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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/669,779	08/04/2017	AmirAli Talasaz	42534-710.303	4580

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EXAMINER
WILDER, CYNTHIA B

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
05/13/2019	ELECTRONIC

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

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

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents@guardanthealth.com
patentdocket@wsgr.com

Guardant - EXHIBIT 2003
Tempus AI, Inc. v. Guardant Health, Inc.
IPR2025-01435

Office Action Summary	**Application No.** 15/669,779	**Applicant(s)** Talasaz et al.	
	Examiner CYNTHIA B WILDER	**Art Unit** 1637	**AIA (FITF) Status** Yes

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
  Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 4/17/2019.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-20 is/are pending in the application.
5a) Of the above claim(s) _____ is/are withdrawn from consideration.
6) ☐ Claim(s) _____ is/are allowed.
7) ☑ Claim(s) 1-20 is/are rejected.
8) ☐ Claim(s) _____ is/are objected to.
9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.
11)☑ The drawing(s) filed on 10/18/2017 is/are: a)☑ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
Certified copies:
a)☐ All b)☐ Some** c)☐ None of the:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date 4/17/2019, 10/9/2018, 12/7/2017.
3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date ______.
4) ☐ Other: ______.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA. Applicant's preliminary amendment filed 10/18/2017 is acknowledged. Claims 1 and 16 have been amended. Claims 21-30 have been canceled. Claims 1-20 are pending.

Specification

2. The disclosure is objected to because of the following informalities:

(a) The use of the term "Qiagen Qibit", "Agilent DNA kit" and "Truseq" at e.g., para. [0227], which is a trade name or a mark used in commerce, has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trade names and marks used in commerce (i.e., trademarks, service marks, certification marks, and collective marks) are permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as commercial marks.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

3. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any

correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

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

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 1-9 and 11-20 is/are rejected under 35 U.S.C. 103 as being unpatentable over Schmitt et al {Schmitt, used interchangeably herein} (20150044687, PgPUB document for US Patent 9752188, effective filing date March 2012, citation made of record on IDS filed 12/7/2017) in view of Fan et al (PNAS, 2008, 105(42), 16266-16271, citation made of record on IDS filed 10/9/2018) and further in view of Forshew (Sci Transl Med (2012 4(136), 1-12 citation made of record on IDS filed 10/9/2018).

Regarding claim 1, Schmitt et al teach a method of detecting mutations in a sample (e.g., [0127] and [0181]) comprising: providing initial starting genetic material obtained from a bodily sample obtained from a subject (see par 00103); converting double stranded polynucleotides from the initial starting genetic material into at least one set of non-uniquely tagged parent polynucleotides (see par. 00090 where ligation of SMI adaptor to double stranded target (DNA or RNA) to form a double stranded SMI-target nucleic acid complex; (double stranded SMI molecule of prior art corresponds to one set of non-uniquely tagged parent polynucleotides recited in instant claim), wherein each polynucleotide in a set is mappable to a reference sequence (and for each set of tagged parent polynucleotides: i. amplifying the tagged parent polynucleotides in the set to produce a corresponding set of amplified progeny polynucleotides; ii. sequencing the set of amplified progeny polynucleotides to produce a set of sequencing reads; (see par. 0010 where amplification of double stranded SMI-target nucleic acid complex followed by sequencing of the amplified SMI-target nucleic acid products is taught) iii. collapsing the set of sequencing reads to generate a set of consensus sequences, wherein collapsing uses sequence information from a tag and at least one of: sequence information at a beginning region of a sequence read, sequence information at an end region of the sequence read and length of the sequence read, each of the consensus sequences corresponding to a unique polynucleotide among the set of tagged parent polynucleotides (see par. 0076 where creation of a single strand consensus sequence from all of the PCR duplicates which arose from an individual molecule of single stranded DNA is taught. Each duplex results in two single stranded consensus sequences (a set of consensus sequences of instant claim). This is referred to as Single Strand Consensus Sequencing

