separate from each other. During the cooler annealing

step of the cycle, the primers will each form a duplex structure (called hybridizing or annealing) with their respective target cognate sequences that flank the target sequence. The temperature for the annealing step is based on the calculated optimal temperature to favor hybridization of the primers to their cognate target sequences, which is called the melting temperature (Tm). During the extension step of each cycle, each primer allows the synthesis of the nucleotide strand complementary to the template sequence strand to which they are bound, forming two duplex molecules of the target sequence. With each cycle, the target sequence between the two primers is amplified.

58. The inventions of the Vogelstein patents are methods for performing digital PCR. Digital PCR is similar to PCR in that genetic sequences of interest are amplified using primers and repeated cycles of denaturation, annealing, and extension. However, unlike in PCR, digital PCR involves separating out the genetic sequences in a DNA sample into parallel reactions for amplification. In the language of the Patents in Suit, the genetic sequences are distributed into "a set of assay samples." After the amplification step, each of the reactions is analyzed to determine how many contain the amplified template sequence of interest. In distributing the genetic sequences in the DNA sample into multiple assay samples, the target sequence is segregated such that only some of the assay samples will contain the target sequence. See **Figure 4**. As such, the majority of the assay samples will either contain only one or no genetic sequences of interest (yielding either a positive or a negative reaction, respectively). However, the method can

also be performed when some of the assay samples contain more than one genetic sequence of interest. Distributing genetic sequences of interest into many parallel amplification reactions enables one to determine an accurate estimate of the amount of the genetic sequences of interest in the original DNA sample by assuming that they have followed the normal Poisson distribution in the set of assay samples. The Poisson distribution is a mathematical algorithm that predicts the probability of a given number of events (*e.g.*, the presence or absence of a genetic sequence) in a fixed interval or time and/or space (*e.g.*, in an assay sample). By assuming this type of distribution, the concentration of genetic sequences of interest in a DNA sample can be accurately calculated based on the number of observed positive or negative assay samples and the amount of DNA present in the DNA sample.

Figure 4. Digital PCR.[2]



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[2] Figure 4 is simplified by showing only the target sequence in each of the partitions. Each partition may in fact contain a number of different DNA molecules from the original starting DNA sample.

59. It is important to note that, *preferably*, DNA samples will be segregated such that each assay sample will contain only one or no template molecules. When assay samples contain at most one template molecule, this is referred to as single molecule analysis. However, single molecule analysis may require partitioning into a very, very large number of assay samples; so large, that it is not practical. As a result, it is possible to conduct the claimed methods where assay samples may contain 0, 1, 2, or 3 template molecules. Use of the Poisson distribution, as described above, will still allow determination of concentration for the template sequence. However, the analytical method used to determine whether an assay sample contains amplified template molecules after the amplification step is a critical factor that determines the extent of dilution that may be required and whether template molecules must be diluted until assay samples contain either 0 or 1 template molecules. These concepts are discussed in the Patents in Suit. (*See, e.g.*, at Col. 3, ll. 65 - Col. 4, ll. 56; Col. 5, ll. 40 – Col. 6, ll. 9.) The idea that template molecules may be preferably segregated to do single molecule analysis is reflected particularly in claim 3 of the '706 patent, claims 1, 8-15, 20 and 21 of the '889 patent, and claims 1, 4, 5, 10, 11, and 16 of the '015 patent.

60. Poisson distribution can be explained using a simple analogy to a bowl of M&Ms. For example, consider a bowl containing red and green M&Ms to represent the DNA sample. An assay sample can be represented by the random selection of a single M&M from the bowl. If 1000 M&Ms are individually and randomly selected from the

bowl, these 100 selections would be a set of assay samples for the analysis. If the number of red and green M&Ms in the bowl was equal, one would expect that about 500 of the selected M&Ms would be red and about 500 would be green. If the red M&Ms are the template sequence, then the positive assay samples are the selected red M&Ms. Even if the split was 480 red to 520 green, or something similar, one would expect that this distribution reflects the fact that the bowl of M&Ms had equal numbers of red and green M&Ms.

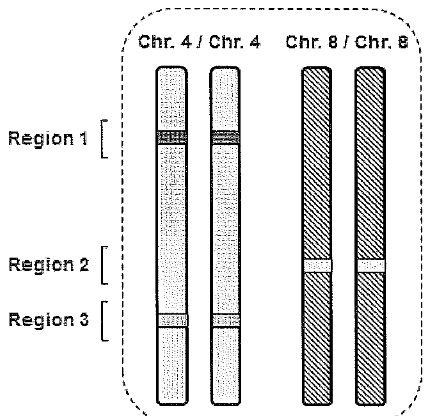
61. Extending this example to the claimed invention, the red and green M&Ms can represent two different template molecules of interest (*e.g.*, a selected genetic sequence and a reference genetic sequence or a first and second allelic form of a marker). If the two template molecules of interest are expected to be present equally in the DNA sample, then they should be detected equally in the set of assay samples. However, if one of the two template sequences of interest has been altered (*e.g.*, changing the sequence, or removing or increasing its presence in the DNA sample), then one would expect that the ratio of the two template sequences would no longer be equal. This would be reflected in the number of positive assay samples for each of the template sequences.

62. As discussed above in the Background section, there are a number of different types of mutations that may be present in a DNA sample. These mutations may be present on one copy of chromosome or both copies of a chromosome in a pair. It was

also discussed that some genetic sequences can be present in different forms (*e.g.*, are polymorphic) in a DNA sample, such as gene alleles and SNPs. This means that in a chromosome pair, the alleles or SNPs for a particular genetic sequence might be the same or may be different.

63. **Figure 5** shows illustrations of some examples of different genetic sequences. Regions 1, 2 and 3 represent three different genetic sequences (*e.g.*, three genetic loci[3]) occurring on two different types of chromosomes (Chromosomes 4 and 8). Each of Regions 1, 2, and 3 have identical sequences on both chromosomes in the pair—*i.e.*, the regions are homozygous alleles or are non-polymorphic loci. Each of these genetic sequences should be present in equal numbers in a DNA sample.

Figure 5. Schematic of Three Homozygous Genetic Loci.

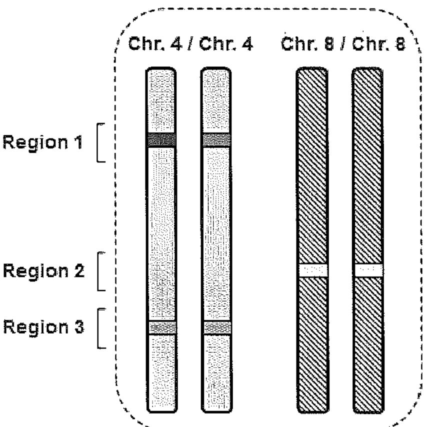


64. In contrast, **Figure 6** shows that Region 1 has two different genetic sequences present at Region 1 (a red sequence and a blue sequence), representing two

[3] "Loci" is the plural of "locus."

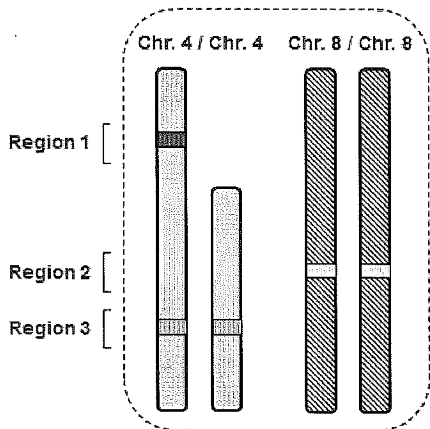
different alleles for a gene, or two different SNPs present at a polymorphic locus. While Regions 2 and 3 would be present in approximately the same amounts in the DNA sample, the red and blue alleles/SNP present at Region 1 would be present at only half the frequency in the DNA sample. However, the red and blue alleles/SNPs at Region 1 would be present in equal amounts to each other in the DNA sample.

Figure 6. Schematic of Two Homozygous Genetic Loci and a Heterozygous Locus.



65. Finally, **Figure 7** shows that part of one chromosome of the Chromosome 4 pair that includes Region 1 is missing (*i.e.*, is deleted). As with Figure 6, Regions 2 and 3 would be present in approximately the same amounts in the DNA sample but Region 1 would only be present in about half the amount compared to Regions 2 and 3.

Figure 7. Schematic of Two Homozygous Genetic Loci and a Deletion Mutation.

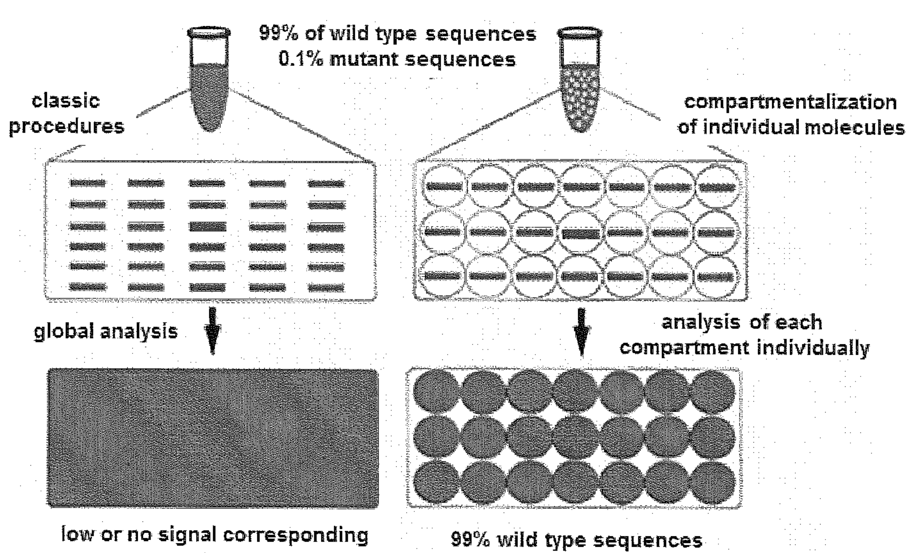


66. Detection of genetic sequences such as those described above is discussed in the Patents in Suit. (*See*, *e.g.*, Col. 4, ll. 66 – Col. 5, ll. 39; Col. 6, ll. 23-44; and Table 1.)

67. One can use the claimed invention to detect a rare template molecule, such as a template DNA containing a mutation that may be present in a heterogeneous (mixed) sample that contains an abundance of wild-type (normal) template. An example of this type of scenario would be a sample (*e.g.*, tissue, blood, or stool) that has normal cells, and mutant cells that contain the mutated template DNA. For example, a mutated template molecule may only be present in 0.1% of the heterogeneous DNA sample. Referring to Figure 6, the mutated template DNA can be the blue allele at Region 1. A reference genetic sequence (or one gene allele)—*i.e.*, a sequence that is suspected to be normal in the DNA sample—can be represented by red M&Ms. The reference genetic sequence

can be the wild-type red allele at Region 1 or the genetic sequences present at Regions 2 or 3. In this scenario, the bowl would contain mostly red M&Ms and only a small number of blue M&Ms (*e.g.*, 0.1%). If only a few M&Ms were selected from the bowl, one might only select red M&Ms and think that the bowl only contained red M&Ms. However, with a sufficiently large number of selections, one would expect that some of the blue M&Ms would also be selected. For example, if 1000 M&M selections were made, one would expect about 1%, (*i.e.*, 1) M&M to be blue (*i.e.*, be positive reactions for the template molecule). The number of blue M&Ms out of the total number of selections made can be used to predict how many total blue M&Ms are present in the bowl. This amount can be compared to the amount of the reference genetic sequence (red M&MS) in the bowl. **Figure 8** shows how the claimed inventions can be used to detect a rare mutation in a heterogeneous DNA sample. In contrast, traditional PCR is unable to detect rare sequences due to the abundance of the normal sequence present in the sample that would act as template DNA for the reaction.

Figure 8. Digital PCR to identify a rare genetic sequence (*e.g.*, mutation).



68. A key factor for detecting rare genetic sequences is that a sufficient number of assay samples are assessed (*i.e.*, how many M&Ms are selected from the bowl). If the number of samples is too small, the number of positive and negative reactions may be skewed. For a rare genetic sequence, if there are too few assay samples, it is possible that none of the assay samples would contain it. Thus, the accuracy of the claimed inventions increases as the number of assay samples increase. This is discussed in the Patents in Suit. (*See*, *e.g.*, Col. 4, ll. 8-65; Col. 6, ll. 10-22.) A number of the claims at issue in this litigation matter relate to the extent to which template molecules must be segregated in the set of assay samples; particularly, claims 7-11 and 39-43 of the ’706 patent, claims 16 and 17 of the ’889 patent, and claims 12 and 13 of the ’015 patent.

69. As another illustrative example, the red and blue M&Ms in the bowl may be two template molecules of interest that are expected to be equal unless a mutation has occurred that impacts the presence of one of the template molecules in the DNA sample. For example, the red M&Ms may represent a reference genetic sequence (or one gene allele)—*i.e.*, a sequence that is suspected to be normal in the DNA sample. As discussed above, each person normally has two copies of each chromosome. Thus, the reference genetic sequence (red M&Ms) is the baseline amount for a given genetic sequence in the DNA sample. The blue M&Ms may represent a selected genetic sequence that may be mutated (or could be a second allele). For example, the blue M&Ms may represent a genetic sequence that may be deleted on one chromosome or from both copies of a chromosome pair. With reference to Figure 5, the selected genetic sequence could be the sequences present at Region 1, while the reference genetic sequence could be the sequences present at Regions 2 and 3. If a selection of 1000 M&Ms is made, the number of red and blue M&Ms selected should be approximately equal (*e.g.*, ~500 each) if no deletion is present. However, if the DNA sample contains a deletion of the selected genetic sequence from one chromosome, such as is shown in Figure 7, then the selected M&Ms (1000) would be expected to have about one third the amount of the selected genetic sequence and two thirds the amount of the reference genetic sequence (*i.e.*, ~250 blue M&Ms to 750 red M&Ms). Also, if the DNA sample contains a deletion of the

selected genetic sequence from both chromosomes in a pair, there would be no blue M&Ms in the bowl and, thus, all the selected M&Ms would be red.

70. In a similar example, the selected genetic sequence might be one that is amplified in the DNA sample. For example, the selected genetic sequence (green M&Ms) may be present twice on one chromosome (*i.e.*, is duplicated), and thus altogether the DNA sample has three copies of the selected genetic sequence (two copies from one chromosome and one copy from the other chromosome in the pair). Again, the red M&Ms may represent a reference genetic sequence—*i.e.*, a sequence that is suspected to have a normal number of copies (*i.e.*, 2) in the DNA sample. If the selected genetic sequence is duplicated, then one would expect that two thirds of the selected M&Ms would be green (750) and only one third would be red (250). In this scenario, the reference genetic sequence (red M&Ms) is again the baseline amount for a given genetic sequence in the DNA sample against which the amount of selected genetic sequence is compared.

71. I note that the above two examples describe scenarios in which the DNA sample being assessed is homogeneous—*i.e.*, contains a uniform set of genetic sequences. An example of a homogeneous DNA sample is DNA from a tissue sample in which all the cells were the same. The difference between the numbers of two sequences (colored M&Ms) is straightforward to detect when there are large differences between the

starting numbers as described above. When the observed differences in the amount of two sequences is small, it is necessary to discern between true differences in the amount of the sequences in the DNA sample and natural variation in sequences represented in the assay samples (*i.e.*, the number of red and green M&Ms in a given number of selected M&Ms). However, the claimed inventions are able to quantify the amount of template molecules so precisely that differences in gene copy can also be detected in a heterogeneous DNA sample containing only a small amount of a template molecule of interest. For example, deletion mutations as described in this example can be rare mutations found in only a small number of cells in a heterogeneous biological sample, similar to those described above. In analyzing heterogeneous DNA samples, the difference in the amount of the selected genetic sequence and the reference genetic sequence will not be nearly as pronounced as in a homogeneous DNA sample. Yet, the claimed inventions are capable of distinguishing the small difference in the amounts of these sequences using statistical methods.

72. At the time of the invention, a wide variety of analytical methods were known that could be used to determine the presence of amplified template molecules in assay samples. A number of these analytical methods used short, single-stranded oligonucleotide molecules. For example, analyses using probe hybridization assays were contemplated (*e.g.*, using the probes described in the Patents in Suit or other oligonucleotide probes, including TaqMan® probes). In these types of assays, a labeled

oligonucleotide probe that is complementary to at least a portion of the template sequence of interest is incubated with the assay samples. If amplified template molecules are present in an assay, the probe will hybridize to the amplified template molecules and label can be detected. The probes can be labeled with molecules that are fluorescent (emit light), colorimetric (can produce a color), or with radioisotopes (emit radiation). Analytical methods using primers were also contemplated, including primer extension assays and sequencing analysis.

73. Different analytical techniques have different degrees of sensitivity and specificity for detecting the amplified template molecules. **Specificity** refers to the ability of the analytical technique to detect only the amplified template molecule of interest and not adventitiously detect a different sequence. Specificity is important because, as discussed above, detecting the amplified template molecule is how an assay sample is designated a positive reaction. If an analytical method is not very specific, it could incorrectly identify assay samples as containing template sequence (*i.e.*, false positives). **Sensitivity** refers to how well the analytical method is able to detect the amplified template molecule. A sensitive analytical method would be able to detect very small amounts of template DNA in an assay sample, while a less sensitive analytical method would require a greater amount of the template to be present for detection.

74. The interplay between these two factors govern both the number of assay samples in a set of assay samples and the amount of the total DNA sample that can be separated amongst the assay samples. If the concentration of the DNA sample is too high, it may require dilution to assure that the template molecules in the DNA sample are sufficiently partitioned in the assay system. However, DNA samples that have a sufficiently low concentration of genetic sequences in them do not require dilution.

75. In addition, out of all the genetic sequences that may be present in an assay sample, the genetic sequences of interest, particularly the selected sequence of interest, which may be rare, must be present in a sufficient amount that the analytical method can detect the amplified molecules with sufficient specificity and selectivity despite the other sequences present in the assay sample. This element goes beyond the notion of simply a detectable amount of the amplified DNA molecules present, as it also contemplates specificity and sensitivity of the analytical method. This concept is expressed in claims 2 and 38 of the '706 patent, which recite that some portion of the assays samples in the set "comprise a number (N) of molecules such that 1/N is larger than the ratio of selected genetic sequences to total genetic sequences required to determine the presence of the selected genetic sequence." These principles underlie the discussion in the Patents in Suit. (*See, e.g.*, Col. 3, ll. 65 - Col. 4, ll. 56; Col. 5, ll. 40 – Col. 6, ll. 9.) Thus, two of the claims at issue in this litigation matter relate to the sensitivity and specificity of the analytical method used in the inventions: claims 2 and 38 of the '706 patent.

B. CLAIM CONSTRUCTION

76. With respect to certain terms contained within the Vogelstein Patents, my understanding is that the parties may disagree with respect to the definition and meaning of certain terms.

77. I understand that Defendants contend that the template molecules to be analyzed must come directly from the biological sample (*i.e.*, not be modified in any way). In my opinion, this is an incorrect interpretation of the specification. The specification contemplates that manipulations, such as amplification or conversion of mRNA to cDNA, could be performed on the sample prior to amplification and analysis. Such manipulations do not alter the relative amounts of different sequences in the DNA sample; they are used simply to facilitate amplification and analysis steps. Thus, template nucleic acid molecules can be manipulated in a number of ways and such modified molecules are still template molecules under the claims of the Patents in Suit. (*See, e.g.*, Col. 6, ll. 45-49 and Examples at Col. 7-12.)

78. For example, the Vogelstein Patents clearly describe the use of the inventions to assess messenger ribonucleic acid (mRNA) by employing reverse-transcription PCR (RT-PCR). (*See*, *e.g.*, Col. 4, ll. 66 – Col. 5, ll. 33.) mRNA is a nucleic acid molecule that is similar to DNA. It is an intermediary molecule in the process of making proteins from genes. mRNA is commonly assessed using RT-PCR, a

modified form of PCR. RT-PCR involves manipulating mRNA that has been obtained from a biological sample to make representative DNA copies called complementary DNA (cDNA). cDNA is not found naturally in cells (or a biological sample) and can only be made in a laboratory. This step is performed due to the inherent instability of mRNA; following conversion to cDNA, the nucleic acid sequence can be effectively handled for laboratory research and diagnostic purposes.

79. Similarly, a preliminary step of amplification may be used to amplify genetic sequences of interest from the DNA sample. Amplification could be conducted in one of two ways. First, whole sample amplification may be performed that would generate more copies of all of the DNA molecules present in the sample. Alternatively, amplification could be done to specific DNA molecules for the purpose of enriching the sample for those genetic sequences of interest. The latter method is used to create a DNA sample with a greater number of genetic sequences of interest, thereby improving the signal to noise ratio for analyzing the DNA sample. Amplifying the genetic sequences of interest in a DNA sample in this manner does not materially alter them and, thus, such amplified sequences are still template molecules under the claims of the Vogelstein Patents.

80. It is also possible to add useful nucleic sequences onto the ends of template molecules from a DNA sample for a variety of reasons that are well known to those of

skill in the art. Examples of modifications include the addition of nucleic acid sequences to aid in the isolation of the sequences of interest, for the purification of the sequences, or for the addition of other identifiers that would be useful when conducting a multiplex analysis of many samples in parallel. These types of manipulations can be readily performed on cDNA template molecules and pre-amplified DNA molecules as described above. These modified molecules are still template molecules under the claims of the Vogelstein Patents.

81. I understand that Defendants may be contending that the analyzing step of the claims is limited to merely an analysis of data. This is also incorrect. The analyzing step described in the Vogelstein Patents involves performing an analytical method on each of the assay samples to determine the number of assay samples that contain amplified template molecules. Also, as discussed above, the specificity and selectivity of the analytical method used in the analyzing step impacts the extent to which template molecules in a DNA sample must be segregated from each other. The selection and use of various analytical methods, and the impact of selecting such methods, is discussed in the Patents in Suit. (*See*, *e.g.*, Col. 3, ll. 66 – Col. 4, ll. 65; Col. 5, ll. 40 – Col. 6, ll. 22.)

82. I understand that Defendants have indicated that claim 38 of the '706 patent, which states that some portion of the assays samples in the set "comprise a number (N) of molecules such that 1/N is larger than the ratio of selected genetic

sequences to total genetic sequences required to determine the presence of the selected genetic sequence," requires diluting the DNA sample. As discussed above, if the concentration of the DNA sample is already sufficiently dilute, there is no need to dilute the DNA sample further prior to partitioning the template molecules amongst the assay samples of the set. This is also clearly stated in the Patents in Suit. (*See*, *e.g.*, Col. 4, ll. 13-34.)

I declare under penalty of perjury that the foregoing is true and correct.

Executed on September 27, 2013 in Ann Arbor, Michigan.

David H. Sherman

Electronic Acknowledgement Receipt

EFS ID:	18029084
Application Number:	90012896
International Application Number:	
Confirmation Number:	8361
Title of Invention:	DIGITAL AMPLIFICATION
First Named Inventor/Applicant Name:	7915015
Customer Number:	11332
Filer:	Sarah Anne Kagan./Jennifer Hazzard
Filer Authorized By:	Sarah Anne Kagan.
Attorney Docket Number:	001107.00988
Receipt Date:	27-JAN-2014
Filing Date:	17-JUN-2013
Time Stamp:	12:22:07
Application Type:	Reexam (Third Party)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	IDSSB08.PDF	612725 96724b075adb82e8f8f5773f43dc551bd93995c7	no	5

Warnings:

Information:

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2	Non Patent Literature	NPL-1.pdf	270942 0887199e2ff5a5b2369181b69f9eb8f7e791319f	no	7
Warnings:					
Information:					
3	Non Patent Literature	NPL-2.pdf	1602260 ee19b3ccbece421ea82e6ddf202bdd44a89ff9b1	no	31
Warnings:					
Information:					
4	Non Patent Literature	NPL-3.pdf	8816248 87febcde97e99964ba5c58c565a2ec5578200f04	no	110
Warnings:					
Information:					
5	Non Patent Literature	NPL-4.pdf	2100308 de213cf9cccd178b58f2fd9916b45181b55d4c8c	no	26
Warnings:					
Information:					
6	Non Patent Literature	NPL-5.pdf	1253136 7ea19c50e28d926e06363bac66ae4d3c008f88f4	no	31
Warnings:					
Information:					
7	Non Patent Literature	NPL-6.pdf	1218520 365cfc46661dd227026b469b6c69abfb5f8ce260	no	16
Warnings:					
Information:					
8	Non Patent Literature	NPL-7.pdf	1780447 b0b9a86407c5f8f21bcfb0749c12b4e7289d8c55	no	38
Warnings:					
Information:					
9	Non Patent Literature	NPL-8.pdf	1679774 498736b96ba6da6608f127a55f63fd34fd6e08d4	no	31
Warnings:					
Information:					

10	Non Patent Literature	NPL-9.pdf	450206 f6e06a26d55df5f0f787773f7f72488eeea4330a	no	6
Warnings:					
Information:					
11	Non Patent Literature	NPL-10.pdf	1375032 212576e91f8996d58026ae34164796a5cf5d59c6	no	31
Warnings:					
Information:					
		Total Files Size (in bytes):	21159598		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Ex Parte* Reexamination:	)	Group Art Unit: 3991
	)	
U.S. Patent No. 7,915,015	)	Docket No. 001107.00988
	)	
Control No. 90/012,896	)	Confirmation No: 8361
	)	
Reexam Filing Date: June 17, 2013	)	Examiner: Bruce R. Campell

For: DIGITAL AMPLIFICATION

DECLARATION OF JAY SHENDURE

1. My name is Jay Shendure. I make this declaration based on my personal knowledge. I am over 21 and otherwise competent to make this declaration.

2. I am currently an Associate Professor in the Department of Genome Sciences at the University of Washington School of Medicine in Seattle, Washington. I have held this position since 2011. Prior to that I was an Assistant Professor in the Department of Genome Sciences at the University of Washington. I held this position from 2007 to 2011. I am also an Affiliate Professor with the Division of Human Biology at the Fred Hutchinson Cancer Research Center in Seattle, Washington; a position I have held since 2010. A copy of my *Curriculum vitae* is attached as Exhibit A.

3. As my *Curriculum vitae* indicates, I obtained my M.D. from Harvard Medical School in Boston, Massachusetts in 2007 and previous to that obtained my Ph.D. in Genetics from Harvard University in 2005.

4. As can be observed from my *Curriculum vitae*, I have been engaged in genetics and genomics research since about 1995. My current research is focused on the development of new technologies for genomics and molecular biology. Throughout my career I have followed new developments in the field by reading of the scientific literature, active research, and interactions with colleagues. Because of my training and experience, I consider myself knowledgeable in various aspects of genomics, technology development, and nucleic acid sequencing. This includes technologies that are used to analyze DNA sequences and variations in DNA sequences.

5. I have been informed that Johns Hopkins University (JHU) owns U.S. patent 7,915,015 ("'015 patent") and has licensed it to Esoterix Genetics Laboratories (EGL), a subsidiary of Laboratory Corporation of America Holdings (LabCorp), and Exact Sciences.

6. I have never been employed by JHU or by EGL, LabCorp, or Exact Sciences.

7. I have reviewed the '015 patent, including the original claims 1-18 (attached as Exhibit B), the re-examination Office Action mailed November 27, 2013, and the cited Bischoff reference (Human Molecular Genetics, 1995, volume 4, pp. 395-399).

8. The statements that I make include my opinions and the bases for them. Although I am being compensated for my time in preparing this declaration, the opinions

are my own, and I have no stake in the outcome of the reexamination proceeding. My compensation does not depend in any way on the outcome of the re-examination.

9. I understand that obviousness is assessed from the standpoint of the hypothetical person of ordinary skill in the art. I believe that such a person would have training in molecular biology techniques, such as PCR and related laboratory procedures, having a bachelor's degree in biological or chemical sciences, and have at least three years of experience in a laboratory, or alternatively have a Master's degree in biological or chemical sciences and have at least one year of laboratory experience.

10. Each of independent claims 1 and 8 of the '015 patent defines an allelic imbalance as a difference between a first and a second allelic form of a marker. Claim 1 recites: "to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker . . .comparing the first number to the second number to ascertain an allelic imbalance in the biological sample . . . ." Claim 8 recites: "to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker . . . comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance between the first allelic form and the second allelic form in the biological sample . . . ."

11. The "allelic imbalance" recited in claims 1 and 8 does not encompass differential expression. Measuring RNA expression is different than quantifying a DNA marker *per se*. One cannot reliably determine an imbalance of a first and a second marker based on an expression product. Differential expression between two alleles may have many causes, including DNA modifications. Some of these causes do not reflect differences in the amount of a first and a second marker.

12. Bischoff studied DNA isolated from single isolated cells in order to distinguish between two genetic mechanisms that would account for the increased amount of paternal allele shown in Fig. 1. Bischoff postulated that either a duplication of a paternal 11p region had occurred in all cells, or that the blood of the patient contained two cell lines with different constituents (normal biparental inheritance and partial paternal isodisomy). Both genetic mechanisms would have yielded the same ratio when analyzed in bulk DNA. In order to distinguish between the two genetic mechanisms, Bischoff performed a single cell analysis. This analysis kept the two chromosome 11 homologs together in a single assay. This permitted Bischoff to distinguish between the two genetic models. If Bischoff had used bulk DNA that was distributed to separate different chromosomes into different assays, she could not have distinguished between the two genetic models.

13. Bischoff teaches micromanipulation of individual, whole cells and then lysing them individually. One of ordinary skill in the art would not understand cell micromanipulation of intact single cells to be a form of distributing nucleic acid

template molecules from a biological sample as required, for example, in claim 8 of the '015 patent.

14. Beckwith-Wiedemann syndrome is not cancer. Beckwith-Wiedemann syndrome, as described in Bischoff, is characterized by numerous growth abnormalities including exomphalos, macroglossia, and gigantism. Page 395, col. 1, lines 22-24. Bischoff's teaching about Beckwith-Wiedemann syndrome would not have motivated one of ordinary skill in the art to look for cancer cells, *e.g.*, to monitor cancer therapy, using the methods of the claimed invention.

15. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the claims or the patent.

Jay Shendure

Jan 27, 2014

Date

Jay Shendure, MD, PhD

Updated January 18, 2014

Current Position

Associate Professor
Department of Genome Sciences
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School of Medicine
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Contact Information

E-mail: shendure@uw.edu
Lab website: http://krishna.gs.washington.edu
Office phone: (206) 685-8543

Education

- 2007 M.D., Harvard Medical School (Boston, Massachusetts)
- 2005 Ph.D. in Genetics, Harvard University (Cambridge, Massachusetts)
  Research Advisor: George M. Church
  Thesis entitled "*Multiplex Genome Sequencing and Analysis*"
- 1996 A.B., *summa cum laude* in Molecular Biology, Princeton University (Princeton, NJ)
  Research Advisor: Lee M. Silver

Professional Experience

- 2011 – Present Associate Professor (with tenure)
  Department of Genome Sciences, University of Washington, Seattle, WA
- 2010 – Present Affiliate Professor
  Division of Human Biology, Fred Hutchinson Cancer Research Center, Seattle, WA
- 2007 – 2011 Assistant Professor
  Department of Genome Sciences, University of Washington, Seattle, WA
- 1998 – 2007 Medical Scientist Training Program (MSTP) Candidate
  Department of Genetics, Harvard Medical School, Boston, WA
- 1997 – 1998 Research Scientist
  Vaccine Division, Merck Research Laboratories, Rahway, NJ
- 1996 – 1997 Fulbright Scholar to India
  Department of Pediatrics, Sassoon General Hospital, Pune, India

Honors and Awards

- 2014 HudsonAlpha Prize for Life Sciences
  HudsonAlpha Institute for Biotechnology
- 2013 FEDERAprijs
  Federation of Dutch Medical Scientific Societies
- 2013 NIH Director's Pioneer Award
  National Institutes of Health

- 2012 Curt Stern Award
  American Society of Human Genetics
- 2010 Lowell Milken Young Investigator (2010-2013)
  Prostate Cancer Foundation
- 2008 Science in Medicine New Investigator Lecture
  University of Washington
- 2008 3rd Annual Tomorrow's PIs
  Genome Technology Magazine
- 2007 James Tolbert Shipley Prize
  Harvard Medical School
- 2006 TR35 Young Innovator Award
  M.I.T. Technology Review
- 1998 Medical Science Training Program Fellowship
  National Institutes of Health
- 1996 Fulbright Scholarship
  U.S. State Department
- 1996 *summa cum laude*
  Princeton University
- 1996 Honorary Major in Anthropology
  Princeton University
- 1996 Sigma Chi Book Award for Molecular Biology Senior Thesis ("*The Genetics of Alcohol Consumption: QTLs Affecting Ethanol Consumption in Inbred Mice*")
  Princeton University
- 1996 Senior Prize for Best Thesis in Anthropology ("*Homunculi, Polyps and the Generation of Beings: Interpreting Theory Change in Biology*")
  Princeton University
- 1996 Phi Beta Kappa
  Princeton University
- 1992 National Merit Scholar
  Solon High School

Editorial Boards, Consortium Leadership & Scientific Advisory Boards

- 2014 – Present Editorial Board of *Human Molecular Genetics*
- 2011 – Present Editorial Board of *Human Genetics*
- 2011 – Present Editorial Board of *Biotechniques*
- 2010 – Present Editorial Advisory Board of *Genome Biology*
- 2009 – Present Editorial Board of *Genome Research*
- 2009 – 2012 Associate Editor of *American Journal of Human Genetics*

- 2012 – Present Member, *Autism Sequencing Consortium (ASC)*
- 2012 – Present Steering Committee, *NHGRI Centers for Mendelian Genomics (CMG)*
- 2009 – 2012 Steering Committee, *NHLBI Exome Sequencing Project (ESP)*

- 2012 – Present Scientific Advisory Board, *Department of Energy - Joint Genome Institute (DOE-JGI)*
- 2009 – Present Technology Development Advisory Group, *International Barcode of Life (iBOL)*
- 2011 – Present External Advisory Committee, *Genomics and Pathology Services at Washington University in St Louis (GPS @ WUSTL)*

Other Activities

- 2012 – Present Faculty of 1000 (F1000), Medical Genetics
- 2011 Guest Editor, *Genome Biology* (special issue on exome sequencing)
- 2009 – Present Member, Fred Hutchinson / University of Washington Cancer Consortium
- 2009 Program Committee, American Association for Cancer Research, 101st Annual Meeting
- 2009 – 2012 Convener, NHLBI Exome Sequencing Project (ESP) Family Studies Working Group

Commercial Advisory Roles

- 2013 – Present Scientific Advisory Board of *Ingenuity Systems*
- 2013 – Present Scientific Advisory Board of *Rubicon Genomics*
- 2013 – Present Scientific Advisory Board of *GenePeeks*
- 2013 – Present Scientific Advisory Board of *Gen9*
- 2010 – Present Consultant to *Ariosa Diagnostics*
- 2010 – Present Scientific Advisory Board of *Adaptive Biotechnologies*
- 2009 – Present Scientific Advisory Board of *Good Start Genetics*
- 2009 – Present Scientific Advisory Board of *Stratos Genomics*
- 2012 Consultant to *Merck Research Laboratories*
- 2010 – 2011 Scientific Advisory Board of *Halo Genomics*
- 2008 – 2009 Consultant to *Complete Genomics*
- 2006 Consultant to *Highland Capital Partners*
- 2004 – 2005 Consultant to *Agencourt Biosciences*

Faculty Administrative Responsibilities (University of Washington)

- 2013 – 2014 Chair, Seminar Series Committee (Genome Sciences)
- 2012 – 2013 Co-chair, Scientific Discovery Subcommittee for Curriculum Renewal
- 2008 – 2013 Member, Faculty Search Committee (Medical Genetics)
- 2011 – 2012 Member, Faculty Search Committee (Genome Sciences)
- 2010 – 2011 Member, Faculty Search Committee (Genome Sciences)
- 2008 – 2009 Member, Faculty Search Committee (Genome Sciences)
- 2010 Co-organizer, Symposium & Panel Discussion – "*New Discoveries in Medicine: Implications for the Cost and Quality of American Healthcare.*" (Genome Sciences)
- 2009 Organizer, Departmental Retreat (Genome Sciences)
- 2009 Member, U.W. "Two Years to Two Decades" (2y2d) initiative, Discovery focus group
- 2008 – 2009 Member, Seminar Series Committee (Genome Sciences)

Reviewer (ad hoc)

Nature
Science
Cell
New England Journal of Medicine
Nature Genetics
Nature Biotechnology
Nature Medicine
Nature Methods
Nature Reviews Genetics
Science Translational Medicine

Analytical Chemistry
Bioinformatics
Biotechniques
BMC Genomics
Cell Stem Cell
Cellular & Molecular Biology Letters
Genomics
Human Mutation
Mammalian Genome
Nature Protocols

Proceedings of the National Academy of Sciences	Neuron
PLoS Genetics	Nucleic Acids Research
Genome Research	PLoS Computational Biology
American Journal of Human Genetics	Trends in Genetics
Genome Biology	Genetics in Medicine

Grant Review & Other Service

- 2013 Grant reviewer, National Institute of Child Health and Human Development Special Emphasis Panel for U01 Male Contraceptive Development Program
- 2013 Abstract reviewer, 63th Annual Meeting of American Society of Human Genetics
- 2013 Grant reviewer, The Wellcome Trust
- 2011 Grant reviewer, W. M. Keck Foundation
- 2011 Grant reviewer, Lasker Clinical Research Scholars Program
- 2010 Grant reviewer, UK Medical Research Council, Molecular and Cellular Medicine Board
- 2009 Grant reviewer, National Science Foundation
- 2009 Grant reviewer, NIH ARRA Challenge Grants (Genes, Genomes and Genetics IRG)
- 2009 Grant reviewer, Ontario Research Fund (GL2 Competition)
- 2008 Grant reviewer, Genome BritishColumbia

Postdoctoral Fellows Trained (University of Washington)

- 2014 – Present Ron Hause, Ph.D.
- 2013 – Present Jacob Kitzman, Ph.D.
- 2012 – Present Martin Kircher, Ph.D.
- 2011 – Present Stephen Salipante, M.D., Ph.D.
- 2009 – 2013 Jerrod Schwartz, Ph.D. (current position: GoogleX)
- 2009 – 2013 Brian O'Roak, Ph.D. (joint trainee with Evan Eichler; current position: Assistant Professor, Department of Molecular & Medical Genetics, Oregon Health & Science University)
- 2007 – 2009 Emily Turner, Ph.D. (current position: Senior Scientist, Genetics & Solid Tumors, Department of Laboratory Medicine, University of Washington)

Graduate Students Trained (University of Washington)

- 2013 – Present Aaron McKenna (Genome Sciences)
- 2012 – Present Matthew Snyder (Genome Sciences)
- 2011 – Present Joshua Burton (Genome Sciences)
- 2010 – Present Akash Kumar (Medical Scientist Training Program, Genome Sciences)
- 2010 – Present Andrew Adey (Molecular & Cellular Biology)
- 2009 – 2013 Jacob Kitzman (Genome Sciences; dissertation entitled "New technologies for sequencing and interpreting genomes"; current position: Postdoctoral Fellow, Shendure Lab)
- 2009 – 2012 Joseph Hiatt (Medical Scientist Training Program, Genome Sciences; dissertation entitled "Molecular tagging to overcome limitations of massively parallel sequencing"; current position: completing medical school)
- 2007 – 2012 Sarah Ng (Genome Sciences; dissertation entitled "Next Generation Mendelian Genetics"; current position: Research Fellow, Institute of Molecular and Cell Biology, Singapore)
- 2007 – 2012 Rupali Patwardhan (Genome Sciences; dissertation entitled "Massively parallel functional dissection of regulatory elements"; current position: Software Engineer, Facebook)

Rotation Students Supervised (University of Washington)

Name	Program	Term
Vijay Ramani	Genome Sciences	Winter 2014
Seungsoo Kim	Genome Sciences	Winter 2014
Jason Klein	MSTP program	Summer 2013
Hugh Haddox	Molecular & Cellular Biology	Spring 2013
Aaron McKenna	Genome Sciences	Winter 2013
Greg Findlay	MSTP program	Summer 2012
Matthew Snyder	Genome Sciences	Spring 2012
Jorgen Nelson	Genome Sciences	Winter 2012
Elyse Hope	Genome Sciences	Winter 2012
Meara Davies	Molecular & Cellular Biology	Fall 2011
Josh Burton	Genome Sciences	Winter 2011
Jenny Wagner	Genome Sciences	Winter 2011
Andrew Adey	Molecular & Cellular Biology	Fall 2009
David Young	MSTP program	Summer 2009
Akash Kumar	MSTP program	Summer 2009
Jacob Kitzman	Genome Sciences	Spring 2009
Keisha Carlson	Genome Sciences	Winter 2009
Jarrett Egerston	Genome Sciences	Winter 2009
Matthew Maurano	Genome Sciences	Fall 2008
Joseph Hiatt	MSTP program	Summer 2008
Sayer Herrin	Genome Sciences	Winter 2008
Rupali Patwardhan	Genome Sciences	Winter 2008
Sarah Ng	Genome Sciences	Fall 2007

