UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ARIOSA DIAGNOSTICS

Petitioner,

v.

THE BOARD OF TRUSTEES OF THE LELAND

STANFORD JUNIOR UNIVERSITY

Patent Owner.

_____

IPR2013- _____

Patent 8,296,076

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PETITION FOR *INTER PARTES* REVIEW
UNDER 35 U.S.C. §§ 311–319 AND 37 C.F.R. § 42.100 ET SEQ.

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I. INTRODUCTION

U.S. Patent No. 8,296,076 (*"the '076 Patent," attached as Ex. 1001*) recently matured from a Track 1 application in a first action allowance. The Patent Owner filed the Track 1 application two months after the publication of a journal article describing Petitioner's commercial fetal aneuploidy test and launched its first lawsuit against Petitioner – alleging infringement of the *'076 Patent* – just two days after the *'076 Patent* issued.

The Patent Owner has used new terms in the claims of the *'076 Patent* that do not appear anywhere in the specification and has used certain terms in the claims in a manner inconsistent with the specification. Furthermore, certain terms, including the Patent Owner's interpretation of those terms, appear to create unresolvable conflicts between elements within certain claims. Petitioner herein attempts to identify the most plausible interpretations of these claims based on reconciling the claim terms with the specification of the *'076 Patent*. For each of these potential "broadest reasonable interpretations," Petitioner sets forth various grounds of invalidity based on anticipation and/or obviousness.

Under a first possible interpretation of the claims, in which the term "sequencing predefined subsequences" is directed to the use of massively parallel sequencing with or without pre-selection of nucleic acids, the claims for which review is requested are anticipated or rendered obvious by U.S. Patent Publication

2009/0029377 to Lo et al. (*"Lo," Ex. 1004*) alone and/or in combination with Dhallan et al., U.S. Patent No. 7,332,277 (*"Dhallan," Ex. 1002*).

Under another possible interpretation of the claims, in which the term "sequencing predefined subsequences" refers to a sequence-dependent sequencing techniques, the claims for which review is requested are rendered obvious by the combination of Kapur et al., U.S. Patent Publication 2008/10138809 (*"Kapur," Ex.1005*) with either Quake et al., U.S. Patent Publication 2007/0202525 (*"Quake," Ex. 1006*) or *Dhallan*. As explained in the accompanying declarations, it would have been obvious to utilize Kapur's sequencing-by-array techniques in connection with either Quake's or Dhallan's use of predetermined targets for detecting fetal aneuploidies.

II. MANDATORY NOTICES

Pursuant to 37 C.F.R. § 42.8(a)(1), Ariosa provides the following mandatory disclosures.

A. Real Party-In-Interest

Pursuant to 37 C.F.R. § 42.8(b)(1) Petitioner certifies that Ariosa Diagnostics, Inc. is the real party-in-interest.

B. Related Matters

Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner states that the '076 Patent is asserted in co-pending litigation captioned *Verinata Health, Inc. et al. v. Ariosa Diagnostics, Inc. et al.*, Civil Action No. 12-05501-SI (N.D. Cal). (*Ex. 1011*) The

complaint (*Ex. 1011*) alleges infringement of the *'076 Patent*. The complaint was filed on October 25, 2012, two days after the *'076 Patent* issued.

The Petitioner previously filed two petitions, 2013IPR-00276 and -00277, requesting review of a related patent which is also asserted by Verinata Health, Inc. against Petitioner in the above captioned lawsuit, U.S. Patent No. 8,318,430. U.S. Patent No. 8,318,430 and the *'076 Patent* are both directed to fetal aneuploidy detection.

C. Lead and Back-Up Counsel

Pursuant to 37 C.F.R. § 42.8(b)(3), Petitioner provides the following designation of counsel: Lead counsel is Greg Gardella (Reg. No. 46,045) and back-up counsel are Scott A. McKeown (Reg. No. 42,866) and Kevin B. Laurence (Reg. No. 38,219).

D. Service Information

Pursuant to 37 C.F.R. § 42.8(b)(4), papers concerning this matter should be served on the following.

Address:	Greg Gardella, Scott McKeown or Kevin Laurence Oblon Spivak 1940 Duke Street Alexandria, VA 22314
Email:	cpdocketgardella@oblon.com cpdocketmckeown@oblon.com cpdocketlaurence@oblon.com
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III. PAYMENT OF FEES

The undersigned authorizes the Office to charge to Deposit Account No. 15-0030 the fee required by 37 C.F.R. § 42.15(a) for this Petition for *inter partes* review. The undersigned further authorizes payment for any additional fees that might be due in connection with this Petition to be charged to the above referenced Deposit Account.

IV. REQUIREMENTS FOR *INTER PARTES* REVIEW

As set forth below and pursuant to 37 C.F.R. § 42.104, each requirement for *inter partes* review of the *'076 Patent* is satisfied.

A. Grounds for Standing

Pursuant to 37 C.F.R. § 42.104(a), Petitioner hereby certifies that the *'076 Patent* is available for *inter partes* review and that the Petitioner is not barred or estopped from requesting *inter partes* review challenging the claims of the *'076 Patent* on the grounds identified herein. The *'076 Patent* has not been subject to a previous estoppel-based proceeding of the AIA, and, the complaint served on Ariosa referenced above in Section II(B) was served within the last 12 months.

B. Identification of Challenge

Pursuant to 37 C.F.R. §§ 42.104(b) and (b)(1), Petitioner requests *inter partes* review of claims 1-13 of the *'076 Patent* and that the Patent Trial and Appeal Board ("PTAB") invalidate the same.

1. The Specific Art and Statutory Ground(s) on Which the Challenge Is Based

Lo et al., U.S. Patent Publication 2009/0029377 (*"Lo," Ex. 1004*) is available as prior art against all the claims of the *'076 Patent* under 35 U.S.C. § 102(e). Dhallan et al., U.S. Patent No. 7,332,277 (*"Dhallan," Ex. 1002*) is available as prior art against all claims of the *'076 Patent* under 35 U.S.C. § 102(b). Brenner, U.S. Patent Publication 2006/0177832 (*"Brenner," Ex. 1003*) is available as prior art against all claims of the *'076 Patent* under 35 U.S.C. § 102(b). Holt et al., Genome Res. 18:839-846, published June, 2008 (*"Holt," Ex. 1010*) is available as prior art against all the claims of the *'076 Patent* under 35 U.S.C. § 102(a). Kapur et al., U.S. Patent Publication 2008/10138809 (*"Kapur," Ex. 1005*) is available as prior art against all the claims of the *'076 Patent* under 35 U.S.C. § 102(e). Quake et al., U.S. Patent Publication 2007/0202525 (*"Quake," Ex. 1006*) is available as prior art against all the claims of the *'076 Patent* under 35 U.S.C. § 102(b). Li et al., Genome Res. 18:8511858 (August 19, 2008) (*"Li," Ex. 1014*) is available as prior art against all claims of the *'076 Patent* under 35 U.S.C. § 102(a).

Claims 1-13 are anticipated by *Lo* (*Ex. 1004*) under 35 U.S.C. §102(e) under a first broadest reasonable interpretation of the claims. If the Board considers the features set forth in claim 4 to be insufficiently disclosed in *Lo*, those features would have been obvious in view of *Holt* (*Ex. 1010*) under 35 U.S.C. §103(a). Claims 10-11 are further rendered obvious by *Lo* (*Ex. 1004*) in view of *Brenner* (*Ex. 1003*) under 35 U.S.C. §103(a). Claims 1-13 are rendered obvious by *Dhallan* (*Ex. 1002*) taken in combination with *Lo* (*Ex. 1004*) under 35 U.S.C. §103(a) under the first broadest reasonable interpretation of the claims.

Claims 10-11 are further rendered obvious by *Dhallan* (*Ex. 1002*) taken in combination with *Lo* (*Ex. 1004*) and *Brenner* (*Ex. 1003*) under 35 U.S.C. §103(a) under the first broadest reasonable interpretation of the claims.

Claims 1-5 and 7-13 are rendered obvious by *Kapur* (*Ex. 1005*) taken in combination with *Quake* (*Ex. 1006*) under 35 U.S.C. §103(a) under a second, alternative broadest reasonable interpretation of the claims.

Claims 1-5 and 7-13 are rendered obvious by *Dhallan* (*Ex. 1002*) in view of either *Brenner* (*Ex. 1003*) or *Kapur* (*Ex. 1005*) under 35 U.S.C. §103(a) under a second broadest reasonable interpretation of these claims.

Claim 6 is rendered obvious by *Lo* (*Ex. 1004*) in view of *Li* (*Ex. 1014*)*; Kapur* (*Ex. 1005*) in view of *Quake* (*Ex. 1006*) and *Li* (*Ex. 1014*)*; Dhallan* (*Ex. 1002*) in view of *Lo* (*Ex. 1004*) and *Li* (*Ex. 1014*)*; Dhallan* (*Ex. 1002*) in view of

Brenner (*Ex. 1003*) and *Li* (*Ex. 1014*); and *Dhallan* (*Ex. 1002*) in view of *Kapur* (*Ex. 1005*) and *Li* (*Ex. 1014*).

2. How the Construed Claims Are Unpatentable under the Statutory Grounds Identified in 37 C.F.R. § 42.204(B)(2)

Pursuant to 37 C.F.R. § 42.104(b)(4), an explanation of how claims 1-13 of the *'076 Patent* are unpatentable under the statutory grounds identified above, including the identification of where each element of the claim is found in the prior art, is provided in Section VII, below, in the form of claim charts. Pursuant to 37 C.F.R. § 42.104(b)(5), the exhibit numbers of the supporting evidence relied upon to support the challenges and the relevance of the evidence to the challenges raised, including identifying specific portions of the evidence supporting the challenges, are provided in Section VII below, in the form of claim charts.

V. FACTUAL BACKGROUND

A. Technical Background

Circulating cell-free fetal DNA was first found to be abundant in the bloodstream of pregnant women in the mid 1990's. (*Morton Dec., Ex. 1008,* ¶¶27-32 and *Nussbaum Dec., Ex. 1009,* ¶27) This discovery fostered techniques using cell-free DNA from maternal samples to detect fetal abnormalities without subjecting a pregnant woman to an invasive test such as amniocentesis. (*Id.*)

The detection of fetal aneuploidies, such as trisomy 21 which is associated with Down syndrome, requires a sensitive quantitative analysis of the chromosome

suspected of having an abnormal copy number. (*Id.*) Quantitative analysis of genomic regions associated with fetal aneuploidies fall into two general categories: the analysis of random cell-free DNA isolated from a maternal sample and the directed analysis of selected DNA regions from the cell-free DNA in a maternal sample. (*Morton Dec.* ¶¶7-15 and *Nussbaum Dec.* ¶23-34)

Analysis of random cell-free DNA can be carried out using a technique called "shotgun sequencing." Shotgun sequencing was developed as a faster and more efficient method for determining the order of the bases, or nucleotides, that form very large pieces of DNA, such as the human genome. (*Id.*) Shotgun sequencing results in the sequencing of small, random fragments from the genome to create products referred to in the *'076 Patent* as "sequence tags." (*Morton Dec.* ¶¶15-18 and *Nussbaum Dec.* ¶¶4-8) The sequence tags described in the *'076 Patent* are of unknown location in the genome unless and until they are aligned to a reference sequence and assigned to a location based on alignment with that reference sequence. (*Id.*) Once assigned, sequence tags can be used, *e.g.*, to assemble a larger, contiguous segment of DNA such as a chromosome or a region thereof, or to identify the quantity of sequences from a chromosome or a region thereof. (*Id.*) A sequence tag arising from shotgun sequencing that is not mapped does not provide any information on the genomic location of the sequence tag and thus cannot be used in any further analysis. (*Id.*)