(SSCS). Thus Schmitt et al. teach meet the limitation--- collapsing the set of sequencing reads to generate a set of consensus sequences; and ii. analyzing the set of consensus sequences for each set of tagged parent molecules separately or in combination (see par. 0077 where comparing the sequence of two single strand consensus sequences arising from a single duplex DNA molecule, and further reducing sequencing or PCR errors by considering only sites at which the sequences of both single-stranded DNA molecules are in agreement. This is referred to as Duplex Consensus Sequencing (DCS) ([0010], [0012], [0014], [0015], [0017])

With regards to the genetic aberrations in cfDNA from a subject, Schmitt et al teach “deep sequencing” of “heterogeneous” samples of DNA, examples of which are tumor/normal DNA in plasma of cancer individuals (abstract) or fetal/maternal DNA in plasma of pregnant mothers (disclosed by way of incorporation by reference ([0182]) which inherently may encompass cfDNA. Schmitt et al teach that the unique identification can be based on either: (1) the use of a large number of barcode sequences such that there is a high probability that a unique barcode sequence is ligated to each parental DNA template; or a “hybrid” approach that attaches a small number of non-unique barcodes to DNA fragments ([0043], [[0112]). Schmitt does not explicitly recite tagging at least 20% or the DNA molecule by ligation, but teaching using state of the art ligation techniques and the use of both blunt-end ligation [0074] and TA ligation [0132].

With regards to the amplification and sequencing steps, Schmitt et al teach amplification of tagged parent polynucleotides to produce amplified tagged progeny polynucleotides, e.g., Figure 1 and 4 and further teaches sequencing of the amplified tagged progeny polynucleotides to produce a plurality of sequence reads from each of

the tagged parent polynucleotides, wherein each sequence read comprise a barcode sequence and a sequence derived from the parental DNA molecule (Figure 3 and Figure 4 and examples). Schmitt et al teaches mapping sequence reads to a human reference genome, grouping sequence reads into families based at least on barcoded sequences and shows that each of the group families comprise sequence reads amplified from the same tagged parent polynucleotide (see Figure 3 and Examples) (see also claims).

While Schmitt et al teach samples that may comprise of cfDNA, Schmitt does not expressly teach analysis of cfDNA. Likewise, Schmitt does not expressly teach tagging at least 20 of the cfDNA but rather teaches methodologies that inherently may result in at least 10%-20% yield of tagged DNA fragments.

Fan et al teach providing cfDNA molecules obtained from the bodily fluid of a subject to detect the genetic aberration known as fetal aneuploidy (abstract). Fan used cell free plasma DNA samples where about 1-8 nanograms of DNA fragments were extracted from 1.3 – 3.2 ml of cell-free plasma for sequencing library preparation Table S1. Fan teaches next generation massively parallel sequencing of the cell free DNA with high throughput shotgun sequencing technology. The method of fan uses massively parallel sequencing to produce millions of short sequence reads in a single run. Fan further teaches counting the number of the sequence reads that map to a predefined window in each chromosome to detect fetal aneuploidy (see abstract and column titled "Approximate amount of input DNA for sequencing library construction")

Forshew teaches tagged amplicon sequencing or "Tam-seq" to identify rare "cancer mutations present in cfDNA. Tam-Seq generally involves pre-amplification of dilute or degraded DNA, followed by PCR that selectively amplifies regions of interest in

the pre-amplified materials, followed by barcoding PCR that attaches adaptors and sample-specific barcodes to the harvested amplicons (Figure 1A, IB; *see also id.*, Figure S1. Forshew further teaches that new platforms for massively parallel sequencing allow for fast turnaround times, which makes this approach [Tam-seq] practical in a clinical setting (page 9, col. 2 and sup. 3-4). Forshew teaches targeting DNA fragments from genomic regions of interest, amplifying and sequencing the fragments and then aligning the sequences to a reference sequence to identify mutations (Figure 1, sup. 1-4). Forshew teaches that the method can be used to monitor mutation frequencies over time using serial samples from a particular patient and to compare mutation frequencies in a particular sample to a reference sample (pages 8-9, Figure 4).