Graduate Student Committees (in addition to trainees)

Years	Name	Department	Advisor
2013 – Present	Jorgen Nelson	U.W. Genome Sciences	Advisor: David Baker
2013 – Present	David Young	U.W. Genome Sciences	Advisor: Stan Fields
2012 – Present	Niklas Krumm	U.W. Genome Sciences	Advisor: Evan Eichler
2012 – Present	Andrew Laszlo	U.W. Physics	Advisor: Jens Gundlach
2012 – Present	Benjamin Vernot	U.W. Genome Sciences	Advisor: Josh Akey
2011 – Present	Jennifer Andrie	U.W. Genome Sciences	Advisor: Josh Akey
2010 – Present	Russell Berg	U.W. Molecular & Cellular Biology	Advisor: Lalita Ramakrishnan
2010 – Present	Leslie Emery	U.W. Genome Sciences	Advisor: Josh Akey
2010 – 2013	Peter Sudmant	U.W. Genome Sciences	Advisor: Evan Eichler
2010 – 2013	Thomas White	U.W. Molecular & Cellular Biology	Advisor: Peter Nelson
2010 – 2013	Benjamin Whiddon	U.W. Genome Sciences	Advisor: Richard Palmiter
2009 – 2013	Cailyn Spurrell	U.W. Genome Sciences	Advisor: Mary-Claire King
2008 – 2013	Alan Rubin	U.W. Genome Sciences	Advisor: Phil Green
2009 – 2012	Joshua Bishop	U.W. Electrical Engineering	Advisor: Eric Klavins
2011 – 2012	Lucas Gray	U.W. Biochemistry	Advisor: Alan Weiner
2009 – 2012	Kyle Minch	U.W. Molecular & Cellular Biology	Advisor: David Sherman
2011	Sung Hang	U.W. Neurobiology and Behavior	Advisor: William Catterall
2010	Carlos Araya	U.W. Genome Sciences	Advisor: Stanley Fields
2008 – 2010	Steven Josefowicz	U.W. Immunology	Advisor: Sasha Rudensky
2008 – 2010	Kevin Schutz	U.W. Genome Sciences	Advisor: Stan Fields

- 2008 – 2010 Marcia Paddock U.W. Immunology Advisor: Andy Scharenberg

Other Trainee Committees

- 2010 – Present Michael Cho, M.D. K08 Advisory Committee Advisor: Ed Silverman

Courses Taught

- 2012 – 2013 CONJOINT 511 – "Genetic Anatomy" (University of Washington)
  Medical school 1st year elective; co-taught w/ Marshall Horwitz and John Clark
- 2012 – 2013 HUBIO 554 – "Genetics" (University of Washington)
  Medical school 2nd year pre-clinical curriculum; co-chaired with Heather Mefford
- 2008 – 2013 GENOME 550 – "Methods and Logic in Genetics" (University of Washington)
  Graduate seminar course; co-taught with Bob Waterston
- 2010 – 2012 GENOME 373 – "Genome Informatics" (University of Washington)
  Undergraduate lecture course; co-taught with Jim Thomas or Elhanan Borenstein
- 2001 – 2003 "Principles of Pharmacology" (Harvard Medical School)
  Teaching assistant, 1st year medical school course

Other Teaching or Outreach Activities

- Dec 2013 Guest session leader for BIOL 485 "Senior Seminar in Cellular, Molecular and Developmental Biology" (UW)
- Nov 2013 Keynote speaker, UW Postdoc Association Symposium
- Nov 2013 Speaker, Pacific Science Center "Science Café" series
- Oct 2013 Guest session leader for MCB 517 "The Developmental Basis of Human Disease" (UW)
- Aug 2013 Co-organizer, UW Center for Mendelian Genomics (CMG) Data Analysis Workshop
- Jul 2013 Speaker, UW Genome Sciences summer research internship program
- Jun 2013 Guest session leader for MEBI 590 "Biomedical and Health Informatics Lecture Series" (UW)
- Apr 2013 Guest speaker, UW MSTP Dinner/Recruitment meeting
- Apr 2013 Guest session leader for EPI 590 "Introduction to Laboratory Methods in Population Research" (UW)
- Oct 2012 Speaker, Seattle Sequencing Interest Group
- Jul 2012 Speaker, "Science on Tap" series
- Jul 2012 Speaker, UW Genome Sciences summer research internship program
- Apr 2012 Guest session leader for GENOME 580 "Ethics in Biomedical Research and Teaching" (UW)
- Apr 2011 Guest session leader for GENOME 580 "Ethics in Biomedical Research and Teaching" (UW)
- Apr 2011 Guest session leader for EPI 590 "Introduction to Laboratory Methods in Population Research" (UW)
- Oct 2010 Lecturer for Medical Genetics "Introduction to Human & Medical Genetics" course (UW)
- Apr 2010 Moderator for UW Genome Sciences 2010 Panel Discussion on ""New Discoveries in Medicine: Implications for the Cost and Quality of American Healthcare"
- Nov 2009 Panelist for Lasker Foundation / UW Dept. of Genome Sciences Round Table: "Personal Genomes: Promise or Hype?"
- Sep 2009 Panelist for "The Two Body Question and Faculty with children" at HHMI Future Faculty Workshop

- Apr 2009 Guest session leader for GENOME 580 "Ethics in Biomedical Research and Teaching" (UW)
- Apr 2009 Guest speaker, UW MSTP Dinner/Recruitment meeting
- Apr 2009 Guest session leader for EPI 590 "Introduction to Laboratory Methods in Population Research" (UW)
- Feb 2009 Guest speaker, Rainier Scholars program (UW)
- Jul 2008 Talk at StarNet 2008 Summer Workshop, UW Genome Sciences Education Outreach
- Jul 2008 Talk at "Wednesdays at the Genome" UW Genome Sciences Public Lecture Series
- Oct 2008 Chalk Talk Workshop, UW Women in Genome Sciences (WiGS)
- May 2008 Guest session leader for GENOME 580 "Ethics in Biomedical Research and Teaching" (UW)

Active Patents & Published Patent Applications

- Polony fluorescent in situ sequencing beads (issued; 7,425,431)
- Sequence tag directed subassembly of short sequencing reads into long sequencing reads (issued; 8,383,345)
- Massively parallel contiguity mapping (application; 20130203605)
- Methods for retrieval of sequence-verified DNA constructs (application; 20120283110)
- Nanogrid rolling circle DNA sequencing (application; 20090018024)
- Multiplex decoding of sequence tags in barcodes (application; 20080269068)
- Wobble sequencing (application; 20070207482)
- Nucleic acid memory device (application; 20100099080)

Peer-Reviewed Research Articles *(* denotes equal contributors; # denotes corresponding author(s))*

1. Melo JA, **Shendure J**, Pociask K, Silver LM#. Identification of sex-specific quantitative trait loci controlling alcohol preference in C57BL/ 6 mice. Nature Genetics 1996 Jun;13(2):147-53.
2. **Shendure J***, Melo JA*, Pociask K, Derr R, Silver LM#. Sex-restricted non-Mendelian inheritance of mouse chromosome 11 in the offspring of crosses between C57BL/6J and (C57BL/6J x DBA/2J)F1 mice. Mammalian Genome 1998 Oct;9(10):812-5.
3. Peirce JL*, Derr R*, **Shendure J**, Kolata T, Silver LM#. A major influence of sex-specific loci on alcohol preference in C57Bl/6 and DBA/2 inbred mice. Mammalian Genome 1998 Dec;9(12):942-8.
4. Liang X#, Munshi S, **Shendure J**, Mark G 3rd, Davies ME, Freed DC, Montefiori DC, Shiver JW. Epitope insertion into variable loops of HIV-1 gp120 as a potential means to improve immunogenicity of viral envelope protein. Vaccine 1999 Jul 16;17(22):2862-72.
5. Aach J*, Bulyk ML, Church GM#, Comander J, Derti A, **Shendure J***. Computational comparison of two draft sequences of the human genome. Nature 2001 Feb 15;409(6822):856-9.
6. Badarinarayana V, Estep PW 3rd, **Shendure J**, Edwards J, Tavazoie S, Lam F, Church GM#. Selection analyses of insertional mutants using subgenic-resolution arrays. Nature Biotechnology 2001 Nov;19(11):1060-5.
7. Weber G*, **Shendure J***, Tanenbaum DM, Church GM, Meyerson M#. Identification of foreign gene sequences by transcript filtering against the human genome. Nature Genetics 2002 Feb;30(2):141-2.
8. **Shendure J**, Church GM#. Computational discovery of sense-antisense transcription in the human and mouse genomes. Genome Biology 2002 Aug 22;3(9):RESEARCH0044.
9. Mitra RD, Butty VL, **Shendure J**, Williams BR, Housman DE, Church GM#. Digital genotyping and haplotyping with polymerase colonies. Proceedings of the National Academy of Sciences 2003 May 13;100(10):5926-31.
10. Zhu J*, **Shendure J***, Mitra RD, Church GM#. Single molecule profiling of alternative pre-mRNA splicing. Science 2003 Aug 8;301(5634):836-8.

11. Mitra RD, **Shendure J**, Olejnik J, Edyta-Krzymanska-Olejnik, Church GM#. Fluorescent in situ sequencing on polymerase colonies. *Analytical Biochemistry* 2003 Sep 1;320(1):55-65.
12. Zhu Z#, **Shendure J**, Church GM#. Discovering functional transcription-factor combinations in the human cell cycle. *Genome Research* 2005 Jun;15(6):848-55.
13. **Shendure J***#, Porreca GJ*#, Reppas NB, Lin X, McCutcheon JP, Rosenbaum AM, Wang MD, Zhang K, Mitra RD, Church GM. Accurate Multiplex Polony Sequencing of an Evolved Bacterial Genome. *Science* 2005 Sep 9;309(5741):1728-32.
14. Zhang K#, Zhu J, **Shendure J**, Porreca GJ, Aach JD, Mitra RD, Church GM#. Polony haplotyping of individual human chromosome molecules. *Nature Genetics* 2006 Mar;38(3):382-7.
15. Turner DJ, **Shendure J**, Porreca G, Church G, Green P, Tyler-Smith C, Hurles ME#. Assaying chromosomal inversions by single-molecule haplotyping. *Nature Methods* 2006 Jun;3(6):439-45.
16. Moskowitz I, Kim JB, Moore M, Wolf C, Peterson MA, **Shendure J**, Norbrega M, Yokota Y, Berul C, Izumo S, Seidman JG*, Seidman CE*#. A Genetic Pathway Including Id2, Tbx5, and Nkx2-5 Required for Cardiac Conduction System Development. *Cell* 2007 Jun 29;129(7):1365-76.
17. Porreca GJ*, Zhang K*, Li JB, Xie B, Austin D, Vassallo SL, LeProust EM, Peck BJ, Emig CJ, Dahl F, Gao Y, Church GM*#, **Shendure J***#. Multiplex Amplification of Large Sets of Human Exons. *Nature Methods* 2007 Nov;4(11):931-6.
18. Higgins AW, Alkuraya FS, Bosco AF, Brown KK, Bruns GA, Donovan DJ, Eisenman R, Fan Y, Farra CG, Ferguson HL, Gusella JF, Harris DJ, Herrick SR, Kelly C, Kim HG, Kishikawa S, Korf BR, Kulkarni S, Lally E, Leach NT, Lemyre E, Lewis J, Ligon AH, Lu W, Maas RL, MacDonald ME, Moore SD, Peters RE, Quade BJ, Quintero-Rivera F, Saadi I, Shen Y, **Shendure J**, Williamson RE, Morton CC#. Characterization of apparently balanced chromosomal rearrangements from the developmental genome anatomy project. *American Journal of Human Genetics* 2008 Mar;82(3):712-22.
19. Turner EH, Lee C, Ng SB, Nickerson DA, **Shendure J#.** Massively parallel exon capture and library-free resequencing across 16 genomes. *Nature Methods* 2009 May;6(5):315-6.
20. Brkanac Z#, Spencer D, **Shendure J**, Robertson PD, Matsushita M, Vu T, Bird TD, Olson MV, Raskind WH. IFRD1 is a candidate gene for SMNA on chromosome 7q22-q23. *American Journal of Human Genetics* 2009 May;84(5):692-7.
21. Ng SB#, Turner EH, Robertson PD, Flygare SD, Bigham AW, Lee C, Shaffer T, Wong M, Bhattacharjee A, Eichler EE, Bamshad M, Nickerson DA, **Shendure J**#. Targeted capture and massively parallel sequencing of 12 human exomes. *Nature* 2009 Aug 16.
22. Vasta V, Ng SB, Turner EH, **Shendure J**#, Hahn SH#. Next generation sequence analysis for mitochondrial disorders. *Genome Medicine* 2009 Oct 23;1(10):100.
23. Ng SB*, Buckingham KJ*, Lee C, Bigham AW, Tabor HK, Dent KM, Huff CD, Shannon PT, Jabs EW, Nickerson DA, **Shendure J**#, Bamshad MJ#. Exome sequencing identifies the cause of a mendelian disorder. *Nature Genetics* 2010 Jan;42(1):30-5.
24. Patwardhan RP#, Lee C, Litvin O, Young DL, Pe'er D, **Shendure J#.** High-resolution analysis of DNA regulatory elements by synthetic saturation mutagenesis. *Nature Biotechnology* 2009 Dec;27(12):1173-5.
26. Hiatt JB*#, Patwardhan RP*, Turner EH, Lee C, **Shendure J**#. Parallel, tag-directed assembly of locally derived short sequence reads. *Nature Methods* 2010 Feb;7(2):119-22.
27. Thomas JH#, Emerson RO, **Shendure J**. Extraordinary molecular evolution in the PRDM9 fertility gene. *PLoS One*. 2009 Dec 30;4(12):e8505.
28. Roach JC*, Glusman G*, Smit AF*, Huff CD*, Hubley R, Shannon PT, Rowen L, Pant KP, Goodman N, Bamshad M, **Shendure J**, Drmanac R, Jorde LB#, Hood L#, Galas DJ. Analysis of Genetic Inheritance in a Family Quartet by Whole-Genome Sequencing. *Science* Apr 30;328(5978):636-9.
29. Cooper GM#, Goode DL, Ng SB, Sidow A, Bamshad MJ, **Shendure J**, Nickerson DA. Single-nucleotide evolutionary constraint scores highlight disease-causing mutations. *Nature Methods* 2010 Apr;7(4):250-1.
30. Yang F, Babak T, **Shendure J**, Disteche CM#. Global survey of escape from X inactivation by RNA-sequencing in mouse. *Genome Research* 2010 May;20(5):614-22.
31. Duan Z*, Andronescu M*, Schutz K, McIlwain S, Kim YJ, Lee C, **Shendure J**, Fields S, Blau CA#, Noble WS#. A three-dimensional model of the yeast genome. *Nature* 2010 May 20;465(7296):363-7.

32. Ng SB*, Bigham AW*, Buckingham KJ, Hannibal MC, McMillin MJ, Gildersleeve HI, Beck AE, Tabor HK, Cooper GM, Mefford HC, Lee C, Turner EH, Smith JD, Rieder MJ, Yoshiura KI, Matsumoto N, Ohta T, Niikawa N, Nickerson DA, Bamshad MJ#, **Shendure J**#. Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. *Nature Genetics* 2010 Sep;42(9):790-3.
33. Rios J, Stein E, **Shendure J**, Hobbs HH#, Cohen JC#. Identification by whole-genome resequencing of gene defect responsible for severe hypercholesterolemia. *Human Molecular Genetics* 2010 Nov 15;19(22):4313-8.
34. Sudmant PH*, Kitzman JO*, Antonacci F, Alkan C, Malig M, Tsalenko A, Sampas N, Bruhn L, **Shendure J**; 1000 Genomes Project, Eichler EE#. Diversity of human copy number variation and multicopy genes. *Science* 2010 Oct 29;330(6004):641-6.
35. Adey A* Morrison HG*, Asan*, Xun X*, Kitzman JO, Turner EH, Stackhouse B, Mackenzie AP, Caruccio NC, Zhang X#, **Shendure J**#. Rapid, low-input, low-bias construction of shotgun fragment libraries by high-density in vitro transposition. *Genome Biology* 2010 Dec 8;11(12):R119.
36. Kitzman JO#, Mackenzie AP, Adey A, Hiatt JB, Patwardhan RP, Sudmant PH, Ng SB, Alkan C, Qiu R, Eichler EE, **Shendure J**#. Haplotype-resolved genome sequencing of a Gujarati Indian individual. *Nature Biotechnology* 2011 Jan;29(1):59-63.
37. Muthappan V*, Lee A*, Lamprecht T, Akileswaran L, Dintzis S, Lee C, Magrini V, Mardis E, **Shendure J**, Van Gelder R#. Biome representational in silico karyotyping. *Genome Research* 2011 Apr;21(4):626-33.
38. Gallagher LA, **Shendure J**, Manoil C#. Genome-Scale Identification of Resistance Functions in Pseudomonas aeruginosa Using Tn-seq. *MBio* 2011 Jan 18;2(1). pii: e00315-10.
39. O'Roak BJ, Deriziotis P, Lee C, Vives L, Schwartz JJ, Girirajan S, Karakoc E, Mackenzie AP, Ng SB, Baker C, Rieder MJ, Nickerson DA, Bernier R, Fisher SE, **Shendure J**#, Eichler EE#. Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations. *Nature Genetics* 2011 Jun;43(6):585-9.
40. Hannibal MC*, Buckingham KJ*, Ng SB*, Ming JE, Beck AE, McMillin MJ, Gildersleeve HI, Bigham AW, Tabor HK, Mefford HC, Cook J, Yoshiura K, Matsumoto T, Matsumoto N, Miyake N, Tonoki H, Naritomi K, Kaname T, Nagai T, Ohashi H, Kurosawa K, Hou JW, Ohta T, Liang D, Sudo A, Morris CA, Banka S, Black GC, Clayton-Smith J, Nickerson DA, Zackai EH, Shaikh TH, Donnai D, Niikawa N, **Shendure J**, Bamshad MJ#. Spectrum of MLL2 (ALR) mutations in 110 cases of Kabuki syndrome. *American Journal of Medical Genetics* 2011 Jul;155A(7):1511-6.
41. Cosart T#, Beja-Pereira A#, Chen S, Ng SB, **Shendure J**, Luikart G. Exome-wide DNA capture and next generation sequencing in domestic and wild species. *BMC Genomics* 2011 Jul 5;12:347.
42. Regalado ES, Guo DC, Villamizar C, Avidan N, Gilchrist D, McGillivray B, Clarke L, Bernier F, Santos-Cortez RL, Leal SM, Bertoli-Avella AM, **Shendure J**, Rieder MJ, Nickerson DA; NHLBI GO Exome Sequencing Project, Milewicz DM#. Exome Sequencing Identifies SMAD3 Mutations as a Cause of Familial Thoracic Aortic Aneurysm and Dissection With Intracranial and Other Arterial Aneurysms. *Circulation Research* 2011 Sep 2;109(6):680-6.
43. Kumar A, White TA, Mackenzie AP, Clegg N, Lee C, Dumpit RF, Coleman I, Ng SB, Salipante SJ, Rieder MJ, Nickerson DA, Corey E, Lange PH, Morrissey C, Vessella RL, Nelson PS#, **Shendure J**#. Exome sequencing identifies a spectrum of mutation frequencies in advanced and lethal prostate cancers. *Proceedings of the National Academy of Sciences* 2011 Oct 11;108(41):17087-92.
44. Ventura M, Catacchio CR, Alkan C, Marques-Bonet T, Sajjadian S, Graves TA, Hormozdiari F, Navarro A, Malig M, Baker C, Lee C, Turner EH, Chen L, Kidd JM, Archidiacono N, **Shendure J**, Wilson RK, Eichler EE#. Gorilla genome structural variation reveals evolutionary parallelisms with chimpanzee. *Genome Research* 2011 Oct;21(10):1640-9.
45. George RD#, McVicker G, Diederich R, Ng SB, Mackenzie AP, Swanson WJ, **Shendure J**#, Thomas JH#. Trans genomic capture and sequencing of primate exomes reveals new targets of positive selection. *Genome Research* 2011 Oct;21(10):1686-94.
46. Fairfield H, Gilbert GJ, Barter M, Corrigan RR, Curtain M, Ding Y, D'Ascenzo M, Gerhardt DJ, He C, Huang W, Richmond T, Rowe L, Probst FJ, Bergstrom DE, Murray SA, Bult C, Richardson J, Kile BT, Gut I, Hager J, Sigurdsson S, Mauceli E, Di Palma F, Lindblad-Toh K, Cunningham ML, Cox TC, Justice MJ, Spector

MS, Lowe SW, Albert T, Donahue LR, Jeddeloh J, **Shendure J**, Reinholdt LG#. Mutation discovery in mice by whole exome sequencing. Genome Biology 2011 Sep 14;12(9):R86.

47. Deng X, Hiatt JB, Nguyen DK, Ercan S, Sturgill D, Hillier LW, Schlesinger F, Davis CA, Reinke VJ, Gingeras TR, **Shendure J**, Waterston RH, Oliver B, Lieb JD, Disteche CM#. Evidence for compensatory upregulation of expressed X-linked genes in mammals, Caenorhabditis elegans and Drosophila melanogaster. Nature Genetics 2011 Oct 23;43(12):1179-85.
48. Hondowicz BD, Schwedhelm KV, Kas A, Tasch MA, Rawlings C, Ramchurren N, McIntosh M, D'Amico LA, Sanda S, Standifer NE, **Shendure J**, Stone B#. Discovery of T cell antigens by high-throughput screening of synthetic minigene libraries. PLoS One 2012;7(1):e29949.
49. Rivière JB*, van Bon BW*, Hoischen A, Kholmanskikh SS, O'Roak BJ, Gilissen C, Gijsen S, Sullivan CT, Christian SL, Abdul-Rahman OA, Atkin JF, Chassaing N, Drouin-Garraud V, Fry AE, Fryns JP, Gripp KW, Kempers M, Kleefstra T, Mancini GM, Nowaczyk MJ, van Ravenswaaij-Arts CM, Roscioli T, Marble M, Rosenfeld JA, Siu VM, de Vries BB, **Shendure J**, Verloes A, Veltman JA, Brunner HG, Ross ME, Pilz DT#, Dobyns WB#. De novo mutations in the actin genes ACTB and ACTG1 cause Baraitser-Winter syndrome. Nature Genetics 2012 Feb 26;44(4):440-4, S1-2.
50. Patwardhan RP*, Hiatt JB*, Witten DM, Kim MJ, Smith RP, May D, Lee C, Andrie JM, Lee SI, Cooper GM, Ahituv N#, Pennacchio LA#, **Shendure J#**. Massively parallel functional dissection of mammalian enhancers in vivo. Nature Biotechnology 2012 Feb 26;30(3):265-70.
51. Adey A, **Shendure J#**. Ultra-low-input, tagmentation-based whole-genome bisulfite sequencing. Genome Research 2012 Jun;22(6):1139-43.
52. O'Roak BJ, Vives L, Girirajan S, Karakoc E, Krumm N, Coe BP, Levy R, Ko A, Lee C, Smith JD, Turner EH, Stanaway IB, Vernot B, Malig M, Baker C, Reilly B, Akey JM, Borenstein E, Rieder MJ, Nickerson DA, Bernier R, **Shendure J#**, Eichler EE#. Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations. Nature 2012 Apr 4;485(7397):246-50.
53. Tabor HK, Stock J, Brazg T, McMillin MJ, Dent KM, Yu JH, **Shendure J**, Bamshad MJ. Informed consent for whole genome sequencing: A qualitative analysis of participant expectations and perceptions of risks, benefits, and harms. American Journal of Medical Genetics (A) 2012 Apr 24.
54. Bernier FP, Caluseriu O, Ng S, Schwartzentruber J, Buckingham KJ, Innes AM, Jabs EW, Innis JW, Schuette JL, Gorski JL, Byers PH, Andelfinger G, Siu V, Lauzon J, Fernandez BA, McMillin M, Scott RH, Racher H; FORGE Canada Consortium, Majewski J, Nickerson DA, **Shendure J**, Bamshad MJ#, Parboosingh JS#. Haploinsufficiency of SF3B4, a Component of the Pre-mRNA Spliceosomal Complex, Causes Nager Syndrome. American Journal of Human Genetics 2012 May 4;90(5):925-33.
55. Kitzman JO#, Snyder MW, Ventura M, Lewis AP, Qiu R, Simmons LE, Gammill HS, Rubens CE, Santillan DA, Murray JC, Tabor HK, Bamshad MJ, Eichler EE, **Shendure J#**. Noninvasive whole-genome sequencing of a human fetus. Science Translational Medicine 2012 Jun 6;4(137):137ra76.
56. Boileau C#, Guo DC, Hanna N, Regalado ES, Detaint D, Gong L, Varret M, Prakash SK, Li AH, d'Indy H, Braverman AC, Grandchamp B, Kwartler CS, Gouya L, Santos-Cortez RL, Abifadel M, Leal SM, Muti C, **Shendure J**, Gross MS, Rieder MJ, Vahanian A, Nickerson DA, Michel JB; National Heart, Lung, and Blood Institute (NHLBI) Go Exome Sequencing Project, Jondeau G, Milewicz DM#. TGFB2 mutations cause familial thoracic aortic aneurysms and dissections associated with mild systemic features of Marfan syndrome. Nature Genetics 2012 Jul 8;44(8):916-921.
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58. Schwartz JJ#, Lee C, **Shendure J#**. Accurate gene synthesis with tag-directed retrieval of sequence-verified DNA molecules. Nature Methods 2012 Sep;9(9):913-5.

59. Elde NC#, Child SJ, Eickbush MT, Kitzman JO, Rogers KS, **Shendure J**, Geballe AP, Malik HS#. Poxviruses deploy genomic accordions to adapt rapidly against host antiviral defenses. *Cell* 2012 Aug 17;150(4):831-41.
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61. Peifer M, Fernández-Cuesta L, Sos ML, George J, Seidel D, Kasper LH, Plenker D, Leenders F, Sun R, Zander T, Menon R, Koker M, Dahmen I, Müller C, Di Cerbo V, Schildhaus HU, Altmüller J, Baessmann I, Becker C, de Wilde B, Vandesompele J, Böhm D, Ansén S, Gabler F, Wilkening I, Heynck S, Heuckmann JM, Lu X, Carter SL, Cibulskis K, Banerji S, Getz G, Park KS, Rauh D, Grütter C, Fischer M, Pasqualucci L, Wright G, Wainer Z, Russell P, Petersen I, Chen Y, Stoelben E, Ludwig C, Schnabel P, Hoffmann H, Muley T, Brockmann M, Engel-Riedel W, Muscarella LA, Fazio VM, Groen H, Timens W, Sietsma H, Thunnissen E, Smit E, Heideman DA, Snijders PJ, Cappuzzo F, Ligorio C, Damiani S, Field J, Solberg S, Brustugun OT, Lund-Iversen M, Sänger J, Clement JH, Soltermann A, Moch H, Weder W, Solomon B, Soria JC, Validire P, Besse B, Brambilla E, Brambilla C, Lantuejoul S, Lorimier P, Schneider PM, Hallek M, Pao W, Meyerson M, Sage J, **Shendure J**, Schneider R, Büttner R, Wolf J, Nürnberg P, Perner S, Heukamp LC, Brindle PK, Haas S, Thomas RK#. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nature Genetics* 2012 Oct;44(10):1104-10.
62. Campbell CD, Chong JX, Malig M, Ko A, Dumont BL, Han L, Vives L, O'Roak BJ, Sudmant PH, **Shendure J**, Abney M, Ober C, Eichler EE#. Estimating the human mutation rate using autozygosity in a founder population. *Nature Genetics* 2012 Nov;44(11):1277-81.
63. Horani A*, Druley TE*, Zariwala MA, Patel AC, Levinson BT, Van Arendonk LG, Thornton KC, Giacalone JC, Albee AJ, Wilson KS, Turner EH, Nickerson DA, **Shendure J**, Bayly PV, Leigh MW, Knowles MR, Brody SL, Dutcher SK, Ferkol TW#. Whole-Exome Capture and Sequencing Identifies HEATR2 Mutation as a Cause of Primary Ciliary Dyskinesia. *American Journal of Human Genetics* 2012 Oct 5;91(4):685-93.
64. Stone B#, Rieck M, Rawlings CA, Kas A, **Shendure J**, Jones H, Buckner JH. Identification of novel HLA class II target epitopes for generation of donor-specific T regulatory cells. *Clinical Immunology* 2012 Nov;145(2):153-60.
65. Schwartz JJ, Lee C, Hiatt JB, Adey A, **Shendure J#**. Capturing native long-range contiguity by in situ library construction and optical sequencing. *Proceedings of the National Academy of Sciences* 2012 Nov 13;109(46):18749-54.
66. Loeb GB*, Khan AA*, Canner D, Hiatt JB, **Shendure J**, Darnell RB, Leslie CS, Rudensky AY#. Transcriptome-wide miR-155 Binding Map Reveals Widespread Noncanonical MicroRNA Targeting. *Molecular Cell* 2012 Nov 6.
67. O'Roak BJ, Vives L, Fu W, Egertson JD, Stanaway IB, Phelps IG, Carvill G, Kumar A, Lee C, Ankenman K, Munson J, Hiatt JB, Turner EH, Levy R, O'Day DR, Krumm N, Coe BP, Martin BK, Borenstein E, Nickerson DA, Mefford HC, Doherty D, Akey JM, Bernier R, Eichler EE#, **Shendure J#**. Multiplex Targeted Sequencing Identifies Recurrently Mutated Genes in Autism Spectrum Disorders. *Science* 2012 Dec 21;338(6114):1619-22.
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Reviews, Perspectives and Book Chapters

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Active Research Support

1DP1HG007811 (NIH/OD) 09/23/13 – 07/31/18
Interpreting genetic variants of uncertain significance (Shendure)
This project aims to develop novel experimental and computational paradigms for predicting the functional consequences of all possible single residue variants in clinically significant genes, thereby informing the interpretation of variants newly observed in patients.
Role: PI

ETOP2013 (DOE/JGI) 10/01/13 – 09/30/15
Accurate gene synthesis with tag-directed retrieval of sequence-verified DNA molecules (Shendure)
The goals of this project include the implementation and further development of dial-out PCR and other technologies for synthetic biology at the DOE's Joint Genome Institute.
Role: PI

1R01HG006768 (NIH/NHGRI) 04/01/12 – 3/31/15
Massively parallel, in vivo functional testing of regulatory elements (MPI: Ahituv, Shendure)
The major goal of this project is to develop novel, multiplexed assays that can easily be adopted by other researchers to clone and simultaneously test tens-of-thousands of candidate regulatory elements for their in vivo functional potential.
Role: PI (MPI award)

1U54HG006493 (NIH/NHGRI) 12/05/11 – 11/30/15
UW Center for Mendelian Genomics (MPI: Bamshad, Nickerson, Shendure)
The goal of the proposed research is to establish the UW Center for Mendelian Genomics (UW-CMG) that will apply exome sequencing and analysis to discover the candidate genes and sequence variants underlying rare Mendelian disorders and other human health-related Mendelian phenotypes.
Role: PI (MPI award)

1R01HG006283 (NIH/NHGRI) 08/15/11 – 07/31/14
Massively parallel contiguity mapping (Shendure)
The aim of this grant is to develop massively parallel methods that facilitate the recovery of contiguity information in genomic DNA at various scales, thereby facilitating high-quality de novo genome assembly and haplotype-resolved human genome sequencing.
Role: PI

1R21CA160080 (NCI/NIH) 07/01/11 – 06/30/14
Ultrasensitive identification and precise quantitation of low frequency somatic mutations by molecular counting (Shendure)
The goal of the proposed research will be to develop novel, robust molecular technologies for sensitively and specifically identifying low frequency mutations in the context of genetically heterogeneous, stromally contaminated cancer samples.
Role: PI

1R01CA160674-01A1 (NIH/NCI) 06/06/12 – 03/31/17
Clonally Expanded Mutations Identify Cancer Precursors in Chronic Inflammation (MPI: Loeb, Brentnall)
The major goal of this project is to develop better methods for identifying early cancers with greater ease and at less cost using state-of-the-art DNA sequencing technology that can be rapidly commercialized for translation to patient care settings.
Role: Co-investigator

1R01MH101221-01 (NIH/NIMH) 08/01/13 – 06/30/17
Sporadic Mutations and Autism Spectrum Disorders (Eichler)
The major goal of this project is to identify genes responsible for autism spectrum disorder (ASD) and developmental delay.
Role: Co-Investigator

SFARI 191889EE (Simons Foundation) 01/01/12 – 12/31/13
Whole Exome Sequencing of Simons Simplex Collection Quads (Eichler)
The goal of this project is to complete exome sequencing of the Simons Simplex Collection.
Role: Co-investigator

Completed Research Support

5U54AI057141-08REV (NIH/NIAID) 03/01/11 – 02/28/14

NW Research Center for Excellence in Biodefense and Emerging Infectious Diseases (Miller)
The major goal is to develop and implement methods for the whole genome sequencing and epidemiological analysis of clinical isolates of gram-negative bacteria at unprecedented speed and low cost.
Role: PI of Developmental Project

University of Washington Cystic Fibrosis Foundation 10/01/11 – 09/30/13
Studying Cystic Fibrosis Infections Using Massively Parallel Sequencing Technology (Shendure)
We test the hypotheses that CF P. aeruginosa populations are highly diverse, and that population composition is stable in the absence of overt changes in symptoms. We will measure diversity using whole genome sequencing of isolate pools to measure allelic variation. We will also test the hypothesis that the abundance of variant alleles changes at the onset of exacerbations, during antibiotic treatment, and upon restoration of the "well" state.
Role: PI

1R011AG039700 (NIH/NIMH) 05/01/11 – 04/30/16
Next Generation Mendelian Genetics in Familial Alzheimer Disease (Brkanac)
The goal of this proposal is to apply novel analytic approaches to identify families in which Alzheimer disease (AD) is likely to have a single gene etiology and to utilize next generation sequencing technologies to find these genes.
Role: Co-investigator

1R01HL110879-01 (NIH/NHLBI) 09/01/11 – 05/31/15
Investigating bacterial-host interactions driving CF Pulmonary Exacerbations (MPI: Bruce, Singh)
The major goal is to test the hypothesis that at the onset of exacerbations, changes in the composition of infecting *P. aeruginosa* populations elicit host responses leading to lung inflammation and injury.
Role: Co-investigator

5R01NS069719 (NIH/NINDS) 04/01/10 – 03/31/14
Next Generation Gene Discovery in Neurogenetics (Raskind)
This proposal seeks to perform massively parallel whole exome sequencing and array comparative genomic hybridization to identify candidate genes for Mendelian neurogenetics disorders.
Role: Co-investigator

W81XWH-10-1-0589 (Department of Defense) 07/01/10 – 08/14/13
Global Characterization of Protein Altering Mutations in Prostate Cancer (Shendure)
The goal of this proposal is to perform comprehensive identification of protein-coding alterations in both primary and metastatic prostate tumors.
Role: PI (synergy award with Nelson at FHCRC)

5P01CA078902 (NIH/NCI) 02/01/09 – 01/31/14
Identification of Canine Minor Histocompatability Antigens (Storb)
The major goal of this subproject is to develop a novel genomics-driven approach for identifying minor histocompatability antigens in a canine transplantation model.
Role: PI of Project 1

5RC2HG005608 (NIH/NHGRI) 09/30/09 – 08/31/12
Next Generation Mendelian Genetics (MPI: Bamshad, Nickerson, Raskind, Shendure)
The goal of this proposal is to sequence and identify the candidate genes responsible for more than 20 Mendelian diseases/disorders.
Role: PI (MPI award)

5UC2HL102926 (NIH/NHLBI) 09/30/09 – 06/30/12
Northwest Genomics Center (MPI: Green, Nickerson, Rieder, Shendure)
The goal of the Northwest Genomics Center is to apply next-generation exome sequencing to medically relevant DNA sample cohorts selected by the NHLBI.
Role: PI (MPI award)

5R01HL094976 (NIH/NHLBI) 09/30/08 – 06/30/12
SeattleSeq (MPI: Eichler, Green, Nickerson, Shendure)
The major goal of this project is to develop a high-throughput pipeline for the comprehensive capture and high-throughput sequencing of all protein-coding sequences in individual human genomes.
Role: PI (MPI award)

Young Investigator Award (Prostate Cancer Foundation) 04/01/10 – 03/31/13
Methods & Tools for Next-Generation Analysis of Prostate Cancer Genomes (Shendure)
The aim of this grant is to develop and deploy methods that enable the efficient characterization of primary and metastatic prostate cancer genomes in large numbers of samples.
Role: PI

3U54AI057141-06S1880509 (NIH/NIAID) 09/12/09 – 02/29/12
Massively parallel genome sequencing of antibiotic-resistant emerging pathogens (Shendure)
The goal of this proposal is to sequence the genomes of over 1,000 antibiotic-resistant bacterial strains representing emerging pathogens.
Role: PI

1R21HG004749 (NIH/NHGRI) 07/23/08 – 06/30/10
Molecular Tools for Genome Partitioning (Shendure)
The major goal of this project is to develop and optimize methods for selective capture of gene families or long contiguous genomic regions.
Role: PI

5R01NS069605 (NIH/NINDS) 02/15/10 – 02/14/14
A Genomic Approach to Epilepsy (Mefford)
The aim of this grant to identify novel candidate genes and pathways for epilepsy through a combination of genome-wide approaches including array comparative genomic hybridization and exome sequencing.
Role: Co-investigator

5R01HG004348 (NIH/NHGRI) 07/01/11 – 06/30/12
Advances in Computational Gene Finding (Korf)
The goal of the proposed research will be to use fosmid-pool-based sequencing to provide contiguity informative validation data for the Assemblathon competition for de novo genome assemblies of the snake, parrot and cichlid genomes.
Role: Co-investigator

2P50HG003233 (NIH/NHGRI) 05/01/09 – 04/30/14
Center for the Epigenetics of Common Human Disease (Feinberg)
The major goal of the UW component of this program is to develop and apply technology for large-scale targeted profiling of DNA methylation in epidemiological samples.
Role: Co-investigator

5R01HD065285 (NIH/NICHD) 09/30/09 – 08/31/12
Genomic Identification of Autism Loci (Eichler)

The aim of this grant is to explore the hypothesis that autism is caused by highly-penetrant, rare mutations using emerging technologies that screen regions for autism-specific copy-number variation (CNV) mutations and exonic point mutations.
Role: Co-investigator

1RC2HG005921 (NIH/NHGRI) 08/20/10 – 01/31/12
A Genome-wide Mutation Resource for C. elegans (Waterston)
The aim of this grant is to construct a community resource of several thousand chemically mutagenized C. elegans strains that have been whole genome sequenced.
Role: Co-investigator

SFARI 191889 (Simons Foundation) 12/01/10 – 11/30/11
Exome Sequencing of Simons Simplex Collection (SSC) Trios (Eichler)
The goal of this project is to perform exome sequencing of 400 SSC autism trios in collaboration with Matt State at Yale University to discover pathogenic SNPs associated with disease.
Role: Co-investigator

1RC2CA148317 (NIH/NCI) 09/30/09 – 09/29/11
An infrastructure for cancer virus discovery from next-generation sequencing data (Meyerson)
The aim of this grant is to develop automated pipelines for identifying virus-derived sequences in next-generation sequencing data from all public sources by computational subtraction.
Role: Co-investigator

1RC1AG035681 (NIH/NIA) 09/30/09 – 09/29/11
Mutational Cloning in Familial Dementia and Alzheimer's Disease (Raskind)
The goal of this proposal is to apply whole exome sequencing in well-characterized pedigrees to identify functional mutations leading to familial dementia and/or Alzheimer's disease.
Role: Co-investigator

1RC2CA148232 (NIH/NCI) 09/30/09 – 09/29/11
Application of RiboTag-seq to Exploration of Tumor Microenvironments (Morris)
The aim of this grant is to develop and apply methods for tagging of ribosome-associated RNAs to study cell-type specific gene expression in complex tissues.
Role: Co-investigator

1I01BX000531 (Department of Veterans Affairs) 10/01/09 – 09/30/13
Genetic Risk Factors for Parkinson's Disease (Zabetian)
The major goal of this project is to validate findings from an ongoing genome-wide association study on PD using next generation sequencing and brain/CSF proteomic analyses.
Role: Consultant