In a second example of analysis of random DNA fragments, random fragments from a sample can be identified and quantified using a sequence-specific sequencing method, *e.g.*, a capture-based sequencing method. (*Morton Dec.* ¶¶11-15, 21-24 and *Nussbaum Dec.* ¶¶31-33) One example of this is sequencing by array, in which the random DNA fragments are captured by probe nucleic acids of known sequence attached to a solid substrate (an "array"). (*Id.*) In this example, all or a representative portion of the random DNA fragments from a sample are fluorescently labeled, and the fragments complementary to the probes of known sequence on the array are captured by hybridization and visualized by the fluorescent label. (*Id.*) As the array probes are of a known genomic location and sequence, the sequence of the random fragment is effectively identified by virtue of its hybridization to a probe. (*Id.*) Although sequencing by array is different from shotgun sequencing in that there is no need to map or "align" the sequence to a reference genome, like shotgun sequencing this technique analyzes randomly generated DNA fragments. (*Id.*) However, in sequencing by array the vast majority of sequences from the sample are not of use in the actual hybridization and quantification analysis. (*Id.*)

In contrast to random analysis, directed analysis of nucleic acids selected from a maternal sample isolates specific informative cell-free DNA fragments known to correspond to genomic regions prior to the use of any sequencing

technique. (*Morton Dec.* ¶15 and *Nussbaum Dec.* ¶27) Selection techniques for directed analysis include use of loci-specific oligonucleotides to isolate regions of interest, where these loci-specific oligonucleotides can be used in, *e.g.*, selective amplification and/or ligation processes to select the informative cell-free DNA fragments for analysis. At least one copy (or "amplicon") of the DNA fragment is made and often the DNA fragments are amplified to create multiple copies. (*Morton Dec.* ¶17) These selected informative DNA fragments are isolated from the remaining cell-free DNA prior to any sequencing technique; thus, in contrast to random analysis, only the informative DNA fragments are analyzed, *e.g.*, by any conventional DNA sequencing method, including next-generation or "massively parallel" sequencing. (*Morton Dec.* ¶17) Directed analysis is a more efficient analysis technique as the cell-free DNA copies analyzed are informative DNA fragments that are used in the determination of fetal aneuploidies. (*Morton Dec.* ¶18 and *Nussbaum Dec.* ¶¶26-27)

A summary of the aforementioned analysis and sequencing techniques is provided below:

Molecular Input to Sequencing	**Type of Sequencing**	
	Sequence Independent	**Sequence Dependent**
Random DNA Fragments (Random Analysis)	Massively Parallel Shotgun Sequencing	Sequencing by Array (Hybridization)
Selected DNA Fragments (Directed Analysis)	Pre-selection + Massively Parallel Sequencing	Pre-selection + Sequencing by Array (Hybridization)

B. The ‘083 Patent Application and Prosecution History

The ‘083 Application was filed on April 20, 2012 along with a Track 1 Request for prioritized examination under 37 CFR §1.102(e)(1).

The Applicant disclosed to Examiner on the order of one thousand references. The listing of the disclosed references spans the first eleven pages of the issued patent. (*’076 Patent*) The Examiner cited just three of the references listed on those eleven pages; the Applicant cited the remainder.

The Examiner issued a first action notice of allowance. The statement of reasons for allowance recited the entire text of claim 1 and thus does not provide substantial insight into the particular features that the Examiner considered to be most significant.

However, the statement of reasons for allowance is noteworthy in that it discusses what appears to be marginally relevant references from other areas of molecular biology, namely 1) the suppression of proto-oncogenes using RNA interference techniques; 2) detection of protein and nucleic acid biomarkers associated with diseases including inflammatory disease; and 3) detection of newborn phenotypic traits including sudden infant death syndrome, cardiomyopathy, cognitive ability and lactose intolerance. (*See also Morton Dec.* ¶33)

VI. BROADEST REASONABLE INTERPRETATION

Pursuant to 37 C.F.R. § 42.100, a claim in an unexpired patent subject to *inter partes* review shall receive the "broadest reasonable construction in light of the specification of the patent in which it appears." All claim terms not specifically addressed in this subsection have been accorded their broadest reasonable interpretation in light of the patent specification including their plain and ordinary meaning to the extent such a meaning could be determined by a skilled artisan.

A. "Sequencing Predefined Subsequences"

The '083 application introduced the term "predefined subsequence." This term does not appear anywhere in the specification, so we have looked at the context of the terms and similar language in the specification to interpret this term. (*Morton Dec.* ¶¶33-48 and *Nussbaum Dec.* ¶¶48-65)

Similar terms – "predefined sequences" and "selected subsequences" – are used in the specification. The term "predefined sequences" is used in the specification in the context of a "sequencing method which selectively captures sample molecules containing certain predefined sequences." (*'076 Patent* 14: 26-28). The term "selected subsequences" is used once in the specification to describe molecules that are sequenced using sequence-based methodologies. (*'076 Patent 13:66*). In Claim 1, "predefined subsequences" are sequenced "to obtain sequence tags," so the initial use of this term should be interpreted as referring to a molecule

rather than sequence data. The most reasonable interpretation of this term based on the provided guidance would be a sample molecule having an *a priori* selected sequence. (*Morton Dec.* ¶¶33-48 and *Nussbaum Dec.* ¶¶48-65)

The description that most closely teaches the sequencing of a predefined subsequence is found at columns 13 and 14 of the specification, which teaches the use of sequence-dependent sequencing techniques, such as sequencing by array, in "sequencing selected subsequences." (*'076 Patent* 13:1-67 and 14:1-67) The only disclosure in the *'076 Patent* on sequencing predefined subsequences describes "sequence-based methodologies such as sequencing by array, or capture beads with specific genomic sequences used as capture probes . . ." (*'076 Patent* 13: 65 to 14: 1) These techniques require hybridizing of nucleic acids to probes of known sequence to selectively sample molecules containing sequences selected *a priori*." Accordingly, a broadest reasonable interpretation of "sequencing predefined sequences" is "using sequence-dependent sequencing to identify capture sample molecules containing sequences selected *a priori."* (*Morton Dec.* ¶¶33-48 and *Nussbaum Dec.* ¶¶48-65)

The Patent Owner, however, has construed the phrase "sequencing predefined subsequences" in the accompanying litigation as a "sequencing predetermined polymorphism independent subsequences." (*See Ex. 1015*) The only sequencing technique described as being polymorphism-independent in the

'076 Patent is shotgun sequencing. *See '076 Patent* 4:19-25 and 20:30-39. However, as discussed above, it is not clear how a **random** sequencing technique such as shotgun sequencing could meet the recitation "sequencing **predefined** subsequences," unless these molecules containing the *a priori* selected sequences are merely included in the sequencing of other randomly generated nucleic acids, *e.g.*, in the shotgun sequencing of DNA fragments of a genome. The claim language of the preamble of independent claim 1 is consistent with such a reading of the claim, as each claimed method *comprises* sequencing predefined subsequences, *i.e.*, would include sequencing of predefined subsequences along with sequencing of other nucleic acids. Thus, based on the statements of the Patent Owner an alternative interpretation of "sequencing predefined subsequences" would be "shotgun sequencing of random fragments from a sample which include sample molecules those having predefined sequences."

The foregoing interpretations of "sequencing predefined subsequences" are mutually exclusive. As described, shotgun sequencing is polymorphism independent and thus more closely aligns with the interpretation set forth by the Patent Owner. Sequence-dependent sequencing, the method actually taught in the specification, utilizes hybridization techniques dependent upon DNA complementarity and thus by definition is not "polymorphism independent." (*Morton Dec.* ¶¶33-48 and *Nussbaum Dec.* ¶57 *et seq.*)

For the purposes of this petition, Petitioner has applied these interpretations separately in the analysis of the prior art. Below, Petitioner explains which grounds of unpatentability apply to each potential interpretation of the term "sequencing predetermined subsequences."

B. "Predetermined Subsequence"

The term "predetermined subsequence" is also newly introduced in the claims of the '083 application and used nowhere in the specification of the *'076 Patent* or any of the priority applications. Unlike "predefined subsequence," which in certain usages in the claims clearly refer to a molecule, "predetermined subsequences" only refer to a data set containing sequences to which a sequence tag aligns, *e.g.*, within a predefined window in a genomic reference. (*Morton Dec.* ¶¶*49-52* and *Nussbaum Dec.* ¶¶*48-55*) Thus, although both terms share the word "subsequences," they appear to be directed to different elements within the claim. (*See id.*) Thus "predetermined subsequence" under the broadest reasonable interpretation refers to a reference data set containing predetermined sequences, *e.g.*, a predefined window. (*Id.*)

C. "Sequence Tag"

The claims submitted in the '083 application recite "sequencing of predefined subsequences" to "obtain a plurality of sequence tags." The '076 Patent sets forth two definitions of sequence tag:

> As is known in the art, the term "sequence tag" refers to a relatively short (*e.g.*, 15-100) nucleic acid sequence that can be used to identify a certain larger sequence, *e.g.*, be mapped to a chromosome or genomic region or gene. These can be ESTs or expressed sequence tags obtained from mRNA. (*'076 Patent* 2:24-26)
>
> . . .
>
> A "sequence tag" is a DNA sequence of sufficient length that it may be assigned specifically to one of chromosomes 1-22, X or Y. (*'076 Patent* 8:53-55)

Consistent with these definitions, the *'076 Patent* uses the term "sequence tag" solely in the context of an intermediate product of random DNA sequencing – *i.e.*, the sequence reads of DNA fragments randomly generated using shotgun sequencing. (*Morton Dec.* ¶¶15-19 and *Nussbaum Dec.* ¶¶40-47) As described, the use of the term "sequence tag" in the '076 is rational only when read in this context. (*Morton Dec.* ¶¶15-19 and *Nussbaum Dec.* ¶¶40-47)

In pending litigation the parties have agreed on the following definition: "relatively short nucleic acid sequences that can be used to identify certain larger sequences." (*Ex. 1015*) This interpretation does not require the sequence tag to actually be mapped back to a reference genome to identify its genomic position – it just must be of sufficient length to do so.

If the term "sequencing predefined subsequences" is interpreted as including sequencing using shotgun sequencing, the term sequence tag would

necessarily include sequenced fragments which are not informative until and unless they are aligned to a reference to assign their genomic location. (*Morton Dec.* ¶¶15-19, 33-52 and *Nussbaum Dec.* ¶¶36-65)

If the term "sequencing predefined subsequences" is interpreted as including sequence-dependent sequencing of sample molecules, such sequencing mechanisms cannot be used to obtain sequence tags even under the broadest interpretation of "sequence tag." (*Morton Dec.* ¶¶15-19, 33-52 and *Nussbaum Dec.* ¶¶36-65) In sequence-dependent sequencing, the sequences are determined through hybridization, which means the sequence indicator is the probe used in the sequencing itself. (*Id.*) For purposes of analysis herein, this inconsistency is not discussed in detail, and the claim is read as though the data generated in the sequence-specific sequencing would be covered by the claim.

D. "Align" and "Assign"

As with "sequence tag," the terms "align" and "assign" are only used in the *'076 Patent* to describe techniques used in the shotgun sequencing of random DNA fragments. In every instance of its use in the *'076 Patent*, the term "align" is used in conjunction with comparison to a reference genome, *e.g.*:

> Short sequence reads are aligned against a reference genome. (*'076 Patent* 9:47-48)
>
> Mapping shotgun sequence information (i.e., sequence information from a fragment whose physical genomic

> position is unknown) can be done in a number of ways, which involve alignment of the obtained sequence with a matching sequence in a reference genome. (‘*076 Patent* 11:46-50)

Similarly, the term “assign” is used in the *‘076 Patent* to describe using alignment information to determine the genomic location for a sequence tag obtained from shotgun sequencing:

> Using a reference sequence, one assigns the sequence tags to their corresponding chromosomes including at least the specified chromosome by comparing the sequence to reference genomic sequence. Often there will be on the order of millions of short sequence tags that are assigned to certain chromosomes, and, importantly, certain positions along the chromosomes. (‘*076 Patent* 4:43-49)

Patent Owner has taken the position that “assigning the plurality of sequence tags to their corresponding predetermined subsequences” should be construed as “assigning the plurality of sequence tags to the corresponding predetermined subsequences to which they uniquely align.” (*Ex. 1015*) As discussed, the term “predetermined subsequence” is most reasonably construed as a predefined reference sequence, as discussed above. Step c) of claim 1 requires alignment of the sequence tag to a predefined reference sequence and assignment of the genomic location of

the sequence tags based on this unique alignment. If "predetermined subsequence" is read more broadly, alignment would include comparison of directed analysis products to preselected genomic sequences. (*See Morton Dec.* ¶53) Although there is no support in the specification for the broader reading, directed analysis is taught in the prior art and considered in the claim charts.