It would have been prima facie obvious at the time of the effective filing date of the claimed invention to have been motivated to combine the mutation detection method of Schmitt with that Fan to target cell-free DNA using the sequencing methodologies recited therein to detect genetic aberrations since Schmitt specifically cites Fan which expressly disclose sequencing cell free DNA and further such substitution of sample type as type by Fan is within the ordinary artisan capabilities and within the scope of the Duplex Consensus Sequencing (DCS) as taught by Schmitt. The ordinary artisan would have been further motivated to combine Schmitt with Fan or Forshew because the problems of accurately detecting rare mutation by sequencing, the problem by which Schmitt's DCS method is purported to solve was known to be particularly significant for sample containing heterogeneous mixtures (which inherently encompasses cfDNA) was known in the art to be useful for detection genetic mutation. The ordinary artisan would have been motivated at the time of the effective filing date of the claimed invention to have

targeted cfDNA as taught by Fan and Forshew and utilize in a detection method as taught by Schmitt for the obvious benefit of improving diagnostic and therapeutic options with a reasonable expectation of success.

Regarding claims 2 and 3, Fan et al teach extracting about 1-8 ng of DNA from cfDNA for sequencing library preparation. (see Table S1 and section entitled "approximate amount of input DNA se for sequencing library construction". Forshew et al teach extracting about 0.9 – 19.7 ng of DNA from cell free plasm for sequencing library preparation (Table 2).

Regarding claims 4 and 5, both Fan and Forshew disclose providing between 100 or 100,000 or between 1000 and 50000 human haploid genome equivalents of the cfDNA molecules. Forshew teaches the standard scientific formula that 1 haploid genome is about 3.3 pg of DNA (Table S1 of supplementary Materials). Fan reported between 1-8 ng (1000-8000 pg) of plasma DNA used for library construction which corresponds to about 303 and 2424 human haploid genome equivalent (Table S1). Forshew used about 1-20 ng (1000 – 20, 000 pg) of plasma DNA, which corresponds to about 303-6060 human haploid genome equivalents (Table S6). Schmitt discloses tagging parental fragments like cfDNA with between 2 and 1,000,000 unique identifier ([0043] and [0092]).

Regarding claim 6, Schmitt discloses 23 mer tags, which are 12 nucleotides in length, ligated to parental DNA fragments (Figure 1, [0012]).

Regarding claim 7, Schmitt et al teach a hybrid approach wherein short n-mers of length 1-4 are ligated to parental fragments [0043]. This hybrid approach for tagging DNA inherently results in non-unique tagging.

Regarding claim 8, Schmitt discloses uniquely tagging parental DNA molecules. Because the use if SMI tags (or double stranded SMI sequences) allows every molecule to be uniquely labeled prior to PCR duplication, tur PCR duplicates may be unambiguously identified by virtue of having a common SMI sequence ([0094]).

Regarding claim 9, Schmitt et al teach wherein the method may comprise of blunt end ligation or sticky end ligation ([0030], [0074], [0082]).

Regarding claim 11, Fan or Forshew discloses the sequencing of hundreds to thousands of human haploid genome equivalents as previous discussed for the claims 4 and 5. Given that Schmitt teaches embodiments wherein a 2-mer SMI sequence on each end (256 different sequence combination) and a 4-mer SMI in each end (65,536 different sequence combination (Figure 4, [0014], [0015], [0026] and [0043]. Based on mathematical probability, tagging 2-mers or 4-mers on each end of millions of cfDNA fragments would inherently result in no more than 5% of the tagged parent polynucleotide having the SMI sequence.

Regarding claim 12, Fan or Forshew discloses the sequencing of hundreds to thousands of human haploid genome equivalents as previous discussed for the claims 4 and 5. Given that Schmitt teaches embodiments wherein a 2-mer SMI sequence on each ed (256 different sequence combination) and a 4-mer SMI in each end (65,536 different sequence combination (Figure 4, [0014], [0015], [0026] and [0043]. Based on mathematical probability, tagging 2-mers or 4-mers on each end of millions of cfDNA fragments would inherently result in no more than 5% of the tagged parent polynucleotide having the SMI sequence.