Invited Talks or Workshops

Jan 2014	*Keynote speaker*, UCLA Center for Neurobehavioral Genetics Annual Retreat (Los Angeles, CA)
Dec 2013	*Workshop participant*, NCI Center for Cancer Genomics Think Tank (Bethesda, MD)
Nov 2013	*Speaker*, NIH / NCI Innovative Molecular Analysis Technologies (IMAT) Grantee Meeting (Bethesda, MD)
Oct 2013	*Invited speaker*, FederaDAG: Next Generation DNA Sequencing: impact on clinical care and society (Utrecht, Netherlands)
Oct 2013	*Invited seminar*, Nijmegen Centre for Molecular Life Sciences (Nijmegen, Netherlands)

Oct 2013 *Participant & speaker,* NHGRI Sequencing Network Meeting (Washington DC)
July 2013 *Invited seminar*, Fred Hutchinson Cancer Research Center, Computational Biology Seminar Series (Seattle, WA)
July 2013 *Invited speaker*, The Human Genetics & Genomics Gordon Research Conference, Bryant University (Smithfield, RI)
June 2013 *Keynote speaker,* Functional Genomics Data Society (FGED) 15th International Conference (Seattle, WA)
May 2013 *Invited seminar*, Department of Cellular and Molecular Medicine, University of California, San Diego (San Diego, CA)
May 2013 *Invited seminar*, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine (Baltimore, MD)
Apr 2013 *Invited seminar*, Institute for Genomics & Systems Biology, University of Chicago (Chicago, IL)
Apr 2013 *Speaker*, NIH / NHGRI Advanced Sequencing Technology Grantee Meeting (San Diego, CA)
Mar 2013 *Invited seminar*, HudsonAlpha Institute for Biotechnology (Huntsville, AL)
Mar 2013 *Invited seminar*, Seminars in Integrative Genomics, Vanderbilt University (Nashville, TN)
Mar 2013 *Plenary speaker*, 2013 Annual Meeting of the Association of Biomolecular Resource Facilities (Palm Springs, CA)
Feb 2013 *Plenary speaker,* Advances in Genome Biology and Technology (AGBT) (Marco Island, FL)
Jan 2013 *Keynote speaker,* The Eleventh Asia Pacific Bioinformatics Conference (Vancouver, BC)
Dec 2012 *Invited seminar*, Dept. of Molecular and Medical Genetics, Oregon Health & Science University (Portland, OR)
Nov 2012 *Invited speaker*, CSHL Personal Genomes meeting (Cold Spring Harbor, NY)
Nov 2012 *Invited participant in closing symposium,* 62th Annual Meeting of American Society of Human Genetics, "Human Genetics 2012 and Beyond: Present Progress and Future Frontiers" (San Francisco, CA)
Nov 2012 *Invited session moderator & speaker,* 62th Annual Meeting of American Society of Human Genetics, "Genomic Approaches to Mendelian Disorders" (San Francisco, CA)
Nov 2012 *Curt Stern Award: Presentation and Lecture,* 62th Annual Meeting of American Society of Human Genetics (San Francisco, CA)
Nov 2012 *Invited speaker,* Institute of Translational Health Sciences 'Omics Workshop - "Lessons Learned and the Path Forward" University of Washington, South Lake Union (Seattle, WA)
Oct 2012 *Participant & speaker,* NHGRI Sequencing Network Meeting (Houston, TX)
Sep 2012 *Invited speaker,* Nature Genetics "Genomics of Common Disease" meeting (Washington DC)
Sep 2012 *Workshop co-organizer & attendee,*" Implicating Sequence Variants in Human Disease" (Washington DC)
Aug 2012 *Invited speaker,* 43rd Annual Meeting of the Environmental Mutagen Society (Seattle, WA)
Jul 2012 *Invited speaker,* 1000 Genomes Community Meeting (Ann Arbor, MI)
Jun 2012 *Invited seminar*, Department of Pathology, University of Washington (Seattle, WA)
Jun 2012 *Invited speaker,* ESHG European Human Genetics Conference 2012 (Nürnberg, Germany)
Jun 2012 *Invited seminar*, UCLA Molecular Biology Institute (Los Angeles, CA)
May 2012 *Grand Rounds,* Division of Hematology, University of Washington Medical Center (Seattle, WA)
May 2012 *Invited seminar,* Institute for Systems Biology (Seattle, WA)
Apr 2012 *Invited speaker,* Chemical & Engineering News Webinar
Apr 2012 *Invited seminar*, NIH / NHGRI Division of Intramural Research (Bethesda, MD)
Apr 2012 *Speaker*, NIH / NHGRI Advanced Sequencing Technology Grantee Meeting (San Diego, CA)
Mar 2012 *Distinguished Lecture Series,* Duke University Program in Genetics and Genomics (Chapel Hill, NC)
Mar 2012 *Co-organizer & speaker,* NIH / NIDDK "Workshop on Rare Syndromic Body Fat Disorders-What Can They Teach Us?" (Bethesda, MD)
Feb 2012 *Invited seminar*, Program in Medical & Population Genetics, Broad Institute of M.I.T. and Harvard (Cambridge, MA)

Feb 2012	*Invited seminar*, Division of Genetics, Brigham and Women's Hospital, Harvard Medical School (Boston, MA)
Jan 2012	*Invited seminar*, Cystic Fibrosis Seminar Series, Seattle Children's Research Institute / University of Washington (Seattle, WA)
Jan 2012	*Grand Rounds*, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School (Boston, MA)
Dec 2011	*Invited seminar*, Department of Biology, University of Pennsylvania (Philadelphia, PA)
Oct 2011	*Guest speaker*, Fred Hutchinson Cancer Research Center, 8th Human Biology Division Retreat (Seattle, WA)
Oct 2011	*Keynote address*, "The Genome and Beyond", BioTechniques Virtual Symposium
Oct 2011	*Chair & organizer*, IPAM (Institute for Pure & Applied Mathematics): Mathematical and Computational Approaches in High-Throughput Genomics; Workshop I: Next-generation Sequencing Technology and Algorithms for Primary Data Analysis (Los Angeles, CA)
Sep 2011	*Invited speaker & session chair*, Beyond the Genome 2011 (Rockville, MD)
Sep 2011	*Invited speaker*, NHLBI Symposium: Genomics: Gene Discovery and Clinical Applications for Cardiovascular, Lung, and Blood Diseases (Bethesda, MD)
Jul 2011	*Workshop speaker*, Illumina Sequencing Expert Panel 2011 (Woodinville, WA)
Jul 2011	*Invited speaker*, "Revolution of Genome Science", 9th International Workshop on Advanced Genomics (Tokyo, Japan)
Jul 2011	*Invited speaker*, University of Tokyo, "Cutting Edge of Human Genome Science", 4th Symposium of the IMSUT & RCAST Global COE (Tokyo, Japan)
Apr 2011	*Invited seminar*, Princeton University and Lewis-Sigler Institute, Quantitative and Computational Biology seminar series (Princeton, NJ)
Mar 2011	*Invited speaker*, Genome 10K Workshop (Santa Cruz, CA)
Feb 2011	*Invited seminar*, Stanford University, Frontiers in Biology Seminar Series (Palo Alto, CA)
Jan 2011	*Invited seminar*, Institute for Molecular Medicine, UT Houston (Houston, TX)
Dec 2010	*Invited speaker*, Illumina Webinar
Dec 2010	*Invited seminar*, UCSF Biomedical Sciences Seminar Series (San Francisco, CA)
Dec 2010	*Invited seminar*, Amgen, Molecular and Computational Toxicology Seminar Series (Seattle, WA)
Nov 2010	*Invited speaker*, American Heart Association, Scientific Sessions 2010, "Whole Genome Sequencing and Integrative Genomics" session (Chicago, IL)
Nov 2010	*Invited speaker*, American Heart Association, Scientific Sessions 2010, "Whole Exome Resequencing: Methods and Early Findings" session (Chicago, IL)
Nov 2010	*Invited session moderator & speaker*, 60th Annual Meeting of American Society of Human Genetics, "Exome Sequencing and Human Genetics" (Washington DC)
Oct 2010	*Invited seminar*, Department of Global Health, University of Washington, Pathobiology Seminar Series (Seattle, WA)
Oct 2010	*Invited speaker*, Beyond the Genome 2010 (Boston, MA)
Sep 2010	*Invited speaker*, Prostate Cancer Foundation, 17th Annual Scientific Retreat (Washington DC)
Jul 2010	*Invited speaker*, Illumina PNW User Group Meeting (Seattle, WA)
Jul 2010	*Invited speaker*, BioC 2010 (Seattle, WA)
Jul 2010	*Workshop attendee*, Planning the Future of Genomics: Foundational Research and Applications in Genomic Medicine, NHGRI (Warrenton, VA)
Jul 2010	*Invited speaker*, 13th International MGED Meeting (Boston, MA)
Jul 2010	*Invited speaker*, Merck (Boston, MA)
Jul 2010	*Evening lecture*, 51st Annual Short Course on Medical and Experimental Mammalian Genetics, The Jackson Laboratory (Bar Harbor, ME)
Jun 2010	*Invited seminar*, PNW Prostate Cancer SPORE Seminar Series (Seattle, WA)
May 2010	*Colloquium co-convener & speaker*, American Society for Microbiology 110th General Meeting, "Ultra-Deep Sequencing in Infectious Diseases" (San Diego, CA)
May 2010	*Invited speaker*, University of Washington, Computational Molecular Biology Spring Symposium

	(Seattle, WA)
May 2010	*Invited seminar*, University of Washington, Department of Medical Genetics Seminar Series (Seattle, WA)
May 2010	*Session co-chair & speaker*, The Biology of Genomes, Cold Spring Harbor Laboratories, "High Throughput Genomics & Genetics" (Cold Spring Harbor, NY)
May 2010	*Workshop participant*, NIH Director's "Big Think" Meeting (Bethesda, MD)
Apr 2010	*Invited speaker*, 4th International Conference on Primate Genomics (Seattle, WA)
Jan 2010	*Invited seminar*, Washington University in St. Louis, Department of Genetics (St. Louis, MO)
Jan 2010	*Invited seminar*, University of Chicago, Department of Human Genetics (Chicago, IL)
Dec 2009	*Invited speaker*, Simons Foundation, workshop on sequencing (New York City, NY)
Dec 2009	*Invited speaker*, Cardiovascular Center Breakfast Club, University of Washington (Seattle, WA)
Oct 2009	*Plenary speaker*, 59th Annual Meeting of American Society of Human Genetics (Honolulu, HI)
Sep 2009	*Invited speaker*, Grand Rounds in Laboratory Medicine, University of Washington (Seattle, WA)
Sep 2009	*Invited speaker*, CSHL Personal Genomes meeting (Cold Spring Harbor, NY)
Aug 2009	*Invited speaker*, eMERGE Network Steering Committee meeting (Seattle, WA)
Aug 2009	*Invited seminar*, McDermott Center, Excellence in Human Genetics Lecture Series, UT Southwestern (Dallas, TX)
Jun 2009	*Invited speaker*, Genomic Tools and Technologies Summit, Cambridge Healthtech Institute (San Francisco, CA)
May 2009	*Invited speaker*, Northwest Institute of Genetic Medicine, 2009 Retreat (Seattle, WA)
Mar 2009	*Invited seminar*, University of Michigan, Center for Translational Pathology (Ann Arbor, MI)
Mar 2009	*Invited speaker*, Next-Generation Sequencing meeting, Cambridge Healthtech Institute (San Diego, CA)
Feb 2009	*Invited speaker*, Advances in Genome Biology and Technology (AGBT) (Marco Island, FL)
Feb 2009	*Invited speaker*, Advances in Genome Biology and Technology (AGBT), pre-meeting workshop (Marco Island, FL)
Dec 2008	*Invited seminar*, Puget Sound Blood Center Research (Seattle, WA)
Oct 2008	*Invited speaker*, Discovery2Diagnostics conference (San Diego, CA)
Sep 2008	*New Investigator Science in Medicine Lecture*, University of Washington (Seattle, WA)
Sep 2008	*Keynote address*, Institute for Systems Biology, Annual Retreat (Seabeck, WA)
Sep 2008	*Invited speaker*, Nature Genetics "Genomics of Common Disease" meeting (Cambridge, MA)
Aug 2008	*Invited seminar*, BC Cancer Agency, Genome Sciences Centre (Vancouver, BC)
Mar 2008	*Invited seminar*, Fred Hutchinson Cancer Research Center, Computational Biology Working Group Seminar Series (Seattle, WA)
Mar 2008	*Invited seminar*, University of Washington, Department of Medical Genetics Seminar Series (Seattle, WA)
Mar 2008	*Invited speaker*, Joint Genome Institute (JGI) User 3rd Annual Meeting (Walnut Creek, CA)
Feb 2008	*Invited speaker*, Association of Biomolecular Resource Facilities (ABRF) Annual Meeting (Salt Lake City, UT)
Feb 2008	*Plenary speaker*, Advances in Genome Biology and Technology (AGBT) (Marco Island, FL)
Nov 2007	*Invited seminar*, Stanford University, Frontiers in Biology Seminar Series (Palo Alto, CA)
Nov 2007	*Invited speaker*, 1st Annual Parallel Sequencing Genomics Meeting, Stanford Genome Technology Center, Stanford University (Palo Alto, CA)
Sep 2007	*Invited seminar*, Fred Hutchinson Cancer Research Center, Program in Prostate Cancer Research Seminar Series, (Seattle, WA)
May 2007	*Invited speaker*, Stanford Genome Technology Center, Stanford University (Palo Alto, CA)
Mar 2007	*Invited seminar*, Institute for Molecular Pediatric Sciences, University of Chicago (Chicago, IL)
Mar 2007	*Invited speaker*, Next Generation Sequencing: Applications and Case Studies, Cambridge Healthtech Institute (San Diego, CA)
Feb 2007	*Invited seminar*, Department of Genetics, University of Pennsylvania (Philadelphia, PA)
Feb 2007	*Invited seminar*, Department of Bioengineering, University of California, Berkeley (Berkeley, CA)

Feb 2007	*Invited seminar*, Division of Genetics, Brigham and Women's Hospital, Harvard Medical School (Boston, MA)
Feb 2007	*Invited seminar*, Department of Pathology, Massachusetts General Hospital, Harvard Medical School (Boston, MA)
Feb 2007	*Invited seminar*, Department of Genome Sciences, University of Washington (Seattle, WA)
Feb 2007	*Invited seminar*, Broad Institute of M.I.T. and Harvard (Cambridge, MA)
Jan 2007	*Invited seminar*, Department of Molecular & Cell Biology, University of California, Berkeley (Berkeley, CA)
Jan 2007	*Invited seminar*, National Human Genome Research Institute, National Institutes of Health (Bethesda, MD)
Jan 2007	*Workshop speaker*, Workshop on Systems Biology and Information Medicine in a Global Society, Princeton University (Princeton, NJ)
Jan 2007	*Invited seminar*, Institute for Systems Biology (Seattle, WA)
Mar 2006	*Invited seminar*, Biological Physics & Biophysical Chemistry Seminar, State University of New York, Stony Brook (Stony Brook, NY)

Exhibit B

U.S. Patent No. 7,915,015

1. (Original) A method for determining an allelic imbalance in a biological sample, comprising the steps of:

amplifying template molecules within a set comprising a plurality of assay samples to form a population of amplified molecules in each of the assay samples of the set, wherein the template molecules are obtained from the biological sample;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker, wherein between 0.1 and 0.9 of the assay samples yield an amplification product;

comparing the first number to the second number to ascertain an allelic imbalance in the biological sample; and

identifying an allelic imbalance in the biological sample.

2. (Original) The method of claim 1 wherein the step of amplifying employs real-time polymerase chain reactions.

3. (Original) The method of claim 2 wherein the real-time polymerase chain reactions comprise a dual-labeled fluorogenic probe.

4. (Original) The method of claim 1 wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the first allelic form of the marker.

5. (Original) The method of claim 1 wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the second allelic form of the marker.

6. (Original) The method of claim 1 wherein the amplified molecules in each of the assay samples within the first and second numbers of assay samples are homogeneous such that the first

number of assay samples do not contain the second allelic form of the marker and the second number of assay samples do not contain the first allelic form of the marker.

7. (Original) The method of claim 1 wherein the sample is from blood.

8. (Original) A method for determining an allelic imbalance in a biological sample, comprising the steps of:

distributing nucleic acid template molecules from a biological sample to form a set comprising a plurality of assay samples;

amplifying the template molecules within the assay samples to form a population of amplified molecules in the assay samples of the set;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker;

comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance between the first allelic form and the second allelic form in the biological sample.

9. (Original) The method of claim 8 wherein the sample is from blood.

10. (Original) The method of claim 1 or 8 wherein between 0.1 and 0.6 of the assay samples yield an amplification product.

11. (Original) The method of claim 1 or 8 wherein between 0.3 and 0.5 of the assay samples yield an amplification product.

12. (Original) The method of claim 1 or 8 wherein the set comprises at least 500 assay samples.

13. (Original) The method of claim 1 or 8 wherein the set comprises at least 1000 assay samples.

14. (Original) The method of claim 8 wherein the step of amplifying employs real-time polymerase chain reactions.

15. (Original) The method of claim 14 wherein the real-time polymerase chain reactions comprise a dual-labeled fluorogenic probe.

16. (Original) The method of claim 8 wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the first allelic form of the marker.

17. (Original) The method of claim 8 wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the second allelic form of the marker.

18. (Original) The method of claim 8 wherein the amplified molecules in each of the assay samples within the first and second numbers of assay samples are homogeneous such that the first number of assay samples do not contain the second allelic form of the marker and the second number of assay samples do not contain the first allelic form of the marker.

Electronic Acknowledgement Receipt

EFS ID:	18037026
Application Number:	90012896
International Application Number:	
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Title of Invention:	DIGITAL AMPLIFICATION
First Named Inventor/Applicant Name:	7915015
Customer Number:	11332
Filer:	Sarah Anne Kagan.
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1	Affidavit-traversing rejectns or objectns rule 132	shendure132dec00988binderReprint.pdf	1789446 582de6e5c8aa8616d55be26d491cd3b8c829695f	no	31

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Ex Parte* Reexamination:	)	Group Art Unit: 3991
	)	
U.S. Patent No. 7,915,015	)	Docket No. 001107.00988
	)	
Control No. 90/012,896	)	Confirmation No: 8361
	)	
Reexam Filing Date: June 17, 2013	)	Examiner: Bruce R. Campell

For: DIGITAL AMPLIFICATION

RESPONSE TO OFFICE ACTION

U.S. Patent and Trademark Office
Customer Service Window
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Commissioner:

This paper is in response to the Non-Final Office Action mailed November 27, 2013 ("Office Action"). Johns Hopkins University ("the Patent Owner") respectfully requests reconsideration of the rejections made in the Office Action in view of the following remarks. Although no claims are currently amended, a listing of the claims is provided for the convenience of the Office.

A **Listing of the Claims** begins on page 2.

Remarks begin on page 5.

Conclusion begins on page 18 of this paper.

LISTING OF CLAIMS SUBJECT TO REEXAMINATION

The claims subject to reexamination are listed below.

1. (Original) A method for determining an allelic imbalance in a biological sample, comprising the steps of:

amplifying template molecules within a set comprising a plurality of assay samples to form a population of amplified molecules in each of the assay samples of the set, wherein the template molecules are obtained from the biological sample;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker, wherein between 0.1 and 0.9 of the assay samples yield an amplification product;

comparing the first number to the second number to ascertain an allelic imbalance in the biological sample; and

identifying an allelic imbalance in the biological sample.

2. (Original) The method of claim 1 wherein the step of amplifying employs real-time polymerase chain reactions.

3. (Original) The method of claim 2 wherein the real-time polymerase chain reactions comprise a dual-labeled fluorogenic probe.

4. (Original) The method of claim 1 wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the first allelic form of the marker.

5. (Original) The method of claim 1 wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the second allelic form of the marker.

6. (Original) The method of claim 1 wherein the amplified molecules in each of the assay

samples within the first and second numbers of assay samples are homogeneous such that the first number of assay samples do not contain the second allelic form of the marker and the second number of assay samples do not contain the first allelic form of the marker.

7. (Original) The method of claim 1 wherein the sample is from blood.

8. (Original) A method for determining an allelic imbalance in a biological sample, comprising the steps of:

distributing nucleic acid template molecules from a biological sample to form a set comprising a plurality of assay samples;

amplifying the template molecules within the assay samples to form a population of amplified molecules in the assay samples of the set;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker;

comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance between the first allelic form and the second allelic form in the biological sample.

9. (Original) The method of claim 8 wherein the sample is from blood.

10. (Original) The method of claim 1 or 8 wherein between 0.1 and 0.6 of the assay samples yield an amplification product.

11. (Original) The method of claim 1 or 8 wherein between 0.3 and 0.5 of the assay samples yield an amplification product.

12. (Original) The method of claim 1 or 8 wherein the set comprises at least 500 assay samples.

13. (Original) The method of claim 1 or 8 wherein the set comprises at least 1000 assay

samples.

14. (Original) The method of claim 8 wherein the step of amplifying employs real-time polymerase chain reactions.

15. (Original) The method of claim 14 wherein the real-time polymerase chain reactions comprise a dual-labeled fluorogenic probe.

16. (Original) The method of claim 8 wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the first allelic form of the marker.

17. (Original) The method of claim 8 wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the second allelic form of the marker.

18. (Original) The method of claim 8 wherein the amplified molecules in each of the assay samples within the first and second numbers of assay samples are homogeneous such that the first number of assay samples do not contain the second allelic form of the marker and the second number of assay samples do not contain the first allelic form of the marker.

REMARKS

Claims 1-18 are subject to the reexamination of U.S. Patent No. 7,915,015 ("the '015 patent").

The Office Action cites Bischoff *et al*., Human Molecular Genetics 4(3):395-99 (1995) ("Bischoff") as allegedly anticipating claims 1, 4, 5, 7-11, 16, and 17. The present Office Action also asserts that claims 12 and 13 are allegedly obvious over Bischoff; that claims 2, 3, 14, and 15 are allegedly obvious over Bischoff in view of U.S. Patent No. 5,928,907 to Woudenberg *et al*. ("Woudenberg"); and that claims 6 and 18 are allegedly obvious over Bischoff in view of Jeffreys *et al*., Nucl. Acids Res. 16(23):10953-71 (1988) ("Jeffreys"). As detailed herein, Bischoff fails to disclose or suggest each and every limitation of the claims under reexamination. Woudenberg and Jeffreys fail to compensate for the deficiencies of Bischoff. Based on the following remarks, the Patent Owner respectfully requests issuance of a Reexamination Certificate confirming patentability of all claims.

I. Overview

The '015 patent issued on March 29, 2011. The issued claims of the '015 patent are directed to methods for determining the genetic composition of a biological sample as a whole. In particular, the methods determine an allelic imbalance in a biological sample. Col. 7, lines 8-9 of the '015 patent. The thrust of the invention is to separate or isolate the components of a mixed population of genetic sequences down to a level where each of a first and a second allelic form of a marker are more readily detected. *See* Table 1 of the '015 patent.

In the claimed methods, the nucleic acid template molecules are obtained from a biological sample. The specification discloses that the

> [b]iological samples which can be used as the *starting material* for the analyses may be from any tissue or body sample from which DNA or mRNA can be isolated. Preferred sources include stool, blood, and lymph nodes. Preferably the biological sample is a cell-free lysate.

Col. 7, lines 10-14 of the '015 patent (emphasis added). The specification does not teach that the method be performed on "individual cells" or "single cells." Rather, the method is concerned with the detection of genetic sequences within a mixed population of genetic sequences from a

biological sample without requiring the isolation of single cells as was described in the prior art.

The specification teaches that the nucleic acid template molecules obtained from the biological sample are diluted to form a set comprising a plurality of assay samples. Figure 1A; Col. 2, lines 11-16 of the '015 patent. The nucleic acid template molecules in each of the assay samples is then amplified, and the amplified molecules are analyzed to determine the number of assay samples across the entire set that contain a selected genetic sequence (*i.e.*, the first allelic form of a marker) and the number of assay samples across the entire set that contain a reference genetic sequence (*i.e.*, the second allelic form of the marker). Col. 2, lines 16-20 of the '015 patent. By comparing the two numbers, the allelic imbalance between the first and second allelic forms of the marker is determined, which reflects whether an allelic imbalance is present *in the biological sample as a whole*. Col. 2, lines 20-22 of the '015 patent.

It is critical that the analysis step in the described methods be performed across the set of assay samples because this number of assay samples containing the first and the second allelic forms of the marker provides information with respect to the composition of the population of sequences in the biological sample, *as a whole*. This type of analysis is different from, and provides very different information from, an analysis of a single intact cell.

II. Novelty

Claims 1, 4, 5, 7-11, 16 and 17 were rejected under § 102(b) as allegedly being anticipated by Bischoff. The Patent Owner traverses this rejection. Claims 4, 5, and 7 are dependent from claim 1, and claims 9-11, 16, and 17 are dependent from claim 8. Therefore, for the ease of discussion, the novelty of claims 1, 4, 5, and 7 are discussed first, and then the novelty of claims 8-11, 16, and 17 are discussed.

To anticipate a claim, the cited reference must disclose each and every element of the claims. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987). Here, Bischoff does not anticipate the claims because Bischoff fails to disclose each element of the claims.

A. Claims 1, 4, 5, and 7

Independent claim 1 includes four steps. The first step requires amplifying template molecules within a set comprising a plurality of assay samples to form a population of amplified molecules in each of the assay samples of the set, wherein the *template molecules are obtained from the biological sample*. The second step requires analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker, wherein between 0.1 and 0.9 of the assay samples yield an amplification product. The third step requires comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance in the biological sample. And the final step requires identifying an allelic imbalance *in the biological sample*.

In a re-examination, the Patent and Trademark Office ("the Office") must construe claims using the broadest reasonable interpretation *consistent with the specification. In re Yamamoto,* 740 F.2d 1569, 1571 (Fed. Cir. 1984). The Patent Owner respectfully submits that the Office erred in its initial construction in a number of ways.

First, the Office erred in the construction of the term "assay sample." The Office states that the "'assay sample' is a portion of the biological sample" but then argues that each assay sample may comprise a single cell. This is contrary to the teachings of the specification as a whole. The specification teaches that it is the nucleic acid template molecules obtained from a biological sample that are diluted to create the assay samples. Figure 1A, Col. 2, lines 9-13 of the '015 patent. The specification is clear and not only supports, but also mandates, this construction. Relevant portions of the specification include, but are not limited to, the following:

> Figure 1A showing that isolated DNA template molecules are diluted.
>
> Thus there is a need in the art for methods for accurately and quantitatively detecting genetic sequences in mixed populations of sequences. Col. 1, lines 65-67 of the '015 patent.
>
> It is an object of the present invention to provide methods for determining the presence of a selected genetic sequence in a population of genetic sequences. Col. 2, lines 3-5 of the '015 patent.

> The first number is then compared to the second number to ascertain a ratio which reflects the composition of the biological sample. Col. 2, lines 20-22 of the '015 patent.
>
> The invention thus provides the art with the means to obtain quantitative assessments of particular DNA or RNA sequences in mixed populations of sequences using digital (binary) signals. Col. 2, lines 56-59 of the '015 patent.
>
> The method requires analyzing a large number of amplified products simply and reliably. Techniques for such assessments were developed, with the output providing a digital readout of the fraction of mutant alleles in the analyzed population. Col. 4, lines 15-19 of the '015 patent.
>
> Desirably each assay sample prior to amplification will contain less than a hundred or less than ten template molecules. Col. 4, lines 39-41 of the '015 patent.
>
> Digital amplification can be used to detect mutations present at relatively low levels in the samples to be analyzed. Col. 4, lines 42-43 of the '015 patent.
>
> In one preferred embodiment each diluted sample has on average one half a template molecule. Col. 6, lines 3-4 of the '015 patent.

As noted above, it is clear that the specification aims to quantify the proportion of two nucleic acid sequences relative to each other in a mixed population of nucleic acid sequences in a biological sample. The biological sample is the *starting material* from which the nucleic acid template molecules are obtained, and the "set comprising a plurality of assay samples" is produced by distributing the *nucleic acid template molecules from the biological sample* into a set of assay samples. Moreover, this understanding is consistent with the teaching of the specification. *See*, *e.g.*, Col. 9, lines 15-18 of the '015 patent ("Principles underlying experiment. The experiment is outlined in FIG. 1A. First, the DNA is diluted into multiwell plates so that there is on average, one template molecule per two wells, and PCR is performed."). Based on the claim language, and supported by the specification, the assay samples are not isolated cells or DNA released from single isolated cells.

The recitation of "template molecules within a set comprising a plurality of assay samples . . . wherein the template molecules are obtained from the biological sample" in step 1 of claim 1 requires that the nucleic acid template molecules be obtained from a biological sample as

a whole, rather than portions thereof (*i.e.*, single cells). As taught in the specification, each of the assay samples is prepared identically from the biological sample such that they differ only by the statistical fluctuations inherent in the sampling of the template molecules to make the assay samples. Col. 4, line 67 – Col. 5, line 2 of the '015 patent. The specification describes the assay samples as being prepared in parallel. Col. 9, lines 15-20; Col. 10, lines 59-61 of the '015 patent. The specification further teaches that the number of assay samples containing template molecules are dependent on the relative fraction of alleles within the template population of the biological sample. Col. 11, lines 1-5 of the '015 patent. Thus, consistent with the specification, claim 1, step 1, is directed to analysis of a biological sample by amplification of nucleic acid template molecules in a set comprising a plurality of assay samples. When the allelic imbalance is ascertained among the entire set of assay samples, it reflects the composition of the biological sample as a whole, rather than determining the composition of portions of the biological sample individually.

Second, the Office asserted that the term "allelic imbalance" is not defined in the specification. This is not correct because each of the original independent claims defines the term. *See In re Koller*, 613 F.2d 819 (CCPA 1980) (finding that original claims constitute their own description). Each of the independent claims defines an allelic imbalance as the difference between the number of a first allelic form of a marker and the number of a second allelic form of a marker. Therefore, the Office erred in construing "allelic imbalance" to also encompass differential expression. Measuring expression is different than quantifying a marker *per se*. Shendure Declaration at paragraph 11.

Third, the Office construed the limitation "wherein between 0.1 and 0.9 of the assay samples yield an amplification product" in claims 1, 4, and 5 erroneously. The Office misapplied the doctrine of claim differentiation to interpret claim 1 to conclude that the limitations of claims 4 and 5 "explicitly allow this limitation to refer to the number of samples in which *either* the first or second allele is amplified." Because each of claims 4 and 5 recite an alternative within the scope of claim 1, the Office read an alternative into claim 1 – *i.e.*, A ***or*** B instead of A *and* B. This is faulty claim interpretation. Claim 1 recites "an amplification product," which includes the amplification products of both the first and second allelic forms. According to the claims, the total number of assay samples containing an amplification

product—whether of the first allele or the second allele—must be between 0.1 and 0.9 of the assay samples. While claims 4 and 5 recite that between 0.1 and 0.9 of the assay samples yield an amplification, as determined by amplification of the first or second allelic forms of the marker, respectively, these dependent recitations do not negate the recitation of claim 1, *i.e.,* the total amplification products cannot comprise greater than 0.9 of the assay samples. The limitations of claims 4 and 5 complement the limitations of claim 1; they do not replace its limitations.

Bischoff is cited as demonstrating somatic mosaicism in an individual with Beckwith Wiedemann syndrome (BWS). Bischoff fails to anticipate the issued claims of the '015 patent because Bischoff fails to disclose each and every element of the claims.

First, Bischoff fails to disclose step 1 of claim 1 because Bischoff does not disclose a set comprising a plurality of assay samples with template molecules obtained or derived from a biological sample.

In a first experiment, Bischoff determined the presence of an allelic imbalance of chromosome 11p as shown in Figure 1. Bischoff, pg. 396, Col. 2, first paragraph. In this experiment, genomic DNA samples in from a child and its mother and father were assessed at twelve different loci using PCR. *See id.* at pg. 398, Col. 2 ("Molecular analysis of genomic DNA"). A separate PCR reaction wa run for each marker (*i.e.*, each PCR reaction contained the primers to amplify only one of the twelve different loci). The amplification products in each PCR reaction were then analyzed individually to determine the intensity of the maternal and paternal alleles in the sample from the child at each loci. *Id.* at pg. 396, Figure 1. Because each PCR reaction utilized primers for a different locus, Bischoff did not, and could not, analyze a first number of assay samples that contain a first allelic form of a marker and a second number of assay samples that contain a second allelic form of a marker.Therefore, this experiment fails to disclose claim 1, step 3.

Bischoff postulated that the presence of the allelic imbalance in the individual could have arisen either from duplication of chromosome 11p in all cells or from somatic mosaicism (*i.e.*, only some of the individual's cells contain the chromosome 11p duplication). To determine which mechanism caused the allelic imbalance, Bischoff assessed markers on chromosome 11p

in single cells. As Bischoff clearly states, they "used this single cell approach to demonstrate somatic mosaicism in a patient with BWS." Bischoff, pg. 397, col. 2, lines 6-10. Therefore, this second experiment fails to disclose the set comprising the plurality of assay samples of claim 1, step 1, because this experiment comprises isolating single cells at one stage and then DNA from the single cells after lysis of the cells. Neither single cells nor nucleic acids isolated from single cells are "assay samples" as taught by the specification (*i.e.*, nucleic acid template molecules obtained from a biological sample that are diluted to create the assay samples). In addition, construction of claim 1 consistent with the specification requires that the nucleic acid template molecules are representative of the biological sample as a whole. Bischoff's experiment analyzes nucleic acid sequences in single cells (*i.e.*, the assay samples are not representative of a biological sample as a whole). Bischoff does not describe a single biological sample comprising a population of template molecules that can be separated, as described in the specification, because individual cells, each with a unique genotype, are not representative of the biological sample as a whole. Because this second experiment fails to disclose the generation of a set comprising a plurality of assay samples containing nucleic acid template molecules obtained from a biological sample, Bischoff also fails to disclose the second step of "analyzing the amplified molecules in the assay samples of the set," the third step of "comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance in the biological sample," and the fourth step of "identifying an allelic imbalance in the biological sample" of claim 1.

Bischoff also fails to disclose the limitation that "between 0.1 and 0.9 of the assay samples yield an amplification product." The markers assessed included two 11p markers (D11S904 and HBB), one 11q marker (CD3D), and one chromosome 21 control marker (INFAR). *Id*. at pg. 397, col. 1, first paragraph. Bischoff assessed whether individual cells had a maternal and a paternal allele (normal parental inheritance) or just a paternal allele (parental isodisomy) for these markers. *Id*., *see also* Table 2. Bischoff relied on the presence of each allele in a cell to make the determination. As is clearly shown in Table 2, *all* the single-cell samples yielded an amplification product, which is outside of the range (between 0.1 and 0.9) recited in claim 1. Therefore, Bischoff fails to disclose this element of the claim.

For at least the reasons set forth above, claim 1 is novel over Bischoff. Claims 4, 5, and 7

depend directly or indirectly from claim 1 and, therefore, incorporate all of the limitations of claim 1. These claims are novel over Bischoff for at least the same reasons discussed above with respect to claim 1.

Accordingly, the Patent Owner respectfully requests that the rejection of claims 1, 4, 5, and 7 under 35 U.S.C. § 102(b) based on Bischoff be withdrawn.

B. Claims 8-11, 16, and 17

Independent claim 8 includes four steps. The first step requires distributing *nucleic acid template molecules from a biological sample* to form a set comprising a plurality of assay samples. The second step requires amplifying template molecules within the assay samples to form a population of amplified molecules in the assay samples of the set. The third step requires analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker. The fourth step requires comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance between the first allelic form and the second allelic form *in the biological sample*.

As set forth above with respect to claim 1 and its dependent claims, the Patent Owner submits that the Office has incorrectly construed the terms "assay sample," "allelic imbalance," and "wherein between 0.1 and 0.9 of the assay samples yield an amplification product" with respect to claim 8 and its dependent claims as well.

In addition, with regard to the distributing step of claim 8, which recites "distributing nucleic acid template molecules from the biological sample," the preposition "from" modifies the nucleic acid template molecules. That is, "from" denotes from where the template molecules are obtained or derived (*i.e.*, a mixed population of nucleic acid molecules within a biological sample). The plain meaning of the claim language is that the nucleic acid template molecules are *from a biological sample* and that they themselves are distributed. One of ordinary skill in the art would not recognize this step as being fulfilled by single cell analyses because the nucleic acid template molecules have not been isolated from the biological sample for distribution. Thus, the nucleic acids themselves are not being distributed directly. Rather the nucleic acids are

passive passengers in the cells when the cells containing them are distributed. As such, the nucleic acid template molecules in a single cell do not represent a mixed population of nucleic acids *from the biological sample* as a whole, but represent nucleic acid molecules from only part (*i.e.*, a single cell) of a biological sample.

Bischoff fails to disclose all of steps 1-3 of claim 8. As discussed above, in Bischoff's first experiment, the different loci were each assessed in a separate PCR reaction. Thus, Bischoff did not, and could not, analyze a first number of assay samples that contain a first allelic form of a marker and a second number of assay samples that contain a second allelic form of a marker. In Bischoff's second experiment, single isolated cells, and not nucleic acid template molecules, are placed in separate reaction tubes. The single cells are lysed, but the DNA from the single cells is not distributed to produce a set comprising a plurality of assay samples.

In addition, Bischoff fails to disclose a set comprising a plurality of assay samples with template molecules obtained or derived from a biological sample. Bischoff's assay samples use nucleic acid sequences from individual cells (*i.e.*, assay samples that are not representative of a biological sample as a whole). Bischoff does not describe a single biological sample comprising a population of template molecules that are separated as described in the specification because individual cells each with a unique genotype, are not representative of template molecules from the biological sample as a whole. Construction of claim 1 in a manner consistent with the specification requires that the nucleic acid template molecules are representative of the biological sample as a whole.

Because Bischoff fails to disclose the generation of a set comprising a plurality of assay samples containing nucleic acid template molecules obtained from a biological sample, Bischoff also fails to disclose the fourth step of claim 8 of "comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance between the first allelic form and the second allelic form in the biological sample."

For at least the reasons set forth above, claim 8 is novel over Bischoff. Claims 9-11, 16, and 17 depend directly or indirectly from claim 8 and, therefore, incorporate all of the limitations of claim 8. These claims are novel over Bischoff for at least the same reasons discussed above with respect to claim 8.

Accordingly, the Patent Owner respectfully requests that the rejection of claims 8-11, 16, and 17 under 35 U.S.C. § 102(b) based on Bischoff be withdrawn.

III. Nonobviousness

A. Claims 12 and 13 – Bischoff

Claims 12 and 13 were rejected under § 103(a) as allegedly being obvious over Bischoff. Claims 12 and 13 depend from claims 1 and 8 and further recite sets of at least 500 and at least 1000 assay samples, respectively. The Office acknowledges that Bischoff fails to disclose at least 500 and at least 1000 assay samples because Bischoff discloses only six samples. Nonetheless, the Office asserts that this massive enlargement of the set would have been obvious to one of ordinary skill in the art to provide greater statistical accuracy. The Patent Owner traverses this rejection.

First, for all of the reasons that independent claim 1 is not anticipated by Bischoff, dependent claims 12 and 13 are not obvious over Bischoff. Claims 12 and 13 contain elements that Bischoff fails to disclose or suggest, and the Office provides no appropriate reason why these elements would have been facially obvious to one of ordinary skill in the art reading Bischoff. *See KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

Second, the rationales for rejection of these claims in particular are not grounded in the reference itself, but rather in the subject specification. Bischoff was investigating mosaicism in a patient with Beckwith Wiedemann Syndrome. Bischoff found a 1:1 ratio of cell types (paternal isodisomy to normal biparental inheritance) in her analysis of six cells. There simply would have been no motivation for examining a larger number of assay samples based on Bischoff. Moreover, given the tedious means of isolating individual cells (micromanipulation), 500 or 1000 assay samples would have been prohibitively tedious. And, further, regardless of the number of cells assessed, as discussed above, single cell analyses do not meet the limitation of the claim for a set comprising a plurality of "assay samples."

Additionally, Beckwith Wiedemann Syndrome is not cancer. Beckwith Wiedemann Syndrome is characterized by numerous growth abnormalities including exomphalos, macroglossia, and gigantism. Bischoff, pg. 395, col. 1, lines 22-24. Bischoff alone would not

have motivated one of ordinary skill in the art to look for cancer cells to monitor cancer therapy, as the Office suggests it would have. Shendure Declaration at paragraph 14. The suggestion to look for rare cancer cells in a population of cells or rare cancer genes in a population of nucleic acid molecules to monitor therapy comes from the subject application, not from the cited reference.

For at least these reasons, claims 12 and 13 are not obvious over the disclosures of Bischoff. The Patent Owner respectfully requests that this rejection under 35 U.S.C. § 103(a) be withdrawn.

B. Claims 2, 3, 14, and 15 – Bischoff in view of Woudenberg

Claims 2, 3, 14, and 15 were rejected under § 103(a) as allegedly being obvious over Bischoff and further in view of Woudenberg. The Patent Owner traverses this rejection.