VII. GROUNDS OF UNPATENTABILITY

Although some ambiguity exists as to the correct interpretation of the claims in the *'076 Patent,* the prior art either anticipates or renders obvious under 35 U.S.C. §§102 or 103 any of the interpretations that could be reasonably construed in view of the specification. The following chart briefly summarizes the art that is available for the possible combinations of molecular analysis and sequencing technique which could be deemed to fall within the internally inconsistent claim language.

Molecular Input to Sequencing	**Type of Sequencing**	
	Sequence Independent	**Sequence Dependent**
Random DNA Fragments (Random Analysis)	Massively Parallel Shotgun Sequencing 102 art: *Lo*	Sequencing by Array (Hybridization) 103 art: *Kapur* and *Dhallan*
Selected DNA Fragments (Directed Analysis)	Pre-selection + Massively Parallel Sequencing 103 art: *Dhallan* + *Lo*	Pre-selection + Sequencing by Array (Hybridization) 103 art: *Dhallan* + *Kapur*

A. Claims 1-9 and 12-13 Are Anticipated by Lo

U.S. Patent Publication 2009/0029377 to Lo et al. (*"Lo," Ex. 1004*) is cited on the face of the *'076 Patent;* however, it was not applied in any rejection during prosecution of the *'076 Patent* and is not cumulative of any prior art specifically applied by the examiner during examination.

It should be noted that in Application No.12/560,708, to which the '076 Patent claims priority, the Examiner recently rejected claims of similar scope as being anticipated by *Lo* under §102(e). That Office action and the pending claims are attached hereto (*Ex. 1012*). Petitioner notes that *Lo* is also involved in Interference No. 105,922 against U.S. Pat. No. 8,195,415, which claims priority to U.S. Application No. 12/560,708, and *Lo* was found to be senior by 14 months.

The Declaration of Dr. Morton (*Ex. 1008 at ¶¶56-73*) and the Declaration of Dr. Nussbaum (*Ex. 1009 at ¶¶66-91*) explain that *Lo* anticipates the claims for which review is requested under the interpretations of the claim terms as discussed above. More particularly, *Lo* covers the claims if interpreted as directed to shotgun sequencing (which is the only disclosed method for obtaining sequence tags) and Lo also meets the claims if this step is interpreted as directed to sequencing of selected targeted subsequences. (*Id.*)

The claim chart below shows the correspondence between *Lo* and claims 1-3, 7-9 and 12-13 of the *'076 Patent*.

Correspondence between claims 1-3, 7-9 and 12-13 of the *'076 Patent* and *Lo*, US 2009/0029377	
1. A method of testing for an abnormal distribution of a chromosome in	*Lo* discloses that "[t]he term 'chromosomal aneuploidy' as used herein means a variation in the quantitative amount of a chromosome from that of a diploid genome. The variation may be a gain or a loss. It may involve the whole of one chromosome or a region of a chromosome." (*Lo* ¶[0046]; *see Morton Dec.* ¶57 and *Nussbaum Dec.* ¶67) "Fetal chromosomal aneuploidy results from the presence of abnormal dose(s) of a chromosome or chromosomal region." (*Lo* ¶[0004]; *see Morton Dec.* ¶57 and *Nussbaum Dec*. ¶67)
a sample comprising a mixture of maternal and fetal DNA, comprising the steps of:	"In step 110, a biological sample from the pregnant female is received. The biological sample may be plasma, urine, serum, or any other suitable sample. The sample contains nucleic acid molecules from the fetus and the pregnant female. For example, the nucleic acid molecules may be fragments from chromosomes." (*Lo* ¶[0054]; *see Morton Dec.* ¶57 and *Nussbaum Dec.* ¶*67*)
(a) obtaining maternal and fetal DNA from said sample;	"In one aspect, an amount of chromosomes is determined from a sequencing of nucleic acid molecules in a maternal sample, such as urine, plasma, serum, and other suitable biological samples. Nucleic acid molecules of the biological sample are sequenced, such that a fraction of the genome is sequenced." (*Lo* ¶[0014]; *see Morton Dec.* ¶58 and *Nussbaum Dec.* ¶¶68-69; *see also Lo* ¶[0052])
(b) sequencing predefined subsequences of the maternal and fetal DNA to obtain a plurality of sequence tags aligning to the predefined subsequences,	*If the claims are construed as including sequencing of selected subsequences:* "In another embodiment, the fraction of the nucleic acid pool that is sequenced in a run is further sub-selected prior to sequencing. For example, hybridization based techniques such as oligonucleotide array could be used to first sub-select for nucleic acid sequences from certain chromosomes, *e.g.* a potentially aneuploid chromosome and other chromosome(s) not involved in the aneuploidy

	tested." (*Lo* ¶[0072]) The Lo method produces multiple sequence tags long enough to be aligned to the human reference genome to note their chromosomal origin, ¶[0070] and an amount of the chromosome of interest and of one or more other chromosomes may thus be determined ¶[0058]. (*Morton Dec.* ¶59 and *Nussbaum Dec.* ¶¶70-72) *If the claims are construed to include shotgun sequencing of predefined subsequences* "The term "random sequencing" as used herein refers to sequencing whereby the nucleic acid fragments sequenced have not been specifically identified or targeted before the sequencing procedure. Sequence-specific primers to target specific gene loci are not required." (*Lo* ¶[0047], *see Morton Dec.* ¶59 and *Nussbaum Dec.* ¶¶70-72) "In one aspect for the massively parallel sequencing approach, representative data from all of the chromosomes may be generated at the same time. The origin of a particular fragment is not selected ahead of time. The sequencing is done at random and then a database search may be performed to see where a particular fragment is coming from." (*Lo* ¶[0080]; *see Morton Dec.* ¶10-12, 51; *see also Morton Dec.* ¶*59* and *Nussbaum Dec.* ¶¶*70-72*)
wherein said sequence tags are of sufficient length to be assigned to a specific predefined subsequence,	"The short sequence tags generated were aligned to the human reference genome sequence and the chromosomal origin was noted." (*Lo* ¶[0070], *see Morton Dec.* ¶*60* and *Nussbaum Dec.* ¶*73*)
wherein the predefined subsequences are from a plurality of different chromosomes, and wherein said plurality of different chromosomes	"In step 130, based on the sequencing (*e.g.* data from the sequencing), a first amount of a first chromosome (*e.g.* the clinically relevant chromosome) is determined. The first amount is determined from sequences identified as originating from the first chromosome. For example, a bioinformatics procedure may then be used to locate each of these DNA sequences to the human genome. It is

comprise at least one first chromosome suspected of having an abnormal distribution in said sample and at least one second chromosome presumed to be normally distributed in said sample;	possible that a proportion of such sequences will be discarded from subsequent analysis because they are present in the repeat regions of the human genome, or in regions subjected to inter-individual variations, *e.g.* copy number variations. An amount of the chromosome of interest and of one or more other chromosomes may thus be determined." (*Lo* ¶[0058]; *see Morton Dec.* ¶61 and *Nussbaum Dec.* ¶73-74)
(c) assigning the plurality of sequence tags to their corresponding predetermined subsequences;	Paragraphs [0016], [0058-59], [0074] and [0075] of *Lo* describe methods for assigning tags to predetermined sequences (sequences from a putative aneuploid chromosome and normal chromosomes), determining numbers of sequence tags on these chromosomes and assessing aneuploidy by comparing the numbers of tags on the test and control chromosomes. (*Morton Dec.* ¶62 and *Nussbaum Dec.* ¶¶*75-77*) See discussion of step 130, *supra*. "In step 140, based on the sequencing, a second amount of one or more second chromosomes is determined from sequences identified as originating from one of the second chromosomes. In one embodiment, the second chromosomes are all of the other chromosomes besides the first one (*i.e.* the one being tested). In another embodiment, the second chromosome is just a single other chromosome." (*Lo* ¶[0059])
(d) determining a number of sequence tags aligning to the predetermined subsequences of said first chromosome and a number of sequence tags to the predetermined subsequences of the second chromosome;	"After the massively parallel sequencing, bioinformatics analysis was performed to locate the chromosomal origin of the sequenced tags. After this procedure, tags identified as originating from the potentially aneuploid chromosome, *i.e.* chromosome 21 in this study, are compared quantitatively to all of the sequenced tags or tags originating from one of more chromosomes not involved in the aneuploidy." (*Lo* ¶[0074]; *see Morton Dec.* ¶63 and *Nussbaum Dec.*¶*78*)

and	
(e) comparing the numbers from step (d) to determine the presence or absence of an abnormal distribution of said first chromosome.	See discussion of Lo's use of the term sequence tags, *supra* at Section VI.C. "A number of different amounts include but not limited to the following could be derived from the sequenced tags. For example, the number of sequenced tags, *i.e.* absolute count, aligned to a particular chromosome could be compared to the absolute count of sequenced tags aligned to other chromosomes." (*Lo* ¶[0075]; *see Morton Dec.* ¶64 and *Nussbaum Dec.* ¶79) "Based on the sequencing, a first amount of a first chromosome is determined from sequences identified as originating from the first chromosome. A second amount of one or more second chromosomes is determined from sequences identified as originating from one of the second chromosomes. A parameter from the first amount and the second amount is then compared to one or more cutoff values. Based on the comparison, a classification of whether a fetal chromosomal aneuploidy exists for the first chromosome is determined." (*Lo* ¶[0016]; *see Morton Dec.* ¶64 and *Nussbaum Dec.* ¶79) "The bioinformatics, computational and statistical approaches used to determine if a maternal plasma specimen is obtained from a pregnant woman conceived with a trisomy 21 or euploid fetus could be compiled into a computer program product used to determine parameters from the sequencing output. The operation of the computer program would involve the determining of a quantitative amount from the potentially aneuploid chromosome as well as amount(s) from one or more of the other chromosomes." (*Lo* ¶[0090]; *see Morton Dec.* ¶64 and *Nussbaum Dec.* ¶79)
2. The method of claim 1 wherein the sample is a maternal serum or plasma sample, wherein the	Lo's claim 3 reads as follows: "The method of claim 1, wherein the biological sample is maternal blood, plasma, serum, urine or saliva." "After this procedure, tags identified as originating from the potentially aneuploid chromosome, *i.e.* chromosome

abnormal distribution of said first chromosome is a fetal aneuploidy, and wherein said second chromosome is a euploid chromosome.	21 in this study, are compared quantitatively to all of the sequenced tags or tags originating from one of more chromosomes not involved in the aneuploidy." (*Lo* ¶[0074]; *see Morton Dec.* ¶65 and *Nussbaum Dec.* ¶¶80-81)
3. The method of claim 2 wherein the sequencing comprises massively parallel sequencing of the predefined subsequences.	"In one embodiment, the sequencing is done using massively parallel sequencing. Massively parallel sequencing, such as that achievable on the 454 platform (Roche) (Margulies, M. et al. 2005 Nature 437, 376-380), Illumina Genome Analyzer (or Solexa platform) or SOLiD System (Applied Biosystems) or the Helicos True Single Molecule DNA sequencing technology (Harris T D et al. 2008 Science, 320, 106-109), the single molecule, real-time (SMRT™) technology of Pacific Biosciences, and nanopore sequencing (SoniGV and Meller A. 2007 ClinChem 53: 1996-2001), allow the sequencing of many nucleic acid molecules isolated from a specimen at high orders of multiplexing in a parallel fashion (Dear Brief Funct Genomic Proteomic 2003; 1: 397-416)." (*Lo* ¶[0056]; *see Morton Dec.* ¶66 and *Nussbaum Dec.* ¶82)
4. The method of claim 3 wherein said massively parallel sequencing comprises attaching DNA fragments to an optically transparent surface, conducting solid phase amplification of the attached DNA fragments to create a high density sequencing flow cell with millions of DNA clusters, and . . . dyes.	In one embodiment, we used the Illumina Genome Analyzer for single-end sequencing of human genomic DNA and human plasma DNA samples. The Illumina Genome Analyzer sequences clonally-expanded single DNA molecules captured on a solid surface termed a flow cell. (*Lo* [0070]; *see Morton Dec.* ¶67 and *Nussbaum Dec.* ¶¶ 83-84) As explained in the Declarations of Dr. Morton and Dr. Nussbaum, the features required by claim 4 were understood to be inherent in the Illumina system as of the date of filing. (*Morton Dec. ¶67 and Nussbaum Dec. ¶¶ 83-84*)