Regarding claims 13-14, Schmitt et al in view of Fan and Forshew provides sufficient evidence that one of ordinary skill in the art at the time of the effective filing date could achieve at least 50% of the cfDNA molecules being tagged using the ligation methodology taught by the cited prior art and commercial ligation kit commonly known and utilized in the technical field. Such methodologies would require no more than routine optimization of known reaction components and reaction condition

Regarding claim 15, Schmitt et al teach the use of Agilent SureSelect system, which is an enrichment system based on target capture ([0110], [0132], see also para. -0052] for discussion on enriching for product using affinity probes).

Regarding claim 16, Forshew teaches wherein the enriching may comprise of a target, such as TP53, PTEN, KRAS, BRAF or EGFR (page 3, section entitled "Validation an sensitivity for mutation identification ovarian tumor samples").

Regarding claim 17, Schmitt et al teach sequencing using massively parallel sequencing (Figure 1).

Regarding claim 18, Schmitt et al teach for example in Figures 3(a) –(c) three separate tagged progeny polynucleotide families, where each family is depicted with five amplicons (i.e., progeny polynucleotides) per sense and antisense strand. Each amplicon is sequence at least once thereby generating at least 5 to 10 sequence reads for each family per Figure 3. [0014]. Schmitt et al teach families should have 3 or more members for error correction analysis and in one examples, describes a base-calling requirement for 90% of sequences to agree such that if all families are of size 9 or less, the 90% cutoff requires perfect agreement at any given position (para [0142].

Regarding claim 19, Schmitt discloses an error rate below 0.0001%. With regards to DCS, Schmitt teach an error rate of $1.2x10^{-9}$ [0172].

Regarding claim 20, this claim merely recites routine optimization of known parameters and methodologies known in the technical field as evidence by the combination of the cited prior art. For example, in Schmitt's experiment that showed SSCS or DCS could detect one mutant molecule per 10,000 wild-type molecules, the sequence depth (i.e., sequence coverage) was at about ~20,000 {0181]. Thus, Schmitt in combination with the common knowledge on sequence coverage makes obvious ensuring each base has a 99% chance of being represented by at least one sequence read.

4. Claim 10 is/are rejected under 35 U.S.C. 103 as being unpatentable over Schmitt et al in view of Fan and Forshew as previously applied above and further in view of Pinter et al (US 20040209299, citation made of record on IDS filed 10/9/2018).

Regarding claim 10, Schmitt et al in view of Fan and Forshew teach a method for detecting genetic aberrations in cfDNA from a subject as previously discussed above. Schmitt et al teach wherein SMI adaptor molecules in excess are used in ligation and sequencing reaction ([0012], [0023], [0030] and [0052]). Schmitt et al teach wherein the SMI adaptor molecules may be utilized in e.g., Illumina sequencing platform [0083].

Schmitt et al in view of Fan and Forshew do not expressly stated wherein the SMI adaptors are utilized at more than 10X molar excess as compared to the starting DNA molecule.

In a general teaching for preparing high quality next-generation sequencing libraries from picogram quantities of target DNA, Parkinson discusses wherein the

preparation comprises 10X molar Illumina PE adaptor (page 131, column 2 and page 132, column 2 at "Sequencing Adapters". Parkinson et al that the adapters were produced with staggered barcode sequence allowing for sticky-end ligation ("Sequencing adapters", page 132, col. 2). Parkinson et al teach that their modification to the standard Illumina PE adaptor sequence results in the repeated sequencing of a mandatory CAG motif at the start of all reads. This may result in a failure of some Illumina base calling software. To avoid this, they used a variable length in-line barcoding region in their adapters to offset these constant sequences and simultaneously allow library multiplexing. Parkinson teaches that this barcoding indexes both reads of a paired-end fragment, allowing important quality checks such as the identification of interlibrary chimeras, which are not possible using standard indexing systems (page 131, column 1, third full paragraph).