Claims 2, 3, 14 and 15 recite using RT-PCR (real time PCR) to amplify, and claims 14 and 15 further recite dual-labeled, fluorogenic probes. Claims 2 and 3 are dependent on claim 1. Claims 14 and 15 depend from claim 8.

For all of the reasons that independent claims 1 and 8 are novel over Bischoff, dependent claims 2, 3, 14, and 15 are not obvious over Bischoff. Woudenberg does not remedy the deficiencies of Bischoff because Woudenberg lacks a relevant disclosure or suggestion regarding the composition of the set comprising a plurality of assay samples (*i.e.*, nucleic acid template molecules obtained from a biological sample), the analysis of the number of assay samples in the set which contain a first allelic form of a marker and the number of samples which contain a second allelic form of the marker, the number of assay samples in the set that yield an amplification product, or the distribution of nucleic acid template molecules from a biological sample to form a set comprising a plurality of assay samples.

For at least these reasons, claims 2, 3, 14, and 15 are not obvious over the disclosures of Bischoff in view of Woudenberg. The Patent Owner respectfully requests that this rejection under 35 U.S.C. § 103(a) be withdrawn.

C. Claims 6 and 18 – Bischoff in view of Jeffreys

Claims 6 and 18 were rejected under § 103(a) as allegedly being obvious over Bischoff and further in view of Jeffreys. Office Action, pgs. 7-9. Claims 6 and 18 are dependent on independent claims 1 and 8, respectively. Claims 6 and 18 further recite that the amplified molecules in each of the assay samples within the first and second numbers of assay samples are homogenous such that the first number of assay samples do not contain the second allelic form of the marker and the second number of assay sample do not contain the first allelic form of the marker. The Office concedes that the samples used in Bischoff's experiments are not homogeneous. However, the Office asserts that it would have been obvious to modify the method of Bischoff by obtaining DNA from a cell free sample, then diluting it into multiple assay samples which each contain approximately as much DNA as a single cell, as taught by Jeffreys. The Patent Owner traverses this rejection.

For all of the reasons that independent claims 1 and 8 are not anticipated by Bischoff, dependent claims 6 and 18 are not obvious over Bischoff. Jeffreys fails to remedy the deficiencies of Bischoff because Jeffreys lacks a relevant disclosure or suggestion regarding the composition of the set comprising a plurality of assay samples (*i.e.*, nucleic acid template molecules obtained from a biological sample), the analysis of the number of assay samples in the set which contain a first allelic form of a marker and the number of samples which contain a second allelic form of the marker, the number of assay samples in the set that yield an amplification product, or the generation of homogenous assay samples containing either a first or a second allelic form of a marker as recited in the claims.

In addition, one of skill in the art would not have found it obvious to combine the teachings of Bischoff and Jeffreys because the combination proposed by the Office would not have allowed Bischoff to perform the desired analysis. The second experiment of Bischoff was designed to distinguish between two genetic possibilities: either the patient had a duplication of a paternal 11p region in all cells or the patient had somatic mosaicism. Both genetic mechanisms would have yielded the same number of alleles if bulk genomic DNA was assessed. Bischoff, pgs. 397-398 (Discussion). This is the reason that single cell analysis was performed. It was critical that Bischoff perform a single cell analysis DNA from the subject to keep the two chromosome 11 homologs in each cell together to distinguish between the two genetic models. Thus, the proposed modification of Bischoff by the technique of Jeffreys would have rendered

Bischoff's method unsuitable for its intended purpose. "If [a] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." MPEP § 2143.01, *citing In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984). As such, the proposed modification would not have been obvious.

For at least these reasons, claims 6 and 18 are not obvious over the disclosures of Bischoff in view of Jeffreys. The Patent Owner respectfully requests that this rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

For at least the reasons set forth above, all claims in this reexamination are patentable and should be confirmed. The absence of additional comments regarding the office action does not signify agreement with or concession of any characterization or requirement. In addition, because the arguments and comments herein may not be exhaustive, there may be additional arguments and comments that have not been expressed.

As such, the issuance of a Reexamination Certificate confirming the patentability of all claims is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 202 824 3100.

No fees are believed to be due with respect to the filing of this response. However, should any such fees be due, the Commissioner is hereby authorized to charge any such fees in connection with this paper to Deposit Account No. 190733

Respectfully submitted,

By: /Sarah A. Kagan/
Sarah A. Kagan
Registration No. 32,141

Dated: 27 January 2014

Banner & Witcoff, Ltd.
Customer No. 11332

CERTIFICATE OF SERVICE

The undersigned certifies that, in accordance with 37 C.F.R. § 1.550(f) and concurrently with the electronic filing of this request to the United States Patent and Trademark Office, a complete copy of this Responsive Amendment to Office Action and rule 132 declaration, has been mailed via first class mail on January 27, 2014 to the third party requester:

Life Technologies Corporation
Attn: IP Department
5791 Van Allen Way
Carlsbad, CA 92008

/Sarah A. Kagan/

Sarah A. Kagan
Registration No. 32,141

Dated: 27 January 2014

Banner & Witcoff, Ltd.
Customer No. 11332

Electronic Acknowledgement Receipt

EFS ID:	18037959
Application Number:	90012896
International Application Number:	
Confirmation Number:	8361
Title of Invention:	DIGITAL AMPLIFICATION
First Named Inventor/Applicant Name:	7915015
Customer Number:	11332
Filer:	Sarah Anne Kagan.
Filer Authorized By:	
Attorney Docket Number:	001107.00988
Receipt Date:	27-JAN-2014
Filing Date:	17-JUN-2013
Time Stamp:	18:00:18
Application Type:	Reexam (Patent Owner)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Req. Reconsideration-After Non-Final Reject	00988Rsp.pdf	164113 b2222c7941eeb542784c4252694b4bf6dc5c955a	no	19

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Total Files Size (in bytes):	164113

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Ex Parte* Reexamination:	)	Group Art Unit: 3991
	)	
U.S. Patent No. 7,915,015	)	Docket No. 001107.00988
	)	
Control No. 90/012,896	)	Confirmation No: 8361
	)	
Reexam Filing Date: June 17, 2013	)	Examiner: Bruce R. Campell

For: DIGITAL AMPLIFICATION

CERTIFICATE OF SERVICE

The undersigned certifies that a complete copy of the Information Disclosure Statement and associated disclosed documents filed in the U.S. Patent and Trademark Office on January 27, 2014, has been mailed via first class mail to the third party requester this day at the following address:

Life Technologies Corporation
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5791 Van Allen Way
Carlsbad, CA 92008

/Sarah A. Kagan/
Sarah A. Kagan
Registration No. 32,141

Dated: 30 January 2014

Banner & Witcoff, Ltd.
Customer No. 11332

Electronic Acknowledgement Receipt

EFS ID:	18072329
Application Number:	90012896
International Application Number:	
Confirmation Number:	8361
Title of Invention:	DIGITAL AMPLIFICATION
First Named Inventor/Applicant Name:	7915015
Customer Number:	11332
Filer:	Sarah Anne Kagan.
Filer Authorized By:	
Attorney Docket Number:	001107.00988
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Time Stamp:	16:05:47
Application Type:	Reexam (Patent Owner)

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Total Files Size (in bytes):	78489

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New Applications Under 35 U.S.C. 111
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New International Application Filed with the USPTO as a Receiving Office
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Electronic Acknowledgement Receipt

EFS ID:	18635766
Application Number:	90012896
International Application Number:	
Confirmation Number:	8361
Title of Invention:	DIGITAL AMPLIFICATION
First Named Inventor/Applicant Name:	7915015
Customer Number:	11332
Filer:	Sarah Anne Kagan./Jennifer Hazzard
Filer Authorized By:	Sarah Anne Kagan.
Attorney Docket Number:	001107.00988
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Filing Date:	17-JUN-2013
Time Stamp:	09:16:08
Application Type:	Reexam (Patent Owner)

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Submitted with Payment	no

File Listing:

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Warnings:					
Information:					
21	Non Patent Literature	Exhibit-67Jeffreys.pdf	427807 9d4667e327ecc893d3c04eb80641c65d032cf1c4	no	59
Warnings:					
Information:					
22	Non Patent Literature	Exhibit-68Kunst.pdf	4906995 1396b954821f584bbb3ff632450d04a27a293c2e	no	25
Warnings:					
Information:					
23	Non Patent Literature	Exhibit-69Leeflang.pdf	5621618 e6418d833e2c0e6f64a046c9ce0f0616a8b4d905	no	32
Warnings:					
Information:					
24	Non Patent Literature	Exhibit-610Levinson.pdf	133207 c3fd30ee6af3ab6b02f2c8c06c7e7529b0fc4efe	no	35
Warnings:					
Information:					
25	Non Patent Literature	Exhibit-611Li1988.pdf	119315 a245e139f59554ef7fff2fbda5b73695c4771f9f	no	30
Warnings:					
Information:					
26	Non Patent Literature	Exhibit-612Lia.pdf	8179466 7ec49817f5d97a3931936fac99fd62e8f9cc3824	no	42
Warnings:					
Information:					
27	Non Patent Literature	Exhibit-613Liu.pdf	164756 25668f7b3f0b07594ece46ba23c46eb7d0cb318f	no	31
Warnings:					
Information:					
28	Non Patent Literature	Exhibit-614Munier.pdf	98525 6fd65204c70a79c7428057462d6cc5e173580114	no	23
Warnings:					
Information:					

29	Non Patent Literature	Exhibit-615Sheehy.pdf	112155 1e5ef805c79dd18ef2491cc8b25fae5737fd b080	no	27
Warnings:					
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30	Non Patent Literature	Exhibit-616Simmonds.pdf	92165 e9fb9b3d3f19fc4076204c667bf9210a2030 1a64	no	21
Warnings:					
Information:					
31	Non Patent Literature	Exhibit-617Stark.pdf	105316 9bbe21d80d53f29f37fa068fdf5fe00e8943e 9b9	no	25
Warnings:					
Information:					
32	Non Patent Literature	Exhibit-618Sykes.pdf	88210 5f0408f5c0bb35896f7d010cb7df35f5e7bb 8441	no	18
Warnings:					
Information:					
33	Non Patent Literature	Exhibit-619Zhang1992.pdf	199879 f435eeb4ee74088ca37f718b113c9be5558 de1cb	no	31
Warnings:					
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34	Non Patent Literature	Exhibit-620Zhang1993.pdf	94661 8479f9e84705d487fecb74d3e45ef8041a36 a480	no	21
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	Application Number	90012896
	Filing Date	2013-06-17
	First Named Inventor	
	Art Unit	3991
	Examiner Name	Bruce R. Campell
	Attorney Docket Number	001107.00988

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	1	Defendants Life Technologies Corporation, Applied Biosystems, LLC, and Ion Torrent Systems, Inc.'s Preliminary Non-Infringement and Patent invalidity Contensions pursuant to Local Rule 103.3, filed in Case No. Case No. 1:12-CV-1173 on August 22, 2013	☐
	2	Deposition of Michael Metzker, Ph.D., dated October 25, 2013	☐
	3	Declaration of Michael Metzker, Ph.D. executed September 27, 2013	☐
	4	BAKER et al., "Male Mice Defective in the DNA Mismatch Repair Gene PMS2 Exhibit Abnormal Chromosome Synapsis in Meiosis," Cell, vol. 82, 309-319, July 28, 1995	☐
	5	BISCHOFF et al., "Single cell analysis demonstrating somatic mosaicism involving 11p in a patient with paternal isodisomy and Beckwith-Wiedemann syndrome," Human Molecular Genetics, 1995, vol. 4, no. 3, 395-399	☐
	6	BRISCO et al., "Detection and quantitation of neoplastic cells in acute lymphoblastic leukaemia, by use of teh polymerase chain reaction," British Journal of Haematology, 1991, 79, 211-217	☐
	7	DREESEN et al., "Preimplantation genetic diagnosis of spinal muscular atrophy," Molecular Human Reproduction, vol. 4, no. 9, pp. 881-885, 1998	☐
	8	FLINT et al., "NR2A Subunit Expression Shortens NMDA Receptor Synaptic Currents in Developing Neocortex," The Journal of Neuroscience, April 1, 1997, 17(7):2469-2476	☐
	9	GAYNOR et al., "Use of Flow Cytometry and RT-PCR for Detecting Gene Expression by Single Cells," BioTechniques, vol. 21, no. 2 (1996)	☐
	10	GRAVEL et al., "Single-Cell Analysis of the t(14;18)(q32;q21) Chromosomal Translocation in Hodgkin's Disease Demonstrates the Absence of This Translocation in Neoplastic Hodgkin and Reed-Sternberg Cells," Blood, 1998, 91:2866-2874	☐
	11	GREWAL et al., "The mutation properties of spinal and bulbar muscular atrophy disease alleles," Neurogenetics (1998) 1:249-252	☐

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	12	JEFFREYS et al., "Complex gene conversion events in germline mutation at human minisatellites," Nature Genetics, vol. 6, February 1994	☐
	13	JENA et al., "Amplification of genes, single transcripts and cDNA libraries from one cell and direct sequence analysis of amplified products derived from one molecule," Journal of Immunological Methods 190 (1996) 199-213	☐
	14	KUNST et al., "The effect of FMR1 CFF repeat interruptions on mutation frequency as measured by sperm typing," J. Med. Genet., 1997; 34:627-631	☐
	15	LEEFLANG et al., "Single sperm analysis of the trinucleotide repeats in the Huntington's disease gene: quantification of the mutation frequency spectrum," Human Molecular Genetics, 1995, vol. 4, no. 9, 1519-1526	☐
	16	LEVINSON et al., "Molecular Characterization of Transgene-induced Immunodeficiency in B-less Mice Using a Novel Quantitative Limiting Dilution Polymerase Chain Reaction Method," J. Exp. Med, vol. 178, July 1993, 317-329	☐
	17	LI et al., "Amplification and analysis of DNA sequences in single human sperm and diploid cells," Nature, vol. 335, September 29, 1988	☐
	18	LIA et al., "Somatic instability of the CTG repeat in mice transgenic for the myotonic dystrophy region is age dependent but not correlated to the relative intertissue transcription levels and proliferative capacities," Human Molecular Genetics, 1998, vol. 7, no. 8, 1285-1291	☐
	19	LIU et al., "Efficiency and accuracy of polymerase-chain-reaction assay for cystic fibrosis allele F508 in single cell," The Lancet, vol. 339, May 16, 1992	☐
	20	SHEEHY et al., "Concurrent evolution of regions of the envelope and polymerase genes of human immunodeficiency virus type 1 observed during zidovudine (AZT) therapy," Journal of General Virology, (1996), 76, 1071-1081	☐
	21	SIMMONDS et al., "Human immunodeficiency virus-infected individuals contain provirus in small numbers of peripheral mononuclear cells and at low copy numbers," Journal of Virology, February 1990, vol. 64, no. 2, p. 864-872	☐
	22	STARK et al., "Single-cell PCR performed with neurofibroma Schwann cells reveals the presence of both alleles of the neurofibromatosis type 1 (NF1) gene," Hum Genet (1995) 96:619-523	☐

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	23	SYKES et al., "Quantitation of Targets for PCR by Use of Limiting Dilution," BioTechniques, vol. 13, no. 3 (1992)	☐
	24	ZHANG et al., "Whole genome amplification from a single cell: Implications for genetic analysis," Proc. Natl. Acad. Sci., vol. 89, pp. 5847-5851, July 1992	☐
	25	ZHANG et al., "Selection for Specific Sequences in the External Envelope Protein of Human Immunodeficiency Virus Type 1 upon Primary Infection," Journal of Virology, June 1993, vol. 67, no. 6, p. 3345-3356	☐
	26	Exhibit 4.1 (Baker)	☐
	27	Exhibit 4.10 (Levinson)	☐
	28	Exhibit 4.11 (Li 1988)	☐
	29	Exhibit 4.12 (Lia)	☐
	30	Exhibit 4.13 (Liu)	☐
	31	Exhibit 4.14 (Munier)	☐
	32	Exhibit 4.15 (Sheehy)	☐
	33	Exhibit 4.16 (Simmonds)	☐

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	34	Exhibit 4.17 (Stark)	☐
	35	Exhibit 4.18 (Sykes)	☐
	36	Exhibit 4.19 (Zhang 1992)	☐
	37	Exhibit 4.2 (Bischoff)	☐
	38	Exhibit 4.20 (Zhang 1993)	☐
	39	Exhibit 4.21 (Flint)	☐
	40	Exhibit 4.22 ((Gaynor)	☐
	41	Exhibit 4.23 (Jena)	☐
	42	Exhibit 4.3 (Brisco)	☐
	43	Exhibit 4.4 (Dreesen)	☐
	44	Exhibit 4.5 (Gravel)	☐

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	45	Exhibit 4.6 (Grewal)	☐
	46	Exhibit 4.7 (Jeffreys)	☐
	47	Exhibit 4.8 (Kunst)	☐
	48	Exhibit 4.9 (Leeflang)	☐
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Signature	/Sarah A. Kagan/	Date (YYYY-MM-DD)	2014-03-26
Name/Print	Sarah A. Kagan	Registration Number	32141

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	1	Exhibit 5.11 (Li 1988)	☐
	2	Exhibit 5.12 (Lia)	☐
	3	Exhibit 5.13 (Liu)	☐
	4	Exhibit 5.14 (Munier)	☐
	5	Exhibit 5.15 (Sheehy)	☐
	6	Exhibit 5.16 (Simmonds)	☐
	7	Exhibit 5.17 (Stark)	☐
	8	Exhibit 5.18 (Sykes)	☐
	9	Exhibit 5.19 (Zhang 1992)	☐
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	24	Exhibit 6.11 (Li 1988)	☐
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☐ See attached certification statement.

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

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Signature	/Sarah A. Kagan/	Date (YYYY-MM-DD)	2014-03-26
Name/Print	Sarah A. Kagan	Registration Number	32141

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EFS ID:	18635738
Application Number:	90012896
International Application Number:	
Confirmation Number:	8361
Title of Invention:	DIGITAL AMPLIFICATION
First Named Inventor/Applicant Name:	7915015
Customer Number:	11332
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Application Type:	Reexam (Patent Owner)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Preliminary-Non-Infringement-and-Patent-invalidity-Contensions.pdf	1405522 b85f24dfe9782365924da42ec65dda71db612e08	no	30

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4	Non Patent Literature	Baker.pdf	2470260 8143663aa919c76808a9df2ae6a1219a0ad 9eed1	no	11
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33	Non Patent Literature	Exhibit-47Jeffreys.pdf	532447 0eac915e1ab23cf78790bea35257e75439f7d685	no	93
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/012,896	06/17/2013	7915015	001107.00988	8361

11332 7590 05/09/2014

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ART UNIT *3991*.

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Ex Parte Reexamination
Detailed Final Office Action

This is a reexamination of U.S. Patent 7,915,015, issued March 29, 2011. A Request pursuant to 37 CFR 1.510 for ex parte reexamination of claims 1-18 of U.S. Patent 7,915,015 was filed on June 17, 2013 by a third party requester. An Order granting the request was mailed on August 22, 2013. A non-final Office action was mailed on November 27, 2013. Patent Owner filed a response including a declaration of Jay Shendure on January 27, 2014.

Status of the Claims

Claims 1-18 of U.S. Patent 7,915,015 are subject to reexamination. No claim has been amended.

Scope of the Claims

In reexamination, patent claims are construed broadly. In re Yamamoto, 740 F.2d 1569, 1571, 222 USPQ 934, 936 (Fed. Cir. 1984) (claims given "their broadest reasonable interpretation consistent with the specification"). The independent claims subject to reexamination read as follows:

1. A method for determining an allelic imbalance in a biological sample, comprising the steps of:

amplifying template molecules within a set comprising a plurality of assay samples to form a population of amplified molecules in each of the assay samples of the set, wherein the template molecules are obtained from the biological sample;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker, wherein between 0.1 and 0.9 of the assay samples yield an amplification product;

comparing the first number to the second number to ascertain an allelic imbalance in the biological sample; and

identifying an allelic imbalance in the biological sample.

8. A method for determining an allelic imbalance in a biological sample, comprising the steps of:

distributing nucleic acid template molecules from a biological sample to form a set comprising a plurality of assay samples;

amplifying the template molecules within the assay samples to form a population of amplified molecules in the assay samples of the set;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker;

comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance between the first allelic form and the second allelic form in the biological sample.

Claim Interpretation

The “biological sample” can either be comprised of cells, tissues, bodily fluids, etc. or cell free. See col. 7, lines 10-14. In either case, nucleic acids are distributed throughout the sample. Therefore any process in which the sample is diluted is considered "distributing nucleic acid template molecules from a biological sample.” An “assay sample” is a portion of the biological sample. "Allelic imbalance" is not defined in the specification. The term is used in the art to refer to situations in which one allele (of a pair) is expressed at a lower level than the other due to gene silencing, imprinting, mutations in regulatory sequences, etc., as well as situations in which one allele is duplicated or deleted from the genome. The claims encompass both possibilities, since the specification discloses amplification of both genomic DNA and cDNA produced by reverse transcription.

Patent Owner argues (Response filed January 27, 2014, pp. 5-9) that the “biological sample” refers to isolated nucleic acids and that the claims exclude methods in which single cells are analyzed, as in the Bischoff reference. This argument is not persuasive because it is not supported by the specification or the claims. Claims 1 and

8 recite "determining an allelic imbalance in a biological sample," claims 7 and 9 recite that the biological sample is "from blood," which contains cells. The claims do not recite a step in which nucleic acids are purified in any way prior to making a set of assay samples or distributing the nucleic acids. Patent Owner cites the '015 patent specification, which recites, "Biological samples which can be used as the starting material for the analyses may be from any tissue or body sample from which DNA or mRNA can be isolated," but does not explain why this precludes the use of blood or cells isolated therefrom (used by Bischoff), as starting material for analyses. The '015 patent does not require that "assay samples" consist of purified nucleic acids; "assay sample" is not defined at all in the specification. Therefore there is no reason why a group of single cells isolated from a biological sample cannot be construed as a set of assay samples. Patent Owner is correct in stating that the quoted portion of the specification does not require isolation of single cells, but neither is such a step excluded. Patent Owner attempts to prove its point by quoting 9 sections from the specification (Response, pp. 7-8), but does not explain how they exclude the methods of Bischoff. The first citation is to Fig. 1A, which recites "dilution" of nucleic acids, but the claims have no "dilution" step. Methods requiring "dilution" are claimed in U.S. patent 6,440,706. Furthermore, the '015 patent specification states, "The dilution can be performed from more concentrated samples. Alternatively, dilute sources of template nucleic acids can be used." See col. 4, lines 35-38. Isolated single cells are dilute sources of template nucleic acids, obtained from a biological sample. The next 7 citations do not exclude methods in which a set of cells (assay samples) is isolated from blood (biological sample), and the template nucleic acid molecules contained within the assay samples are then amplified. A population of intact cells should contain the same "population of genetic sequences" before DNA is extracted as the extracted DNA will contain afterwards. The ninth citation is only describing a preferred embodiment. A particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment (MPEP 2111.01 (II)). In addition, with regard to Fig. 1A and other portions of Example 4 cited by Patent Owner as support for its position, the '015 patent clearly states, "specific examples…are

provided herein for purposes of illustration only, and are not intended to limit the scope of the invention" (col. 7, lines 59-61).

Patent Owner argues (Response, p. 9) that "allelic imbalance" does not include differential gene expression, citing the Shendure declaration (¶ 11). This is incorrect. As stated above, "allelic imbalance" is sometimes used in the art to refer to situations in which one allele (of a pair) is expressed at a lower level than the other. For example, see the Shen reference. Methods of measuring gene expression are specifically contemplated at col. 5, lines 6-28, of the '015 patent. Moreover, this is a moot point because none of the cited prior art measures gene expression.

Patent Owner argues (Response, pp. 9-10) that claim 1 requires that 0.1 to 0.9 of the assay samples yield an amplification product which can be from either the first or second allele (or both). It is agreed that this is within the scope of the claim, but the claim is not limited to this method of determining what proportion of assay samples produce an amplification product. For example, if the limitations of claim 4 (or 5) are "read into" claim 1, claim 1 becomes "… analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker, wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the first (or second) allelic form of the marker; comparing the first number to the second number …" Claim 1 is a broad claim in which the "between 0.1 and 0.9 of the assay samples" can be determined in several different ways. It can be determined by 1) the number of assay samples in which the first allele is amplified, as in claim 4, 2) the number of assay samples in which the second allele is amplified, as in claim 5, 3) the number of assay samples in which either the first or second allele is amplified, as argued by Patent Owner, or 4) the number of assay samples containing any amplification product (including non-specific products which can be detected by gel electrophoresis – see Fig. 3; col. 3, lines 39-41). This is considered the broadest reasonable interpretation of claim 1, even though only options 1) and 2) are specifically contemplated in the '015 patent specification (col. 6,

lines 6-21). Patent Owner has not pointed out any portion of the specification that supports its claim interpretation.

Documents Submitted by Requester

Bischoff et al., "Single cell analysis demonstrating somatic mosaicism involving 11p in a patient with paternal isodisomy and Beckwith-Wiedemann syndrome", Human Molecular Genetics, Vol. 4, No. 3, 1995, 395-399

Documents Cited by Examiner

U.S. Patent 5,928,907, issued July 27, 1999 to Woudenberg et al.

Jeffreys *et al.,* "Amplification of human minisatellites by the polymerase chain reaction: towards DNA fingerprinting of single cells." *Nucl. Acids. Res.,* vol 16, no. 23, pages 10953-10971 (1988)

J Shen et al. “Allelic Imbalance in BRCA1 and BRCA2 Gene Expression and Familial Ovarian Cancer.” Cancer Epidemiol Biomarkers Prev 20(1): 50-56 (2011)

https://education.yahoo.com/reference/dictionary/entry/from, accessed 5/1/2014 “Yahoo”)

Maintained Claim Rejections – 35 U.S.C. §§ 102 and 103

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 5, 7-11, 16 and 17 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Bischoff.

Bischoff discloses a study which demonstrated somatic mosaicism (i.e. the somatic cells of an individual are not all genetically identical) in a patient with Beckwith-Wiedemann syndrome (BWS). The study focused on a segment of chromosome 11 between the 11p15.5 and 11p13 regions. It was found that the patient had two populations of cells. One population of cells contained a maternally inherited copy of chromosome 11 and a paternally inherited copy, as expected. The other population of cells displayed partial paternal isodisomy, i.e. the segment of interest on the maternal chromosome was actually derived from the paternal chromosome. (Abstract. See Fig. 3 for diagrammatic explanation of how this can occur.) This situation is "allelic imbalance" because genes on the affected cells do not show the expected 1:1 ratio of maternal and paternal alleles. The procedure used by Bischoff meets the limitations of the claims as follows.

In a preliminary experiment, Bischoff isolated genomic DNA from blood samples obtained from the patient and both parents and subjected it to PCR using primers designed to amplify 6 markers from the 11p region, 4 markers from the 11q region and one from the 21q region (chromosome 21). The markers comprise dinucleotide repeats and there are as many as 4 alleles for each marker. Results are shown in Fig. 1 and Table 1. For example, marker HRAS was uninformative because both parents had the same genotype. Marker DHS922 was informative; the mother had alleles 1 and 3, while the father had the alleles 2 and 3. The patient had allele 1 from the mother and allele 2 from the father, but the probe for allele 2 produced a much stronger signal. This was interpreted as evidence for mosaic paternal disomy, i.e. some cells contain alleles 1 and 2 while other cells contain 2 copies of the (paternal) allele 2. A total of 4 markers for the 11p region were informative and all suggested mosaic paternal disomy. Only one

marker from the 11q region proved informative, and it indicated normal biparental disomy (i.e. one allele from each parent). The marker from chromosome 21 also indicated normal biparental disomy.

Bischoff then produced a set of “assay samples” by isolating 6 individual lymphocytes from a “biological sample” of the patient’s blood (“distributing” step). The cells were lysed and genomic DNA was subjected to primer extension preamplification (PEP), which amplifies essentially the entire genome by extension of a complete set of random oligonucleotide primers. Following PEP, the DNA from each cell was subjected to PCR using the primer sets previously shown to amplify informative alleles (“amplifying” step). Results are shown in Fig. 2 and Table 2. Cells 1, 5 and 6 were found to show paternal isodisomy and cells 2, 3 and 4 showed normal biparental disomy (“analyzing” step). It is arbitrary which allele is considered the first form and which the second form. For example, marker HBB showed that all 6 cells contained allele 1 from the paternal chromosome, but only 3 cells contained allele 2 from the maternal chromosome, thereby demonstrating an allelic imbalance (“comparing” step). Therefore claim 8 is anticipated.

With regard to the limitation “between 0.1 and 0.9 of the assay samples yield an amplification product,” claims 4 and 5 explicitly allow this limitation to refer to the number of samples in which <u>either</u> the first or second allele is amplified. Since 50% (0.5) of the samples contained amplified maternal HBB sequence, and the maternal sequence can be considered either the first or second allele, this result meets the limitations of claims 1, 4, 5, 10, 11, 16 and 17.

With regard to claims 7 and 9, the biological sample was from blood.

Claims 12 and 13 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Bischoff.

Bischoff is described above. Bischoff does not disclose a method wherein at least 500 or 1,000 assay samples are produced from the biological sample. This modification would have been obvious to the skilled artisan, however, because it is

readily apparent that assaying a larger number of samples (cells) would provide a more accurate (statistically) determination of the number of cells containing the allelic imbalance (or any given allele of interest). Moreover, in cases where an allelic imbalance (or a particular allele) is associated with a disease state (e.g. cancer), it would be obvious to assay a large number of cells before and after therapy in order to assess the efficacy of the therapy employed, or to assay a large number of cells from surrounding tissues to search for possible metastatic cells. Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 2, 3, 14 and 15 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Bischoff as applied to claim 1 and further in view of Woudenberg.

Bischoff is relied upon as described above. Bischoff does not disclose a method wherein DNA is amplified by real-time PCR using a dual labeled fluorogenic probe.

Woudenberg describes a method and apparatus for real time PCR with detection by a dual labelled fluorogenic probe. See entire document, especially claim 12; col. 7, line 47 - col. 8, line 61; col. 9, line 61 - col. 10, line 67.

It would have been obvious to one of ordinary skill in the art to modify the method of Bischoff by amplifying DNA using real time PCR with detection by a dual labelled fluorogenic probe as taught by Woudenberg. One would have been motivated to do this in order to obtain the benefits noted by Woudenberg, i.e. more accurate quantitation of template nucleic acids, less sample handling, reduced reagent use, etc. (col. 3, lines 31-41). Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 6 and 18 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Bischoff as applied to claim 1 and further in view of Jeffreys.

Bischoff is relied upon as described above. Bischoff does not disclose a method wherein the amplified DNA sequences in the assay samples are homogenous.

Bischoff is relied upon as described above. Bischoff does not disclose a method wherein the amplified DNA sequences in the assay samples are homogenous.

Jeffreys discloses methods for amplification of human minisatellite DNA for the purpose of producing DNA fingerprints of individuals. In one method, a biological sample is split into multiple assay samples by isolating single cells, then analyzed in much the same way as in Bischoff (pp. 10955-10956). In an alternative method, isolated (cell free) DNA was diluted into multiple assay samples, each containing 6 pg DNA. This amount was estimated to be equivalent to the amount of DNA in a single cell. It was concluded that single DNA molecules could be faithfully amplified (pp. 10960-10962). In the experiment shown in Fig. 4, each assay sample was subjected to PCR with 4 sets of primers (in a single reaction), the primers designed to amplify two alleles for each of 2 minisatellites. Successful amplification was obtained, with a mean failure rate of 63% per allele per reaction, equating to an estimated 0.46 successful amplification events per 6 pg sample (because statistically one would not expect the template sequence to be present in every sample; p. 10961). Of the 16 samples shown in Fig. 4, 3 were a+/b+ (positive for both markers a and b), 5 were a-/b- (negative for both markers), 8 were a-/b+ and 0 were a+/b-. Therefore the proportion of samples homogenous for marker b was 0.5 (8/16) or, if doubly negative samples are excluded, 0.73 (8/11). Similar results were obtained for markers c and d; 2 samples were c+/d+, 8 were c-/d-, 4 were c+/d- and 2 were c-/d+.

It would have been obvious to one of ordinary skill in the art to modify the method of Bischoff by obtaining DNA from a cell free sample, then diluting it into multiple assay samples which each contain approximately as much DNA as a single cell, as taught by Jeffreys. Jeffreys shows that some assay samples will contain a single copy of the marker in question, some will contain more than one, and others will not contain any copies, as expected with a random distribution of genomic DNA in each sample. If genomic DNA from the patient studied by Bischoff were analyzed in this manner (diluting DNA into a plurality of assay samples, each containing approximately one copy

of an informative marker sequence), the result would be that, of the samples testing positive for a single allele, more than 50% would be positive for the paternal allele. This result (allelic imbalance, i.e not a 1:1 ratio of maternal:paternal alleles) would indicate paternal isodisomy in some of the patient's cells. (If half the cells in the patient's blood had the paternal isodisomic genotype, as in the small sample reported by Bischoff, the expected ratio would be 1 maternal allele : 3 paternal alleles.) One would have been motivated to analyze DNA from a cell free biological sample as taught by Jeffreys in order to eliminate the labor intensive process of isolating single cells. Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Patent Owner's remarks and the Shendure declaration, submitted on January 27, 2014, have been considered but are not found persuasive.

§ 102(b) rejection over Bischoff

With regard to claims 1, 4, 5 and 7, Patent Owner's arguments concerning the scope of the claims (Response, pp. 7-10) have been rebutted above in the "Claim Interpretation" section. While Patent Owner has made clear how it would like the claims to be interpreted, it has not shown that the broader interpretation adopted by the Office is unreasonable. As stated in *In re Yamamoto*, 222 USPQ 934, claims subject to reexamination are given their broadest reasonable interpretation because a patent owner has "an opportunity … to amend his claims to correspond with his contribution to the art" (p. 937), just as an applicant can amend claims in a pending application. And as stated in *In re Prater and Wei*, 162 USPQ 541, 551 (cited in *Yamamoto*), "We are not persuaded by any sound reason why, at any time before the patent is granted, an applicant should have limitations of the specification read into a claim where no express statement of the limitation is included in the claim."

Patent Owner argues (Response, p. 10) that the preliminary experiment disclosed in Bischoff does not anticipate the claims. This is correct. The preliminary experiment is described in the rejection only to facilitate understanding of the additional experiment disclosed in Bischoff.

Patent Owner argues (Response, pp. 10-11) that the second experiment disclosed by Bischoff does not anticipate the claims because 1) single cells are not assay samples and 2) the claims require that the nucleic acids in each assay sample be representative of the nucleic acids in the biological sample as a whole. With regard to the first point, Patent Owner is arguing limitations not found in the claims. The claims do not include a step in which nucleic acids in the biological sample are extracted, isolated or purified in any way prior to preparation of the assay samples. The six isolated cells analyzed by Bischoff make up a set of assay samples upon which PCR amplification was independently performed. As noted above, "assay sample" is not defined in the specification, and a "biological sample" can be comprised of cells, tissues or bodily fluids. The working example in the specification utilizes purified DNA as the biological sample from which assay samples are prepared, but this is not a limiting definition. With regard to the second point, not only is Patent Owner arguing limitations not found in the claim, but the limitation is also not found in the specification and the argument is simply incorrect. There should be at least two copies of the marker per cell in most cases (exceptions would be genes on X or Y chromosomes, situations in which there are deletions, etc.). But the claims (as interpreted by Patent Owner) allow up to 90% of the assay samples to contain <u>no</u> amplifiable copies of either allele. Since each cell contains the entire genome, the assay samples of Bischoff are actually much more representative of the DNA in the test subject's blood (the biological sample) than what is allowed by claim 1.

Patent Owner's argument (Response, p. 11) regarding the "0.1 to 0.9" limitation has been rebutted above in the "Claim Interpretation" section.

With regard to claims 8-11, 16 and 17, Patent Owner reiterates (Response, p. 12) its arguments regarding claim interpretation, which have been addressed above. Patent Owner further argues (Response, pp. 12-13) that "distributing nucleic acid

template molecules from a biological sample" (claim 19) means that the nucleic acids have been removed from the biological sample. Turning to the dictionary (Yahoo), definition 3 of "from" is indeed "used to indicate separation, removal, or exclusion" as argued by Patent Owner. However, definition 2 reads "used to indicate a source." Cells contain nucleic acids. When Bischoff distributed individual blood cells the nucleic acids contained therein were also distributed, and the nucleic acids were "from" the biological sample (blood). This is a reasonable interpretation of the claim and the prior art.

Patent Owner argues (Response, p. 13) that, in Bischoff, DNA from lysed cells is not further distributed. This argument is not persuasive because no second distribution step is recited in the claims. Patent Owner's position appears to be that cells cannot be assay samples, but as noted above this is not stated in the claims or the specification. It is agreed that Bischoff did not use the same procedure as the '899 patent's non-limiting working example, but the plain, broad language of the claims encompasses the Bischoff procedure and it is improper to read limitations from the specification into the claims. Moreover Patent Owner's requirement that "the nucleic acid template molecules are representative of the biological sample as a whole" is not found in the specification, and is also indefinite.

§ 103 rejection over Bischoff

Patent Owner reiterates (Response, pp. 14-15) the arguments made in traversing the anticipation rejection, which are not persuasive as explained above. Patent Owner further argues that the motivation to analyze more assay samples (cells) is not found in the reference itself. This argument is not persuasive because the rationale to modify the prior art need not be expressly stated in the prior art; the rationale may be reasoned from knowledge generally available to one of ordinary skill in the art or from established scientific principles (MPEP 2144(I)). In this case, the rejection provides three motivations to analyze a greater number of cells, each reasoned from common knowledge and/or established scientific principles.

Patent Owner argues (Response, p. 14) that analyzing more cells would be "prohibitively tedious." This argument is not persuasive because it is not supported by any evidence, and also because the fact that this process could possibly be labor intensive (expensive) does not mean that a person of ordinary skill in the art would not undertake it because of some technological incompatibility. See MPEP 2145(I) and (VII).

Patent Owner argues (Response, pp. 14-15) that Beckwith-Wiedemann syndrome is not cancer, citing the Shendure declaration (¶ 14). Patent Owner's point is unclear, since nothing of the kind was asserted in the rejection. It was notoriously well known in the art that chromosomal abnormalities which result in allelic imbalance are associated with many types of cancer (see Brenner, exhibit 8 submitted with the Request, p. 2892, col. 1); therefore it would have been obvious to use the Bischoff method to look for allelic imbalances in cells of patients suffering from cancer (or any other disease involving allelic imbalance) .

§ 103 rejection over Bischoff in view of Woudenberg

Patent Owner argues (Response, p. 15) that Woudenberg does not remedy the deficiencies of Bischoff. Since Bischoff is not deficient for the reasons discussed at length above, this argument is not persuasive.

§ 103 rejection over Bischoff in view of Jeffreys

Patent Owner argues (Response, pp. 16-17) that Jeffreys does not remedy the deficiencies of Bischoff. Since Bischoff is not deficient for the reasons discussed at length above, this argument is not persuasive. Patent Owner further argues that analysis of "bulk" DNA rather than single cells would not allow one to distinguish between mosaicism (duplication of the paternal allele in some cells) and duplication of the paternal allele in all cells. This argument is not persuasive for three reasons. First, the claims are drawn to a method for determining an allelic imbalance, not

distinguishing between mosaicism and complete paternal isodisomy. The use of bulk DNA would accomplish that as explained in the rejection. Patent Owner has not pointed out any error in Examiner's analysis. Second, the preliminary experiment of Bischoff demonstrates that allelic imbalance can be detected with bulk DNA by visual inspection of Southern blots (Fig.1; p. 396, col. 1). Third, a cell free method could readily distinguish between mosaic and complete paternal isodisomy because in the case of complete paternal isodisomy, there would be no assay samples at all containing the maternal allele, whereas in the case of mosaicism, there would be some assay samples containing the maternal allele as explained in the rejection.

Conclusion

Claims 1-18 are rejected.

Extensions of Time

THIS ACTION IS MADE FINAL.

A shortened statutory period for response to this action is set to expire 2 months from the mailing date of this action.

Extensions of time under 37 CFR 1.136(a) do not apply in reexamination proceedings. The provisions of 37 CFR 1.136 apply only to "an applicant" and not to parties in a reexamination proceeding. Further, in 35 U.S.C. 305 and in 37 CFR 1.550(a), it is required that reexamination proceedings "will be conducted with special dispatch within the Office."

Extensions of time in reexamination proceedings are provided for in 37 CFR 1.550(c). A request for extension of time must be filed on or before the day on which a response to this action is due, and it must be accompanied by the petition fee set forth in 37 CFR 1.17(g). The mere filing of a request will not effect any extension of time. An extension of time will be granted only for sufficient cause, and for a reasonable time specified.