5. The method of claim 2 wherein the fetal aneuploidy is an aneuploidy of a chromosome selected from the group consisting of chromosome 13, chromosome 18 and chromosome 21.	"The term "clinically relevant nucleic acid sequence" as used herein can refer to a polynucleotide sequence corresponding to a segment of a larger genomic sequence whose potential imbalance is being tested or to the larger genomic sequence itself. One example is the sequence of chromosome 21. Other examples include chromosome 18, 13, X and Y." (*Lo* ¶[0037]; *see Morton Dec.* ¶68 and *Nussbaum Dec.* ¶ 85)
6. The method of claim 2 wherein the step of assigning sequence tags to corresponding chromosome portions allows one mismatch.	"Dhallan et al (Dhallan, R, et al. 2007, supra Dhallan, R, et al. 2007 *Lancet* 369,474-481) described an alternative strategy of enriching the proportion of circulating fetal DNA by adding formaldehyde to maternal plasma. The proportion of chromosome 21 sequences contributed by the fetus in maternal plasma was determined by assessing the ratio of paternally-inherited fetal-specific alleles to non-fetal-specific alleles for single nucleotide polymorphisms (SNPs) on chromosome 21." (*Lo* ¶[0008]) An example of this method would be to target polymorphic sites at which the pregnant woman is homozygous and the fetus is heterozygous, wherein the amount of fetal-specific allele can be compared with the amount of the common allele to determine the fractional concentration of fetal DNA. By definition the alignment of a polymorphic region to a single reference will have a mismatch in either the fetal or the maternal DNA, as they differ by one base pair.
7. The method of claim 2 wherein the length of the sequence tags is from about 25 bp to about 100 bp in length.	"For example, sequencing output corresponding to nucleic acid fragments of a specified size range could be selected after the bioinformatics analysis. Examples of the size ranges are about <300 bp, <200 bp or <100 bp." (*Lo* [0061]; *see Morton Dec.* ¶*69* and *Nussbaum Dec.* ¶*86*) "In the present experiment, because 36 bp were sequenced from each DNA fragment, the number of nucleotides sequenced from a particular chromosome could easily be derived from 36 bp multiplied by the

	sequenced tag count." (*Lo* ¶[0075]; see *Morton Dec.* ¶69)
8. The method of claim 2 wherein the DNA is genomic DNA.	"In one embodiment, random sequencing is performed on DNA fragments that are present in the plasma of a pregnant woman, and one obtains genomic sequences which would originally have come from either the fetus or the mother." (*Lo* [0083]; *see Morton Dec.* ¶*70* and *Nussbaum Dec.* ¶*87*)
9. The method of claim 2 wherein said sequencing comprises selectively sequencing nucleic acid molecules comprising the predefined sequences.	"In another embodiment, the fraction of the nucleic acid pool that is sequenced in a run is further sub-selected prior to sequencing. For example, hybridization based techniques such as oligonucleotide array could be used to first sub-select for nucleic acid sequences from certain chromosomes, *e.g.* a potentially aneuploid chromosome and other chromosome(s) not involved in the aneuploidy tested." (*Lo* ¶[0072]; see *Morton Dec.* ¶*71 and Nussbaum Dec.* ¶*88*)
12. The method of claim 2 further comprising determination of fetal DNA fraction of the DNA obtained from the maternal serum or plasma sample.	"Yet another alternative way of determining the fractional concentration of fetal DNA would be through the quantification of polymorphic differences between the pregnant women and the fetus (Dhallan R, et al. 2007 Lancet, 369, 474-481). An example of this method would be to target polymorphic sites at which the pregnant woman is homozygous and the fetus is heterozygous. The amount of fetal-specific allele can be compared with the amount of the common allele to determine the fractional concentration of fetal DNA." (*Lo* ¶[0107]; *see Morton Dec.* ¶72and *Nussbaum Dec.* ¶¶*89-90*)
13. The method of claim 12 wherein the fetal DNA fraction is determined by digital PCR.	"The determination of the fractional concentration of fetal DNA in maternal plasma can also be done separate to the sequencing run. For example, the Y chromosome DNA concentration could be pre-determined using real-time PCR, microfluidics PCR or mass spectrometry." (*Lo* ¶[0105]; *Morton Dec.* ¶73 and *Nussbaum Dec.* ¶91)

B. Claim 4 is Rendered Obvious by *Lo* Taken in Combination with *Holt*

This rejection is offered in the alternative to the rejection of claim 4 set forth in section VII.A. If the Board considers features set forth in claim 4 to be insufficiently disclosed in *Lo*, those features would have been obvious in view of *Holt*, which was not disclosed in connection with the prosecution of the *'076 Patent*. *Holt* expressly discloses the claimed aspects of the Illumina Genome Analyzer identified in *Lo*. (*Holt, Ex. 1010* at p. 840, col. 1, last paragraph, *see Declaration of Dr. Morton, Ex. 1008* at ¶74 and *Declaration of Dr. Nussbaum, Ex. 1009* at ¶¶92-95)

C. Claims 10-11 Are Rendered Obvious by *Lo* Taken in Combination with *Brenner*

In this combination, *Brenner* provides motivation for sequencing a predetermined subsequence for the purpose of reducing the complexity of a sequencing procedure. (*Morton Dec.* ¶75 and *Nussbaum Dec.* ¶96) The DNA sorting methods of *Brenner* would have permitted one to select particular fractions of the maternal and fetal DNA for sequencing. (*Morton Dec.* ¶75-77 and *Nussbaum Dec.* ¶¶96-104) This would have been expected to focus the sequencing procedure on putative aneuploid chromosome sequences and reduce the complexity of the method of *Lo*. (*Id.*)

The claim chart below shows the correspondence between *Lo*, *Brenner* and claims 10-11 of the *'076 Patent*.

Correspondence between claims 10 and 11 of the *'076 Patent* and *Lo*, US 2009/0029377 and *Brenner*, U.S. 2006/0177832	
10. The method of claim 9 wherein said sequencing comprises the use of a sequencing array.	"In another aspect, the method of the invention is carried out on a population of tagged polynucleotides so that after a subpopulation is selected, the members of the subpopulation may be simultaneously analyzed using the unique tags on the polynucleotides to convey analytical information to a hybridization array for a readout." (*Brenner Abstract; see Brenner* ¶[0041], *Morton Dec.* ¶76, and *Nussbaum Dec.* ¶¶98-101)
11. The method of claim 10 wherein said selected defined subsequences of the genomic DNA are rendered single-stranded and captured under hybridizing conditions by single-stranded probes physically separated on an array.	"In another aspect, the method of the invention is carried out on a population of tagged polynucleotides so that after a subpopulation is selected, the members of the subpopulation may be simultaneously analyzed using the unique tags on the polynucleotides to convey analytical information to a hybridization array for a readout." (*Brenner Abstract; see Morton Dec.* ¶77 and *Nussbaum Dec.* ¶¶*102-104*) "'Hybridization" refers to the process in which two single-stranded polynucleotides bind non-covalently to form a stable double-stranded polynucleotide." (*Brenner* ¶[0026]; *see Morton Dec.* ¶*77* and *Nussbaum Dec.* ¶102-104)

D. Claims 1-5, 7-13 Are Rendered Obvious by *Quake* in view of *Kapur*

If the interpretation of "sequencing predefined subsequences" includes the use of sequence-based sequencing, *e.g.*, sequencing by array, the claims of the *'076 Patent* would have been obvious to one of ordinary skill in the art over *Kapur* in combination with *Quake*.

It would have been obvious to use the sequencing by array methods taught by *Kapur* in combination with analysis of targeted gene loci taught by *Quake* to identify fetal abnormalities. (*Morton Dec.* ¶79 and *Nussbaum Dec.* ¶105) A skilled artisan would have been motivated to combine these techniques since sequencing techniques were well-known in the art, the use of cell-free DNA as a source for determining aneuploidy was well-known, both *Kapur* and *Quake* are in the same sub-specialty (*e.g.*, molecular testing for prenatal abnormalities), and both patent applications were controlled by the same licensee at the time of their respective filings. (*Id.*)

In addition, it would have been obvious to substitute the maternal and fetal cell-derived DNA used in *Kapur* with the maternal and fetal cell-free DNA used in *Quake*. (*Morton Dec.* ¶*78 et seq.*) Both references teach DNA samples useful for sequence analysis, thus the results of these substitutions would have been predictable and would not have required undue experimentation.

The following claim chart demonstrates, on a limitation-by-limitation basis, how claims 1-5 and 7-13 of the *'076 Patent* are obvious over *Kapur* taken in combination with *Quake*.

Correspondence between claims 1-5 and 7-13 of the *'076 Patent* and *Kapur*, U.S. 2008/10138809 and *Quake*, U.S. 2007/0202525	
1. A method of testing for an abnormal distribution of a chromosome in a sample	*Quake* at claim 1 recites detection of chromosomal aneuploidy in "differential detection of target sequences in a mixture of maternal and fetal genetic

comprising a mixture of maternal and fetal DNA, comprising the steps of:	material." (Claim 1 of *Quake*) *Kapur* teaches obtaining a sample comprising both maternal and fetal DNA and analyzing the maternal and fetal DNA from cells for genetic conditions including various trisomies. (Kapur ¶[0007]; *see Morton Dec.* ¶80 and *Nussbaum Dec.* ¶¶107-108)
(a) obtaining maternal and fetal DNA from said sample;	*Quake* teaches obtaining maternal and fetal DNA from a maternal tissue. (*See e.g., Quake* [Abstract] and ¶[0026]; *see also Morton Dec.* ¶81 and *Nussbaum Dec.* ¶¶107-108) *Kapur* teaches obtaining DNA from maternal and fetal cells by "obtaining a blood sample from the female pregnant with the fetus, [and] enriching the sample for cells…" (*Kapur* ¶[0076]; *see Morton Dec.* ¶81 and *Nussbaum Dec.* ¶¶107-108)
(b) sequencing predefined subsequences of the maternal and fetal DNA to obtain a plurality of sequence tags aligning to the predefined subsequences,	*If the claims are construed as including sequencing of selected subsequences:* *Quake* discloses "It is also possible to sequence the target sequence in the reaction sample directly, either after amplification or at the single molecule level." (*Quake* ¶[0117]; *see Morton Dec.* ¶82 and *Nussbaum Dec.* ¶¶*109-110*) *Quake* states "In one aspect, the present method of differential detection of target sequences may involve direct sequencing of target sequences the genetic material [sic]." (*Quake* ¶[0033] *see Morton Dec.* ¶82 and *Nussbaum Dec.* ¶¶109-110) *Kapur* at Figure 6 and 7 teaches a method for sequence determination of randomly generated DNA fragments using arrays having oligonucleotides of known sequence. Sequencing of a randomly generated genomic fragment via binding to a predefined sequence on an array aligns a random sequence to a probe indicative of a specific genomic region. (*Morton Dec.* ¶82 and *Nussbaum Dec.* ¶¶109-110)
wherein said sequence	*Quake* teaches that "only about 30 bp of random