Pinter et al teach a method of converting double stranded DNA into adapter ligated DNA libraries by fragmenting DNA and ligating adaptors to the ends of the DNA fragments and amplifying the adaptor-ligated DNA (para. 0067-0069, page 7; para. 0071, page 8; para. 0096-0097, page 10). Pinter teaches these adaptors are blunt-end adaptors (page 8, para. 0079, page 10, para. 0098). Pinter teaches that the adaptors are added at a 10-100 fold molar excess (para. 0099, page 10; para. 0228, page 20; para 0232, page 21; and claims 107-108). Pinter teaches wherein the target DNA us cell-free DNA in maternal blood.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the effective filing date of the claimed invention to have been motivated to have modified the method of Schmitt et al in view of Fan and Forshew to encompass molar

excess of 10X or more of barcoded oligonucleotides as compared to the starting material for the benefit of facilitating detection of rare variants as taught by Pinter because this was particular known technique recognized as part of the ordinary artisans capabilities and was recognized in the art for achieving the predictable outcome of a method for detecting genetic abnormalities in cell free DNA using tagged adaptors to target dell free DNA and iterative and optimized analysis of sequencing and contig assembly as noted by Pinter.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly

owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

6. Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting over the claims 1-33 of US Patent 9902992.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the claims 1-20 of the instant invention and the claims 1-33 of US Patent 9902992 are directed to a method of detecting genetic abberrations in a cfDNA of a sample comprising the steps of a) providing cfDNA molecules obtained from a bodily sample of the subject; b) attaching to the cfDNA molecules, tags comprising barcodes having distinct barcode sequences to generate tagged parent polynucleotides, wherein at least 10% of the cfDNA is tagged by the attaching step; c) amplifying the tagged parent polynucleotides to produce tagged progeny polynucleotides; d) sequencing the tagged progeny polynucleotides to produce sequence reads, wherein each sequence read comprises a barcode sequence and a sequence derived from a cfDNA molecule; e) grouping the sequence reads into families based at least on the barcode sequence; f) comparing the sequence reads grouped within each family to determine consensus sequences for each family, wherein each of the consensus sequences corresponds to a unique polynucleotide among the tagged parent polynucleotides; and g) detecting, at one or more genetic loci, a plurality of genetic aberrations. The claims 1-20 of the instant invention and the claims 1-33 of US Patent 9902992 falls entirely within the scope of each other and only vary slightly in wording.

As the court stated in *In re Goodman*, 29 USPQ2d 2010 (CAFC 1993), "a second application-- "containing a broader claim, more generical in its character than the specific claim in the prior patent"--typically cannot support an independent valid patent. Miller, 151, U.S. at 198; See Stanley, 214 F.2d at 153. Thus, the generic invention, as noted above is "anticipated" by the species of the patented invention. Cf., Titanium metal corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (holding that an earlier species

disclosure in the prior art defeats any generic claims). This court's predecessor has held that, without a terminal disclaimer, the species claims preclude issuance of the generical application. "*In re Van Ornum*, 686 F.2d 937, 944, 214 USPQ 761, 767 (CCPA 1982); *Schneller*, 397 F.2d at 354".

7. **Claims 1, 2, 3, 9-11 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4, 6-11 of US 9598731.**

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant invention and the claims of US 9598731 are obvious variants of each other and falls entirely within the scope of each other.

As the court stated in *In re Goodman*, 29 USPQ2d 2010 (CAFC 1993), “a second application-- "containing a broader claim, more generical in its character than the specific claim in the prior patent"--typically cannot support an independent valid patent. Miller, 151, U.S. at 198; See Stanley, 214 F.2d at 153. Thus, the generic invention, as noted above is "anticipated" by the species of the patented invention. Cf., Titanium metal corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (holding that an earlier species disclosure in the prior art defeats any generic claims). This court's predecessor has held

that, without a terminal disclaimer, the species claims preclude issuance of the generical application. "*In re Van Ornum*, 686 F.2d 937, 944, 214 USPQ 761, 767 (CCPA 1982); *Schneller*, 397 F.2d at 354".