The filing of a timely first response to this final rejection will be construed as including a request to extend the shortened statutory period for an additional month, which will be granted even if previous extensions have been granted. In no event however, will the statutory period for response expire later than SIX MONTHS from the mailing date of the final action. See MPEP § 2265.

Duty to Disclose

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving U.S. Patent No. 7,915,015 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRUCE CAMPELL whose telephone number is (571)272-0974. The examiner can normally be reached on Monday - Thursday from 8:00 to 5:00. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Jones, can be reached on 571-272-1535.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this ex parte reexamination proceeding should be directed:

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Supervisory Patent Examiner, Art Unit 3991

Office Action in Ex Parte Reexamination	**Control No.** 90/012,896	**Patent Under Reexamination** 7915015	
	Examiner BRUCE CAMPELL	**Art Unit** 3991	**AIA (First Inventor to File) Status** No

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

a. ☒ Responsive to the communication(s) filed on *1/27/2014* .
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ______.

b. ☒ This action is made FINAL.

c. ☐ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire *2* month(s) from the mailing date of this letter.
Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).**
If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Information Disclosure Statement, PTO/SB/08.
3. ☐ Interview Summary, PTO-474.
4. ☐ ______.

Part II SUMMARY OF ACTION

1a. ☒ Claims *1-18* are subject to reexamination.
1b. ☐ Claims ______ are not subject to reexamination.
2. ☐ Claims ______ have been canceled in the present reexamination proceeding.
3. ☐ Claims ______ are patentable and/or confirmed.
4. ☒ Claims *1-18* are rejected.
5. ☐ Claims ______ are objected to.
6. ☐ The drawings, filed on ______ are acceptable.
7. ☐ The proposed drawing correction, filed on ______ has been (7a) ☐ approved (7b) ☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the certified copies have
   1 ☐ been received.
   2 ☐ not been received.
   3 ☐ been filed in Application No. ______ .
   4 ☐ been filed in reexamination Control No. ______.
   5 ☐ been received by the International Bureau in PCT application No. ______.
   * See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. ☐ Other: ______

cc: Requester (if third party requester)

Notice of References Cited	Application/Control No. 90/012,896	Applicant(s)/Patent Under Reexamination 7915015	
	Examiner BRUCE CAMPELL	Art Unit 3991	Page 1 of 1

U.S. PATENT DOCUMENTS

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*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	J Shen et al. “Allelic Imbalance in BRCA1 and BRCA2 Gene Expression and Familial Ovarian Cancer.” Cancer Epidemiol Biomarkers Prev 20(1): 50-56 (2011)
	V	https://education.yahoo.com/reference/dictionary/entry/from, accessed 5/1/2014
	W	
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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)	Application Number	90012896
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	First Named Inventor	
	Art Unit	3991
	Examiner Name	Bruce R. Campell
	Attorney Docket Number	001107.00988

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /B.C./

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	1	Defendants Life Technologies Corporation, Applied Biosystems, LLC, and Ion Torrent Systems, Inc.'s Preliminary Non-Infringement and Patent invalidity Contensions pursuant to Local Rule 103.3, filed in Case No. Case No. 1:12-CV-1173 on August 22, 2013	☐
	2	Deposition of Michael Metzker, Ph.D., dated October 25, 2013	☐
	3	Declaration of Michael Metzker, Ph.D. executed September 27, 2013	☐
	4	BAKER et al., "Male Mice Defective in the DNA Mismatch Repair Gene PMS2 Exhibit Abnormal Chromosome Synapsis in Meiosis," Cell, vol. 82, 309-319, July 28, 1995	☐
	5	BISCHOFF et al., "Single cell analysis demonstrating somatic mosaicism involving 11p in a patient with paternal isodisomy and Beckwith-Wiedemann syndrome," Human Molecular Genetics, 1995, vol. 4, no. 3, 395-399	☐
	6	BRISCO et al., "Detection and quantitation of neoplastic cells in acute lymphoblastic leukaemia, by use of teh polymerase chain reaction," British Journal of Haematology, 1991, 79, 211-217	☐
	7	DREESEN et al., "Preimplantation genetic diagnosis of spinal muscular atrophy," Molecular Human Reproduction, vol. 4, no. 9, pp. 881-885, 1998	☐
	8	FLINT et al., "NR2A Subunit Expression Shortens NMDA Receptor Synaptic Currents in Developing Neocortex," The Journal of Neuroscience, April 1, 1997, 17(7):2469-2476	☐
	9	GAYNOR et al., "Use of Flow Cytometry and RT-PCR for Detecting Gene Expression by Single Cells," BioTechniques, vol. 21, no. 2 (1996)	☐
	10	GRAVEL et al., "Single-Cell Analysis of the t(14;18)(q32;q21) Chromosomal Translocation in Hodgkin's Disease Demonstrates the Absence of This Translocation in Neoplastic Hodgkin and Reed-Sternberg Cells," Blood, 1998, 91:2866-2874	☐
	11	GREWAL et al., "The mutation properties of spinal and bulbar muscular atrophy disease alleles," Neurogenetics (1998) 1:249-252	☐

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	Art Unit	3991
	Examiner Name	Bruce R. Campell
	Attorney Docket Number	001107.00988

	12	JEFFREYS et al., "Complex gene conversion events in germline mutation at human minisatellites," Nature Genetics, vol. 6, February 1994	☐
	13	JENA et al., "Amplification of genes, single transcripts and cDNA libraries from one cell and direct sequence analysis of amplified products derived from one molecule," Journal of Immunological Methods 190 (1996) 199-213	☐
	14	KUNST et al., "The effect of FMR1 CFF repeat interruptions on mutation frequency as measured by sperm typing," J. Med. Genet., 1997; 34:627-631	☐
	15	LEEFLANG et al., "Single sperm analysis of the trinucleotide repeats in the Huntington's disease gene: quantification of the mutation frequency spectrum," Human Molecular Genetics, 1995, vol. 4, no. 9, 1519-1526	☐
	16	LEVINSON et al., "Molecular Characterization of Transgene-induced Immunodeficiency in B-less Mice Using a Novel Quantitative Limiting Dilution Polymerase Chain Reaction Method," J. Exp. Med, vol. 178, July 1993, 317-329	☐
	17	LI et al., "Amplification and analysis of DNA sequences in single human sperm and diploid cells," Nature, vol. 335, September 29, 1988	☐
	18	LIA et al., "Somatic instability of the CTG repeat in mice transgenic for the myotonic dystrophy region is age dependent but not correlated to the relative intertissue transcription levels and proliferative capacities," Human Molecular Genetics, 1998, vol. 7, no. 8, 1285-1291	☐
	19	LIU et al., "Efficiency and accuracy of polymerase-chain-reaction assay for cystic fibrosis allele F508 in single cell," The Lancet, vol. 339, May 16, 1992	☐
	20	SHEEHY et al., "Concurrent evolution of regions of the envelope and polymerase genes of human immunodeficiency virus type 1 observed during zidovudine (AZT) therapy," Journal of General Virology, (1996), 76, 1071-1081	☐
	21	SIMMONDS et al., "Human immunodeficiency virus-infected individuals contain provirus in small numbers of peripheral mononuclear cells and at low copy numbers," Journal of Virology, February 1990, vol. 64, no. 2, p. 864-872	☐
	22	STARK et al., "Single-cell PCR performed with neurofibroma Schwann cells reveals the presence of both alleles of the neurofibromatosis type 1 (NF1) gene," Hum Genet (1995) 96:619-523	☐

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	23	SYKES et al., "Quantitation of Targets for PCR by Use of Limiting Dilution," BioTechniques, vol. 13, no. 3 (1992)	☐
	24	ZHANG et al., "Whole genome amplification from a single cell: Implications for genetic analysis," Proc. Natl. Acad. Sci., vol. 89, pp. 5847-5851, July 1992	☐
	25	ZHANG et al., "Selection for Specific Sequences in the External Envelope Protein of Human Immunodeficiency Virus Type 1 upon Primary Infection," Journal of Virology, June 1993, vol. 67, no. 6, p. 3345-3356	☐
	26	Exhibit 4.1 (Baker)	☐
	27	Exhibit 4.10 (Levinson)	☐
	28	Exhibit 4.11 (Li 1988)	☐
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	34	Exhibit 4.17 (Stark)	☐
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	45	Exhibit 4.6 (Grewal)	☐
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☐ See attached certification statement.

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Signature	/Sarah A. Kagan/	Date (YYYY-MM-DD)	2014-03-26
Name/Print	Sarah A. Kagan	Registration Number	32141

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	90012896	7915015
	Examiner	**Art Unit**
	BRUCE CAMPELL	3991

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SEARCH NOTES

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	1	Supplemental Joint Claim Construction Statement filed in Civil Action No. 12-cv-1173-CCE-JEP on October 28, 2013 (filed with exhibits A, B, and C)	☐
	2	Defendants' Responsive Claim Construction Brief filed in Case No. 1:12-CV-1173 on November 26, 2013	☐
	3	Deposition of David Sherman, Ph.D., dated October 17, 2013	☐
	4	Supplemental Joint Claim Construction Statement Exhibit C filed in Civil Action No. 12-cv-1173-CCE-JEP on October 28, 2013 (filed with Supplemental Joint Claim Construction Statement filed in Civil Action No. 12-cv-1173-CCE-JEP on October 28, 2013)	☐
	5	Plaintiffs' Responsive Claim Construction Brief filed in filed in Civil Action No. 12-cv-1173-CCE-JEP on November 26, 2013	☐
	6	Plaintiffs' Proposed Construction of Disputed Terms, Supporting Evidence, and Rebuttal Evidence Exhibit B, filed in filed in Civil Action No. 12-cv-1173-CCE-JEP on October 28, 2013 (filed with Supplemental Joint Claim Construction Statement filed in Civil Action No. 12-cv-1173-CCE-JEP on October 28, 2013)	☐
	7	Declaration of David H. Sherman in Support of Esoterix Genetic Laboratories' Claim Construction Brief filed in Civil Action Nos. 12-cv-411-CCE-JEP and 12-cv-1173-CCE-JEP, executed September 27, 2013	☐
	8	Defendants' Opening Claim Construction Brief filed in Case No. 1:12-CV-1173 on November 5, 2013	☐
	9	Exhibit A filed in Civil Action No. 12-cv-1173-CCE-JEP on October 28, 2013 (filed with Supplemental Joint Claim Construction Statement filed in Civil Action No. 12-cv-1173-CCE-JEP on October 28, 2013)	☐
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	Filing Date	2013-06-17
	First Named Inventor	
	Art Unit	3991
	Examiner Name	Bruce R. Campell
	Attorney Docket Number	001107.00988

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Sarah A. Kagan/	Date (YYYY-MM-DD)	2014-03-26
Name/Print	Sarah A. Kagan	Registration Number	32141

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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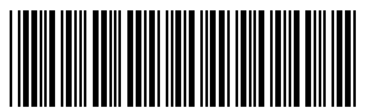
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Reexamination 	Application/Control No. 90012896	Applicant(s)/Patent Under Reexamination 7915015
	Certificate Date	**Certificate Number** C1

Requester Correspondence Address: ☐ **Patent Owner** ☒ **Third Party**

LIFE TECHNOLOGIES CORPORATION
ATTN: IP DEPARTMENT
5791 VAN ALLEN WAY
CARLSBAD, CA 92008

LITIGATION REVIEW ☒	/BC/ (examiner initials)	06/18/2013 (date)
Case Name		Director Initials
Esoterix Genetic Laboratories v Life Technolgies Corporation		
US District NC MIddle 1:12cv1173		

COPENDING OFFICE PROCEEDINGS	
TYPE OF PROCEEDING	**NUMBER**
1. none	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Ex Parte* Reexamination of
U.S. Patent No. 7,915,015

Examiner: Bruce R. Campell

Issued: March 29, 2011

Art Unit: 3991

Reexam Control No.: 90/012,896

Reexam Filing Date: June 17, 2013

Confirmation No.: 8361

For: DIGITAL AMPLIFICATION

NOTIFICATION OF ACTION (EXTENSION OF STAY) IN CONCURRENT LITIGATION

Mail Stop *Ex Parte* Reexam
Attn: Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Examiner:

Third-Party Requester hereby provides notice that the Court, upon mutual request by both parties, has extended the stay of the concurrent litigation proceeding at least until September 29, 2014 (*Esoterix Genetic Laboratories, LLC v. Life Technologies Corporation* (Civil Action No. 1:12-cv-01173-CCE-JEP)). A copy of the Court Order extending the stay is attached.

Dated: 5/13/14

Respectfully submitted,

By: /Ashita Doshi/
Ashita A. Doshi
Reg. No. 57,327

Life Technologies Corporation
5791 Van Allen Way
Carlsbad, California 92008
(760) 845-2798

U.S. Patent No.: 7,915,015
Reexam No.: 90/012,896
Filing Date: June 17, 2013
Title: DIGITAL AMPLIFICATION
Inventor: BERT VOGELSTEIN
Issue Date: March 29, 2011
Examiner: Bruce R. Campell

CERTIFICATE OF SERVICE

I hereby certify that a true and accurate copy of the above-identified Notification of Action (Extension of Stay) in Concurrent Litigation by Third Party Requester Life Technologies Corporation was served on the patent owner through its attorney/agent of record on May 14, 2014 by First Class mail to the following address:

Banner & Witcoff, Ltd.
1100 13th Street N.W.
Suite 1200
Washington DC 20005-4051

Dated: May 14, 2014

Respectfully submitted,

By: /Elizabeth Morgan/
Elizabeth Morgan
Patent Paralegal

Life Technologies Corporation
2130 Woodward St., Bldg. 1
Austin, TX 78744
Customer No.: 52059

From: ECF@ncmd.uscourts.gov [mailto:ECF@ncmd.uscourts.gov]
Sent: Tuesday, April 29, 2014 11:00 AM
To: ecf@ncmd.uscourts.gov
Subject: Activity in Case 1:12-cv-01173-CCE-JEP ESOTERIX GENETIC LABORATORIES, LLC et al v. LIFE TECHNOLOGIES CORPORATION, et al Order

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U.S. District Court

North Carolina Middle District

Notice of Electronic Filing

The following transaction was entered on 4/29/2014 at 2:00 PM EST and filed on 4/29/2014

Case Name:	ESOTERIX GENETIC LABORATORIES, LLC et al v. LIFE TECHNOLOGIES CORPORATION, et al
Case Number:	1:12-cv-01173-CCE-JEP
Filer:	
Document Number:	No document attached

Docket Text:
TEXT ORDER: Consistent with the request of the parties, (see Doc. 87), the stay in this case is extended through September 29, 2014. The parties shall confer in August 2014 and shall, no later than August 28, 2014, inform the Court of the status of the patent re-examinations, in a joint submission if possible. To the extent the parties agree that the stay should be extended or allowed to expire, they will inform the Court in the status report. To the extent they do not agree, each party may file a brief no longer than ten pages supporting its position. SO ORDERED. Signed by JUDGE CATHERINE C. EAGLES on April 29, 2014. (EAGLES, CATHERINE)

1:12-cv-01173-CCE-JEP Notice has been electronically mailed to:

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1:12-cv-01173-CCE-JEP Notice will not be electronically mailed to:

Electronic Acknowledgement Receipt

EFS ID:	19026186
Application Number:	90012896
International Application Number:	
Confirmation Number:	8361
Title of Invention:	DIGITAL AMPLIFICATION
First Named Inventor/Applicant Name:	7915015
Customer Number:	11332
Filer:	Ashita Amu Doshi/Elizabeth Morgan
Filer Authorized By:	Ashita Amu Doshi
Attorney Docket Number:	001107.00988
Receipt Date:	14-MAY-2014
Filing Date:	17-JUN-2013
Time Stamp:	10:12:05
Application Type:	Reexam (Third Party)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		LT00831REX3-notification-EXT-stay-w-serv-cert-5-14-14.pdf	188229 ebdbfba02561f311709b4bd3951eb4a34021c8bf	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Notice of concurrent proceeding(s)	1	1
	Reexam Certificate of Service	2	2
	Notice of concurrent proceeding(s)	3	4
Warnings:			
Information:			
	Total Files Size (in bytes):	188229	

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

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Ex Parte* Reexamination:	)	Group Art Unit: 3991
	)	
U.S. Patent No. 7,915,015	)	Docket No. 001107.00988
	)	
Control No. 90/012,896	)	Confirmation No: 8361
	)	
Reexam Filing Date: June 17, 2013	)	Examiner: Bruce R. Campell

For: DIGITAL AMPLIFICATION

RESPONSIVE AMENDMENT TO FINAL OFFICE ACTION

U.S. Patent and Trademark Office
Customer Service Window
Randolph Building
401 Dulany Street
Alexandria, VA 22314
Sir:

This paper is in response to the final Office Action mailed May 9, 2014.

Amendments to the Claims are reflected in the Listing of Claims, which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

IN THE CLAIMS

Please amend the following claims as indicated by the status identifier. Patent claims under reexamination but not amended are indicated as "original." Patent claims not subject to reexamination are not shown.

1. (Amended) A method for determining an allelic imbalance in a biological sample, comprising the steps of:

distributing isolated nucleic acid template molecules to form a set comprising a plurality of assay samples, wherein the nucleic acid template molecules are isolated from the biological sample;

amplifying the isolated nucleic acid template molecules within [a] the set [comprising a plurality of assay samples] to form a population of amplified molecules in [each of the] individual assay samples of the set[, wherein the template molecules are obtained from the biological sample];

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker, wherein between 0.1 and 0.9 of the assay samples yield an amplification product of at least one of the first and second allelic forms of the marker;

comparing the first number to the second number to ascertain an allelic imbalance in the biological sample; and

identifying an allelic imbalance in the biological sample.

2. (Original) The method of claim 1 wherein the step of amplifying employs real-time polymerase chain reactions.

3. (Original) The method of claim 2 wherein the real-time polymerase chain reactions comprise a dual-labeled fluorogenic probe.

4. (Amended) The method of claim 1 further comprising the step of isolating template nucleic acid molecules from the biological sample prior to the step of distributing [wherein

between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the first allelic form of the marker].

5. (Amended) The method of claim 1 wherein the step of distributing the isolated nucleic acid template molecules is performed by diluting [wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the second allelic form of the marker].

6. (Original) The method of claim 1 wherein the amplified molecules in each of the assay samples within the first and second numbers of assay samples are homogeneous such that the first number of assay samples do not contain the second allelic form of the marker and the second number of assay samples do not contain the first allelic form of the marker.

7. (Original) The method of claim 1 wherein the sample is from blood.

8. (Amended) A method for determining an allelic imbalance in a biological sample, comprising the steps of:

distributing cell-free nucleic acid template molecules from a biological sample to form a set comprising a plurality of assay samples;

amplifying the template molecules within the assay samples to form a population of amplified molecules in the assay samples of the set;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker;

comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance between the first allelic form and the second allelic form in the biological sample.

9. (Original) The method of claim 8 wherein the sample is from blood.

10. (Amended) The method of claim 1 or 8 wherein between 0.1 and 0.6 of the assay

samples yield an amplification product of at least one of the first and second allelic forms of the marker.

11. (Amended) The method of claim 1 or 8 wherein between 0.3 and 0.5 of the assay samples yield an amplification product of at least one of the first and second allelic forms of the marker.

12. (Original) The method of claim 1 or 8 wherein the set comprises at least 500 assay samples.

13. (Original) The method of claim 1 or 8 wherein the set comprises at least 1000 assay samples.

14. (Original) The method of claim 8 wherein the step of amplifying employs real-time polymerase chain reactions.

15. (Original) The method of claim 14 wherein the real-time polymerase chain reactions comprise a dual-labeled fluorogenic probe.

16. (Amended) The method of claim 8 wherein the step of distributing is performed by diluting [between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the first allelic form of the marker] .

17. (Amended) The method of claim 8 further comprising the step of isolating cell-free nucleic acid template molecules from the biological sample prior to the step of distributing [wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the second allelic form of the marker].

18. (Original) The method of claim 8 wherein the amplified molecules in each of the assay samples within the first and second numbers of assay samples are homogeneous such that

the first number of assay samples do not contain the second allelic form of the marker and the second number of assay samples do not contain the first allelic form of the marker.

Remarks

Status of all claims

Claims 1-18 are subject to re-examination. Claims 1, 4, 5, 8, 10, 11, 16, and 17 are amended.

Support for amendments

Claim 1 is amended to recite a step of distributing isolated nucleic acid template molecules. This is supported at col. 4, lines 37-41, and col. 7, lines 10-12.

Claim 1 is amended to recite that *individual* assay samples are formed with amplified molecules rather than *each* assay sample. This is a clarifying amendment to make it consistent with the recitation later in the claims of between 0.1 and 0.9 of the assay samples yielding an amplification product. See col. 6, lines 15-20.

Claim 1 is amended to recite that the amplification products in 0.1 to 0.9 of the assay samples are of at least one of the first and second allelic forms of the marker. Again this is an attempt to clarify the intended meaning of the original recitation. Claims 10 and 11 are similarly amended for clarification purposes. See col. 6, lines 3-20.

Claims 4 and 17 recite a step of isolating nucleic acid template molecules from the biological sample. This is supported at col. 7, lines 10-12.

Claim 5 and 16 are amended to recite that the distribution of nucleic acid template molecules is by dilution. This is supported at col. 4, lines 20-41.

Claim 8 is amended to recite cell-free nucleic acid template. This is supported at col. 7, lines 10-14, col. 8, lines 6-7, col. 9, lines 16-18, col. 9, lines 59-61, col. 11, line 29, and col. 12, lines 24-25.

The claims amendments do not expand the scope of the claims

None of the amendments enlarge the scope of the patent claims. The amendments add limitations such that no claim as amended is broader in scope than all of the patented claims.

1. Novelty

Claims 1, 4, 5, 7-11, 16 and 17 stand rejected under §102(b) as allegedly anticipated by Bischoff (*Human Molec. Genet. 4:*395-399, 1995). As described by the Patent and Trademark Office, Bischoff determines an allelic imbalance in Figure 1, Table 1. The Patent and Trademark Office concedes that Figure 1 and Table 1 do not anticipate the claims. Final Office Action at page 12, lines 1-4.

The next experiment Bischoff describes was aimed at determining whether the allelic imbalance occurred in all cells or only in a subset of the cells. As Bischoff clearly states, "we have used this single cell approach to demonstrate somatic mosaicism in a patient with BWS" (Beckwith Wiedemann Syndrome). Page 397, col. 2, lines 6-10. Bischoff identifies normal biparental inheritance when both alleles are present in a cell and identifies partial paternal isodisomy when only one allele was present in a single sample. This teaching of Bischoff fails to anticipate the invention of independent claims 1 and 8, as amended for at least the following reasons.

Bischoff does not teach a step of distributing isolated nucleic acid template molecules, as recited in amended claim 1. Bischoff does not teach a step of distributing cell-free nucleic acid template molecules as recited in claim 8 as amended. Bischoff teaches distributing single lymphocytic cells to separate compartments. One of ordinary skill in the art would not recognize single cell micromanipulation as fulfilling a step of distribution of either cell-free or isolated nucleic acid template molecules to form a set comprising a plurality of assay samples.

Bischoff also fails to teach the recitation in claim 1 of "between 0.1 and 0.9 of the assay samples yield an amplification product of at least one of the first and second allelic forms of the marker." In Bischoff, Table 2, all single-cell samples yielded an amplification product. "All" is equivalent to the ratio 1, 1:1, or 100%, which is outside of the recited range recited in amended claim 1.

Dependent claims 4, 5, 7, 9-11, 16 and 17, dependent on either claim 1 or claim 8, are not anticipated for at least the same reasons. Therefore all the claims are novel over Bischoff.

Please withdraw this rejection.

2. Nonobviousness

a. Bischoff (*Human Molec. Genet. 4*:395-399, 1995)

Claims 12 and 13 stand rejected under §103(a) as allegedly obvious over Bischoff alone. Claims 12 and 13, dependent on claims 1 or 8, further recite sets of at least 500 and at least 1000 assay samples, respectively. The Patent and Trademark Office acknowledges that Bischoff did not teach this element, because Bischoff taught only a set of six. Nonetheless, the Patent and Trademark Office asserts this massive enlargement of the set would have been obvious to one of ordinary skill in the art to provide greater statistical accuracy.

To establish a proper *prima facie* case of obviousness, the following criteria must be established: (1) the prior art reference, or references when combined, must disclose or suggest all the claim limitations (*See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991)); (2) the Patent Office must provide an apparent reason to combine the known elements in the claims (*See KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007)); and (3) there must be a reasonable expectation of success in combining the teachings of the reference(s) (*See id.*). Here, the Patent and Trademark Office fails to establish a *prima facie* case of obviousness because the cited reference does not disclose or suggest each of the claim limitations.

The reasons discussed above with respect to lack of anticipation of claim 1 by Bischoff, apply to the rejection of these claims as well. Thus the prior art reference fails to disclose all the claim limitations, even before considering the additional recitations of claims 12 and 13.

The rationale asserted in the rejection for modifying the teaching of Bischoff (greater statistical accuracy) bears no connection to Bischoff's teaching. Bischoff was trying to ascertain whether a duplication or mosaicism had occurred. Bischoff got her answer assaying only six cells (six assay samples). One of ordinary skill in the art would not have been motivated to assay more individual cells in more assay samples because statistical accuracy was irrelevant to Bischoff's determination of genetic mechanism. Bischoff's analysis was qualitative, not quantitative, and could be determined quite accurately with six cells. Increasing the number or cells would not have increased the accuracy of the determination.

Additionally, other alleged motivations provided in the rejection do not apply to Beckwith-Wiedemann disease as studied by Bischoff, but rather relate to other uses that appear to be derived from the subject patent. For example, there would have been no motivation for one of skill in the art

to apply Bischoff's method to study tumor margins or monitor reactions to anti-tumor treatments without impermissible hindsight analysis.

For all these reasons, Bischoff does not render claims 12 and 13 obvious. Please withdraw this rejection.

b. Bischoff in view of Woudenberg (U.S. 5,928,907)

Claims 2, 3, 14, and 15 stand rejected under §103(a) as allegedly obvious over Bischoff and further in view of Woudenberg.

Claims 2 and 3 are dependent on claim 1. Claims 14 and 15 depend from claim 8. Claims 2, 3, 14 and 15 recite using RT-PCR (real time PCR) to amplify, and claims 3 and 15 further recite dual-labeled, fluorogenic probes.

The Office Action fails to establish a *prima facie* case of obviousness because the cited references fail to disclose or suggest each of the claim limitations. The deficiencies of Bischoff as an anticipatory reference are discussed above. Woudenberg does not remedy these deficiencies. Woudenberg has no relevant teaching regarding distributing isolated or cell-free nucleic acid template molecules to form a set comprising a plurality of assay samples.

Claims 2, 3, 14, and 15 are therefore not obvious over Bischoff in view of Woudenberg. Please withdraw this rejection.

c. Bischoff in view of Jeffreys (*Nuc. Acids Res. 16:* 10953-10971, 1988)

Claims 6 and 18 stand rejected under §103(a) as allegedly obvious over Bischoff and further in view of Jeffreys. Claims 6 and 18 are dependent on independent claims 1 and 8, respectively. Claims 6 and 18 further recite that the first and second numbers of assay samples are homogeneously first or second allelic form "such that the first number of assay samples do not contain the second allelic form of the marker and the second number of assay samples do not contain the first allelic form of the marker."

The Office Action fails to establish a *prima facie* case of obviousness because the cited references fail to disclose or suggest each of the claim limitations and there is no apparent reason to combine the elements from the cited references. For all of the reasons that independent claims 1 and 8 are not anticipated by Bischoff, dependent claims 6 and 18 are also not obvious over Bischoff and Jeffreys. In addition, as the Office Action concedes, Bischoff fails to disclose the limitation that the amplified DNA sequences in the assay samples are homogeneous. However, the Office Action

asserts that Jeffreys teaches this aspect.

Jeffreys fails to remedy the deficiencies of Bischoff because Jeffreys, like Bischoff, lacks a relevant disclosure or suggestion regarding the analysis of the number of assay samples in the set which contain a first allelic form of a marker and the number of samples which contain a second allelic form of the marker, or the formation of homogenous assay samples containing either the first allelic form or the second allelic form of the marker as recited in the claims.

Moreover, it would not have been obvious to one of ordinary skill in the art to combine Jeffreys with Bischoff to meet the limitation of the claims. The combination has been made improperly using hindsight knowledge obtained from the present invention. It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the prior art so that the claimed invention is rendered obvious. *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992). Indeed, this proposed combination would have destroyed the intended purpose of Bischoff.

Bischoff already knew what the ratio of alleles was in her patient's blood cell population. At page 395, col. 2, last paragraph, Bischoff describes extracting genomic DNA from the patient's blood sample. By visual inspection on a polyacrylamide gel electrophoresis, Bischoff determined that four markers had a greater amount of paternal allele. Fig. 1. But that is not the experiment that the Patent and Trademark Office proposes to modify. The Patent and Trademark Office proposes that the molecular analysis of single cells be modified to incorporate the analysis of diluted, bulk DNA. This second experiment of Bischoff was designed to distinguish between two genetic possibilities: either a duplication of a paternal 11p region had occurred in all cells, or two cell lines had different constituents (normal biparental inheritance and partial paternal isodisomy). Shendure declaration under rule 132, at ¶12. Both genetic models would have yielded the same ratio if analyzed in bulk. Shendure declaration under rule 132, at ¶12. See also Fig. 1 of Bischoff. That is why it was critical that Bischoff perform a single cell analysis. Bischoff *needed* to keep the two chromosome 11 homologs together to distinguish between the two genetic models. Shendure declaration at ¶12. Thus, the proposed modification of Bischoff by the technique of Jeffreys would have rendered Bischoff's method unsuitable for its intended purpose.

If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon,* 733 F.2d 900(Fed. Cir. 1984). See also MPEP § 2143.01(V).

Additionally, the Patent and Trademark Office did not explain how the proposed modification of Bischoff's experiment using a diploid amount of DNA (6 pg) would have resulted in

a set of assay samples with sufficient assay samples comprising homogeneous first and second allelic forms as recited in claims 6 and 18.

Please withdraw this rejection as the combination of references is improper and would not have yielded the claimed invention.

Conclusion

For at least the reasons stated above, and for the reasons stated in the prior response and declaration under rule 132, all claims in this reexamination are patentable and should be confirmed. Therefore, we request that the Patent and Trademark Office issue a certificate of reexamination confirming the patentability of all claims. The absence of additional comments regarding the Office Action does not indicate agreement with or concession of any characterization or requirement. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 202 824 3000.

We thank the examiners for agreeing to conduct an interview in this case on July 10, 2014.

No fees are believed to be due with respect to the filing of this response. However, should any such fees be due, the Commissioner is hereby authorized to charge any such fees in connection with this paper to Deposit Account No. 19-0733.

Respectfully submitted,

By: /Sarah A Kagan/
Sarah A. Kagan
Registration No. 32,141

Dated: July 9, 2014

Banner & Witcoff, Ltd.
Customer No. 11332

Electronic Acknowledgement Receipt

EFS ID:	19531523
Application Number:	90012896
International Application Number:	
Confirmation Number:	8361
Title of Invention:	DIGITAL AMPLIFICATION
First Named Inventor/Applicant Name:	7915015
Customer Number:	11332
Filer:	Sarah Anne Kagan./Jennifer Hazzard
Filer Authorized By:	Sarah Anne Kagan.
Attorney Docket Number:	001107.00988
Receipt Date:	09-JUL-2014
Filing Date:	17-JUN-2013
Time Stamp:	15:11:27
Application Type:	Reexam (Patent Owner)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Response-to-FOA-90012896.pdf	151510 fb32c91e0130a2abd5082c85a18b7a9372389c07	yes	12

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response After Final Action	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	12

Warnings:

Information:

Total Files Size (in bytes):	151510

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Ex Parte* Reexamination:	)	Group Art Unit: 3991
	)	
U.S. Patent No. 7,915,015	)	Docket No. 001107.00988
	)	
Control No. 90/012,896	)	Confirmation No: 8361
	)	
Reexam Filing Date: June 17, 2013	)	Examiner: Bruce R. Campell

For: DIGITAL AMPLIFICATION

CERTIFICATE OF SERVICE

The undersigned certifies that a complete copy of the Responsive Amendment to Final Office Action filed in the U.S. Patent and Trademark Office on July 9, 2014, has been mailed via first class mail to the third party requester this day at the following address:

Life Technologies Corporation
Attn: IP Department
5791 Van Allen Way
Carlsbad, CA 92008

/Sarah A. Kagan/
Sarah A. Kagan
Registration No. 32,141

Dated: July 9, 2014

Banner & Witcoff, Ltd.
Customer No. 11332

Electronic Acknowledgement Receipt

EFS ID:	19532709
Application Number:	90012896
International Application Number:	
Confirmation Number:	8361
Title of Invention:	DIGITAL AMPLIFICATION
First Named Inventor/Applicant Name:	7915015
Customer Number:	11332
Filer:	Sarah Anne Kagan./Jennifer Hazzard
Filer Authorized By:	Sarah Anne Kagan.
Attorney Docket Number:	001107.00988
Receipt Date:	09-JUL-2014
Filing Date:	17-JUN-2013
Time Stamp:	15:50:05
Application Type:	Reexam (Patent Owner)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Reexam Certificate of Service	Certificate-of-Service.pdf	78456 b7d9686d99f60de90efd60f0d8b24a648ab0ded9	no	1

Warnings:

Information:

Total Files Size (in bytes):	78456

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UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/012,896	06/17/2013	7915015	001107.00988	8361

11332 7590 07/22/2014

Banner & Witcoff, Ltd.
Attorneys for client 001107
1100 13th Street N.W.
Suite 1200
Washington, DC 20005-4051

EXAMINER	
CAMPELL, BRUCE R	

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
07/22/2014	PAPER

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

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

PTOL-90A (Rev. 04/07)

UNITED STATES PATENT AND TRADEMARK OFFICE

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LIFE TECHNOLOGIES CORPORATION

ATTN: IP DEPARTMENT

5791 VAN ALLEN WAY

CARLSBAD, CA 92008

EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. *90/012,896*.

PATENT NO. *7915015*.

ART UNIT *3991*.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

<table>
<tr><td rowspan="2">Ex Parte Reexamination Interview Summary</td><td>Control No.
90/012,896</td><td>Patent Under Reexamination
7915015</td></tr>
<tr><td>Examiner
BRUCE CAMPELL</td><td>Art Unit
3991</td></tr>
</table>

All participants (USPTO personnel, patent owner, patent owner's representative):

(1) *BRUCE CAMPELL*	(3) *Sarah Kagan, Joseph Skerpon*
(2) *Deborah Jones, Padmashri Ponnaluri*	(4) *Kathryn Wade, Tina McEwan*

Date of Interview: *10 July 2014*

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal (copy given to: 1)☐ patent owner 2)☐ patent owner's representative)

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: ______

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.
Any other agreement(s) are set forth below under "Description of the general nature of what was agreed to…"

Claim(s) discussed: *all*.

Identification of prior art discussed: *Bischoff, Jeffreys*.

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
Discussed the amendment filed 7/9/2014. It was agreed that the amendments, if entered, overcome the 102 rejection over Bischoff. Amendment alone appears insufficient to overcome 103 rejection over Bischoff Jeffreys(as presently applied to claims 6 and 18, but would be applicable to all claims in combination with other references of record), since Jeffreys discloses every physical step of the method of claim 1. Exrs will fully consider PO's submission after final. PO intends to file evidence (declaration) to support argument of non-obviousness. .

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims patentable, if available, must be attached. Also, where no copy of the amendments that would render the claims patentable is available, a summary thereof must be attached.)

A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION MUST INCLUDE PATENT OWNER'S STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. (See MPEP § 2281). IF A RESPONSE TO THE LAST OFFICE ACTION HAS ALREADY BEEN FILED, THEN PATENT OWNER IS GIVEN **ONE MONTH** FROM THIS INTERVIEW DATE TO PROVIDE THE MANDATORY STATEMENT OF THE SUBSTANCE OF THE INTERVIEW (37 CFR 1.560(b)). THE REQUIREMENT FOR PATENT OWNER'S STATEMENT CAN NOT BE WAIVED. **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).**

/Bruce Campell/ Patent Reexamination Specialist Central Reexamination Unit 3991	/Padmashri Ponnaluri/ Patent Reexamination Specialist Central Reexamination Unit 3991	/Deborah Jones/ Supervisory Patent Reexamination Specialist Central Reexamination Unit 3991

cc: Requester (if third party requester)

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/012,896	06/17/2013	7915015	001107.00988	8361

11332 7590 07/22/2014

Banner & Witcoff, Ltd.
Attorneys for client 001107
1100 13th Street N.W.
Suite 1200
Washington, DC 20005-4051

EXAMINER	
CAMPELL, BRUCE R	

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
07/22/2014	PAPER

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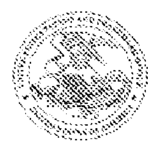
The time period for reply, if any, is set in the attached communication.



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LIFE TECHNOLOGIES CORPORATION

ATTN: IP DEPARTMENT

5791 VAN ALLEN WAY

CARLSBAD, CA 92008

EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. *90/012,896*.

PATENT NO. *7915015*.

ART UNIT *3991*.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Ex Parte Reexamination Advisory Action	**Control Number** 90/012,896	**Patent Under Reexamination** 7915015	
	Examiner BRUCE CAMPELL	**Art Unit** 3991	**AIA (First Inventor to File) Status** No

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

THE PROPOSED RESPONSE FILED *09 July 2014* FAILS TO OVERCOME ALL OF THE REJECTIONS IN THE FINAL REJECTION MAILED *09 May 2014*. Therefore, unless a timely appeal is filed, or other appropriate action by the patent owner is taken to overcome all of the outstanding rejection(s), this *ex parte* reexamination proceeding WILL BE TERMINATED and a Notice of Intent to Issue *Ex Parte* Reexamination Certificate will be mailed in due course. Any finally rejected claims, or claims objected to, will be CANCELLED.

THE PERIOD FOR RESPONSE IS EXTENDED TO RUN *4* MONTHS FROM THE MAILING DATE OF THE FINAL REJECTION.

(Extensions of time are governed by 37 CFR 1.550(c))

1. ☐ Appellant's Brief is due two months from the date of the Notice of Appeal filed on _____ (or within the extended period for response set forth above, whichever is later). See 37 CFR 1.191(d) and 37 CFR 1.192(a).

2. ☒ The proposed amendment(s) will not be entered because:
   - (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
   - (b) ☒ they raise the issue of new matter (see NOTE below);
   - (c) ☐ they are not deemed to place the proceeding in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   - (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*

3. ☐ Patent owner's proposed response filed _____ has overcome the following rejection(s):_____

4. ☐ The proposed new or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☐ An affidavit(s)/declaration(s) under **37 CFR 1.130(b)** was/were filed on _____.

6. ☐ The a)☐ affidavit/declaration, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT overcome the rejection(s) because: __ .

7. ☐ The affidavit/declaration or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

8. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) patentable and/or confirmed: _____
   Claim(s) objected to: _____
   Claim(s) rejected: *1-18*
   Claim(s) not subject to reexamination: _____

9. ☐ The drawing correction filed on _____ a)☐ has b)☐ has not been approved by the Examiner.

10. ☐ Note the attached Information Disclosure Statement(s), PTO-1449, Paper No(s) _____.

11. ☒ Other:*The proposed amendment would have overcome the § 102 rejection over Bischoff. However the § 103 rejection over Bischoff in combination with Jeffreys, presently applied to claims 6 and 18, would render the claims obvious because Jeffreys performs the "distributing," "amplifying" and "analyzing" steps recited in claims 1 and 8. Patent Owner's response does not explain why it would not have been obvious to use this method to determine whether an allelic imbalance such as that disclosed by Bischoff was present in a subject. Bischoff was able to detect allelic imbalance using isolated DNA (Fig. 1). It is noted that in the interview of 7/10/2014 Patent Owner indicated that it intends to submit evidence (declaration) addressing this question.*

	Bruce Campell Primary Examiner Art Unit: 3991
cc: Requester (if third party requester)	

Continuation of 2. (d) NOTE: The amendment raises the issue of new matter because claims 1 and 8 use "isolated" or "cell free" nucleic acid template molecules as starting materials. Adding a further "isolating" step in claims 4 and 17 implies that the methods of claims 1 and 8 can somehow be practiced without first isolating template nucleic acids (otherwise claims 4 and 17 would not be further limiting). This is new matter because no such alternative method is disclosed in the specification. .

/Bruce Campell/
Patent Reexamination Specialist

/Padmashri Ponnaluri/
Patent Reexamination Specialist

/Deborah Jones/
Supervisory Patent Reexamination Specialist
Central Rexamination Unit 3991

DO NOT ENTER: /B.C./

IN THE CLAIMS

Please amend the following claims as indicated by the status identifier. Patent claims under reexamination but not amended are indicated as "original." Patent claims not subject to reexamination are not shown.