tags are of sufficient length to be assigned to a specific predefined subsequence,	sequence information are needed to identify a sequence as belonging to a specific human chromosome. Longer sequences can uniquely identify more particular targets." (*Quake* ¶[0121]; *see Morton Dec.* ¶83 and *Nussbaum Dec.* ¶¶111-113) In *Kapur* at Figures 6 and 7, and the description of these figures within the specification, *Kapur* describes the use of arrays of known sequences to identify random sequences from a genomic sample of maternal and fetal DNA to obtain sequence tags of sufficient length to "autocall genotypes." In an exemplary array assay, *Kapur* at [0213] teaches that "each SNP would be assigned a 22 bp DNA tag [on the array] which allows the SNP to be uniquely identified during the highly parallel genotyping assay." (*Morton Dec.* ¶83 and *Nussbaum Dec.* ¶¶111-113)
wherein the predefined subsequences are from a plurality of different chromosomes, and wherein said plurality of different chromosomes comprise at least one first chromosome suspected of having an abnormal distribution in said sample and at least one second chromosome presumed to be normally distributed in said sample;	*Quake* ¶[0034]: "Thus is provided a kit for differential detection of target sequences in maternal and fetal DNA in a mixed DNA sample, comprising primers specific for a genetically abnormal sequence and a control sequence, such as two chromosomes, one of which is possibly aneuploid and one of which is presumed diploid." (*see Morton Dec.* ¶84 and *Nussbaum Dec.* ¶¶114-115) *Kapur* teaches, for example, that the array probes "can be designed along chromosomes 13, 18, 21 and X to detect the most frequent aneuploidies, and along control regions of the genome where aneuploidy is not expected." (*Kapur* ¶[0212]; *see Morton Dec.* ¶84 and *Nussbaum Dec.* ¶¶114-115)
(c) assigning the plurality of sequence tags to their corresponding predetermined subsequences	*Quake* describes "software methods that can be used to identify a sequence in comparison to the known genome sequence." (*Quake* ¶[0121]; *see Morton Dec.* ¶85 and *Nussbaum Dec.* ¶¶116-117) *Kapur* teaches at ¶[0116] "mapping analysis using fixed content arrays." At ¶[0119], *Kapur* describes the use of the arrays for assigning sequence of random

	fragments: "Computer implemented methods for determining genotype using data from mapping arrays are disclosed, for example: in Liu, et al., Bioinformatics 19:2397-2403, 2003; and Diet al., Bioinformatics 21:1958-63, 2005. Computer implemented methods for linkage analysis using mapping array data are disclosed, for example, in Ruschendorf and Nurnberg, Bioinformatics 21:2123-5, 2005; and Leykin et al., BMC Genet. 6.7, 2005; and in U.S. Pat. No. 5,733,729." (*See Morton Dec.* ¶85 and *Nussbaum Dec.* ¶¶116-117)
(d) determining a number of sequence tags aligning to the predetermined subsequences of said first chromosome and a number of sequence tags to the predetermined subsequences of the second chromosome; and	*Quake* teaches "[q]uantitative analysis of the detection of the maternal and fetal target sequences. In some cases this may include targets to different regions, such as probes to a target on a chromosome suspected of being present in an abnormal copy number (trisonomy) [*sic*] compared to a normal diploid chromosome which is used as a control." (*Quake* ¶[0061]; *see Morton Dec.* ¶86 and *Nussbaum Dec.* ¶¶118-119) *Kapur* describes determining the number of random DNA fragments that bind to an array with predetermined sequence probes thereon based on the number of fragments that bind to the array probes: "Computer implemented methods for estimation of copy number based on hybridization intensity are disclosed in U.S. Publication Application Nos. 20040157243; 20050064476; and 20050130217." (*Kapur* ¶[0115]; *see Morton Dec.* ¶86 and *Nussbaum Dec.* ¶¶118-119). *Kapur* discloses that "quantification of amplified target nucleic acid can be used to determined gene/or allele copy number." (*Kapur* ¶[0113]; *see Morton Dec.* ¶86 and *Nussbaum Dec.* ¶¶118-119)
(e) comparing the numbers from step (d) to determine the presence or absence of an abnormal distribution of	*Quake* describes calculating a ratio based on the detected sequences by comparing the number to a cutoff value (*i.e.* an expected ratio) and determining whether an aneuploidy exists or not. (*Quake* ¶¶[0119]-[0121]; *see Morton Dec.* ¶87 and *Nussbaum Dec.*

said first chromosome.	¶¶120-123) *Quake* teaches that "The presence or absence of different target sequences in the discrete samples is detected; and the results are analyzed whereby the number of results from the discrete samples will provide data sufficient to obtain results distinguishing different target sequences. In one aspect, the method involves an analysis of a trisomy. In this method, one of the different target sequences (*e.g.* chromosome 21) is diploid in maternal genetic material and aneuploid in fetal genetic material and another of the different target sequences (*e.g.,* chromosome 12) is diploid in both maternal and fetal genetic material." (*Quake* ¶[0027]; *see Morton Dec.* ¶87 and *Nussbaum Dec.* ¶¶120-123) *Kapur* teaches that "quantification of amplified target nucleic acid can be used to determine gene/or allele copy number…" (*Kapur* ¶[0113]; *see Morton Dec.* ¶87 and *Nussbaum Dec.* ¶¶120-123) *Kapur* teaches detection of aneuploidy for chromosomes 13, 18, and 21: "After identifying approximately 10 bins that contain fetal cells, the next step would be to determine the ploidy of chromosomes 13, 18, 21 and X by comparing ratio of maternal to paternal alleles for each of the 10 SNPs on each chromosome. The ratios for the multiple SNPs on each chromosome can be combined (averaged) to increase the confidence of the aneuploidy call for that chromosome." (*Kapur* ¶[0216]; *see Morton Dec.* ¶87 and *Nussbaum Dec.* ¶¶120-123)
2. The method of claim 1 wherein the sample is a maternal serum or plasma sample, wherein the abnormal distribution of said first chromosome is a fetal aneuploidy, and wherein said second chromosome is a euploid	*Quake* ¶[0053] "The methods and materials described below apply techniques for analyzing numerous nucleic acids contained in a tissue sample (preferably serum or, more preferably, plasma) containing a mixture of DNA from both the mother and the fetus, and allowing detection of small but statistically significant differences." (*Morton Dec.* ¶88 and *Nussbaum Dec.* ¶¶124-125) *Quake* teaches that "The presence or absence of

chromosome.	different target sequences in the discrete samples is detected; and the results are analyzed whereby the number of results from the discrete samples will provide data sufficient to obtain results distinguishing different target sequences. In one aspect, the method involves an analysis of a trisomy. In this method, one of the different target sequences (*e.g.*, chromosome 21) is diploid in maternal genetic material and aneuploid in fetal genetic material and another of the different target sequences (*e.g.*, chromosome 12) is diploid in both maternal and fetal genetic material." (*Quake* ¶[0027]; *see Morton Dec.* ¶88 and *Nussbaum Dec.* ¶¶124-125)
3. The method of claim 2 wherein the sequencing comprises massively parallel sequencing of the predefined subsequences.	*Quake* at ¶[0120] "A methodology useful in the present invention platform is based on massively parallel sequencing." (*Morton Dec.* ¶88 and *Nussbaum Dec.* ¶¶126-127) *Kapur* teaches "In some embodiments, high-throughput sequencing is performed using Clonal Single Molecule Array (Solexa, Inc.) or sequencing-by-synthesis (SBS) utilizing reversible terminator chemistry. These technologies are described in part in U.S. Pat. Nos. 6,969,488; 6,897,023; 6,833,246; 6,787,308; and US Publication Application Nos. 20040106110; 20030064398; 20030022207; and Constans, A., The Scientist 2003, 17(13):36." (*Kapur* ¶[0163]; *see Morton Dec.* ¶88 and *Nussbaum Dec.* ¶¶126-127)
4. The method of claim 3 wherein said massively parallel sequencing comprises attaching DNA fragments to an optically transparent surface, conducing solid phase amplification of the attached DNA fragments to create a high density sequencing flow cell with millions of DNA clusters, and	*Quake* teaches A methodology useful in the present invention platform is based on massively parallel sequencing of millions of fragments using attachment of randomly fragmented genomic DNA to a planar, optically transparent surface and solid phase amplification to create a high density sequencing flow cell with millions of clusters, each containing -1,000 copies of template per cm^2. These templates are sequenced using four-color DNA sequencing-by-synthesis technology. See, products offered by Illumina,

sequencing the DNA clusters by a four-color DNA sequencing-by-synthesis method employing reversible terminators with removable fluorescent dyes.	Inc., San Diego Calif. Also, see US 2003/0022207 to Balasubramanian, et al., published Jan. 30, 2003, entitled "Arrayed polynucleotides and their use in genome analysis." (*Quake* ¶[0120]; *see Morton Dec.* ¶89 and *Nussbaum Dec.* ¶¶128-129) *Kapur* also teaches solid phase amplification to create high density clusters of DNA and "a sequencing-by-synthesis (SBS) method [which] utilizes four fluorescently labeled modified nucleotides that are especially created to possess a reversible termination property, which allow each cycle of the sequencing reaction to occur simultaneously in the presence of all four nucleotides (A, C, T, G)." (*Kapur* ¶[0166]; *see Morton Dec.* ¶89 and *Nussbaum Dec.* ¶¶128-129)
5. The method of claim 2 wherein the fetal aneuploidy is an aneuploidy of a chromosome selected from the group consisting of chromosome 13, chromosome 18 and chromosome 21.	*Quake* teaches that "The present method may be used for detection of a translocation, addition, amplification, transversion, inversion, aneuploidy, polyploidy, monosomy, trisomy, trisomy 21, trisomy 13, trisomy 14, trisomy 15, trisomy 16, trisomy 18, trisomy 22, triploidy, tetraploidy, and sex chromosome abnormalities including but not limited to XO, XXY, XYY, and XXX." (*Quake* ¶[0129]; *see Morton Dec.* ¶90 and *Nussbaum Dec.* ¶¶130-132) *Kapur* teach that "genetic conditions that can be determined in one or more fetal cells include trisomy 13, trisomy 18, trisomy 21…" (*Kapur* ¶[0007]; *see Morton Dec.* ¶90 and *Nussbaum Dec.* ¶¶130-132)
7. The method of claim 2 wherein the length of the sequence tags is from about 25 bp to about 100 bp in length.	*Quake* teaches "Only about 30 bp of random sequence information are needed to identify a sequence as belonging to a specific human chromosome. Longer sequences can uniquely identify more particular targets." (*Quake* ¶[0121]; *see Morton Dec.* ¶91 and *Nussbaum Dec.* ¶¶133-135) *Kapur*: "For generating sequence data that can be compared with a reference database (for instance human mRNA database of the NCBI), length of the sequence snippets has to exceed 15-20 nucleotides."

	(*Kapur* ¶[0171]; *see Morton Dec.* ¶91 and *Nussbaum Dec.* ¶¶133-135)
8. The method of claim 2 wherein the DNA is genomic DNA.	*Quake* teaches: "Briefly, the present invention is directed to a method of differential detection of target sequences in a mixture of maternal and fetal genetic material. One obtains maternal tissue containing both maternal and fetal genetic material. Preferably, the maternal tissue is maternal peripheral blood or blood plasma. The term "plasma" may include plasma or serum. The genetic material may be genomic DNA or RNA, preferably mRNA." (*Quake* ¶[0026]; *see Morton Dec.* ¶92 and *Nussbaum Dec.* ¶¶136-138) Kapur teaches "Preferably, the nucleic acid is genomic DNA." (*Kapur* ¶[0009]; *see Morton Dec.* ¶92 and *Nussbaum Dec.* ¶¶136-138)
9. The method of claim 2 wherein said sequencing comprises selectively sequencing nucleic acid molecules comprising the predefined sequences.	*Quake* teaches "In one aspect, the present method of differential detection of target sequences may involve direct sequencing of target sequences the genetic material [sic]." (*Quake* ¶[0033]; *see Morton Dec.* ¶93 and *Nussbaum Dec.* ¶¶139-141) *Kapur* at Figures 6 and 7 and the descriptions therefor teaches a method for sequence determination of randomly generated DNA fragments using arrays having oligonucleotides of known sequence. The techniques described are sequencing by array technologies, as these arrays identify the sequence of the randomly generated sequences resulting from the genomic library. Sequencing of a randomly generated genomic fragment via binding to a predefined sequence on an array aligns a random sequence to a probe indicative of a specific genomic region. (*Morton Dec.* ¶93 and *Nussbaum Dec.* ¶¶139-141)
10. The method of claim 9 wherein said sequencing comprises the use of a sequencing array.	*Kapur* at Figures 6 and 7 and the descriptions therefor teaches a method for sequence determination of randomly generated DNA fragments using arrays having probes of known sequence. The techniques described are sequencing by array technologies, as these arrays identify the sequence of the randomly