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

8. **Claims 1, 2, 4, 10, 11, 12, 13, 14, 15, 17 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1, 2, 4, 5, 9, 10, 21, 22, 41 and 44 of copending Application No. 14855301.**

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claim 1 of the instant invention is drawn to a method for detecting genetic aberrations in cfDNA (“cfDNA”) from a subject, comprising: a) providing cfDNA molecules obtained from a bodily sample of the subject; b) attaching to the cfDNA molecules, tags comprising barcodes having distinct barcode sequences to generate tagged parent polynucleotides, wherein at least 10% of the cfDNA is tagged by the attaching step; c) amplifying the tagged parent polynucleotides to produce tagged progeny polynucleotides; d) sequencing the tagged

progeny polynucleotides to produce sequence reads, wherein each sequence read comprises a barcode sequence and a sequence derived from a cfDNA molecule; e) grouping the sequence reads into families based at least on the barcode sequence; f) comparing the sequence reads grouped within each family to determine consensus sequences for each family, wherein each of the consensus sequences corresponds to a unique polynucleotide among the tagged parent polynucleotides; and g) detecting, at one or more genetic loci, a plurality of genetic aberrations.

The claim 1 of the **14/855301** is directed to a method comprising: (a) providing a sample comprising double-stranded deoxyribonucleic acid (DNA) molecules; (b) incubating said sample with a molar excess of polynucleotide adapters comprising barcodes as compared to said DNA molecules, wherein said polynucleotide adapters are bidirectional adapters that support amplification: and (c) ligating said polynucleotide adapters to one or more ends of said DNA molecules, thereby providing tagged DNA molecules, wherein said molar excess is sufficient to tag at least 20% of said DNA molecules (d) enriching said tagged DNA molecules mapping to one or more selected reference sequences by selective sequence capture of at least a subset of said tagged DNA molecules, thereby providing enriched DNA molecules: (e) sequencing at least a portion of said enriched DNA molecules, thereby providing a set of sequencing reads: and (f) analyzing said set of sequencing reads to detect rare variants in said DNA molecules.

The limitation of using cell free DNA as recited in the instant invention (claim 1) is recited in the claim 33 of copending application. The limitation of grouping the sequences

reads of the instant invention (claims 1) is recited in the claim in the claims 21-22 of copending application.

The limitation of ligating polynucleotide adapter one or more ends of the DNA molecule as recited in copending application is recited in the claim 11 of the instant invention. The limitation of enriching sequence of interest as recited in copending application is recited in the claims 15 and 16 of the instant invention.

The limitation of providing at least of 100 ng of the cfDNA as instantly claimed in claims 2 and 4 is recited in copending application 14851301 at claim 41. The limitation of sequencing comprising massively parallel sequencing as recited in the claim 8 of the instant invention is recited in the claim 44 of copending application. The limitation of uniquely tagging as recited in the claims 12 and 18 of the instant invention is recited in claim 9 of the copending application.

The limitation of using more than 10X molar excess of a tag as recited in the claim 10 of the instant invention is recited in the claims 1 of the copending application.

The limitation at least 30% or 50% of the DNA molecule being tagged as recited in the claims 13 and 14 in the instant invention is recited in the claims 2 and 4 of the copending application.

The claims of the instant invention recited above only differs from the claims of copending application 14/855301 in that the claims of copending application 14/855301 are broader in scope.

Thus, the claims of the instant invention falls entirely within the scope of the claims of copending application 14/855301.

As the court stated in *In re Goodman*, 29 USPQ2d 2010 (CAFC 1993), "a second application-- "containing a broader claim, more generical in its character than the specific claim in the prior patent"--typically cannot support an independent valid patent. Miller, 151, U.S. at 198; See Stanley, 214 F.2d at 153. Thus, the generic invention, as noted above is "anticipated" by the species of the patented invention. Cf., Titanium metal corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (holding that an earlier species disclosure in the prior art defeats any generic claims). This court's predecessor has held that, without a terminal disclaimer, the species claims preclude issuance of the generical application. "*In re Van Ornum*, 686 F.2d 937, 944, 214 USPQ 761, 767 (CCPA 1982); *Schneller*, 397 F.2d at 354".

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

9. NO claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on Flexible.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, GARY BENZION can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CYNTHIA B WILDER/
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