1. (Amended) A method for determining an allelic imbalance in a biological sample, comprising the steps of:

distributing isolated nucleic acid template molecules to form a set comprising a plurality of assay samples, wherein the nucleic acid template molecules are isolated from the biological sample;

amplifying the isolated nucleic acid template molecules within [a] the set [comprising a plurality of assay samples] to form a population of amplified molecules in [each of the] individual assay samples of the set[, wherein the template molecules are obtained from the biological sample];

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker, wherein between 0.1 and 0.9 of the assay samples yield an amplification product of at least one of the first and second allelic forms of the marker;

comparing the first number to the second number to ascertain an allelic imbalance in the biological sample; and

identifying an allelic imbalance in the biological sample.

2. (Original) The method of claim 1 wherein the step of amplifying employs real-time polymerase chain reactions.

3. (Original) The method of claim 2 wherein the real-time polymerase chain reactions comprise a dual-labeled fluorogenic probe.

4. (Amended) The method of claim 1 further comprising the step of isolating template nucleic acid molecules from the biological sample prior to the step of distributing [wherein

between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the first allelic form of the marker].

5. (Amended) The method of claim 1 wherein the step of distributing the isolated nucleic acid template molecules is performed by diluting [wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the second allelic form of the marker].

6. (Original) The method of claim 1 wherein the amplified molecules in each of the assay samples within the first and second numbers of assay samples are homogeneous such that the first number of assay samples do not contain the second allelic form of the marker and the second number of assay samples do not contain the first allelic form of the marker.

7. (Original) The method of claim 1 wherein the sample is from blood.

8. (Amended) A method for determining an allelic imbalance in a biological sample, comprising the steps of:

distributing cell-free nucleic acid template molecules from a biological sample to form a set comprising a plurality of assay samples;

amplifying the template molecules within the assay samples to form a population of amplified molecules in the assay samples of the set;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker;

comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance between the first allelic form and the second allelic form in the biological sample.

9. (Original) The method of claim 8 wherein the sample is from blood.

10. (Amended) The method of claim 1 or 8 wherein between 0.1 and 0.6 of the assay

samples yield an amplification product of at least one of the first and second allelic forms of the marker.

11. (Amended) The method of claim 1 or 8 wherein between 0.3 and 0.5 of the assay samples yield an amplification product of at least one of the first and second allelic forms of the marker.

12. (Original) The method of claim 1 or 8 wherein the set comprises at least 500 assay samples.

13. (Original) The method of claim 1 or 8 wherein the set comprises at least 1000 assay samples.

14. (Original) The method of claim 8 wherein the step of amplifying employs real-time polymerase chain reactions.

15. (Original) The method of claim 14 wherein the real-time polymerase chain reactions comprise a dual-labeled fluorogenic probe.

16. (Amended) The method of claim 8 wherein the step of distributing is performed by diluting [between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the first allelic form of the marker] .

17. (Amended) The method of claim 8 further comprising the step of isolating cell-free nucleic acid template molecules from the biological sample prior to the step of distributing [wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the second allelic form of the marker].

18. (Original) The method of claim 8 wherein the amplified molecules in each of the assay samples within the first and second numbers of assay samples are homogeneous such that

the first number of assay samples do not contain the second allelic form of the marker and the second number of assay samples do not contain the first allelic form of the marker.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Ex Parte* Reexamination:	)	Group Art Unit: 3991
	)	
U.S. Patent No. 7,915,015	)	Docket No. 001107.00988
	)	
Control No. 90/012,896	)	Confirmation No: 8361
	)	
Reexam Filing Date: June 17, 2013	)	Examiner: Bruce R. Campell

For: DIGITAL AMPLIFICATION

PATENT OWNER'S INTERVIEW SUMMARY

Examiners Campell, Jones, and Ponnaluri graciously conducted an interview with representatives of the patent owner and a licensee on July 10, 2014. During the interview the patent owner presented the various amendments to the claims that were submitted on July 9, 2014. An advance copy of the amendments had been provided to the examiners on July 7, for their review. The following amendments were raised for comment:

i. Claim 1
   1. add step of distributing nucleic acid template molecules
   2. specify that the nucleic acid template molecule distributed are ***isolated***
   3. clarify that 0.1 to 0.9 of assay samples have ***at least one of*** two allelic forms of template amplified

ii. Claims 4, 17--add step of isolation of nucleic acid template molecule

iii. Claims 5, 16—specify that distribution is performed by ***dilution***

iv. Claim 8—specify that nucleic acid template molecule is cell free

v. Claims 10, 11—clarify that 0.1 to 0.9 of assay samples have ***at least one of*** two allelic forms of template amplified

The patent owner indicated that the amendments distinguish the claims over the references, particularly with regard to the rejections of certain claims for anticipation and obviousness based on Bischoff (Human Genetics 4:395-399, 1995) and other claims for obviousness over Bischoff in view of Jeffreys (Nucleic

Acid Research 16:10953-71, 1988).

The patent owner emphasized that different goals and purposes of the prior art from the nonobvious goals and purposes of the claimed methods. In almost all cases the prior art taught qualitative methods, whereas the claimed methods are directed to quantitative methods. The prior art taught methods involving a very small number of assay samples which were sufficient for the qualitative determinations sought. The success of the prior art in their qualitative determinations would not have motivated the ordinary skilled artisan (nor have made obvious the changes needed) to change to a quantitative assessment based on statistics or to change to a method involving large numbers of assay samples, such as greater than 500 or 1000 assay samples.

The examiners suggested that the patent owner may improve the record by submitting declarations demonstrating that the claimed method is commercially used and is considered in the art as a breakthrough technology.

The patent owner acknowledges receipt of the Examiner's Interview Summary mailed July 22, 2014. The patent owner agrees with the report of the proceedings, but not with the interpretation of the claims and the interpretation of the prior art.

/Sarah A. Kagan/
Sarah A. Kagan
Registration No. 32,141

Dated: July 22, 2014

Banner & Witcoff, Ltd.
Customer No. 11332

Electronic Acknowledgement Receipt

EFS ID:	19646128
Application Number:	90012896
International Application Number:	
Confirmation Number:	8361
Title of Invention:	DIGITAL AMPLIFICATION
First Named Inventor/Applicant Name:	7915015
Customer Number:	11332
Filer:	Sarah Anne Kagan./Jennifer Hazzard
Filer Authorized By:	Sarah Anne Kagan.
Attorney Docket Number:	001107.00988
Receipt Date:	22-JUL-2014
Filing Date:	17-JUN-2013
Time Stamp:	14:00:56
Application Type:	Reexam (Patent Owner)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	Interview-Summary.pdf	108674 184c012b86d0f8c49a8dee64bc29a3c0571319da	no	2

Warnings:

Information:

Total Files Size (in bytes):	108674

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Ex Parte* Reexamination:	)	Group Art Unit: 3991
	)	
U.S. Patent No. 7,915,015	)	Docket No. 001107.00988
	)	
Control No. 90/012,896	)	Confirmation No: 8361
	)	
Reexam Filing Date: June 17, 2013	)	Examiner: Bruce R. Campell

For: DIGITAL AMPLIFICATION

RESPONSIVE AMENDMENT TO FINAL OFFICE ACTION

U.S. Patent and Trademark Office
Customer Service Window
Randolph Building
401 Dulany Street
Alexandria, VA 22314
Sir:

This paper is in response to the final Office Action mailed May 9, 2014, and comments made in the Advisory Action mailed July 22, 2014.

Amendments to the Claims are reflected in the Listing of Claims, which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

Two **declarations under rule 132** accompany this amendment.

A **notice of appeal** is filed with this amendment.

IN THE CLAIMS

Please amend the following claims as indicated by the status identifier. Patent claims under reexamination but not amended are indicated as "original." Patent claims not subject to reexamination are not shown.

1. (Amended) A method for determining an allelic imbalance in a biological sample, comprising the steps of:

distributing isolated nucleic acid template molecules to form a set comprising a plurality of assay samples, wherein the nucleic acid template molecules are isolated from the biological sample;

amplifying the isolated nucleic acid template molecules within [a] the set [comprising a plurality of assay samples] to form a population of amplified molecules in [each of the] individual assay samples of the set[, wherein the template molecules are obtained from the biological sample];

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker, wherein between 0.1 and 0.9 of the assay samples yield an amplification product of at least one of the first and second allelic forms of the marker;

comparing the first number to the second number to ascertain an allelic imbalance in the biological sample; and

identifying an allelic imbalance in the biological sample.

2. (Original) The method of claim 1 wherein the step of amplifying employs real-time polymerase chain reactions.

3. (Original) The method of claim 2 wherein the real-time polymerase chain reactions comprise a dual-labeled fluorogenic probe.

4. (Cancelled)

5. (Amended) The method of claim 1 wherein the step of distributing the isolated nucleic acid template molecules is performed by diluting [wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the second allelic form of the marker].

6. (Original) The method of claim 1 wherein the amplified molecules in each of the assay samples within the first and second numbers of assay samples are homogeneous such that the first number of assay samples do not contain the second allelic form of the marker and the second number of assay samples do not contain the first allelic form of the marker.

7. (Original) The method of claim 1 wherein the sample is from blood.

8. (Amended) A method for determining an allelic imbalance in a biological sample, comprising the steps of:

distributing cell-free nucleic acid template molecules from a biological sample to form a set comprising a plurality of assay samples;

amplifying the template molecules within the assay samples to form a population of amplified molecules in the assay samples of the set;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker;

comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance between the first allelic form and the second allelic form in the biological sample.

9. (Original) The method of claim 8 wherein the sample is from blood.

10. (Amended) The method of claim 1 or 8 wherein between 0.1 and 0.6 of the assay samples yield an amplification product of at least one of the first and second allelic forms of the marker.

11. (Amended) The method of claim 1 or 8 wherein between 0.3 and 0.5 of the assay samples yield an amplification product of at least one of the first and second allelic forms of the marker.

12. (Original) The method of claim 1 or 8 wherein the set comprises at least 500 assay samples.

13. (Original) The method of claim 1 or 8 wherein the set comprises at least 1000 assay samples.

14. (Original) The method of claim 8 wherein the step of amplifying employs real-time polymerase chain reactions.

15. (Original) The method of claim 14 wherein the real-time polymerase chain reactions comprise a dual-labeled fluorogenic probe.

16. (Amended) The method of claim 8 wherein the step of distributing is performed by diluting [between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the first allelic form of the marker].

17. (Cancelled)

18. (Original) The method of claim 8 wherein the amplified molecules in each of the assay samples within the first and second numbers of assay samples are homogeneous such that the first number of assay samples do not contain the second allelic form of the marker and the second number of assay samples do not contain the first allelic form of the marker.

Remarks

Status of all claims

Claims 1-18 are subject to re-examination. Claims 1, 5, 8, 10, 11, and 16 are amended and claims 4 and 17 are cancelled. The amended claims 1, 5, 8, 10, 11, and 16 are the same as those proposed in the non-entered amendment.

Support for amendments

Claim 1 is amended to recite a step of distributing isolated nucleic acid template molecules. This is supported at col. 4, lines 37-41, and col. 7, lines 10-12.

Claim 1 is amended to recite that *individual* assay samples are formed with amplified molecules rather than *each* assay sample. This is a clarifying amendment to make it consistent with the recitation later in the claims of between 0.1 and 0.9 of the assay samples yielding an amplification product. See col. 6, lines 15-20.

Claim 1 is amended to recite that the amplification products in 0.1 to 0.9 of the assay samples are of at least one of the first and second allelic forms of the marker. Again this is an attempt to clarify the intended meaning of the original recitation. Claims 10 and 11 are similarly amended for clarification purposes. See col. 6, lines 3-20.

Claim 5 and 16 are amended to recite that the distribution of nucleic acid template molecules is by dilution. This is supported at col. 4, lines 20-41.

Claim 8 is amended to recite cell-free nucleic acid template. This is supported at col. 7, lines 10-14, col. 8, lines 6-7, col. 9, lines 16-18, col. 9, lines 59-61, col. 11, line 29, and col. 12, lines 24-25.

The claims amendments do not expand the scope of the claims

None of the amendments enlarge the scope of the patent claims. The amendments add limitations such that no claim as amended is broader in scope than all of the patented claims.

1. Novelty

Claims 1, 5, 7-11, and 16 stand rejected under §102(b) as allegedly anticipated by Bischoff (*Human Molec. Genet. 4:*395-399, 1995). As described by the Patent and Trademark Office, Bischoff determines an allelic imbalance in Figure 1, Table 1. The Patent and Trademark Office concedes that the experiment described in Figure 1 and Table 1 does not anticipate the claims. Final Office Action at page 12, lines 1-4.

The next experiment Bischoff describes was aimed at determining whether the allelic imbalance occurred in all cells or only in a subset of the cells. As Bischoff clearly states, "we have used this single cell approach to demonstrate somatic mosaicism in a patient with BWS" (Beckwith Wiedemann Syndrome). Page 397, col. 2, lines 6-10. Bischoff identifies normal biparental inheritance when both alleles are present in a cell and identifies partial paternal isodisomy when only one allele was present in a single sample. This teaching of Bischoff fails to anticipate the invention of independent claims 1 and 8, as amended for at least the following reasons.

Bischoff does not teach a step of distributing isolated nucleic acid template molecules, as recited in amended claim 1. Bischoff does not teach a step of distributing cell-free nucleic acid template molecules as recited in claim 8 as amended. Bischoff teaches distributing single lymphocytic cells to separate compartments. One of ordinary skill in the art would not recognize single cell micromanipulation as disclosing a step of distribution of either cell-free or isolated nucleic acid template molecules to form a set comprising a plurality of assay samples.

Bischoff also fails to teach the recitation in claim 1 of "between 0.1 and 0.9 of the assay samples yield an amplification product of at least one of the first and second allelic forms of the marker." In Bischoff, Table 2, all single-cell samples yielded an amplification product. "All" is equivalent to the ratio 1, 1:1, or 100%, which is outside of the range recited in amended claim 1.

Dependent claims 5, 7, 9-11, and 16, dependent on either claim 1 or claim 8, are not anticipated for at least the same reasons. Therefore all the claims are novel over Bischoff.

Please withdraw this rejection.

2. Nonobviousness

a. Bischoff (*Human Molec. Genet. 4*:395-399, 1995)

Claims 12 and 13 stand rejected under §103(a) as allegedly obvious over Bischoff alone. Claims 12 and 13, dependent on claims 1 or 8, further recite sets of at least 500 and at least 1000 assay samples, respectively. The Patent and Trademark Office acknowledges that Bischoff did not teach this element, because Bischoff taught only a set of six. Nonetheless, the Patent and Trademark Office asserts this massive enlargement of the set would have been obvious to one of ordinary skill in the art to provide greater statistical accuracy.

To establish a proper *prima facie* case of obviousness, the following criteria must be established: (1) the prior art reference, or references when combined, must disclose or suggest all the claim limitations (*See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991)); (2) the Patent Office must provide an apparent reason to combine the known elements in the claims (*See KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007)); and (3) there must be a reasonable expectation of success in combining the teachings of the reference(s) (*See id.*). Here, the Patent and Trademark Office fails to establish a *prima facie* case of obviousness because the cited reference does not disclose or suggest each of the claim limitations.

The reasons discussed above with respect to lack of anticipation of claim 1 by Bischoff, apply to the rejection of these claims as well. Thus the prior art reference fails to disclose all the claim limitations, even before considering the additional recitations of claims 12 and 13.

The rationale asserted in the rejection for modifying the teaching of Bischoff to include at least 500 or 1,000 assay samples (greater statistical accuracy) bears no connection to Bischoff's teaching. Bischoff was trying to ascertain whether a duplication or mosaicism had occurred. Bischoff got her answer by assaying just six cells (six assay samples). One of ordinary skill in the art would not have been motivated to assay more individual cells in more assay samples because statistical accuracy was irrelevant to Bischoff's determination of genetic mechanism. Bischoff's analysis was qualitative, not quantitative, and could be determined quite accurately with six cells. Increasing the number of cells would not have increased the accuracy of the determination.

Additionally, other alleged motivations provided in the rejection do not apply to Beckwith-Wiedemann disease as studied by Bischoff, but rather relate to other uses that appear to be derived from the subject patent. For example, there would have been no motivation for one of skill in the art to apply Bischoff's method to study tumor margins or monitor reactions to anti-tumor treatments without impermissible hindsight analysis.

For all these reasons, Bischoff does not render claims 12 and 13 obvious. Please withdraw this rejection.

b. Bischoff in view of Woudenberg (U.S. 5,928,907)

Claims 2, 3, 14, and 15 stand rejected under §103(a) as allegedly obvious over Bischoff and further in view of Woudenberg.

Claims 2 and 3 are dependent on claim 1. Claims 14 and 15 depend from claim 8. Claims 2, 3, 14, and 15 recite using RT-PCR (real time PCR) to amplify, and claims 3 and 15 further recite dual-labeled, fluorogenic probes.

The Office Action fails to establish a *prima facie* case of obviousness because the cited references fail to disclose or suggest each of the claim limitations. The deficiencies of Bischoff as an anticipatory reference are discussed above. Woudenberg does not remedy these deficiencies. Woudenberg has no relevant teaching regarding distributing isolated or cell-free nucleic acid template molecules to form a set comprising a plurality of assay samples.

Claims 2, 3, 14, and 15 are therefore not obvious over Bischoff in view of Woudenberg. Please withdraw this rejection.

c. Bischoff in view of Jeffreys (*Nuc. Acids Res. 16:* 10953-10971, 1988)

Claims 6 and 18 stand rejected under §103(a) as allegedly obvious over Bischoff and further in view of Jeffreys. Claims 6 and 18 are dependent on independent claims 1 and 8, respectively. Claims 6 and 18 further recite that the first and second numbers of assay samples are homogeneously first or second allelic form "such that the first number of assay samples do not contain the second allelic form of the marker and the second number of assay samples do not contain the first allelic form of the marker."

The Office Action fails to establish a *prima facie* case of obviousness because the cited references fail to disclose or suggest each of the claim limitations and because there is no

apparent reason to combine the elements from the cited references.

Jeffreys fails to remedy the deficiencies of Bischoff because Jeffreys, like Bischoff, lacks a relevant disclosure or suggestion to analyze the number of assay samples in the set which contain a first allelic form of a marker and the number of samples which contain a second allelic form of the marker. Neither of the two references teaches or suggests this active step of the claimed method of the independent claims. Moreover, neither of the two references teaches or suggests analyzing the number of assay samples which are homogenous for the first allelic form and the number of assay samples which are homogeneous for the second allelic form of the marker, as recited in the dependent claims. Neither of the two references teaches or suggests this active step. Additionally, neither Jeffreys nor Bischoff's single cell analysis method discloses identification of an allelic imbalance.

Bischoff in Table 2 taught distribution and analysis of single, whole cells, rather than distribution of isolated or cell-free nucleic acid template molecules to form a set comprising a plurality of assay samples as recited in claims 1 and 8. Bischoff's method could not have separated first and second allelic forms into separate assay samples to form homogeneous amplification products that reflect an allelic imbalance, as recited in dependent claims 6 and 18.

Bischoff in Figure 1 taught the analysis of bulk DNA without distributing it to form a plurality of assay samples which were separately amplified, analyzed, and counted for first and second forms of an allelic marker. There was no plurality of assay samples to analyze and count and compare.

Jeffreys fails to cure the deficiencies of Bischoff. Jeffreys taught that, indeed, single target minisatellite molecules can be amplified by PCR. Jeffreys taught that upon dilution of DNA (from an individual heterozygous at two markers) down to the diploid level (*i.e.,* two alleles per assay sample) that both alleles could be amplified. Some assay samples amplified neither allele, some assay samples amplified one allele or the other, and some assay samples amplified both alleles. Both alleles were presumed by Jeffreys to be present, and the failure to amplify both alleles was interpreted by Jeffreys as a failure to amplify. Jeffreys does not disclose analyzing the assay samples to determine the number of assay samples that contain a first allelic form of a marker and the number of assay samples that contain a second allelic form of the marker any more than he discloses determining the number of assay samples that had a homogeneous amplification product. What Jeffreys sought to determine was whether two

minisatellite markers could be successfully co-amplified in a single reaction. He demonstrated that they could. He further concluded that a single target molecule can be amplified by PCR. Nowhere does Jeffreys teach counting samples to determine the quantitative properties of the original source. The only quantitative determination that Jeffreys makes is the success/failure rate of the PCR reaction itself. See page 10961, lines 3-8.

Even if, *arguendo*, the teachings of these two references were combined, they would not be sufficient to teach the method of the independent claims or the dependent claims. Neither of the two references teaches or suggests the step of analyzing a plurality of assay samples to determine a first number of assay samples which contain the first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker. All the more so did neither of them teach or suggest the step of analyzing a plurality of assay samples to determine a first number of assay samples which contain the first allelic form of a marker homogeneously and a second number of assay samples which contain a second allelic form of the marker homogeneously. This is an active step which the references do not teach or suggest.

Moreover, one of ordinary skill in the art would not have been motivated to combine elements of the disclosures of Jeffreys with Bischoff. The combination has been made improperly using hindsight knowledge obtained from the present invention. It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the prior art so that the claimed invention is rendered obvious. *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992). Indeed, this proposed combination would have destroyed the intended purpose of Bischoff.

Bischoff already knew what the ratio of alleles was in her patient's blood cell population. At page 395, col. 2, last paragraph, Bischoff describes extracting genomic DNA from the patient's blood sample. By visual inspection of a polyacrylamide gel after electrophoresis, Bischoff determined that four markers had a greater amount of paternal allele. Bischoff, page 396, Fig. 1. But that is not the experiment that the Patent and Trademark Office proposes to modify. The Patent and Trademark Office proposes that Bischoff's molecular analysis of single cells be modified to incorporate the analysis of diluted, bulk DNA. This second experiment of Bischoff was designed to distinguish between two genetic possibilities: either a duplication of a paternal 11p region had occurred in all cells, or two cell lines had different constituents (normal biparental inheritance and partial paternal isodisomy). Shendure

declaration under rule 132, at ¶12. Both genetic models would have yielded the same ratio if analyzed in bulk. Shendure declaration under rule 132, at ¶12. See also Bischoff, page 396, Fig. 1. That is why it was critical that Bischoff perform a single cell analysis. Bischoff *needed* to keep the two chromosome 11 homologs together to distinguish between the two genetic models. Shendure declaration at ¶12. Thus, the proposed modification of Bischoff by the technique of Jeffreys would have rendered Bischoff's method unsuitable for its intended purpose.

If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon,* 733 F.2d 900 (Fed. Cir. 1984); see also MPEP § 2143.01(V).

The Patent and Trademark Office asserts that Bischoff was able in Figure 1 to ascertain allelic imbalance using isolated DNA. Indeed, the success of that determination would have provided absolutely no motivation to modify Bischoff's method. Even if one postulated that one of skill in the art would have modified the method to make it more precise, there would have been no suggestion or motivation to utilize the method of Jeffreys. Jeffreys, as discussed above, did not disclose a quantitative assay. Jeffreys was determining whether amplification could occur under certain circumstances. Therefore, one of skill in the art would not have looked to Jeffreys to improve quantitative precision.

Accordingly, for at least these reasons, there would have been no reason to combine Bischoff and Jeffreys. As also discussed, even if, *arguendo*, Bischoff and Jeffreys were combined, they would not have been sufficient to disclose or suggest each of the limitations of the claimed methods. Neither of the two references discloses or suggests the step of analyzing a plurality of assay samples to determine a first number of assay samples which contain the first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker. In addition, neither of them discloses or suggests the step of analyzing a plurality of assay samples to determine a first number of assay samples which contain *only* the first allelic form of a marker and a second number of assay samples which contain *only* a second allelic form of the marker. This is an active step which the references do not disclose or suggest.

Additionally, the Patent Owner provides evidence of secondary considerations of non-obviousness in the form of two declarations under 37 C.F.R. § 1.132. Evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results "may also serve to 'guard

against slipping into use of hindsight' and to resist the temptation to read into the prior art the teachings of the invention in issue." *Graham v. John Deere,* 383 U.S. 1, 36 (1966) (quoting *Monroe Auto Equip. Co. v. Heckethorn Mfg. & Supply Co.,* 332 F.2d 406, 412 (6th Cir. 1964). Furthermore, "such evidence must always be considered in connection with the determination of obviousness." *In re Fielder,* 471 F.2d 640, 644)(C.C.P.A. 1973); see also MPEP § 716.01(a).

The declaration under rule 132 of Dr. Shih (Exhibit A) provides additional evidence of nonobviousness. The Shih declaration, introduces evidence regarding the reception of the invention in the technological art and adoption by commercial entities. The declaration demonstrates that those of skill in the art consider digital PCR to be a significant advance in the art. Many articles have cited the original publication of the invention. ¶15. Expensive machines have been developed by commercial vendors to efficiently carry out the claimed method. ¶¶25, 27, and 28. The claimed method has been compared to the prior quantitative amplification method and the claimed method has been found to yield results that are more precise and less ambiguous. ¶17, 27. The claimed method achieves a finer degree of quantitative discrimination. ¶21. The claimed method achieves a higher degree of precision. ¶22. It makes possible the precise evaluation of balance/imbalance between mutant and wild-type alleles. ¶20. Annual meetings have been organized on the topic of digital PCR by at least three different organizations. ¶¶16, 17. The claimed method solves a need in the art: its precision is needed in the screening and detection of aneuploidy. ¶¶20, 21. It achieves the long sought goal of non-invasive detection of Down syndrome. ¶18.

Additional objective evidence of nonobviousness is provided in the Declaration of Stanley N. Lapidus (Exhibit B). Mr. Lapidus considers digital PCR to be a brilliant innovation that made a tremendous impact on the field, particularly for generating quantitative data concerning rare genetic sequences. ¶ 11. At the time of the Vogelstein and Kinzler invention, Mr. Lapidus and others skilled in the art were genuinely surprised by the success of the method. ¶ 11. Furthermore, Mr. Lapidus notes that digital PCR addressed a previously unmet need as evidenced by numerous publications that related to how to determine mutant to wild-type genetic ratios and the like. None of these publications, however, described digital enumeration by spatial separation, as used in digital PCR. ¶¶ 11, 12. Additionally, Mr. Lapidus notes that digital PCR was a substantial improvement over other methods in use at the time for determining the ratio of rare or mutant alleles. ¶ 13. Mr. Lapidus is also aware of a number of companies that have

marketed or are currently marketing products for use in digital PCR. ¶ 14.

Thus, even if any of the combinations of art which have been asserted were properly made and formed a proper *prima facie* case, which the patent owner does not concede, the secondary considerations indicate that the non-obviousness of the claimed method.

Please withdraw this rejection as the combination of references is improper and would not have yielded the claimed invention.

Conclusion

For at least the reasons stated above, and for the reasons stated in the prior response and prior submitted Shendure declaration under rule 132, all claims in this reexamination are patentable and should be confirmed. Therefore, we request that the Patent and Trademark Office issue a certificate of reexamination confirming the patentability of all claims. The absence of additional comments regarding the Office Action does not indicate agreement with or concession of any characterization or requirement. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 202 824 3000.

No fees are believed to be due with respect to the filing of this response. However, should any such fees be due, the Commissioner is hereby authorized to charge any such fees in connection with this paper to Deposit Account No. 19-0733.

Respectfully submitted,

By: /Sarah A. Kagan/
Sarah A. Kagan
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Dated: September 8, 2014

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Education

BS Engineering, Cooper Union, New York City, 1970

Employment history

SynapDx Corp. 2009-present

Founder and CEO
Founder and leader of neurodevelopmental diagnostics testing laboratory

Helicos BioSciences Corp. 2003-present

Co-founder, President, CEO, Chairman, BOD member
Co-founded and led single molecule sequencing company

EXACT Sciences Corp. 1995-2006

Founder, President, Chairman, BOD member
Founded and led colorectal cancer early detection company

Cytyc Corp. 1987-1994

Founder, President
Founded and led pap smear diagnostic company.

Itran Corp. 1983-1987

Founder, President
Founded and led industrial machine-vision company

Gentech Inc. 1979-1983

Founder President
Principal at contract engineering company

Raytheon Medical Electronics 1976-1978

Engineering Group Leader, Engineering Manager
Led and managed engineering team at nuclear medicine instrument manufacturer

Elscint Ltd. 1971-1976

Design Engineer, Engineering Group Leader
Designed and led design of nuclear medicine instrumentation

Academic Appointments
Instructor, Harvard/MIT of division of Health Sciences Technology, MIT Sloan School of Management 2002-present

Research Assistant Professor, Department of Pathology, Tufts University School of Medicine 1994-present

Board Appointments

Harvard School of Public Health Center for Cancer Prevention, Advisory Board Member 1995-2000

EXACT Sciences, Director 1995-2006

Cooper Union School of Engineering, Advisory Board Member 1999-present

Precision Therapeutics Director 2001-2013

Harvard MIT Division of Health Sciences and Technology, Advisor 2001-present

Cooper Union Board of Trustees 2002-2012

Helicos Biosciences, Director 2003-2011

T2 Biosystems, Inc., Director 2008 – present

Advisory Board of Technology Fund of Boston Children's Hospital 2009 – present

Daktari DX, Corp. Director 2009-present

Institutes of Medicine, Committee on the Evolution of Translational Omics 2011 – 2012

Fractyl Laboratories Director 2013-present

Honors
Elected as Fellow at American Institute of Medical and Biological Engineering. 2014

Patents and Publications*
Inventor of >30 issued US patents and 20+ pending patent applications.

Patent	Date	Inventor	Title	Subject Matter

	Number	Issued			
1	4,093,857	6-Jun-78	**Lapidus, Stanley N.**	Radiographic normalizing system	Uniformity correction for gamma cameras
2	4,281,249	28-Jul-81	**Lapidus, Stanley N.**	Stepped scanner imaging system	Whole-body gamma camera imaged using step and repeat
3	4,570,217	11-Feb-86	Allen; Bruce S. (East Kingston, NH), Dunalvey; Michael R. (Needham, MA), King; Bruce A. (Bolton, MA), DuPrie; Harold J. (Andover, MA), Hudnall; Richard E. (Nashua, NH), **Lapidus; Stanely N.** (Bedford, NH), Gilbert; Daniel R. (Dracut, MA), Carlson; Anne M. (Wakefield, MA), Thakrar; Kiran (Salem, NH), Doig; Robert C. (Salem, NH), Kimerer; Brian S. (Reading, MA), Sirois; Andrew F. (Lawrence, MA), Poirer; Bruce A. (Bradford, MA), Hunt; Philip G. (Derry, NH), Dziezanowski; Joseph J. (Brighton, MA), Bromberg; Michael A. (Nashua, NH), Brown; Michael (Salem, NH), Friedel; Seymour A. (Merrimack, NH)	Man machine interface	Computer hardware for high-speed graphics
4	4,581,762	8-Apr-86	**Lapidus; Stanley N.** (Bedford, NH), Dziezanowski; Joseph J. (Weare, NH), Friedel; Seymour A. (Goffstown, NH), Greenberg; Michael P. (Manchester, NH)	Vision inspection system	A vision inspection system operable with foreground illumination provides user identification of selected regions of a known object for later comparison to an unknown object.
5	5,143,627	1-Sep-92	**Lapidus; Stanley N.** (Bedford, NH), Polk, Jr.; Lewis T. (Bedford, MA), Farber; Fredric L. (Chestnut Hill, MA), Barlas; J. Morgan (Malden, MA), Hurley; Anne A. (Carver, MA)	Method and apparatus for preparing cells for examination	An apparatus and method provide automated collection and transfer of particles from a liquid suspension to a glass slide for visual examination.
6	5,185,084	9-Feb-93	**Lapidus; Stanley N.** (Bedford, NH), Kamen; Dean (Bedford, NH), Villeneuve; Richard R. (Bedford, NH), Polk, Jr.; Lewis T. (Bedford, MA)	Method and apparatus for control of flow through a filter chamber by measured chamber equilibration pressure	A method and apparatus for the controlled instrumentation processing of cells and other paricles with a filter device measures a parameter of the flow through the filter device of a fluid carrying the particles.
7	5,240,606	31-Aug-93	**Lapidus; Stanley N.** (Bedford, NH), Polk, Jr.; Lewis T. (Bedford, MA), Farber; Fredric L. (Chestnut Hill, MA), Barlas; J. Morgan (Malden, MA), Hurley; Anne A. (Carver, MA)	Apparatus for preparing cells for examination	An apparatus and method provide automated collection and transfer of particles from a liquid suspension to a glass slide for visual examination.
8	5,266,495	30-Nov-93	**Lapidus; Stanley N.**	Method and apparatus for controlled instrumentation of particles with a filter device	A method and apparatus for the controlled instrumentation processing of cells and other particles with a filter device measures a parameter of the flow through the filter device of a fluid carrying the particles.

9	5,269,918	14-Dec-93	**Lapidus; Stanley N.** (Bedford, NH), Polk, Jr.; Lewis T. (Bedford, MA), O'Lari; Arlen M. (Chelmsford, MA)	Clinical cartridge apparatus	A cartridge-like holder or carrier for automatic operation with a specimen processor has a frame for removable and replaceable alignment in operative engagement with the specimen processor and has multiple supports, each of which removably and replaceably supports an implement such as a container of a biological specimen having cellular particles suspended in a liquid, a filter device for use in collecting cellular particles from the liquid in the sample container, a viewing screen onto which the collected cellular particles can be transferred from the filter device and, further, an output container for receiving the viewing screen with the cellular particles thereon.
10	5,670,325	23-Sep-97	**Lapidus; Stanley N.** (Bedford, NH), Shuber; Anthony P. (Milford, MA), Ulmer; Kevin M. (Cohasset, MA)	Method for the detection of clonal populations of transformed cells in a genomically heterogeneous cellular sample	Methods are provided for detecting the presence of mutant sequences in a subpopulation of gene sequences in a biological sample.
11	5,741,650	21-Apr-98	**Lapidus; Stanley N.** (Bedford, NH), Shuber; Anthony P. (Milford, MA), Ulmer; Kevin M. (Cohasset, MA)	Methods for detecting colon cancer from stool samples	The present invention provides methods for screening for the presence of a subpopulation of cancerous or precancerous cells in a heterogeneous cellular sample, such as a stool sample.
12	5,928,870	27-Jul-99	**Lapidus; Stanley N.** (Bedford, NH), Shuber; Anthony P. (Milford, MA)	Methods for the detection of loss of heterozygosity	Methods are provided for detecting loss of heterozygosity in a nucleic acid sample.
13	5,952,178	14-Sep-99	**Lapidus; Stanley N.** (Bedford, NH), Shuber; Anthony P. (Milford, MA)	Methods for disease diagnosis from stool samples	The present invention provides methods for preparing a stool sample in order to screen for the presence of indicators of a disease, for example a subpopulation of cancerous or precancerous cells.
14	6,010,909	4-Jan-00	**Lapidus; Stanley N.** (Bedford, NH)	Method and apparatus for controlled instrumentation of particles with a filter device	A method and apparatus for the controlled instrumentation processing of cells and other particles with a filter device measures a parameter of the flow through the filter device of a fluid carrying the particles.
15	6,020,137	1-Feb-00	**Lapidus; Stanley N.** (Bedford, NH), Shuber; Anthony P. (Milford, MA)	Methods for the detection of loss of heterozygosity	Methods are provided for detecting loss of heterozygosity in a pooled nucleic acid sample obtained from a patient population.
16	6,100,029	8-Aug-00	**Lapidus; Stanley N.** (Bedford, NH), Shuber; Anthony P. (Milford, MA)	Methods for the detection of chromosomal aberrations	Methods are provided for detecting fetal chromosomal aberrations by detecting statistically-significant differences between normal and aberrant chromosomes.
17	6,143,529	7-Nov-00	**Lapidus; Stanley N.** (Bedford, NH), Shuber; Anthony P. (Milford, MA)	Methods for improving sensitivity and specificity of screening assays	Methods of the invention comprise assays for markers indicative of cancer or precancer.
18	6,146,828	14-Nov-00	**Lapidus; Stanley N.** (Bedford, NH), Shuber; Anthony P. (Milford, MA)	Methods for detecting differences in RNA expression levels and uses therefor	Methods are disclosed for the detection and diagnosis of disease by determining differences in the number of RNA molecules in a patient sample compared to an expected number

19	6,203,993	20-Mar-01	Shuber; Anthony P. (Milford, MA), **Lapidus; Stanley N.** (Bedford, NH), Daley; George Q. (Weston, MA)	Methods for the detection of nucleic acids	Methods are provided for identifying nucleic acids. Methods of the invention are useful for identifying and analyzing nucleic acids, especially variants of single nucleotide polymorphisms, that are indicative of disease or the predisposition for disease.
20	6,214,558	10-Apr-01	**Lapidus; Stanley N.** (Bedford, NH), Shuber; Anthony P. (Milford, MA)	Methods for the detection of chromosomal aberrations	Methods are provided for detecting fetal chromosomal aberrations by detecting statistically-significant differences between normal and aberrant chromosomes
21	6,225,125	1-May-01	**Lapidus; Stanley N.** (Bedford, NH)	Method and apparatus for controlled instrumentation of particles with a filter device	A method and apparatus for the controlled instrumentation processing of cells and other particles with a filter device measures a parameter of the flow through the filter device of fluid carrying the particles.
22	6,268,136	31-Jul-01	Shuber; Anthony P. (Milford, MA), **Lapidus; Stanley N.** (Bedford, NH), Radcliffe; Gail E. (Worcester, MA)	Methods for stool sample preparation	The present invention provides methods for the preparation of stool samples to increase the yield of relevant DNA, and further provides methods for isolating and analyzing target DNA for characteristics indicative of colorectal cancer.
23	6,300,077	9-Oct-01	Shuber; Anthony P. (Milford, MA), **Lapidus; Stanley N.** (Bedford, NH)	Methods for the detection of nucleic acids	Methods are provided for identifying nucleic acids. Methods of the invention are useful for identifying and analyzing nucleic acids, especially variants of single nucleotide polymorphisms, that are indicative of disease or the predisposition for disease.
24	6,303,304	16-Oct-01	Shuber; Anthony P. (Milford, MA), **Lapidus; Stanley N.** (Bedford, NH)	Methods for disease diagnosis from stool samples	The present invention provides methods for preparing a stool sample in order to screen for the presence of indicators of a disease, for example a subpopulation of cancerous or precancerous cells.
25	6,351,857	5-Mar-02	Slaon [sic, should be Sloan], III; Walker M. (Berlin, MA), **Lapidus; Stanley N**. (Bedford, NH)	Stool specimen collector	An apparatus for obtaining a stool specimen. The apparatus comprises a housing, a collection bag, a slider to close the collection bag and a draw string to move the slider.
26	6,406,857	18-Jun-02	Shuber; Anthony P. (Milford, MA), **Lapidus; Stanley N.** (Bedford, NH), Radcliffe; Gail E. (Worcester, MA)	Methods for stool sample preparation	The present invention provides methods for the preparation of stool samples to increase the yield of relevant DNA, and further provides methods for isolating and analyzing target DNA for characteristics indicative of colorectal cancer.
27	6,415,455	9-Jul-02	Slaon [sic, should be Sloan], III; Walker M. (Berlin, MA), **Lapidus; Stanley N**. (Bedford, NH)	Stool specimen collector	The invention provides an apparatus for obtaining a stool specimen. The apparatus comprises a housing, a collection bag, a slider to close the collection bag and a draw string to move the slider.
28	6,566,101	20-May-03	Shuber; Anthony P. (Milford, MA), **Lapidus; Stanley N.** (Bedford, NH)	Primer extension methods for detecting nucleic acids	Methods are provided for selective nucleic acid sequence detection in single base primer extension reactions of high sensitivity. These methods are useful for detecting small amounts of mutant nucleic acid in a heterogeneous biological sample. These methods are particularly useful for identifying individuals with gene mutations indicative of early colorectal cancer.

29	7,269,560	30-Jan-07	**Lapidus; Stanley N** (Bedford, NH), Buzby; Philip Richard (Brockton, MA), Harris; Timothy (Ocean County, NJ)	Short cycle methods for sequencing polynucleotides	The invention provides methods for sequencing a polynucleotide comprising stopping an extension cycle in a sequence by synthesis reaction before the reaction has run to near or full completion.
30	7,491,498	17-Feb-09	**Lapidus; Stanley N** (Bedford, NH), Buzby; Philip Richard (Brockton, MA), Harris; Timothy (Ocean County, NJ)	Short cycle methods for sequencing polynucleotides	The invention provides methods for sequencing a polynucleotide comprising stopping an extension cycle in a sequence by synthesis reaction before the reaction has run to near or full completion.
31	7,666,593	23-Feb-10	**Lapidus; Stanley** (Bedford, NH)	Single molecule sequencing of captured nucleic acids	The invention provides methods and devices for detecting, enumerating or identifying target nucleic acid molecules using immobilized capture probes and single molecule sequencing techniques.
32	7,897,345	1-Mar-11	**Lapidus; Stanley N** (Bedford, NH), Buzby; Philip Richard (Brockton, MA), Harris; Timothy (Ocean County, NJ)	Short cycle methods for sequencing polynucleotides	The invention provides methods for sequencing a polynucleotide comprising stopping an extension cycle in a sequence by synthesis reaction before the reaction has run to near or fill completion.