	generated sequences resulting from the genomic library. (*Morton Dec.* ¶94 and *Nussbaum Dec.* ¶142)
11. The method of claim 10 wherein said selected defined subsequences of the genomic DNA are rendered single-stranded and captured under hybridizing conditions by single-stranded probes physically separated on an array.	*Kapur* describes in relation to Figure 7, "In step 706, the single-stranded, labeled DNAs are eluted and prepared for hybridization. In step 707, the single-stranded, labeled DNAs are hybridized to their complement bead type through their unique address sequence. Hybridization of the GoldenGateAssay™ products onto the Array Matrix™ of Beadchip™ allows for separation of the assay products in solution, onto a solid surface for individual SNP genotype readout." (*Kapur* ¶[0126]; *see Morton Dec.* ¶95 and *Nussbaum Dec.* ¶¶143-144)
12. The method of claim 2 further comprising determination of fetal DNA fraction of the DNA obtained from the maternal serum or plasma sample.	*Quake* states "Lo et al., "Quantitative Analysis of Fetal DNA in Maternal Plasma and Serum: Implications for Noninvasive Prenatal Diagnosis," Am. J. Hum. Genet. 62:768-775 (1998) discloses a real-time quantitative PCR assay to measure the concentration of fetal DNA in maternal plasma and serum. The authors found a mean of 25.4 genome equivalents/ml of fetal DNA in early pregnancy. This corresponds to about 3.4% of total DNA in early pregnancy." (*Quake* ¶[0017]; *see Morton Dec.* ¶96 and *Nussbaum Dec.* ¶¶145-148) Additionally, *Quake* states "The number of discrete samples is chosen according to the results desired. In one aspect, it is preferred that a high degree of statistical significance is obtained, and the number of samples is at least about 10,000. In order to improve statistical confidence, it is preferable to employ large numbers of reactions, preferably between 500 and 100,000, more preferably between 10,000 and 100,000 or more reactions, depending on the percentage of fetal DNA present in the mixture. The results to be obtained should be statistically significant for purposes of the analysis conducted, *e.g.* initial screening, primary diagnosis, etc."(*Quake* ¶[0029]; *see Morton Dec.* ¶96 and *Nussbaum Dec.* ¶¶145-148)
13. The method of claim	Quake *states* that detection of the presence of the target

12 wherein the fetal DNA fraction is determined by digital PCR.	in the DNA can be carried out by digital PCR: "The detection step is referred to here as "digital PCR" and may be carried out by a variety of methods, such as (a) by PCR on samples diluted into individual wells of a microtiter plate; (b) PCR on samples diluted into emulsions containing primers immobilized to beads; or (c) PCR on samples trapped in a microfluidic chamber." (*Quake* ¶[0060]; *see Morton Dec.* ¶97 and *Nussbaum Dec.* ¶¶149-150)

E. Claims 1-10 and 12-13 are Rendered Obvious by *Dhallan* Viewed in Combination with *Lo*

The Declarations of Dr. Morton and Dr. Nussbaum explain that the combination of *Dhallan* and *Lo* renders the 'claims of the *'076 Patent* obvious under an interpretation of the claims covering sequencing of pre-selected sequences. (*Morton Dec.* ¶98 and *Nussbaum Dec.* ¶151) The following claim chart demonstrates, on a limitation-by-limitation basis, how claims 1-5, 7-10 and 12-13 of the *'076 Patent* are obvious over *Dhallan* when viewed in combination with *Lo*.

Correspondence between claims 1-10 and 12-13 of the *'076 Patent* and *Dhallan*, U.S. 7,332,277 and *Lo*, US 2009/0029377	
1. A method of testing for an abnormal distribution of a chromosome in	See claim chart in Section VII.A for the correspondence between this element and *Lo*. *Dhallan* '277 states at 6: 15-16, "In one aspect, the invention is directed to methods for detecting chromosomal abnormalities." (*Morton Dec.* ¶99 and *Nussbaum Dec.* ¶153)
a sample comprising a mixture of maternal and fetal DNA, comprising	See claim chart in Section VII.A for the correspondence between this element and Lo. See also *Morton Dec.*

the steps of:	¶100 and *Nussbaum Dec.* ¶154)
(a) obtaining maternal and fetal DNA from said sample;	*Dhallan* discloses obtaining a maternal and fetal DNA sample (template DNA), *e.g.* from blood plasma: "In an embodiment, the sample is blood obtained from a pregnant female and, *e.g.* , the nucleic acid is isolated from plasma obtained from blood of a pregnant female; the plasma is generated using procedures designed to minimize the amount of maternal cell lysis." (*Dhallan* 16:34-38*; see Morton Dec.* ¶101 and *Nussbaum Dec.* ¶154) See claim chart in Section VII.A for the correspondence between this element and *Lo*.
(b) sequencing predefined subsequences of the maternal and fetal DNA	*If the claims are construed as including sequencing of selected subsequences:* *Dhallan* discloses sequencing predefined portions of the template DNA that can be used for determination of fetal abnormalities: "In one embodiment, the present invention is directed to a method for detecting chromosomal abnormalities, said method comprising quantitating the relative amount of the alleles at a heterozygous locus of interest, where, the heterozygous locus of interest was previously identified by determining the sequence of alleles at a locus of interest from template DNA." (*Dhallan* 6:17-22, Figs. 4-7; *see also Morton Dec.* ¶102 and *Nussbaum Dec.* ¶¶155-161) "In another embodiment, the fraction of the nucleic acid pool that is sequenced in a run is further sub-selected prior to sequencing. For example, hybridization based techniques such as oligonucleotide array could be used to first sub-select for nucleic acid sequences from certain chromosomes, *e.g.* a potentially aneuploid chromosome and other chromosome(s) not involved in the aneuploidy tested." (*Lo* ¶[0072]; *see Morton Dec.* ¶102 and *Nussbaum Dec.* ¶¶155-161) The *Lo* method produces multiple sequence tags long enough to be aligned to the human reference genome to

	note their chromosomal origin, *[0070]* and an amount of the chromosome of interest and of one or more other chromosomes may thus be determined *[0058]*. (*Morton Dec.* ¶102 and *Nussbaum Dec.* ¶¶155-161) *If the claims are construed to include shotgun sequencing of predefined subsequences* "The term "random sequencing" as used herein refers to sequencing whereby the nucleic acid fragments sequenced have not been specifically identified or targeted before the sequencing procedure. Sequence-specific primers to target specific gene loci are not required." (*Lo* [0047], *see Morton Dec.* ¶102 and *Nussbaum Dec.* ¶¶155-161) "In one aspect for the massively parallel sequencing approach, representative data from all of the chromosomes may be generated at the same time. The origin of a particular fragment is not selected ahead of time. The sequencing is done at random and then a database search may be performed to see where a particular fragment is coming from." (*Lo* [0080], *see Morton Dec.* ¶102 and *Nussbaum Dec.* ¶¶155-161)
to obtain a plurality of sequence tags aligning to the predefined subsequences,	*Dhallan* discloses that "[t]he amplified DNA can be pooled together prior to digestion of the amplified DNA. Each of the labeled DNA containing a locus of interest can be separated prior to determining the sequence of the locus of interest. In one embodiment, at least one of the loci of interest is suspected of containing a single nucleotide polymorphism or a mutation." (*Dhallan* 7:23-32; *see Morton Dec.* ¶102 and *Nussbaum Dec.* ¶¶155-161) As explained in the Declaration of Dr. Morton, the amplified DNA contains a plurality of DNA fragments of predefined sequence. (*Morton Dec.* ¶102 and *see also Nussbaum Dec.* ¶¶155-161) See claim chart in Section VII.A for the correspondence between this element and *Lo*
wherein said sequence	*Dhallan* discloses: "By a 'locus of interest' is intended a

tags are of sufficient length to be assigned to a specific predefined subsequence,	selected region of nucleic acid that is within a larger region of nucleic acid. A locus of interest can include but is not limited to 1-100, 1-50, 1-20, or 1-10 nucleotides, preferably 1-6, 1-5, 1-4, 1-3, 1-2, or 1 nucleotide(s). (*Dhallan* 29:5-10; *see also Morton Dec.* ¶*103 and Nussbaum Dec.* ¶162) *Lo* teaches that "[t]he short sequence tags generated were aligned to the human reference genome sequence and the chromosomal origin was noted." (*Lo* ¶[0070]; see *Morton Dec.* ¶103-104 and *Nussbaum Dec.* ¶162)
wherein the predefined subsequences are from a plurality of different chromosomes, and wherein said plurality of different chromosomes comprise at least one first chromosome suspected of having an abnormal distribution in said sample and at least one second chromosome presumed to be normally distributed in said sample;	*Dhallan* teaches that "[a]ny number of loci of interest can be analyzed and processed, especially at the same time, using the method of the invention. The sample(s) can be analyzed to determine the sequence at one locus of interest or at multiple loci of interest at the same time. The loci of interest can be present on a single chromosome or on multiple chromosomes." (*Dhallan* 35:41-47; *see also Morton Dec.* ¶103-104 and *Nussbaum Dec.* ¶163) See claim chart in Section VII.A for the correspondence between this element and *Lo*.
(c) assigning the plurality of sequence tags to their corresponding predetermined subsequences;	*Dhallan* discloses assigning the plurality of sequence tags (amplified loci of interest) to their corresponding predetermined subsequences (the predetermined loci of interest): "In another aspect, the invention provides a method for detecting a chromosomal abnormality by (a) determining the sequence of alleles of a locus of interest from template DNA . . ." (*Dhallan* 16:62-65*; see also Morton Dec.* ¶105 and *Nussbaum Dec.* ¶164) See claim chart in Section VII.A for the correspondence between this element and *Lo*.
(d) determining a number of sequence tags aligning to the	*Dhallan* discloses determining the number of loci of interest known *a priori* to align to a first and a second chromosome: "In another aspect, the invention provides

predetermined subsequences of said first chromosome and a number of sequence tags to the predetermined subsequences of the second chromosome; and	a method for detecting a chromosomal abnormality by . . . (b) quantitating the relative amount of the alleles at a heterozygous locus of interest that was identified from the locus of interest of (a),. . .” (*Dhallan* 16:65-67; *see also Morton Dec.* ¶106 and *Nussbaum Dec.* ¶165-166) See claim chart in Section VII.A for the correspondence between this element and *Lo*.
(e) comparing the numbers from step (d) to determine the presence or absence of an abnormal distribution of said first chromosome.	*Dhallan* discloses comparing the numbers of loci of interest aligned to the first and second chromosome to determine the presence or absence of an abnormal chromosomal distribution: “In another aspect, the invention provides a method for detecting a chromosomal abnormality by . . . (b) quantitating the relative amount of the alleles at a heterozygous locus of interest that was identified from the locus of interest of (a), wherein said relative amount is expressed as a ratio, and wherein said ratio indicates the presence or absence of a chromosomal abnormality.” (*Dhallan* 16: 67- 17:2; *see also Morton Dec.* ¶*107* and *Nussbaum Dec.* ¶167) See claim chart in Section VII.A for the correspondence between this element and *Lo*.
2. The method of claim 1 wherein the sample is a maternal serum or plasma sample, wherein the abnormal distribution of said first chromosome is a fetal aneuploidy, and wherein said second chromosome is a euploid chromosome.	*Dhallan* teaches that “[i]n some embodiments, the template DNA is obtained from a sample that is a cell, fetal cell, tissue, blood, serum, plasma, saliva, urine. . .” (*Dhallan* 6:41-43; *see also Morton Dec.* ¶108 and *Nussbaum Dec.* ¶¶168-171). *See also comments for claim 1, steps (d) and (e).* See claim chart in Section VII.A for the correspondence between this element and Lo.
3. The method of claim 2 wherein the sequencing comprises massively parallel	See claim chart in Section VII.A for the correspondence between this element and Lo. (*See also Morton Dec.* ¶ 109 and *Nussbaum Dec.* ¶¶172-173)

sequencing of the predefined subsequences.	
4. The method of claim 3 wherein said massively parallel sequencing comprises attaching DNA fragments to an optically transparent surface, conducing solid phase amplification . . . removable fluorescent dyes.	See claim chart in Section VII.A for the correspondence between this element and Lo. (*See also Morton Dec.* ¶ 110 and *Nussbaum Dec.* ¶¶174-175)
5. The method of claim 2 wherein the fetal aneuploidy is an aneuploidy of a chromosome selected from the group consisting of chromosome 13, chromosome 18 and chromosome 21.	See claim chart in Section VII.A for the correspondence between this element and Lo. (*See also Morton Dec.* ¶111 and *Nussbaum Dec.* ¶¶176-177)
6. The method of claim 2 wherein the step of assigning sequence tags to corresponding chromosome portions allows one mismatch.	Claim 18 of *Lo* recites: "wherein the fractional concentration of fetal DNA in the biological sample is determined by any one or more of a proportion of Y chromosome sequences, a fetal epigenetic marker, or using single nucleotide polymorphism analysis." An example of this method would be to target polymorphic sites at which the pregnant woman is homozygous and the fetus is heterozygous, wherein the amount of fetal-specific allele can be compared with the amount of the common allele to determine the fractional concentration of fetal DNA. By definition the alignment of a polymorphic region to a single reference will have a mismatch in either the fetal or the maternal DNA, as they differ by one base pair.