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The Johns Hopkins University School of Medicine

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EDUCATION AND TRAINING

Year	Degree	Institution	Discipline
1981-1988	M.D.	Taipei Medical University	Medicine
1989- 1993	Ph.D.	University of Pennsylvania	Pathology
1993-1994	Postdoctoral Fellow	The Wistar Institute	Cancer Biology
1994-1997	Resident	Johns Hopkins Hospital	Pathology
1997-1998	Clinical Fellow	Johns Hopkins Hospital	Gynecologic Pathology
1998-2000	Research Fellow	Johns Hopkins Oncology Ctr. (w/ Dr. Bert Vogelstein)	Cancer Genetics

PROFESSIONAL EXPERIENCE

2000-2001 **Instructor**, Department of Pathology

	Johns Hopkins Medical Institutions, Baltimore, MD
2001-2003	**Assistant Professor**, Department of Pathology Johns Hopkins Medical Institutions, Baltimore, MD
2003-2008	**Associate Professor**, Departments of Pathology, Oncology and Gynecology and Obstetrics Johns Hopkins Medical Institutions, Baltimore, MD
2008-	**Professor**, Departments of Pathology, Oncology and Gynecology/Obstetrics Johns Hopkins Medical Institutions, Baltimore, MD
2014-	**Richard W. TeLinde Distinguished Professor** Department of Gynecology and Obstetrics Johns Hopkins University School of Medicine
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RESEARCH ACTIVITIES

Peer-Reviewed Research Articles

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5. Mancianti ML, Gyorfi T, **Shih IM**, Valyi-Nagy I, Levengood G, Menssen HD, Halpern A, Elder DE, Herlyn M. Growth regulation of cultured human nevus cells. J Invest Dermatol, 100:281S-287S, 1993. PMID: 8440904

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12. **Shih IM**, Kurman RJ. Expression of melanoma cell adhesion molecule in intermediate trophoblast. Lab Invest, 75: 377-388, 1996. (with cover illustration) PMID: 8804361

13. **Shih IM**, Speicher D, Hsu MY, Levine E, Herlyn M. Melanoma cell-cell interactions are mediated through heterophilic Mel-CAM/ligand adhesion. Cancer Res, 57: 3835-3840, 1997. PMID: 9288796

14. **Shih IM**, Hsu MY, Palazzo JP, Herlyn M. The cell-cell adhesion receptor Mel-CAM acts as a tumor suppressor in breast carcinoma. Am J Pathol, 151:745-751, 1997. PMID: 9284823

15. **Shih IM**, Kurman RJ. New concepts in trophoblastic growth and differentiation with practical application for the diagnosis of gestational trophoblastic disease. Verh Dtsch Ges Path, 81: 266-272, 1997. PMID: 9474880

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24. **Shih IM.** The role of CD146 (Mel-CAM) in biology and pathology. J Pathol, 189:4-11,1999. PMID: 10451481

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64. Davidson B, Elstrand MV, McMaster MT, Berner A, Kurman RJ, Risberg B, Trope CG, **Shih IM**. HLA-G expression in effusions is a possible marker of tumor susceptibility to chemotherapy in ovarian carcinoma. Gyn Oncol, 96:42-47, 2005. PMID: 15589578

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purified ovarian serous neoplasms. Cancer Biol Therapy, 5:779-785, 2006. PMID: 16721043

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Book Chapters

1. **Shih IM**, Mazur MT, Kurman RJ. Chapter 49: Gestational trophoblastic disease. In Sternberg's Diagnostic Surgical Pathology. Edited by Stacey E. Mills. pp 2049-2070, Fifth edition. Lippincott Williams & Wilkins Publishers, New York, 2009.

2. **Shih IM**, Mazur MT, Kurman RJ. Chapter 20: Gestational trophoblastic disease. In Blaustein's Pathology of Female Genital Tract. Edited by Robert J. Kurman. Sixth edition. Springer-Verlag, New York, pp1075-1135, 2011.

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Others

1. **Shih IM**. Placental site trophoblastic tumor. In Encyclopedia of Cancer, 2nd edition, Springer-Verlag, Editor: Manfred Schwab, Berlin and Heidelberg, GmbH & Co, 2009. http://www.springerreference.com/docs/featured/978-3-540-47648-1_5715.html

2. Chen L, Xuan J, Gu J, Wang Y, Zhang Z, Wang TL, **Shih IM**. Integrative network analysis to identify aberrant pathway networks in ovarian cancer. Pac Symp Biocomput, 31-42, 2012.

Inventions, Patents, Copyrights

- US patent #6419896: Non-invasive approach for assessing tumor in living animals. Inventors: Vogelstein B, Kinzler WK and Shih I-M
- US patent #20110171741: DNA integrity assay (DIA) for cancer diagnostics, using confocal fluorescence spectroscopy. Inventors: Tza-Hui Wang, Kelvin J. Liu, Ie-Ming Shih
- US patent in process (11/604,183): Application of Rsf-1 expression to predict clinical outcome in cancer patients. Inventors: Shih I-M and Wang T-L
- International patent in progress (PCT/US2008/011948): Detection of cancer by measuring genomic DNA copy number and strand length in cell-free DNA. Inventors: Shih I-M

Extramural Funding

Current awarded Grants

4/1/2011 – 3/31/2016	Notch3 signaling in ovarian cancer RO1 CA148826 (PI: TL Wang) NCI/NIH Role: co-investigator; 0.5 calendar months Purpose: To investigate the molecular mechanism of Notch3 signaling in the pathogenesis of ovarian high-grade serous carcinoma.
10/01/2011 – 09/30/2016	Prevention of Ovarian High-Grade Serous Carcinoma by Elucidating Its Early Changes OC100517 (Director: RJ Kurman; co-Director: I-M Shih) Consortium Award, US Department of Defense (USAMRMC), Directed Medical Research Programs (CDMRP) Role: Co-director and co-investigator; 3.0 calendar months Purpose: To determine the origin and pathogenesis in the development of ovarian high-grade serous carcinomas by employing cancer genetics, cell biology, animal models and epidemiologic studies through multi-institutional research effort. The consortium includes five research projects and three cores.
07/01/2011 - 06/30/2016	Multiplexed Detection of Cell Free DNA Biomarkers for Cancer RO1 CA155305 (PI: TZ Wang) NCI/NIH Role: co-investigator; 1.0 calendar months Purpose: To analyze the potential application of multiplexed detection of cell free DNA as biomarkers for cancer detection.
09/01/2011 - 08/30/2016	Proteome characterization center: a genoproteomics pipeline for cancer biomarker. Clinical Proteomic Technologies for Cancer Initiative. U24CA160036 (PI: D Chan) NCI/NIH Role: co-investigator; 1.0 calendar months Purpose: To identify, verify and characterize biomarkers for ovarian cancer by combining genomics and proteomic approaches. To establish the clinical proteomic technology center and to validate, verify and characterized of ovarian cancer biomarkers using genoproteomic approaches.
12/01/2011 - 11/30/2014	Tumor suppressor role of ARID1A R21 CA165807 (PI: IM Shih) NCI/NIH Role: principal investigator; 1.0 calendar months Purpose: To determine the tumor suppressor roles of ARID1A and its molecular mechanisms in developing gynecological cancer.

Recent Completed Research Grants

12/01/2004 - 11/30/2012	Molecular Diagnostics for Malignant Effusion 2R01 CA103937 (PI: I-M Shih) NCI/NIH Role: principal investigator; 1.0 calendar months Purpose: To study the functional role of NAC-1 in the development of ovarian carcinoma.
4/01/2008 - 1/31/2013	The Roles of HBXAP Gene in Ovarian Cancer 1R01 CA129080 (PI: I-M Shih) NCI/NIH Role: principal investigator; 1.0 calendar months Purpose: To study the molecular mechanism of HBXAP gene product in the progression of ovarian carcinoma.
04/01/2007 - 01/31/2012	Pathogenesis of Ovarian Serous Borderline Tumors RO1 CA116184 (PI: R.J. Kurman) NCI/NIH Role: co-Director, project 1 leader; 0.5 calendar months Purpose: To study the molecular genetic profiles of implants that is associated with ovarian serous borderline tumors. To develop biomarkers to better diagnose the implant and correlate the molecular genetic profiles and biomarker expression with clinical behavior in patients.
07/01/2002- 06/30/2007	Development of a New Technology in Analyzing Allelic Imbalance in Plasma DNA as a Tool for Early Cancer Detection R21/R33 CA97527 (PI: Shih) NCI/NIH Role: principal investigator; 4.0 calendar months Purpose: To develop an innovative molecular method to better diagnose human cancer using cell-free circulating DNA in patients.
07/01/2008 - 06/30/2012	Notch3 Signaling Pathway in the Ovarian Carcinoma GMC-113937 (PI: TL Wang) American Cancer Society Role: co-investigator; 1.0 calendar month Purpose: This project is to characterize the role of Notch3 signaling pathway in ovarian tumorigenesis and identify Notch3 down-stream target genes in ovarian cancer.
06/01/2009 – 05/31/2012	High-throughput intracellular microrheology: a new tool for cancer research 1R21CA137686 (PI: D Wirtz/IM Shih) NCI/NIH Role: Co-PI Purpose: To apply a high-throughput intracellular microrheology in studying ovarian cancer

07/01/2002- 06/30/2006	Diverse Pathways in the Development of Ovarian Serous Tumors OC010017 (PI: RJ Kurman) US Department of Defense (USAMRMC), Directed Medical Research Programs (CDMRP) Role: Project #1 leader; 3.0 calendar months Purpose: To study the molecular pathways that is involved in the development of different types of ovarian serous carcinoma by using several new technologies including SAGE.
09/01/2003- 08/30/2004	Molecular genetic changes in the development of cervical cancer P50CA098252- SPORE (PI: TC Wu) NIH/NCI Role: co-investigator; 1.0 calendar month Purpose: The development project/pilot study in this SPORE of cervical cancer is to investigate the DNA copy number changes involved in the development of cervical cancer.
12/28/2005- 12/27/2006	Marker Discovery for Ovarian Cancer Research agreement Developmental Center of Biotechnology, Taiwan (PI: Shih) Role: principal investigator; 1.0 calendar month Purpose: To identify biomarkers for potential use in ovarian cancer diagnosis and therapy.
10/01/2006 - 09/30/2007	Characterization of Rsf-1 in human cancer China Medical University, Taiwan Research agreement (PI: Shih) Role: principal investigator; no salary requested Purpose: To study the molecular etiology of Rsf-1 expression in oral cancer in Taiwanese patients.
1/1/2008 - 12/31/2009	Notch3 signaling in the pathogenesis of ovarian cancer Ovarian Cancer Research Foundation (OCRF, New York) Individual Investigator Award (PI: T.L. Wang) Role: co-investigator; 0.6 calendar month Purpose: To characterize the Notch3 signaling pathway in the tumor progression of ovarian cancer. Specifically, the proposal is to determine how the Notch3 pathway goes awry in normal ovaries and the molecular mechanisms in which Notch3 pathway aberration contributes to ovarian cancer.
01/01/2009 – 12/31/2010	Screening of Chinese herbal medicine extracts in cancer therapy Research Agreement (PI: IM Shih) China Medical University, Taichung city, Taiwan Role: Principal; investigator

	Purpose: To screen candidate Chinese herbal extracts to inhibit specific cancer-associated targets for potential molecularly targeted therapy.
12/11/2006 - 12/31/2007	Molecular Markers for Clinical Outcome Prediction Oncotech, Inc. Research Agreement (PI: Shih) Role: principal investigator; 0.60 calendar month Purpose: To assess the clinical potential of Rsf-1 and NAC-1 immunohistochemistry in predicting clinical outcome in ovarian cancer patients.
04/01/2008 - 03/31/2010	Nanobiosensing Method for Point Mutation Detection of Cancer 1R21CA120742 (PI: TZ Wang) NCI/NIH Role: co-investigator; 0.60 calendar month Purpose: To develop a nanobiosensing technical platform to detect point sequence mutation of Kras and Braf genes using a relatively small amount of DNA samples without PCR.
07/01/2007 - 06/31/2009	Characterization of Chromatin Remodeling Gene, Rsf-1, in Pathogenesis of Ovarian Cancer Johns Hopkins-Weizmann Inst. (PI: Shih) Role: principal investigator; 0.60 calendar month Purpose: To study the biological function of Rsf-1 gene in the development of ovarian cancer.
01/01/2005 -12/31/2008	Identification and Characterization of Genomic Amplifications in Ovarian Serous Carcinoma OC04-0060 (PI: T.L. Wang) US Department of Defense (USAMRMC), Directed Medical Research Programs (CDMRP), New Investigator Research award Role: co-investigator; 1.0 calendar month Purpose: To identify and characterize ovarian cancer genome using digital karyotyping and SNP array.
07/01/2009 – 06/30/2011	Elucidation of molecular alterations in precursor lesions of ovarian serous carcinoma OC080469 (Director: RJ Kurman; Co-director: IM Shih) Role: Co-director Purpose: To establish ovarian cancer research consortiums to facilitate identify and characterize early lesions of ovarian cancer through multiple institution collaborations

EDUCATIONAL ACTIVITIES

Classroom Instruction (Johns Hopkins University School of Medicine)

- Gynecological Pathology and laboratory/small group, Pathology course for medical students, 1994-
- Graduate course in Pathobiology and Disease Mechanisms, Section of Ovarian Tumors, 2002-
- Graduate course in Functional Anatomy ("Female Reproductive Organ"), for graduate students, Johns Hopkins University, 2006-
- Graduate course in Pathobiology ("Gynecological Pathology") for graduate students, Johns Hopkins University, 2005-

Clinical Instruction (the Johns Hopkins Hospital)

- Microscopic and gross teachings for medical students, residents and fellows rotating to gynecologic pathology, 1999-
- Didactic course on Gynecologic Pathology for residents and fellows, 2002-

CME course speaker

- "Molecular pathways of ovarian cancer". At the Current Concepts in the Multidisciplinary Management of Ovarian Cancer, the Sidney Kimmel Cancer Center and the office of Continuing Medical Education, Johns Hopkins University, Baltimore, September, 2004.
- "Molecular genetics and target-based therapy for low-grade serous cancers of the ovary". At the Current Concepts in the Multidisciplinary Management of Ovarian Cancer, the office of Continuing Medical Education, Johns Hopkins University, Baltimore, September, 2005.
- "Gynecologic neoplasms- trophoblastic tumors and ovarian epithelial neoplasms". Symposium of the Taiwanese Association of Pathology, August 2006.
- "Update in gestational trophoblastic disease". Surgical Pathology Update, Leipzig, Germany, June, 2007.

Mentoring

Research Fellows

- 2000-2002, Hsueh-Wei Chang, PhD, currently Chairman and Professor of the Department of Biological Science and Environmental Biology, Kaohsiung Medical University, Taiwan
- 2001-2003, Gad Singer, M.D., Professor at the Institute of Pathology, Baden, Switzerland
- 2002-2004, Brant G. Wang, MD, PhD, research fellow; currently an attending pathologist at the Washington Medical Center, Washington DC
- 2003-2004, Gudrun Pohl, MD, assistant professor at the University of Vienna, Austria
- 2003-2004, Chung-Liang Ho, MD, PhD, Associate Professor, National Chenug-Kung University School of Medicine, Tainan, Taiwan
- 2003, Ariane Aigelsreiter, MD, visiting research fellow, Austria
- 2003-2004, Reiko Dehari, MD, Visiting research fellow, Japan
- 2003-2004, Chih-Yi Hsu, MD, Visiting research fellow, currently a faculty t the National Yang-Ming University School of Medicine/VGH -Taipei, Taiwan
- 2004-2005, Tsung-Hsuan Lai, MD, Director of Reproductive Endocrinology and Infertility division, Department of Ob and Gyn, Taipei Cathay General Hospital, Taipei, Taiwan

- 2004-2006, Kentaro Nakayma, MD, PhD, Associate Professor, Shimane National University School of Medicine, Japan
- 2005-2007, Jim Sheu, PhD, Professor at the Institute of Biomedical Sciences, National Sun Yat-Sen University, Taiwan
- 2005-2006, Ritu Salani, MD, Assistant Professor and attending physician at the Ohio State University Health System, division of Gynecologic Oncology
- 2007 and 2008, Ayse Ayhan, MD, PhD, attending/consulting pathologist at the Seirei Mikatahara General Hospital, Hamamatsu, Japan
- 2005-2007, Tsui-Lien Mao, MD, research fellow, currently an assistant professor at the National Taiwan University College of Medicine, Taipei, Taiwan
- 2007, Artit Jinawath, MD, PhD, research fellow/visiting resident, Thailand
- 2006-2008, Natini, Jinawath, MD, PhD, research fellow, currently a medical cytogenetics fellow at the Johns Hopkins Hospital
- 2006-2008, Jung Hye Choi, PhD, Assistant Professor at Kyung Hee University, Seoul, South Korea
- 2006-2008, Kuan-Ting Kuo, MD, Assistant Professor at the National Taiwan University Hospital, Taipei, Taiwan
- 2007-2008, Stefanie Ueda, MD, Assistant Profession, Department of Obstetrics and Gynecology, University of California at San Francisco, CA
- 2008-2010, Michelle Thiaville, PhD, Assistant Professor, Department of Biological Science, Nicholls State University, Louisiana
- 2008-2010, Pradeep K. panuganti, MD, currently a resident in Texas Tech University of Health Sciences
- 2010, Daichi Maeda, MD, PhD, Assistant Professor, Department of Pathology, University of Tokyo, Japan
- 2010-2012, Stephanie Gaillard, Assistant Professor, Duke University
- 2009-2012, Alex Stoeck, PhD, Research Scientist Leader, Merck Co.
- 2011-2012, Chen-Hsuan Wu, MD, Instructor, Kaohsiung Chang Gung Memorial Hospital, and Chang Gung University college of medicine, Kaohsiung, Taiwan
- 2012-2013, Laura Ardighieri, MD, a fellow at the Anatomia Patologicaat Spedali Civili Brescia, Italy
- 2009-2013, Elisabetta Kuhn, MD, staff scientist, International Agency for Research on Cancer (IARC), Lyon, France
- 2007-2013, Bin Guan, PhD, NIDDK, NIH
- 2012-2014, Tae Mogami, MD, PhD, Department of Gynecology, Yokolohoma City University Medical Center, Japan

Graduate and Undergraduate Students (Johns Hopkins University except Ms. Mahle)

- 2008-2012, KaiLee Yap, pathobiology graduate student (thesis student), currently a postdoc fellow at the University of Chicago.
- 2010-2012, Min Gao, exchange/visiting graduate student from Shandong University/Zilu hospital, China.
- 2008-2010, Chen Xu, exchange/visiting graduate student from China Scholarship council, currently attending physician in the Department of Urology, the first affiliated hospital, Sun Yat Sen University, China
- 2005- 2009, Joon Park, pathobiology graduate student (thesis student), currently a Senior Scientist, Samsung Advanced Institution for Technology, Seoul, South Korea.

- 2009-2010, Elizabeth Chen, currently medical student in Uniformed Services University of Health Sciences, Bethesda, Maryland.
- 2007-2008, Vivek Murthy, currently a medical student at NYU.
- 2003-2005, Robert J. Oldt III, currently a medical student at UMDNJ, NY.
- 2005, Jim M. Yen, MD, currently a medical resident at the Medical Center of the University of South California, CA.
- 2005, Eric Cheng, currently a medical student at UMDNJ, NY.
- 2005, Ilena Neuberger, currently a medical student at UMDNJ, NY.
- 2007, Rebecca Bush, currently a medical student in Washington University School of Medicine, MO.
- 2007, David Chu, currently a medical student in University of Pittsburg, PA.
- 2007, Mandy Mahle, Queens University of Charlotte, NC, currently, a Biochemistry major
- 2007-2009, Kevin Lee, currently a medical student in Albany Medical College, NY.
- 2007-2009, Paul Markowiski, previously lab assistant, currently a medical student in Robert Wood Johnson Medical School, NJ.
- Marilina Mascaró, visiting PhD student, Facultad de Farmacia Bioquimica, Catedra de Immunologia, Buenos Aires, Argentina

Ph.D. Student Qualification Committee:

- MD/PhD candidates in Cellular & Molecular Medicine Graduate Program: Saurubh Saha, Harith Rajagopalan, Chetan Bettego, Jordan Cummins
- PhD candidates in Cellular & Molecular Medicine Graduate Program: Ian Cheong, Carlo Rago and Jihye Yun
- Pharmacology Graduate Program: Xin Huang, Meng Li, Kibem Kim
- Pathobiology Graduate Program: Yin Yeh, Shaaretha Pelly, Sophie Lin Zhirong; Kah Suan Lim; Byung-Hak Kang, Shu-Han Yu
- Graduate Board Exam, Department of Chemical and Molecular Engineering, Johns Hopkins Univeristy: Serving as the Chair of the Exam committee for Melissa Thompson, CK Wang.

Ph.D. Student Thesis Committee:

- Melissa Thompson, PhD candidate, Department of Chemical and Molecular Engineering, Johns Hopkins University (Homewood campus), 2007- current
- Melissa Landek, PhD candidate, Pathobiology Graduate Program, Johns Hopkins Medical Institutions, 2008
- Hsin Chih Yeh, PhD candidate, Department of Bioengineering, Johns Hopkins University, 2008
- Christopher Puleo, PhD candidate, Department of Bioengineering, Johns Hopkins University, 2009
- Vasudev Bailey, PhD candidate, Department of Bioengineering, Johns Hopkins University, 2010
- Kelvin Liu, PhD candidate, Department of Bioengineering, Johns Hopkins University, 2011
- Yi Zhang, PhD candidate, Department of Bioengineering, Johns Hopkins University, 2013

Participation in mentoring Gynecologic Pathology Fellows (*Johns Hopkins Hospital*):

- 2003 – 2005, Monica Srodon, M.D.
  Staff pathologist
  Greensboro Pathology Associates
  Greensboro, NC
- 2004 – 2006, Saeid Movahedi-Lankarani, M.D.
  Staff pathologist
  Hospital Pathology Associates
  St. Paul, MN
- 2006 – 2007, Dengfeng Cao, M.D., Ph.D.
  Assistant Professor
  Department of Pathology & Immunology
  Washington University School of Medicine
  St. Louis, MO
- 2006 – 2007, Kara Judson, M.D.
  Attending pathologist
  Lenox Hill Hospital
  New York, NY
- 2005 – Current, Anna Yemelyanova, M.D.
  (Current Fellow)
- 2007 – Current, Thomas McConnell, M.D.
  (Current Fellow)
- 2007 – 2008, Emanuela Veras, M.D.
  Memorial Sloan-Kettering Cancer Center

Awards Received by Dr. Shih's Trainees

- **Collen's Dream Foundation for ovarian cancer research award,** 2014, Hiroyasu Kashima, MD, research fellow
- **Keio University School of Medicine Young Investigator Award, Japan,** 2014, Yusuke Kobayashi, research fellow
- **Young Investigator Award in Basic Science, Department of Pathology, JHU,** 2014, Fun Yuyu, postdoctoral fellow
- **Ovarian Cancer Research Foundation (OCRF) award, 2013,** Fun Yuyu, postdoctoral fellow
- **Oppo's Foundation for Ovarian Cancer Young Investigator Award,** 2013, Felix Zeppernick, research fellow
- **Scholar-in-Training Award, American Association for Cancer Research**, 2013, Ren-Chin Wu, graduate student
- **HERA Research Award,** 2013, Fnu Yuyu, PhD, research fellow
- **Collen's Dream Foundation for ovarian cancer research award,** 2013, Felix Zeppernick, MD, research fellow
- **YW Loke Award,** 2012, Yusuke Kobayashi, MD, PhD, research fellow, award from International Federation of Placenta Associations
- **HERA Research Award,** 2012, Elizabeth Kuhn, MD, research fellow
- **Scholar-in-Training Award, American Association for Cancer Research**, 2011, Kai-Lee Yap, graduate student

- **Ovarian Cancer Research Foundation (OCRF) Award**, 2011, Bin Guan, PhD, postdoctoral fellow
- **American Society of Clinical Oncology Young Investigator Research Grant,** 2011, Stephanie Gaillard, MD, PhD, research fellow
- **Scholar-in-Training Award by Aflac, Inc.,** 2011, Kai-Lee Yap, PhD graduate student
- **HERA Research Award,** 2011, Alex Stoeck, PhD, research fellow
- **Pathology Young Investigator Award,** 2011, Kai-Lee Yap, PhD graduate student
- **Pathology Young Investigator Award,** 2011, Elisabetta Kuhn, MD research fellow
- **Pathology Young Investigator Award,** 2011, Alex Stoeck, PhD research fellow
- **International Society of Gynecologic Pathology Fellowship Award**, 2011, Laura Ardigheri, research fellow, 2011
- **HERA Research Award,** 2010, Bin Guan, PhD, research fellow
- **UICC, ICRETT award**. 2010, Marilina Mascaró, visiting PhD student, Argentina
- **Pathology Young Investigator Award,** 2010, Kai-Lee Yap, PhD graduate student
- **HERA Research Award,** 2008, Stefanie Ueda, MD, research fellow
- **Pathology Department Young Investigator First Price Award in Basic Science,** 2008, Joon Park, Johns Hopkins Medical Institutions
- **HERA Research Award,** 2007, Natini Jinawath, MD, PhD, research fellow
- **Provost's undergraduate research award,** 2007, Chanont Vasoontara, Johns Hopkins University
- **Ovarian Cancer Research Fund (OCRF)**, 2006, Ritu Salani, MD, research fellow
- **Best Abstract Award,** 2006, Ritu Salani, MD, research fellow, International Gynecologic Cancer Society biannual meeting, Santa Monica
- **Provost's undergraduate research award**, 2006, Rebecca Busch, JHU undergraduate student
- **HERA Research Award,** 2005, Kentaro Nakayama, MD, PhD, research fellow
- **First Place Award for Research Fellow in Basic Research, Johns Hopkins Oncology,** 2005, Jim Sheu, PhD, research fellow
- **International Union Against Cancer Technology Transfer Fellowship,** 2004, Gudrum Pohl, MD, research fellow
- **HERA Research Award,** 2003, Brant Wang, MD, PhD, research fellow
- **Yong Investigator Award of the International Society of Gynecologic Pathologists**, 2004, Gad Singer, MD, research fellow
- **Howard Hughes Undergraduate Research Award**, 2003, Robert J. Oldt III, JHU undergraduate student
- **Provost's undergraduate research award**, 2002, Robert J. Oldt III, JHU undergraduate student

CLINICAL ACTIVITIES

Certification

- The American Board of Pathology --- Anatomic Pathology, 1997
- Medical Licensure: Maryland, 1997

Clinical Service Responsibilities (20% of total effort) at the Johns Hopkins Hospital

- **Attending Physician**- diagnostic pathology in routine gynecologic specimens

- **Consultant Pathologist**- gynecologic pathology, specifically gestational trophoblastic diseases (nationally and internationally)

ADMINISTRATIVE AND ORGANIZATIONAL ACTIVITIES

Administrative Appointments

- Co-director, the Female Reproductive Cancer Program (in development), Kimmel Cancer Center, Johns Hopkins Medical Institutions, 2011- current. Mainly involved in program development, research planning and educational activities.
- Planning Committee, the 7th Biennial Meeting of Asia-Pacific International Academy of Pathology, 2009-2011
- Johns Hopkins Oncology Center Tissue Core oversight committee, 2013-
- Johns Hopkins Professor Promotion Committee, 2013-
- Symposium organizer, Johns Hopkins Annual Ovarian Cancer Symposium, 2009-current.
- President of International Association of Chinese Pathologists, 2006-2007; received the *Excellent Service Award*, March 2, 2008
- President of North American Taiwanese Medical Association-Baltimore chapter, 2006-2008
- Faculty promotion committee, Department of Pathology, Johns Hopkins Medical Institutions, 2004
- PhD student qualification/thesis committees, 2002-current
- Pathology residency advisory committee, 2009-current

Editorial Board Appointments

- Editor-in-Chief, Current Obstetrics and Gynecology Report (2012-)
- Cancer Research (2013-2015)
- The Journal of Pathology (2012-)
- Guest Editor, Journal of Oncology special issue in ovarian cancer targeted therapy, 2011
- International Journal of Gynecologic Pathology
- ISRN Pathology
- International Journal of Molecular Sciences (Molecular Pathology section)
- Journal of the Formosan Medical Association
- Frontiers in Women's Cancer

Journal Peer Review Activities

- Proceedings of National Academy of Science
- Cancer Research
- Clinical Cancer Research
- Oncogene
- Journal of Clinical Investigation
- Journal of Biological Chemistry
- International Journal of Cancer
- Gynecologic Oncology
- Cancer Letters
- Modern Pathology
- Placenta
- The American Journal of Pathology
- Laboratory Investigation

- Human Pathology
- The Journal of Obstetrics and Gynecology Research
- British Journal of Cancer
- International Journal of Gynecologic Pathology
- Gastroenterology
- Annals of Oncology
- American Journal of Obstetrics and Gynecology
- International Journal of Gynecologic Cancer

Professional Societies Membership

- American Association for Cancer Research, 2004-present
- American Society for Investigative Pathology, 2002-present
- International Association of Gynecologic Pathologists, 1998-present
- United States and Canadian Academy of Pathology, 1998-present
- International Society for the Study of Trophoblastic Disease, 2000-present
- Society for the Study of Reproduction, 2000-present
- American Medical Association, 1998
- International Federation of Placental Associations, 1996-present

Panelist in Study Sections and Grant Review Committees

- National Institute of Health, National Cancer Institute, member of Omnibus- Cancer Biology 1 study section, 2013
- National Institute of Health, National Cancer Institute, member of P50 SPORE study section, 2012-
- National Institute of Health, National Cancer Institute, , Ad Hoc member of Provocative Question study section, 2012
- National Institute of Health, National Cancer Institute, member of Cancer Molecular Pathobiology Study section (CAMP), 2006-2011 (*Recipient of "Brain Award" and "Humanitarian Award")
- National Institute of Health, National Cancer Institute, Ad Hoc member of R15 Academic Research Enhancement Award Study Section, 2011.
- National Institute of Health, National Cancer Institute, site visit adviser, EDRN Early Detection Network, Cancer Biomarkers Research Group, July 15, 2008
- National Institute of Health, National Cancer Institute, member of ZRG1 Onc-L (12)B Cancer Diagnostic & Treatment Study Section, March 2005, October 2005, March 2006, June 2006, February 2007 (member)
- The Wellcome Trust, London, United Kingdom, Research proposal reviewer, 1998 (Ad Hoc)
- National Institute of Health, National Cancer Institute, study section of IMAT, R21: "new innovative technology in cancer", 2002 (Ad Hoc)
- Israel Science Foundation (ISF), Research proposal reviewer, 2004 (Ad Hoc)
- US Department of Defense (USAMRMC/CDMRP) ovarian cancer research program, member of the review committee, April, 2005 (Ad Hoc)
- Cancer Research UK, April 2005, July 2008 (Ad Hoc)
- Netherlands Organization for Health Research and Development (ZonMw), Netherland, grant proposal reviewer for 80-007029-98-07041, March 2006 (Ad Hoc)
- Research Grants Council of Hong Kong, panel member and external reviewer, March 2006, December 2007

- US Department of Defense ovarian cancer research program-concept awards, member of the review committee, April, 2006 (Ad Hoc)
- Cancer Research UK, requested by the Translational Research in Clinical Trials Committee, July 2006 (Ad Hoc)
- U.S. Civilian Research Development Foundation, Arlington, Virginia, October 2006 (Ad Hoc)
- Swiss Nationals Science Foundation, Berne, Switzerland, January, 2007 (Ad Hoc)
- Kansas Masonic Foundation, Kansas Masonic Cancer Research Institute, 2007 (Ad Hoc)
- Invited reviewer requested by the Ministry of Science & Technology, Life Sciences Division, Israel, for Taiwanese Israeli scientific and technological cooperation, 2007
- Invited reviewer requested by the Sheffield Hospital Charitable Trust Medical Research Committee, UK, 2008
- Maryland Industrial Partnerships (MIPS) Program, University of Maryland College Park, 2008
- US Department of Defense (USAMRMC/CDMRP) ovarian cancer research program, member of the review committee, April, 2009 (Ad Hoc)
- American Institute of Biological Sciences (AIBS), May, 2010 (Ad Hoc)
- Calgary Laboratory Services Health Services Research Funding Competition, June, 2010 (Ad Hoc)
- National Medical Research Council, Singapore, January 2011.

Organizer, chair and moderator in conference organizations

- *Chair Moderator*, Poster Section In 4th Conference of the International Federation of Placenta Associations. Tokyo, Japan, 1998.
- *Symposium section chair,* Gestational trophoblastic disease. In XXVI International Congress of the International Academy of Pathology, Montreal, Canada, September 2006.
- *Moderator*, Pathobiology platform section, annual (the 97th) meeting of the United States and Canadian Academy of Pathology (USCAP), Denver, Colorado, March 2008.
- *Symposium organizer,* Ovarian Cancer Symposium- Elucidating Early Ovarian Carcinogenesis: Implications for Early Detection and Treatment. Sponsored by Department of Defense. Baltimore, Maryland, May 28-29, 2009.
- *Moderator,* Gynecologic Pathology platform section, annual (the 99th) meeting of the United States and Canadian Academy of Pathology (USCAP), Washington DC, March 2010.
- *Moderator,* Gynecologic Pathology platform section, annual (the 100th) meeting of the United States and Canadian Academy of Pathology (USCAP), San Antonio, TX, March 2011.
- *Section convener,* gynecologic pathology section, in the (scheduled) 7th Asia-Pacific International Academy of Pathology, Taipei, Taiwan, May 20-24, 2011.

Advisory boards, committees and consultation groups

- **Scientific Advisory Committee,** Ovarian Cancer Research Foundation (OCRF), New York, 2013-.
- **NCI Ovarian Task Force of Gynecologic Cancer Steering Committee,** 2012-2015

- **International Society of Gynecologic Pathology/World Health Organization (WHO) Nomenclature Committee for gynecological neoplasm**, 2012
- **External advisory board**, Ovarian Cancer SPORE at Fox Chase Cancer Center, 2013
- **International Society of Gynecologic Pathology Nomenclature Committee:** Gestational trophoblastic disease subcommittee, 2011-
- **Panelist** of an NIH sponsored consensus meeting for ovarian borderline tumor, Bethesda, 2003
- **Committee member** in the *National Academy for Clinical Biochemistry*-ovarian cancer marker Laboratory Medicine Practice Guidelines (tumor markers). 2003

Ad Hoc member in Award/Fellowship Committee

- Wittgenstein Award, funded by the Austrian Science Fund (FWF), 2007
- Moldovan Young Scientist Scholarship Program, United States Civilian Research & Development Foundation, 2007

RECOGNITION

Awards and Honors

- *The Best Intern Award,* McKay Memorial Hospital, Taiwan, 1988
- *TeLinde Research Award,* Division of Gynecologic Pathology, Department of Pathology, the Johns Hopkins Hospital, 1996-1998
- *Young Investigator Award,* The 13th Rochester Trophoblast Conference, Banff, Canada, 1996
- *Junior Achievement Award,* NIH/FDA Chinese American Association and Washington DC Chapter of Society of Chinese Bioscientists in America, 1998
- *Young Investigator Award,* International Society of Gynecological Pathologists, 2000.
- *Clinician Scientist Award,* Johns Hopkins University School of Medicine, 2002.

Invited Talks and Panels

- *Invited Speaker*, "Pathology of benign and malignant lesions of intermediate trophoblast". In 4th Conference of the International Federation of Placental Associations. Tokyo, Japan, 1998.
- *Invited Speaker* "Molecular surrogates of tumor progression in body fluids". Bowling Green State University, Ohio, 2001.
- *Invited Speaker,* "Molecular Landscape of Ovarian cancer and its implication for early diagnosis". Chang-Gung Memorial Hospital, Taiwan, 2002.
- *Invited Speaker,* "Gestational trophoblastic diseases", Taipei Medical University, Taiwan, 2002.
- *Invited Speaker,* "Molecular Landscape of Ovarian cancer". National Cancer Institute/NIH, 2002.
- *Invited Lecturer,* "Gestational trophoblastic diseases", Pathology Laboratory, National Cancer Institute/NIH, 2002.
- *Invited Speaker,* "Circulating tumor-released DNA as the marker for early detection of cancer". Pathology Grand Round, MD Anderson Cancer Center, January 2003.
- *Invited Lecturer,* "Pathology of gestational trophoblastic diseases", MD Anderson Cancer Center, January 2003.

- *Invited Speaker, "*Digital PCR and clinical applications". At the 11th annual meeting of "Nuclei acid-based technologies" Baltimore, June 2003.
- *Invited Speaker, "*New technologies in exploring disorders of human implantation and trophoblast". Perinatology research branch, NICHD, Detroit, May, 2003.
- *Invited Speaker, "*Pathology of intermediate trophoblastic lesions". NICHD, Detroit, May, 2003.
- *Invited Speaker, "*Allelic imbalance in detecting ovarian and other types of cancer". At the 4th Principal Investigator Meeting of "Innovative Molecular Analysis Technologies (IMAT) Program" sponsored by NIH. San Diego, June 2003.
- *Invited Speaker, "*Molecular Genetic Markers for Cancer Detection in Blood". At the Cambridge Healthtech Institute's 11th Annual Molecular Medicine Tri-Conference, San Francisco, March 2004.
- *Invited Speaker,* "Molecular pathways of ovarian cancer-translational cancer research by analyzing cancer genome". Division of epidemiology and genetics, NCI/NIH, Rockville, Maryland, September 16, 2004.
- *Invited Speaker,* "DNA preparation for cancer genomic study-the pathologist's views". Lecture in the G.O.T. (Getting Optimal Targets) summit series, Genomic and Proteomic Sample Preparation, Boston, May 3-4, 2005.
- *Invited Speaker,* "Identification of novel genes for cancer therapy and diagnosis by exploring cancer genome". 10th Annual Meeting of Chinese Biopharmaceutical Association, Rockville, Maryland, June 18, 2005.
- *Guest Speaker,* "Exploring ovarian cancer genome- new insights and old challenges". Fox Chase Cancer Center, Philadelphia, Pennsylvania, August 9, 2005.
- *Invited Speaker,* "Relationship of serous borderline tumor and carcinoma". The annual companion meeting of the International Association for Gynecologic Pathologists. Atlanta, Georgia, Feb. 12, 2006.
- *Invited Speaker,* "Identification of novel molecular targets for ovarian cancer therapy". University of Oslo. Olso, Norway, Feb. 27, 2006.
- *Invited Speaker,* "Translating Ovarian Cancer Genome- New Genes for Prognostic Prediction and Targeted Therapy". Pathology Grand Round, University of British Columbia, Vancouver, Canada, March 13, 2006.
- *Invited Speaker,* "Trophoblastic tumors and tumor-like lesions". Department of Pathology, Vancouver Hospital, Canada, March 13, 2006.
- *Invited Speaker, "Gestational trophoblastic tumor-an intellectual Odyssey".* Second Investigative Pathology Conference, Cleveland Clinics, Cleveland, Ohio, June 3, 2006
- *Invited Speaker,* "Applications of HLA-G expression in the diagnosis of human neoplastic diseases". Forth International conference on HLA-G, Paris, France, July 12, 2006.
- *Invited Speaker,* "Trophoblastic tumors- molecular classification and pathogenesis". Biennial Meeting of International Gynecological Cancer Society, Santa Monica, October 17, 2006.
- *Invited Speaker,* "Analyzing ovarian cancer genome- from gene discovery to therapeutic targets". Sloan Kettering Memorial Hospital, New York, December 11, 2006.
- *Distinguished Visiting Professor*, "Ovarian cancer- molecular pathways, diagnostic markers and therapeutic targets". Pathology Grand Round, Emory University, March 9, 2007.
- *Distinguished Visiting Professor*, "New concept in ovarian cancer- the dualistic pathway and its implications". Pathology Grand Round, Yale University School of Medicine, April 19, 2007.

- *Invited Speaker*, "Translational Research and New Diagnosis in Ovarian Cancer". The 12th Taiwan Joint Cancer Conference (Gynecologic Oncology section), Taipei, Taiwan, May 5, 2007.
- *Invited Speaker*, "Genomic analysis of ovarian cancer from marker discovery to translational applications". Taipei Medical University, Taipei, Taiwan, May 3, 2007.
- *Invited Speaker*, "Analyzing Ovarian Cancer Genome for Marker Discovery". International Symposium on Biomarkers Discovery in Human Cancers, Tainan, Taiwan, May 7, 2007.
- *Invited Speaker*, "Analyzing ovarian cancer genome for therapeutic target discovery". 12th annual meeting of SCBA, University of Maryland Shady Groove Conference Center, MD, June 2, 2007.
- *Invited Speaker*, "Update in gestational trophoblastic disease". Surgical Pathology Update, Leipzig, Germany, June 15, 2007.
- *Invited Speaker*, "The roles of NAC-1 in chemoresistance in ovarian carcinoma". The Montebello Conference, Norway, June 18, 2007.
- *Invited Speaker*, "Exploring ovarian cancer genome- from marker discovery to therapeutic targeting". Symposium of Toronto Ovarian Cancer Research Network/University of Toronto Health Network, Toronto, Canada, November 2, 2007.
- *Invited Speaker*, "Biological and clinical significance of Rsf-1 gene amplification in ovarian cancer". Grand Round at the Cancer Institute of New Jersey, April 2, 2008.
- *Invited Speaker*, "Analyzing cancer genome to identify new cancer-associated genes in ovarian cancer". In the series of Molecular Pathology seminar, University of Maryland at Baltimore, Baltimore, April 11, 2008.
- *Invited Speaker*, "Molecular etiology of drug resistance in ovarian cancer". Symposium on Ovarian Cancer Research, Medical University of South Carolina, Charleston, South Carolina, May 2, 2008.
- *Invited Speaker*, "Identifying new cancer genes through analyzing cancer genomics- Rsf-1 amplification in ovarian cancer". National Health Research Institution, Taiwan, August 5, 2008.
- *Invited Speaker*, "Early detection and treatment of ovarian cancer: shifting from early stage to minimal volume of disease based on a new model of carcinogenesis". 7th Biennial Ovarian Cancer Symposium, Marsha Rivkin Center for Ovarian Cancer Research, Charleston, Seattle, Washington, September 4-5, 2008
- *Invited Speaker*, "Functional genomic analysis of ovarian cancer", in honor of Dr. Meenhard Herlyn's achievement in cancer research, The Wistar Institute, Philadelphia, PA, August 10, 2009
- *Invited Speaker*, "Notch3 signaling in ovarian cancer", Institute of Genomic Medicine, China Medical University, Taiwan, August 21, 2009
- *Invited Speaker*, "Targeted therapy in ovarian cancer", Ovarian Cancer SPORE meeting, Fox Chase Cancer Center, Philadelphia, PA, September 26, 2009
- *Invited Speaker*, 7th International Seminar at Lake Hamana- Surgical and Molecular Pathology of the Endometrium, Placenta, and Ovary. "Pathology of gestational trophoblastic diseases", and "Molecular pathogenesis of ovarian cancer", Hamamatsu, Shizuoka, Japan, November 7, 8, 2009
- *Invited Speaker*, "Gestational trophoblastic diseases", Grand Round in the Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY, December 7, 2009
- *Invited Speaker*, "The origin and pathogenesis of epithelial ovarian cancer- a proposed unifying theory", Grand Round, Department of Gynecologic Oncology, MD Anderson Cancer Center, Houston, TX, February 1, 2010

- *Invited Speaker*, "Definition and characterization of low-grade and high-grade ovarian serous carcinomas", 2nd Annual European Gynecologic Oncology Congress, Athens, Greece, February 12-13, 2010
- *Invited Speaker*, "Clear cell carcinoma of the ovary", Gynecologic Pathology Specialty Conference, United States & Canadian Academy of Pathology, 99th annual meeting. Washington DC, March 20-26, 2010
- *Invited Speaker*, "Molecular pathology of ovarian clear cell carcinoma", University of British Columbia, Vancouver, Canada, June 24, 2010
- *Invited Speaker*, "The origin and pathogenesis of epithelial ovarian cancer- a proposed unifying theory", Fox Chase Cancer Center, Philadelphia, July 15, 2010
- *Invited Speaker*, "The origin and pathogenesis of epithelial ovarian cancer- a proposed unifying theory", Department of Pathology, Chang-Gang Memorial Hospital at Kaohsiung, Taiwan, August 12, 2010
- *Invited Speaker*, "The biological roles of NAC1 in cancer pathogenesis", Department of Developmental Biology and Regeneration Medicine, Mount Sinai School of Medicine, New York City, New York, September 2, 2010
- *Invited Speaker*, "Chromatin remodeling in ovarian cancer", Department of Molecular and Cellular Biology, Rutgers University, New Jersey, January 11, 2011
- *Invited Speaker*, "Genomic analysis of gynecological cancer", National Cancer Research Center, Tokyo, Japan, June 30, 2011
- *Invited Keynote Speaker*, "Ovarian cancer is an imported disease- fiction or fact", The 10th annual meeting of targeted therapy in gynecologic oncology, Izumo, Shimane, Japan, July 2, 2011
- *Invited Keynote Speaker*, "Pathogenesis of ovarian clear cell carcinoma", The 10th annual meeting of targeted therapy in gynecologic oncology, Izumo, Shimane, Japan, July 2, 2011
- *Invited Speaker*, "Diagnosis of biological implication of serous tubal intraepithelial carcinoma", Chang-Kung Memorial Hospital, Kaohsiung, Taiwan, July 6, 2011
- *Invited Speaker*, "Ovarian cancer genetics- latest insight", The Boehringer Ingelheim Conversations in Oncology, Vienna, Austria, October 28-29, 2011
- *Invited Speaker*, "Integrated molecular analysis of ovarian cancer", Virginia Polytechnic Institute and State University, Arlington, Virginia, February 22, 2012.
- *Invited Speaker,* "Intertumoral heterogeneity- how many types of cancers do my patients have?" In the symposium of "Intratumoral and intertumoral heterogeneity in ovarian cancer", American Association for Cancer Research (AACR) annual meeting, Chicago, April 2, 2012
- *Invited Speaker*, "Genomic landscape in gynecologic cancer and its biological and translation implications", Department of Pathology and Laboratory Medicine, University of California at Irvine, April 16, 2012.
- *Lecture,* "Molecular analysis of serous tubal intraepithelial carcinoma", the 3rd Johns Hopkins Ovarian Cancer Symposium, Baltimore, Maryland, May 18, 2012.
- *Invited Keynote Speaker*, "Endometriosis-related ovarian cancer", The 16th Korea-Japan, the 2nd Korea-Taiwan-Japan Joint Conference for Gynecological Pathology, Kumamoto University, Kumamoto City, Japan, May 26, 2012.
- *Invited Speaker*, "Genomic landscape in gynecologic cancer- a road map to new therapeutics", Bristol-Myers Squibb Lectureship, Kumamoto City, Japan, May 27, 2012.
- *Invited Speaker*, "Genomic landscape in gynecologic cancer- a road map to new therapeutics", Kyoto University, Kyoto, Japan, May 29, 2012.

- *Invited Keynote Speaker*, "Genomic analysis of gynecological cancer and their clinical implications", In annual meeting of Korean Division of International Association of Pathologists, Seoul, South Korea, October 18, 2012.
- *Invited Speaker*, "The tumor suppressor role of ARID1A in human cancer", Kyung Hee University, Seoul, South Korea, October 18, 2012.
- *Invited Speaker*, "The tumor suppressor role of ARID1A in human cancer", Korean National Cancer Center, Seoul, South Korea, October 19, 2012.
- *Invited Speaker*, "The origin of ovarian cancer- clear cell carcinoma", International Society of Gynecologic Pathologists companion meeting of United States and Canadian Association of Pathology annual meeting, Baltimore, Maryland, March 3, 2013.
- *Invited Speaker*, "Genomic landscape of ovarian cancer and its translational implications", The Wistar Institute, Philadelphia, April 15, 2013.
- *Invited Speaker*, "Molecular alterations in serous tubal intraepithelial carcinoma", 4th Ovarian Cancer Symposium, the Memorial Sloan Kettering Cancer Center, New York, May 15, 2013.
- *Invited Speaker*, "Emerging therapeutics in gynecologic cancer", China Medical University, Taichung, Taiwan, July 7, 2013
- *Invited Speaker*, "Bokhman's dualistic model of endometrial carcinoma- revisited", Chang-Kung Memorial Hospital, Kaohsiung, Taiwan, July 8, 2013
- *Invited Speaker*, "Genomic analysis and pathogenesis of uterine carcinoma", Taipei Veterans General Hospital, Taipei, Taiwan, July 11, 2013.
- *Invited Speaker*, "The Genomic landscape and origin of ovarian cancer", The 18th Taiwan Joint Cancer conference, Taipei, Taiwan, July 13, 2013.
- *Invited Lecturer*, "The origin and pathogenesis of ovarian cancer", The 2013 International Diagnostic Pathology Course, Tokyo, Japan, July 14, 2013.
- *Invited Speaker*, "Ovarian cancer is an imported disease- fiction or fact?" Charite Hospital (Mitt campus), Berlin, Germany, September 11, 2013
- *Invited Lecturer*, "Various topics in gynecologic pathology and oncology", Nederland Master Class in ovarian cancer. Berlin, Germany, September 12, 2013
- *Invited Lecturer*, "Understanding the molecular mechanisms in the development of chemoresistance in cancer", Rush University Medical Center, Chicago, October 30, 2013
- *Invited Speaker*, "Ovarian cancer is an imported disease – translational implication and beyond", Ovarian Cancer SPORE meeting, MD Anderson Cancer Center, Houston, TX, May 28, 2014
- *Invited Speaker*, "Molecular pathogenesis of high-grade serous carcinoma". Symposium of the National Gynecologic Oncology Group (NGR, GOG). Chicago, July 9, 2014

OTHER NONPROFESSIONAL ACTIVITIES

Photography website: http://www.shih-photography.com

United States Patent **6,440,706**
Vogelstein , et al. **August 27, 2002**

Digital amplification

Claims

What is claimed is:

1. A method for determining the ratio of a selected genetic sequence in a population of genetic sequences, comprising the steps of: diluting nucleic acid template molecules in a biological sample to form a set comprising a plurality of assay samples; amplifying the template molecules within the assay samples to form a population of amplified molecules in the assay samples of the set; analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain the selected genetic sequence and a second number of assay samples which contain a reference genetic sequence; comparing the first number to the second number to ascertain a ratio which reflects the composition of the biological sample.

2. The method of claim 1 wherein the step of diluting is performed until at least one-tenth of the assay samples in the set comprise a number (N) of molecules such that 1/N is larger than the ratio of selected genetic sequences to total genetic sequences required for the step of analyzing to determine the presence of the selected genetic sequence.

3. The method of claim 1 wherein the step of diluting is performed until between 0.1 and 0.9 of the assay samples yield an amplification product when subjected to a polymerase chain reaction.

4. The method of claim 1 wherein the step of diluting is performed until all of the assay samples yield an amplification product when subjected to a polymerase chain reaction and each assay sample contains less than 10 nucleic acid template molecules containing the reference genetic sequence.

5. The method of claim 1 wherein the step of diluting is performed until all of the assay samples yield an amplification product when subjected to a polymerase chain reaction and each assay sample contains less than 100 nucleic acid template molecules containing the reference genetic sequence.

6. The method of claim 1 wherein the biological sample is cell-free.

7. The method of claim 1 wherein the number of assay samples within the set is greater than 10.

8. The method of claim 1 wherein the number of assay samples within the set is greater than 50.

9. The method of claim 1 wherein the number of assay samples within the set is greater than 100.

10. The method of claim 1 wherein the number of assay samples within the set is greater than 500.

11. The method of claim 1 wherein the number of assay samples within the set is greater than 1000.

12. The method of claim 1 wherein the step of amplifying and the step of analyzing are performed on assay samples in the same receptacle.

13. The method of claim 1 wherein a molecular beacon probe is used in the step of analyzing, wherein a molecular beacon probe is an oligonucleotide with a stem-loop structure having a photoluminescent dye at one of the 5' or 3' ends and a quenching agent at the opposite 5' or 3' end.

14. The method of claim 1 wherein the step of analyzing employs gel electrophoresis.

15. The method of claim 1 wherein the step of analyzing employs hybridization to at least one nucleic acid probe.

16. The method of claim 1 wherein the step of analyzing employs hybridization to at least two nucleic acid probe.

17. The method of claim 13 wherein two molecular beacon probes are used, each having a different photoluminescent dye.

18. The method of claim 13 wherein the molecular beacon probe detects a wild-type selected genetic sequence better than a mutant selected genetic sequence.

19. The method of claim 1 wherein the step of amplifying employs a single pair of primers.

20. The method of claim 1 wherein the step of amplifying employs a polymerase which is activated only after heating.

21. The method of claim 1 wherein the step of amplifying employs at least 40 cycles of heating and cooling.

22. The method of claim 1 wherein the step of amplifying employs at least 50 cycles of heating and cooling.

23. The method of claim 1 wherein the step of amplifying employs at least 60 cycles of heating and cooling.

24. The method of claim 1 wherein the biological sample is selected from the group consisting of stool, blood, and lymph nodes.

25. The method of claim 1 wherein the biological sample is blood or bone marrow of a leukemia or lymphoma patient who has received anti-cancer therapy.

26. The method of claim 1 wherein the selected genetic sequence is a translocated allele.

27. The method of claim 1 wherein the selected genetic sequence is a wild-type allele.

28. The method of claim 1 wherein the selected genetic sequence is within an amplicon which is amplified during neoplastic development.

29. The method of claim 1 wherein the selected genetic sequence is a rare exon sequence.

30. The method of claim 1 wherein the nucleic acid template molecules comprise cDNA of RNA transcripts and the selected genetic sequence is present on a cDNA of a first transcript and the reference genetic sequence is present on a cDNA of a second transcript.

31. The method of claim 1 wherein the selected genetic sequence comprises a first mutation and the reference genetic sequence comprises a second mutation.

32. The method of claim 1 wherein the selected genetic sequence and the reference genetic sequence are on distinct chromosomes.

33. A molecular beacon probe comprising: an oligonucleotide with a stem-loop structure having a photoluminescent dye at one of the 5' or 3' ends and a quenching agent at the opposite 5' or 3' end, wherein the loop consists of 16 base pairs, wherein the loop has a T.sub.m of 50-51.degree. C. and the stem consists of 4 base pairs having a sequence 5'-CACG-3'.

34. The probe of claim 33 wherein the molecular beacon probe detects a wild-type selected genetic sequence better than a mutant selected genetic sequence.

35. The probe of claim 33 wherein the molecular beacon probe detects a mutant genetic sequence better than a wild-type genetic sequence.

36. A molecular beacon probe comprising: an oligonucleotide with a stem-loop structure having a photoluminescent dye at one of the 5' or 3' ends and a quenching agent at the opposite 5' or 3' end, wherein the loop consists of 19-20 base pairs, wherein the loop has a T.sub.m of 54-56.degree. C. and the stem consists of 4 base pairs having a sequence 5'-CACG-3'.

37. A pair of molecular beacon probes comprising: a first molecular beacon probe which is an oligonucleotide with a stem-loop structure having a first photoluminescent dye at one of the 5' or 3' ends and a quenching agent at the opposite 5' or 3' end, wherein the loop consists of 16 base pairs having a T.sub.m of 50-51.degree. C. and the stem consists of 4 base pairs having a sequence 5'-CACG-3'; and a second molecular beacon probe which is an oligonucleotide with a stem-loop structure having a second photoluminescent dye at one of the 5' or 3' ends and a quenching agent at the opposite 5' or 3' end, wherein the loop consists of 19-20 base pairs having a T.sub.m of 54-56.degree. C. and the stem consists of 4 base pairs having a sequence 5'-CACG-

3'; wherein the first and the second photoluminescent dyes are distinct.

38. A method for determining the ratio of a selected genetic sequence in a population of genetic sequences, comprising the steps of: amplifying template molecules within a set comprising a plurality of assay samples to form a population of amplified molecules in each of the assay samples of the set; analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain the selected genetic sequence and a second number of assay samples which contain a reference genetic sequence, wherein at least one-fiftieth of the assay samples in the set comprise a number (N) of molecules such that 1/N is larger than the ratio of selected genetic sequences to total genetic sequences required to determine the presence of the selected genetic sequence; comparing the first number to the second number to ascertain a ratio which reflects the composition of the biological sample.

39. The method of claim 38 wherein the number of assay samples within the set is greater than 10.

40. The method of claim 38 wherein the number of assay samples within the set is greater than 50.

41. The method of claim 38 wherein the number of assay samples within the set is greater than 100.

42. The method of claim 38 wherein the number of assay samples within the set is greater than 500.

43. The method of claim 38 wherein the number of assay samples within the set is greater than 1000.

44. The method of claim 38 wherein the step of amplifying and the step of analyzing are performed on assay samples in the same receptacle.

45. The method of claim 38 wherein a molecular beacon probe is used in the step of analyzing, wherein a molecular beacon probe is an oligonucleotide with a stem-loop structure having a photoluminescent dye at one of the 5' or 3' ends and a quenching agent at the opposite 5' or 3' end.

46. The method of claim 38 wherein the step of analyzing employs gel electrophoresis.

47. The method of claim 38 wherein the step of analyzing employs hybridization to at least one nucleic acid probe.

48. The method of claim 38 wherein the step of analyzing employs hybridization to at least two nucleic acid probe.

49. The method of claim 45 wherein two molecular beacon probes are used, each having a different photoluminescent dye.

50. The method of claim 45 wherein the molecular beacon probe detects a wild-type selected genetic sequence better than a mutant selected genetic sequence.

51. The method of claim 38 wherein the step of amplifying employs a single pair of primers.

52. The method of claim 38 wherein the step of amplifying employs a polymerase which is activated only after heating.

53. The method of claim 38 wherein the step of amplifying employs at least 40 cycles of heating and cooling.

54. The method of claim 38 wherein the step of amplifying employs at least 50 cycles of heating and cooling.

55. The method of claim 38 wherein the step of amplifying employs at least 60 cycles of heating and cooling.

56. The method of claim 38 wherein the template molecules are obtained from a body sample selected from the group consisting of stool, blood, and lymph nodes.

57. The method of claim 38 wherein the template molecules are obtained from a body sample of a leukemia or lymphoma patient who has received anti-cancer therapy, said body sample being selected from the group consisting of blood and bone marrow.

58. The method of claim 38 wherein the selected genetic sequence is a translocated allele.

59. The method of claim 38 wherein the selected genetic sequence is a wild-type allele.

60. The method of claim 38 wherein the selected genetic sequence is within an amplicon which is amplified during neoplastic development.

61. The method of claim 38 wherein the selected genetic sequence is a rare exon sequence.

62. The method of claim 38 wherein the nucleic acid template molecules comprise cDNA of RNA transcripts and the selected genetic sequence is present on a cDNA of a first transcript and the reference genetic sequence is present on a cDNA of a second transcript.

63. The method of claim 38 wherein the selected genetic sequence comprises a first mutation and the reference genetic sequence comprises a second mutation.

64. The method of claim 38 wherein the selected genetic sequence and the reference genetic sequence are on distinct chromosomes.

Digital amplification

Claims

The invention claimed is:

1. A method for determining an allelic imbalance in a biological sample, comprising the steps of: amplifying template molecules within a set comprising a plurality of assay samples to form a population of amplified molecules in each of the assay samples of the set, wherein the template molecules are obtained from a biological sample; analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a selected genetic sequence on a first chromosome and a second number of assay samples which contain a reference genetic sequence on a second chromosome, wherein between 0.1 and 0.9 of the assay samples yield an amplification product; comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance in the biological sample.

2. The method of claim 1 wherein the step of amplifying employs real-time polymerase chain reactions.

3. The method of claim 2 wherein the real-time polymerase chain reactions comprise a dual-labeled fluorogenic probe.

4. The method of claim 1 wherein the selected genetic sequence and the reference genetic sequence are non-polymorphic markers.

5. The method of claim 1 wherein the biological sample is from blood.

6. The method of claim 1 wherein the selected genetic sequence is a non-polymorphic marker.

7. The method of claim 1 wherein the reference genetic sequence is a non-polymorphic marker.

8. The method of claim 1 wherein between 0.1 and 0.6 of the assay samples yield an amplification product.

9. The method of claim 1 wherein between 0.3 and 0.5 of the assay samples yield an amplification product.

10. The method of claim 1 wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the selected genetic sequence.

11. The method of claim 1 wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the reference genetic sequence.

12. The method of claim 1 wherein between 0.1 and 0.6 of the assay samples yield an amplification product as determined by amplification of the selected genetic sequence.

13. The method of claim 1 wherein between 0.1 and 0.6 of the assay samples yield an amplification product as determined by amplification of the reference genetic sequence.

14. The method of claim 1 wherein between 0.3 and 0.5 of the assay samples yield an amplification product as determined by amplification of the selected genetic sequence.

15. The method of claim 1 wherein between 0.3 and 0.5 of the assay samples yield an amplification product as determined by amplification of the reference genetic sequence.

16. The method of claim 1 wherein the set comprises at least 500 assay samples.

17. The method of claim 1 wherein the set comprises at least 1000 assay samples.

18. The method of claim 1 wherein the amplified molecules in each of the assay samples in the first and second numbers of assay samples are homogeneous such that the first number of assay samples do not contain the reference genetic sequence and the second number of assay samples do not contain the selected genetic sequence.

19. A method for determining an allelic imbalance in a biological sample, comprising the steps of: distributing nucleic acid template molecules from a biological sample to form a set comprising a plurality of assay samples; amplifying the template molecules within the assay samples to form a population of amplified molecules in the assay samples of the set; analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a selected genetic sequence on a first chromosome and a second number of assay samples which contain a reference genetic sequence on a second chromosome; comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance between the first chromosome and the second chromosome in the biological sample.

20. The method of claim 19 wherein between 0.1 and 0.9 of the assay samples yield an amplification product.

21. The method of claim 20 wherein between 0.1 and 0.9 of the assay samples yield a homogeneous amplification product.

22. The method of claim 19 wherein the biological sample is blood.

Digital amplification

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Claims

The invention claimed is:

1. A method for determining an allelic imbalance in a biological sample, comprising the steps of: amplifying template molecules within a set comprising a plurality of assay samples to form a population of amplified molecules in each of the assay samples of the set, wherein the template molecules are obtained from the biological sample; analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker, wherein between 0.1 and 0.9 of the assay samples yield an amplification product; comparing the first number to the second number to ascertain an allelic imbalance in the biological sample; and identifying an allelic imbalance in the biological sample.

2. The method of claim 1 wherein the step of amplifying employs real-time polymerase chain reactions.

3. The method of claim 2 wherein the real-time polymerase chain reactions comprise a dual-labeled fluorogenic probe.

4. The method of claim 1 wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the first allelic form of the marker.

5. The method of claim 1 wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the second allelic form of the marker.

6. The method of claim 1 wherein the amplified molecules in each of the assay samples within the first and second numbers of assay samples are homogeneous such that the first number of assay samples do not contain the second allelic form of the marker and the second number of assay samples do not contain the first allelic form of the marker.

7. The method of claim 1 wherein the sample is from blood.

8. A method for determining an allelic imbalance in a biological sample, comprising the steps of: distributing nucleic acid template molecules from a biological sample to form a set comprising a plurality of assay samples; amplifying the template molecules within the assay samples to form a population of amplified molecules in the assay samples of the set; analyzing the amplified

molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker; comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance between the first allelic form and the second allelic form in the biological sample.

9. The method of claim 8 wherein the sample is from blood.

10. The method of claim 1 or 8 wherein between 0.1 and 0.6 of the assay samples yield an amplification product.

11. The method of claim 1 or 8 wherein between 0.3 and 0.5 of the assay samples yield an amplification product.

12. The method of claim 1 or 8 wherein the set comprises at least 500 assay samples.

13. The method of claim 1 or 8 wherein the set comprises at least 1000 assay samples.

14. The method of claim 8 wherein the step of amplifying employs real-time polymerase chain reactions.

15. The method of claim 14 wherein the real-time polymerase chain reactions comprise a dual-labeled fluorogenic probe.

16. The method of claim 8 wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the first allelic form of the marker.

17. The method of claim 8 wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the second allelic form of the marker.

18. The method of claim 8 wherein the amplified molecules in each of the assay samples within the first and second numbers of assay samples are homogeneous such that the first number of assay samples do not contain the second allelic form of the marker and the second number of assay samples do not contain the first allelic form of the marker.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Ex Parte* Reexamination:	)	Group Art Unit: 3991
	)	
U.S. Patent No. 6,440,706	)	Docket No. 001107.00989
	)	
Control No. 90/012,894	)	Confirmation No: 8442
	)	
Reexam Filing Date: June 17, 2013	)	Examiner: Bruce R. Campell

For: DIGITAL AMPLIFICATION

RESPONSIVE AMENDMENT TO FINAL OFFICE ACTION

IN THE CLAIMS

Please amend the following claims as indicated by the status identifier. Patent claims under reexamination but not amended are indicated as "original." Patent claims not subject to reexamination are not shown.

1. (Amended) A method for determining the ratio of a selected genetic sequence in a population of genetic sequences, comprising the steps of:

diluting isolated nucleic acid template molecules [in] isolated from a biological sample to form a set comprising a plurality of assay samples;

amplifying the template molecules within the assay samples to form a population of amplified molecules in the assay samples of the set;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain the selected genetic sequence and a second number of assay samples which contain a reference genetic sequence;

comparing the first number to the second number to ascertain a ratio which reflects the composition of the biological sample.

2. (Original) The method of claim 1 wherein the step of diluting is performed until at least one-tenth of the assay samples in the set comprise a number (N) of molecules such that 1/N is larger than the ratio of selected genetic sequences to total genetic sequences required for the step of analyzing to determine the presence of the selected genetic sequence.

3. (Amended) The method of claim 1 wherein the step of diluting is performed until between 0.1 and 0.9 of the assay samples yield an amplification product of at least one of the selected and reference genetic sequences when subjected to a polymerase chain reaction.

4. (Original) The method of claim 1 wherein the step of diluting is performed until all of the assay samples yield an amplification product when subjected to a polymerase chain reaction and each assay sample contains less than 10 nucleic acid template molecules containing the reference genetic sequence.

5. (Original) The method of claim 1 wherein the step of diluting is performed until all of the assay samples yield an amplification product when subjected to a polymerase chain reaction and each assay sample contains less than 100 nucleic acid template molecules containing the reference genetic sequence.

6. (Original) The method of claim 1 wherein the biological sample is cell-free.

7. (Original) The method of claim 1 wherein the number of assay samples within the set is greater than 10.

8. (Original) The method of claim 1 wherein the number of assay samples within the set is greater than 50.

9. (Original) The method of claim 1 wherein the number of assay samples within the set is greater than 100.

10. (Original) The method of claim 1 wherein the number of assay samples within the set is greater than 500.

11. (Original) The method of claim 1 wherein the number of assay samples within the set is greater than 1000.

12. (Original) The method of claim 1 wherein the step of amplifying and the step of analyzing are performed on assay samples in the same receptacle.

13. (Not subject to reexamination)

14. (Original) The method of claim 1 wherein the step of analyzing employs gel electrophoresis.

15. (Original) The method of claim 1 wherein the step of analyzing employs hybridization to at least one nucleic acid probe.

16. (Original) The method of claim 1 wherein the step of analyzing employs hybridization to at least two nucleic acid probe.

17-18. (Not subject to reexamination)

19. (Original) The method of claim 1 wherein the step of amplifying employs a single pair of primers.

20. (Original) The method of claim 1 wherein the step of amplifying employs a polymerase which is activated only after heating.

21. (Original) The method of claim 1 wherein the step of amplifying employs at least 40 cycles of heating and cooling.

22. (Original) The method of claim 1 wherein the step of amplifying employs at least 50 cycles of heating and cooling.

23. (Original) The method of claim 1 wherein the step of amplifying employs at least 60 cycles of heating and cooling.

24. (Original) The method of claim 1 wherein the biological sample is selected from the group consisting of stool, blood, and lymph nodes.

25. (Original) The method of claim 1 wherein the biological sample is blood or bone marrow of a leukemia or lymphoma patient who has received anti-cancer therapy.

26. (Original) The method of claim 1 wherein the selected genetic sequence is a

translocated allele.

27. (Original) The method of claim 1 wherein the selected genetic sequence is a wild-type allele.

28. (Original) The method of claim 1 wherein the selected genetic sequence is within an amplicon which is amplified during neoplastic development.

29. (Original) The method of claim 1 wherein the selected genetic sequence is a rare exon sequence.

30. (Original) The method of claim 1 wherein the nucleic acid template molecules comprise cDNA of RNA transcripts and the selected genetic sequence is present on a cDNA of a first transcript and the reference genetic sequence is present on a cDNA of a second transcript.

31. (Original) The method of claim 1 wherein the selected genetic sequence comprises a first mutation and the reference genetic sequence comprises a second mutation.

32. (Original) The method of claim 1 wherein the selected genetic sequence and the reference genetic sequence are on distinct chromosomes.

33-37. (Not subject to reexamination)

38. (Twice amended) A method for determining the ratio of a selected genetic sequence in a population of genetic sequences, comprising the steps of:

distributing cell-free nucleic acid template molecules from a biological sample to form a set comprising a plurality of assay samples;

amplifying the nucleic acid template molecules [within a set comprising a plurality of assay samples] to form a population of amplified molecules in [each of the] individual assay samples of the set;

analyzing the amplified molecules in the assay samples of the set to determine a first

number of assay samples which contain the selected genetic sequence and a second number of assay samples which contain a reference genetic sequence, wherein at least one-fiftieth of the assay samples in the set comprise a number (N) of molecules such that 1/N is larger than the ratio of selected genetic sequences to total genetic sequences required to determine the presence of the selected genetic sequence;

comparing the first number to the second number to ascertain a ratio which reflects the composition of the biological sample.

39. (Original) The method of claim 38 wherein the number of assay samples within the set is greater than 10.

40. (Original) The method of claim 38 wherein the number of assay samples within the set is greater than 50.

41. (Original) The method of claim 38 wherein the number of assay samples within the set is greater than 100.

42. (Original) The method of claim 38 wherein the number of assay samples within the set is greater than 500.

43. (Original) The method of claim 38 wherein the number of assay samples within the set is greater than 1000.

44. (Original) The method of claim 38 wherein the step of amplifying and the step of analyzing are performed on assay samples in the same receptacle.

45. (Not subject to reexamination)

46. (Original) The method of claim 38 wherein the step of analyzing employs gel electrophoresis.

47. (Original) The method of claim 38 wherein the step of analyzing employs hybridization to at least one nucleic acid probe.

48. (Amended) The method of claim 38 wherein the step of analyzing employs hybridization to at least two nucleic acid [probe] probes.

49-50. (Not subject to reexamination)

51. (Original) The method of claim 38 wherein the step of amplifying employs a single pair of primers.

52. (Original) The method of claim 38 wherein the step of amplifying employs a polymerase which is activated only after heating.

53. (Original) The method of claim 38 wherein the step of amplifying employs at least 40 cycles of heating and cooling.

54. (Original) The method of claim 38 wherein the step of amplifying employs at least 50 cycles of heating and cooling.

55. (Original) The method of claim 38 wherein the step of amplifying employs at least 60 cycles of heating and cooling.

56. (Original) The method of claim 38 wherein the template molecules are obtained from a body sample selected from the group consisting of stool, blood, and lymph nodes.

57. (Original) The method of claim 38 wherein the template molecules are obtained from a body sample of a leukemia or lymphoma patient who has received anti-cancer therapy, said body sample being selected from the group consisting of blood and bone marrow.

58. (Original) The method of claim 38 wherein the selected genetic sequence is a translocated allele.

59. (Original) The method of claim 38 wherein the selected genetic sequence is a wild-type allele.

60. (Original) The method of claim 38 wherein the selected genetic sequence is within an amplicon which is amplified during neoplastic development.

61. (Original) The method of claim 38 wherein the selected genetic sequence is a rare exon sequence.

62. (Original) The method of claim 38 wherein the nucleic acid template molecules comprise cDNA of RNA transcripts and the selected genetic sequence is present on a cDNA of a first transcript and the reference genetic sequence is present on a cDNA of a second transcript.

63. (Original) The method of claim 38 wherein the selected genetic sequence comprises a first mutation and the reference genetic sequence comprises a second mutation.

64. (Original) The method of claim 38 wherein the selected genetic sequence and the reference genetic sequence are on distinct chromosomes.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Ex Parte* Reexamination:	)	Group Art Unit: 3991
	)	
U.S. Patent No. 7,824,889	)	Docket No. 001107.00990
	)	
Control No. 90/012,895	)	Confirmation No: 7285
	)	
Reexam Filing Date: June 17, 2013	)	Examiner: Bruce R. Campell

For: DIGITAL AMPLIFICATION

RESPONSIVE AMENDMENT TO FINAL OFFICE ACTION

IN THE CLAIMS

Please amend the claims as shown below with the standard markings for re-examination proceedings. Patent claims under reexamination but not amended are indicated as "original." Patent claims not subject to reexamination are not shown.

1. (Amended) A method for determining an allelic imbalance in a biological sample, comprising the steps of:

distributing isolated nucleic acid template molecules to form a set comprising a plurality of assay samples, wherein the nucleic acid template molecules are isolated from the biological sample;

amplifying the template molecules within [a] the set [comprising a plurality of assay samples] to form a population of amplified molecules in [each of the] individual assay samples of the set [, wherein the template molecules are obtained from a biological sample];

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a selected genetic sequence on a first chromosome and a second number of assay samples which contain a reference genetic sequence on a second chromosome, wherein between 0.1 and 0.9 of the assay samples yield an amplification product of at least one of the selected and the reference genetic sequences;

comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance in the biological sample.

2. (Original) The method of claim 1 wherein the step of amplifying employs real-time polymerase chain reactions.

3. (Original) The method of claim 2 wherein the real-time polymerase chain reactions comprise a dual-labeled fluorogenic probe.

4. (Original) The method of claim 1 wherein the selected genetic sequence and the reference genetic sequence are non-polymorphic markers.

5. (Original) The method of claim 1 wherein the biological sample is from blood.

6. (Original) The method of claim 1 wherein the selected genetic sequence is a non-polymorphic marker.

7. (Original) The method of claim 1 wherein the reference genetic sequence is a non-polymorphic marker.

8. (Amended) The method of claim 1 wherein between 0.1 and 0.6 of the assay samples yield an amplification product of at least one of the selected and the reference genetic sequences.

9. (Amended) The method of claim 1 wherein between 0.3 and 0.5 of the assay samples yield an amplification product of at least one of the selected and the reference genetic sequences.

10. (Amended) The method of claim 1 further comprising the step of isolating nucleic acid template molecules from the biological sample prior to the step of distributing [wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the selected genetic sequence].

11. (Amended) The method of claim 19 further comprising the step of isolating nucleic acid template molecules from the biological sample to form cell-free nucleic acid template molecules prior to the step of distributing [wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the reference genetic sequence].

12. (Amended) The method of claim 1 wherein between 0.1 and 0.6 of the assay samples yield [an] a homogeneous amplification product of at least one of the selected and the reference genetic sequences [as determined by amplification of the selected genetic sequence].

13. (Amended) The method of claim [1] 19 wherein between 0.1 and 0.6 of the assay samples yield an amplification of at least one of the selected and the reference genetic sequences [product as determined by amplification of the reference genetic sequence].

14. (Amended) The method of claim 1 wherein between 0.3 and 0.5 of the assay samples

yield [an] a homogeneous amplification product of at least one of the selected and the reference genetic sequences [as determined by amplification of the selected genetic sequence].

15. (Amended) The method of claim [1] 19 wherein between 0.3 and 0.5 of the assay samples yield an amplification product of at least one of the selected and the reference genetic sequences [as determined by amplification of the reference genetic sequence].

16. (Original) The method of claim 1 wherein the set comprises at least 500 assay samples.

17. (Original) The method of claim 1 wherein the set comprises at least 1000 assay samples.

18. (Original) The method of claim 1 wherein the amplified molecules in each of the assay samples in the first and second numbers of assay samples are homogeneous such that the first number of assay samples do not contain the reference genetic sequence and the second number of assay samples do not contain the selected genetic sequence.

19. (Amended) A method for determining an allelic imbalance in a biological sample, comprising the steps of:

distributing cell-free nucleic acid template molecules from a biological sample to form a set comprising a plurality of assay samples;

amplifying the template molecules within the assay samples to form a population of amplified molecules in the assay samples of the set;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a selected genetic sequence on a first chromosome and a second number of assay samples which contain a reference genetic sequence on a second chromosome;

comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance between the first chromosome and the second chromosome in the biological sample.

20. (Amended) The method of claim 19 wherein between 0.1 and 0.9 of the assay samples yield an amplification product of at least one of the selected and the reference genetic sequences.

21. (Amended) The method of claim 20 wherein between 0.1 and 0.9 of the assay samples yield a homogeneous amplification product of at least one of the selected and the reference genetic sequences.

22. (Original) The method of claim 19 wherein the biological sample is blood.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re *Ex Parte* Reexamination:	)	Group Art Unit: 3991
	)	
U.S. Patent No. 7,915,015	)	Docket No. 001107.00988
	)	
Control No. 90/012,896	)	Confirmation No: 8361
	)	
Reexam Filing Date: June 17, 2013	)	Examiner: Bruce R. Campell

For: DIGITAL AMPLIFICATION

RESPONSIVE AMENDMENT TO FINAL OFFICE ACTION

IN THE CLAIMS

Please amend the following claims as indicated by the status identifier. Patent claims under reexamination but not amended are indicated as "original." Patent claims not subject to reexamination are not shown.

1. (Amended) A method for determining an allelic imbalance in a biological sample, comprising the steps of:

distributing isolated nucleic acid template molecules to form a set comprising a plurality of assay samples, wherein the nucleic acid template molecules are isolated from the biological sample;

amplifying the isolated nucleic acid template molecules within [a] the set [comprising a plurality of assay samples] to form a population of amplified molecules in [each of the] individual assay samples of the set[, wherein the template molecules are obtained from the biological sample];

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker, wherein between 0.1 and 0.9 of the assay samples yield an amplification product of at least one of the first and second allelic forms of the marker;

comparing the first number to the second number to ascertain an allelic imbalance in the biological sample; and

identifying an allelic imbalance in the biological sample.

2. (Original) The method of claim 1 wherein the step of amplifying employs real-time polymerase chain reactions.

3. (Original) The method of claim 2 wherein the real-time polymerase chain reactions comprise a dual-labeled fluorogenic probe.

4. (Amended) The method of claim 1 further comprising the step of isolating template nucleic acid molecules from the biological sample prior to the step of distributing [wherein

between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the first allelic form of the marker].

5. (Amended) The method of claim 1 wherein the step of distributing the isolated nucleic acid template molecules is performed by diluting [wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the second allelic form of the marker].

6. (Original) The method of claim 1 wherein the amplified molecules in each of the assay samples within the first and second numbers of assay samples are homogeneous such that the first number of assay samples do not contain the second allelic form of the marker and the second number of assay samples do not contain the first allelic form of the marker.

7. (Original) The method of claim 1 wherein the sample is from blood.

8. (Amended) A method for determining an allelic imbalance in a biological sample, comprising the steps of:

distributing cell-free nucleic acid template molecules from a biological sample to form a set comprising a plurality of assay samples;

amplifying the template molecules within the assay samples to form a population of amplified molecules in the assay samples of the set;

analyzing the amplified molecules in the assay samples of the set to determine a first number of assay samples which contain a first allelic form of a marker and a second number of assay samples which contain a second allelic form of the marker;

comparing the first number of assay samples to the second number of assay samples to ascertain an allelic imbalance between the first allelic form and the second allelic form in the biological sample.

9. (Original) The method of claim 8 wherein the sample is from blood.

10. (Amended) The method of claim 1 or 8 wherein between 0.1 and 0.6 of the assay

samples yield an amplification product of at least one of the first and second allelic forms of the marker.

11. (Amended) The method of claim 1 or 8 wherein between 0.3 and 0.5 of the assay samples yield an amplification product of at least one of the first and second allelic forms of the marker.

12. (Original) The method of claim 1 or 8 wherein the set comprises at least 500 assay samples.

13. (Original) The method of claim 1 or 8 wherein the set comprises at least 1000 assay samples.

14. (Original) The method of claim 8 wherein the step of amplifying employs real-time polymerase chain reactions.

15. (Original) The method of claim 14 wherein the real-time polymerase chain reactions comprise a dual-labeled fluorogenic probe.

16. (Amended) The method of claim 8 wherein the step of distributing is performed by diluting [between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the first allelic form of the marker] .

17. (Amended) The method of claim 8 further comprising the step of isolating cell-free nucleic acid template molecules from the biological sample prior to the step of distributing [wherein between 0.1 and 0.9 of the assay samples yield an amplification product as determined by amplification of the second allelic form of the marker].

18. (Original) The method of claim 8 wherein the amplified molecules in each of the assay samples within the first and second numbers of assay samples are homogeneous such that

the first number of assay samples do not contain the second allelic form of the marker and the second number of assay samples do not contain the first allelic form of the marker.