7. The method of claim 2 wherein the length of the sequence tags is from about 25 bp to about 100 bp in length.	*Dhallan* teaches "[f]or each of the nine SNPs, a primer that annealed approximately 130 bases from the locus of interest and 130 bases downstream of the locus of interest were used. This amplification reaction, which contained a total of 100 different primer sets, was used to amplify the regions containing the loci of interest." (*Dhallan* 25:4-10; *see Morton Dec.* ¶112 and *Nussbaum Dec.* ¶178) See claim chart in Section VII.A for the correspondence between this element and *Lo*.
8. The method of claim 2 wherein the DNA is genomic DNA.	"The nucleic acid that is to be analyzed can be any nucleic acid, *e.g.*, genomic, plasmid, cosmid, yeast artificial chromosomes, artificial or man-made DNA, including unique DNA sequences, and also DNA that has been reverse transcribed from an RNA sample, such as cDNA." (*Dhallan* 33:53-58; *see Morton Dec.* ¶113 and *Nussbaum Dec.* ¶¶179-181) See claim chart in Section VII.A for the correspondence between this element and *Lo*.
9. The method of claim 2 wherein said sequencing comprises selectively sequencing nucleic acid molecules comprising the predefined sequences.	"The labeled DNA loci of interest sites can be analyzed by a variety of methods . . . wherein DNA fragments would be useful as both 'probes' and 'targets'. . ." (*Dhallan* 62:30-48; *see Morton Dec.* ¶114 and *Nussbaum Dec.* ¶¶182-184) See claim chart in Section VII.A for the correspondence between this element and *Lo*.
10. The method of claim 9 wherein said sequencing comprises the use of a sequencing array.	"Any method that provides information on the sequence of a nucleic acid can be used including but not limited to allele specific PCR, PCR, gel electrophoresis, ELISA, mass spectrometry, MALDI-TOF mass spectrometry hybridization, primer extension, fluorescence detection, fluorescence resonance energy transfer (FRET), fluorescence polarization, DNA sequencing, Sanger dideoxy sequencing, DNA sequencing gels, capillary electrophoresis on an automated DNA sequencing machine, microchannel electrophoresis, microarray, southern blot, slot blot, dot blot, single primer linear

	nucleic acid amplification, as described in U.S. Pat. No. 6,251,639, SNP-IT, GeneChips, HuSNP, BeadArray, TaqMan assay, Invader assay, MassExtend, or MassCleave ™ (hMC) method." (*Dhallan* 36: 5-18; *see Morton Dec.*¶115 and *Nussbaum Dec.* ¶185)
12. The method of claim 2 further comprising determination of fetal DNA fraction of the DNA obtained from the maternal serum or plasma sample.	"Plasma isolated from blood of a pregnant female contains both maternal template DNA and fetal template DNA. As discussed earlier, the percentage of fetal DNA in the maternal plasma varies for each pregnant female. However, the percentage of fetal DNA can be determined by analyzing SNPs wherein the maternal template DNA is homozygous and the template DNA obtained." (*Dhallan* 196:45-54; *see Morton Dec.*¶116 and *Nussbaum Dec.* ¶186)
13. The method of claim 12 wherein the fetal DNA fraction is determined by digital PCR.	See claim chart in Section VII.A for the correspondence between this element and Lo. *See also Morton Dec.* ¶117 and *Nussbaum Dec.* ¶187.

F. Claims 10-11 Are Rendered Obvious by *Dhallan* Taken in Combination with *Lo* and *Brenner*

In this combination, *Brenner* provides motivation for sequencing a predefined subsequence for the purpose of reducing the complexity of a sequencing procedure. (*Morton Dec.* ¶*118* and *Nussbaum Dec.* ¶*189*) The DNA sorting methods of *Brenner* would have permitted one to select particular fractions of the maternal and fetal DNA for sequencing. (*See id.*) It would have been expected to focus the sequencing procedure on putative aneuploid chromosome sequences and reduce the complexity of the method of *Lo.* (*Id.*)

The claim chart below shows the correspondence between *Dhallan* (*Ex. 1002*), Lo (*Ex. 1004*), Brenner (*Ex. 1003*) and claims 10-11 of the *'076 Patent*.

Correspondence between claims 10 and 11 of the *'076 Patent* and *Dhallan, Lo* and *Brenner*	
10. The method of claim 9 wherein said sequencing comprises the use of a sequencing array.	"In another aspect, the method of the invention is carried out on a population of tagged polynucleotides so that after a subpopulation is selected, the members of the subpopulation may be simultaneously analyzed using the unique tags on the polynucleotides to convey analytical information to a hybridization array for a readout." (*Brenner Abstract, see Morton Dec.* ¶108) "In one aspect, the invention provides methods for sorting polynucleotides based on predetermined sequence characteristics to form subpopulations of reduced complexity. In another aspect, such sorting methods are used to analyze populations of uniquely tagged polynucleotides, such as genome fragments. That is, mixtures may be formed containing fragments of genomic DNA from different individuals such that each individual's DNA is labeled with a unique oligonucleotide tag. During or at the conclusion of repeated steps of sorting in accordance with the invention, the tags may be replicated, labeled and hybridized to a solid phase support, such as a microarray, to provide a simultaneous readout of sequence information related to the genomic DNA." (*Brenner* ¶[0041]; *see Morton Dec.* ¶119 and *Nussbaum* ¶¶191-195)
11. The method of claim 10 wherein said selected defined subsequences of the genomic DNA are rendered single-stranded and captured under hybridizing conditions by single-stranded	See discussion above in connection with claim 10. "'"Hybridization" refers to the process in which two single-stranded polynucleotides bind non-covalently to form a stable double-stranded polynucleotide." (*Brenner* [0026]; *see Morton Dec.* ¶120 and *Nussbaum Dec.* ¶¶196-198)

probes physically separated on an array.	

G. Claims 1-5 and 7-12 Are Rendered Obvious by *Dhallan* et al. When Viewed in Combination with *Kapur*

As the broadest reasonable interpretation of the limitations "sequencing predefined subsequences" and "sequence tags" includes targeted array sequencing, it would have been obvious to utilize the sequencing by array methods taught by *Kapur* in the analysis of loci of predefined sequences as taught by *Dhallan* to identify abnormal distribution of a chromosome in a sample. (*Morton Dec.* ¶120 and *Nussbaum Dec.* ¶*199*) The following claim chart demonstrates, on a limitation-by-limitation basis, how claims 1-5 and 7-12 of the *'076 Patent* are obvious over *Dhallan* taken in combination with *Kapur*.

Correspondence between claims 1-5 and 7-12 of the *'076 Patent* and *Dhallan*, U.S. 7,332,277 and *Kapur*, U.S. 2008/10138809	
1. A method of testing for an abnormal distribution of a chromosome in a sample comprising a mixture of maternal and fetal DNA, comprising the steps of:	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. See claim chart in Section VII.D for the correspondence between this element and *Kapur*. (*Morton Dec.* ¶121-123 and *Nussbaum Dec.* ¶201)
(a) obtaining maternal and fetal DNA from said sample;	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. See claim chart in Section VII.D for the correspondence between this element and *Kapur*. (*Morton Dec.* ¶124 and *Nussbaum Dec.* ¶202)
(b) sequencing predefined subsequences of the maternal and fetal DNA to obtain a	*If the claims are construed as including sequencing of selected subsequences:*

plurality of sequence tags aligning to the predefined subsequences,	"In one embodiment, the present invention is directed to a method for detecting chromosomal abnormalities, said method comprising quantitating the relative amount of the alleles at a heterozygous locus of interest, where, the heterozygous locus of interest was previously identified by determining the sequence of alleles at a locus of interest from template DNA." (*Dhallan* 6:17-22, Figs. 4-7; *see Morton Dec.* ¶125 and *Nussbaum Dec.* ¶¶203-205) *Dhallan* discloses that "[t]he loci of interest on template DNA can be amplified in one reaction. Alternatively, each of the loci of interest on template DNA can be amplified in a separate reaction. The amplified DNA can be pooled together prior to digestion of the amplified DNA. Each of the labeled DNA containing a locus of interest can be separated prior to determining the sequence of the locus of interest. In one embodiment, at least one of the loci of interest is suspected of containing a single nucleotide polymorphism or a mutation." (*Dhallan* 7:23-32; see *Morton Dec.* ¶125 and *Nussbaum Dec.* ¶¶203-205) As explained in the declarations submitted herewith, the amplified DNA containing the loci of interest represent sequence tags under a broad interpretation of that term. (*Morton Dec.* ¶125 *and Nussbaum Dec.* ¶¶203-205) *Kapur* at Figure 6 and 7 teaches a method for sequence determination of randomly generated DNA fragments using arrays having oligonucleotides of known sequence. Sequencing of a randomly generated genomic fragment via binding to a predefined sequence on an array aligns a random sequence to a probe indicative of a specific genomic region. (*Morton Dec.* ¶125 and *Nussbaum Dec.* ¶¶203-205)

wherein said sequence tags are of sufficient length to be assigned to a specific predefined subsequence,	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. See claim chart in Section VII.D for the correspondence between this element and *Kapur*. (*Morton Dec.* ¶126 and *Nussbaum Dec.* ¶206)
wherein the predefined subsequences are from a plurality of different chromosomes, and wherein said plurality of different chromosomes comprise at least one first chromosome suspected of having an abnormal distribution in said sample and at least one second chromosome presumed to be normally distributed in said sample;	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. See claim chart in Section VII.D for the correspondence between this element and *Kapur*. (*Morton Dec.* ¶127 and *Nussbaum Dec.* ¶207)
(c) assigning the plurality of sequence tags to their corresponding predetermined subsequences;	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. See claim chart in Section VII.D for the correspondence between this element and *Kapur*. (*Morton Dec.* ¶128 and *Nussbaum Dec.* ¶208)
(d) determining a number of sequence tags aligning to the predetermined subsequences of said first chromosome and a number of sequence tags to the predetermined subsequences of the second chromosome; and	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. See claim chart in Section VII.D for the correspondence between this element and *Kapur*. (*Morton Dec.* ¶129 and *Nussbaum Dec.* ¶209)
(e) comparing the numbers from step (d) to determine the presence or absence of an abnormal distribution of said first chromosome.	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. See claim chart in Section VII.D for the correspondence between this element and *Kapur*.

	(*Morton Dec.* ¶130 *and Nussbaum Dec.* ¶210)
2. The method of claim 1 wherein the sample is a maternal serum or plasma sample, wherein the abnormal distribution of said first chromosome is a fetal aneuploidy, and wherein said second chromosome is a euploid chromosome.	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. (*Morton Dec.* ¶131 and *Nussbaum Dec.* ¶211-212)
3. The method of claim 2 wherein the sequencing comprises massively parallel sequencing of the predefined subsequences.	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. See claim chart in Section VII.D for the correspondence between this element and *Kapur*. (*Morton Dec.* ¶132 and *Nussbaum Dec.* ¶213)
4. The method of claim 3 wherein said massively parallel sequencing comprises attaching DNA fragments to an optically transparent surface, conducing solid phase amplification of the attached DNA fragments to create a high density sequencing flow cell with millions of DNA clusters, and sequencing the DNA clusters by a four-color DNA sequencing-by-synthesis method employing reversible terminators with removable fluorescent dyes.	See claim chart in Section VII.D for the correspondence between this element and *Kapur*.
5. The method of claim 2 wherein the fetal aneuploidy is an aneuploidy of a chromosome selected from the group consisting of	See claim chart in Section VII.D for the correspondence between this element and *Kapur*. (*Morton Dec.* ¶133 and *Nussbaum Dec.* ¶214)

chromosome 13, chromosome 18 and chromosome 21.	
7. The method of claim 2 wherein the length of the sequence tags is from about 25 bp to about 100 bp in length.	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. See claim chart in Section VII.D for the correspondence between this element and *Kapur*. (*Morton Dec.* ¶134 and *Nussbaum Dec.* ¶215)
8. The method of claim 2 wherein the DNA is genomic DNA.	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. See claim chart in Section VII.D for the correspondence between this element and *Kapur*. (*Morton Dec.* ¶135 and *Nussbaum Dec.* ¶216)
9. The method of claim 2 wherein said sequencing comprises selectively sequencing nucleic acid molecules comprising the predefined sequences.	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. See claim chart in Section VII.D for the correspondence between this element and *Kapur*. (*Morton Dec.* ¶136 and *Nussbaum Dec.* ¶*217*)
10. The method of claim 9 wherein said sequencing comprises the use of a sequencing array.	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. See claim chart in Section VII.D for the correspondence between this element and Kapur. (*Morton Dec.* ¶137 and *Nussbaum Dec.* ¶218-219)
11. The method of claim 10 wherein said selected defined subsequences of the genomic DNA are rendered single-stranded and captured under hybridizing conditions by single-stranded probes physically separated on an array.	*Kapur* at describes in relation to Figure 7, "In step 706, the single-stranded, labeled DNAs are eluted and prepared for hybridization. In step 707, the single-stranded, labeled DNAs are hybridized to their complement bead type through their unique address sequence." (*Kapur* ¶[0126]; *see Morton Dec.* ¶138 and *Nussbaum Dec.* ¶220)
12. The method of claim 2 further comprising determination of fetal DNA	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*.

fraction of the DNA obtained from the maternal serum or plasma sample.	(*Morton Dec.* ¶139 and *Nussbaum Dec.* ¶221)

H. Claims 1-3, 5 and 7-12 Are Rendered Obvious by *Dhallan* et al. When Viewed in Combination with *Brenner*

As noted above, the broadest reasonable interpretation of the limitations "sequencing predefined subsequences" and "sequence tags" includes targeted array sequencing. This form of sequencing uses hybridization of randomly produced DNA fragments (i.e. "sequence tags") to an array with probes complementary to "preselected subsequences" unique to a genomic region. *Dhallan* taken in view of Brenner is an alternative ground of rejection. In this combination Brenner provides motivation for sequencing a predefined sequence for the purpose of reducing the complexity of a sequencing procedure. (*Morton Dec.* ¶140 and *Nussbaum Dec.* ¶222)

The following claim chart demonstrates, on a limitation-by-limitation basis, how claims 1-3, 5 and 7-13 of the *'076 Patent* are obvious over *Dhallan* taken in combination with *Brenner*.

Correspondence between claims 1-3, 5, and 7-13 of the *'076 Patent* and *Dhallan*, U.S. 7,332,277 and *Brenner*, U.S. 2006/0177832	
1. A method of testing for an abnormal distribution of a chromosome in a sample	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. (*Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶224)
comprising a mixture	See claim chart in Section VII.E for the correspondence

of maternal and fetal DNA, comprising the steps of:	between this element and *Dhallan*. (*Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶225-226)
(a) obtaining maternal and fetal DNA from said sample;	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. (*Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶225-226)
(b) sequencing predefined subsequences of the maternal and fetal DNA	*If the claims are construed as including sequencing of selected subsequences:* Dhallan discloses sequencing predefined portions of the template DNA by amplifying multiple predefined loci of interest in the template DNA using specific primers thus obtaining a plurality of short nucleotide sequences (sequence tags) aligning to each predefined locus of interest on a particular chromosome: "In one embodiment, the present invention is directed to a method for detecting chromosomal abnormalities, said method comprising quantitating the relative amount of the alleles at a heterozygous locus of interest, where the heterozygous locus of interest was previously identified by determining the sequence of alleles at a locus of interest from template DNA." (*Dhallan* 6:17-22, Figs. 4-7; *see also Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶¶227-232) *Brenner*, ¶[0041] discloses "methods for sorting polynucleotides based on predetermined sequence characteristics to form subpopulations of reduced complexity. . .Predetermined sequence characteristics include, but are not limited to, a unique sequence region at a particular locus, or a series of polymorphisms, such as insertions, deletions, or substitutions, at a series of loci. . ." (*See also Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶¶227-232)
to obtain a plurality of sequence tags aligning to the predefined subsequences,	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. As explained in the declarations submitted herewith, the amplified DNA containing the loci of interest represent "sequence tags" under the broadest reasonable

	interpretation of that term. (*See section VI.C, supra*)
wherein said sequence tags are of sufficient length to be assigned to a specific predefined subsequence,	"By a 'locus of interest' is intended a selected region of nucleic acid that is within a larger region of nucleic acid. A locus of interest can include but is not limited to 1-100, 1-50, 1-20, or 1-10 nucleotides, preferably 1-6, 1-5, 1-4, 1-3, 1-2, or 1 nucleotide(s). (*Dhallan* 29: 5-10; *Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶¶233-234)
wherein the predefined subsequences are from a plurality of different chromosomes, and wherein said plurality of different chromosomes comprise at least one first chromosome suspected of having an abnormal distribution in said sample and at least one second chromosome presumed to be normally distributed in said sample;	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. (*Morton Dec.* ¶¶140-141 *and Nussbaum Dec.* ¶¶235-236)
(c) assigning the plurality of sequence tags to their corresponding predetermined subsequences;	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. (*Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶¶237-238)
(d) determining a number of sequence tags aligning to the predetermined subsequences of said first chromosome and a number of sequence tags to the predetermined	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. (*Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶¶239-240)

subsequences of the second chromosome; and	
(e) comparing the numbers from step (d) to determine the presence or absence of an abnormal distribution of said first chromosome.	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. (*Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶¶241-242)
2. The method of claim 1 wherein the sample is a maternal serum or plasma sample, wherein the abnormal distribution of said first chromosome is a fetal aneuploidy, and wherein said second chromosome is a euploid chromosome.	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. (*Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶¶243-244)
3. The method of claim 2 wherein the sequencing comprises massively parallel sequencing of the predefined subsequences.	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. (*Morton Dec.* ¶¶*140-141* and *Nussbaum Dec.* ¶¶245-246)
5. The method of claim 2 wherein the fetal aneuploidy is an aneuploidy of a chromosome selected from the group consisting of chromosome 13, chromosome 18 and chromosome 21.	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. (*Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶¶248-249)

7. The method of claim 2 wherein the length of the sequence tags is from about 25 bp to about 100 bp in length.	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. (*Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶¶250-251)
8. The method of claim 2 wherein the DNA is genomic DNA.	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. (*Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶¶252-254)
9. The method of claim 2 wherein said sequencing comprises selectively sequencing nucleic acid molecules comprising the predefined sequences.	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. (*Morton Dec.* ¶¶140-141 *and Nussbaum Dec.* ¶¶255-257)
10. The method of claim 9 wherein said sequencing comprises the use of a sequencing array.	"In another aspect, the method of the invention is carried out on a population of tagged polynucleotides so that after a subpopulation is selected, the members of the subpopulation may be simultaneously analyzed using the unique tags on the polynucleotides to convey analytical information to a hybridization array for a readout." (*Brenner Abstract*; *see Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶258) "During or at the conclusion of repeated steps of sorting in accordance with the invention, the tags may be replicated, labeled and hybridized to a solid phase support, such as a microarray, to provide a simultaneous readout of sequence information related to the genomic DNA." (*Brenner [0041]*; *see Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶258)
11. The method of claim 10 wherein said selected defined subsequences of the genomic DNA are rendered	"In another aspect, the method of the invention is carried out on a population of tagged polynucleotides so that after a subpopulation is selected, the members of the subpopulation may be simultaneously analyzed using the unique tags on the polynucleotides to convey analytical information to a hybridization array for a readout."

single-stranded and captured under hybridizing conditions by single-stranded probes physically separated on an array.	(*Brenner Abstract*; *see Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶259) “"Hybridization" refers to the process in which two single-stranded polynucleotides bind non-covalently to form a stable double-stranded polynucleotide.” (*Brenner [0026]; see also Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶259)
12. The method of claim 2 further comprising determination of fetal DNA fraction of the DNA obtained from the maternal serum or plasma sample.	See claim chart in Section VII.E for the correspondence between this element and *Dhallan*. (*Morton Dec.* ¶¶140-141 and *Nussbaum Dec.* ¶260)

I. Claim 6 Is Rendered Obvious by Li

Claim 6 of the *‘076 Patent* is directed to allowing one mismatch during the sequencing step or, under the broadest reasonable interpretation and in view of the open ended nature of the claim, at least one mismatch. Allowing an arbitrary number of mismatches, such as one or two mismatches, was a routine design choice at the time of filing.

For instance, Li et al., *Mapping short DNA sequencing reads and calling variants using mapping quality scores*, Genome Res. 18:8511858 (August 19, 2008) (*Ex. 1014*) discloses a program that counts mismatches in order to determine the reads which align most closely to the reference genome:

> MAQ is a program that rapidly aligns short reads to the reference genome and accurately infers variants, including SNPs and short indels, from the

> alignment. At the alignment stage, MAQ first searches for the ungapped match with lowest **mismatch score**, defined as the sum of qualities at mismatching bases. To speed up the alignment, MAQ only considers positions that have **two or fewer mismatches** in the first 28 bp (default parameters) (*Li at page 1852, col. 1 "Overview of MAQ algorithms"*).

Li thus specifically indicates that the mismatching counting algorithm can be programed to flag reads which have one or two mismatches.

A person of ordinary skill in the art having considered i) *Lo* (Section VII.A), ii) *Kapur* in view of *Quake* (Section VII.D), iii) *Dhallan* in view of *Lo* (Section VII.E), iv) *Dhallan* in view of *Brenner* (Section VII.F) or v) *Dhallan* in view of *Kapur* (Section VII.H) would have been informed by *Li* to use an algorithm that permits a small number of mismatches, such as one or two mismatches, when aligning a short sequence read to a reference genome to infer sequence variants. (*Morton Dec. ¶¶142-143 and Nussbaum Dec. ¶¶261-262*) Accordingly, claim 6 is rendered obvious by: *Lo* (*Ex. 1004*) in view of *Li* (*Ex. 1014*)*; Kapur* (*Ex. 1005*) in view of *Quake* (*Ex. 1006*) and further in view of *Li* (*Ex. 1014*)*; Dhallan* (*Ex. 1002*) in view of *Lo* (*Ex. 1004*) and further in view of *Li* (*Ex. 1014*)*; Dhallan* (*Ex. 1002*) in view of *Brenner* (*Ex. 1003*) and further in view of *Li* (*Ex. 1014*) *Dhallan* (*Ex. 1002*) in view of *Kapur* (*Ex. 1005*) and further in view of *Li* (*Ex. 1014*).

These grounds are not redundant because the various combination address different techniques which could fall within the claims under various interpretations of the internally inconsistent claim language:

Molecular Input to Sequencing	**Type of Sequencing**	
	Sequence Independent	**Sequence Dependent**
Random DNA Fragments (Random Analysis)	Massively Parallel Shotgun Sequencing 102 art: *Lo*	Sequencing by Array (Hybridization) 103 art: *Dhallan* + *Kapur*
Selected DNA Fragments (Directed Analysis)	Pre-selection + Massively Parallel Sequencing 103 art: *Dhallan* + *Lo*	Pre-selection + Sequencing by Array (Hybridization) 103 art: *Dhallan* + *Kapur*

VIII. CONCLUSION

Substantial, new and noncumulative technical teachings have been presented for each of claims 1-13 of the *'076 Patent,* which are anticipated or at least are rendered obvious for the reasons set forth above. There is a reasonable likelihood that Petitioner will prevail as to each of the claims. *Inter Partes* Review of claims 1-13 is accordingly requested.

Respectfully submitted,
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Dated: May 24, 2013

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CERTIFICATE OF SERVICE

The undersigned certifies service pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(b) on the Patent Owner by UPS Next Day Delivery of a copy of the Petition for *Inter Partes* Review and supporting materials at the correspondence address of record for the '076 patent:

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