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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEPHEN **QUAKE** and HEI-MUN CHRISTINA FAN
Junior Party
(Patent 8,008,018),

v.

YUK-MING DENNIS **LO**, ROSSA WAI KWUN CHIU,
and KWAN CHEE CHAN
Senior Party

(Application 13/070,275).

Patent Interference No. 105,920 (DK)
(Technology Center 1600)

Judgment

37 C.F.R. § 41.127

Before, SALLY GARDNER LANE, JAMES T. MOORE, and DEBORAH KATZ, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

Interference 105,920

Following the Decision on Remand ("Decision," Paper 273), Quake was ordered to show why the interference should continue to a priority or derivation phase. (*See* "Order," Paper 274.) The Order was issued because Quake asserted dates of conception and derivation in its Priority Statement earlier than the dates accorded to and asserted by Lo. (Compare Quake Priority Statement, Paper 57, with Redeclaration, Paper 43, and Lo Priority Statement, Paper 52.) Quake failed, though, to "[p]rovide a copy of the earliest document upon which [Quake] will rely to show conception" with its Priority Statement as required under 37 C.F.R. § 41.204(2)(iv). Instead, Quake asserted that "the earliest document proving conception is a communication between Dr. Stephen Quake and his attorney dated January 2, 2006, that is subject to attorney client privilege." (Quake Priority Statement, Paper 57, at 2:25-3:1.) The Order to Show Cause provided Quake an opportunity to submit this document.

In its Response to the Order to Show Cause, Quake did not submit a copy of the communication between Dr. Quake and his attorney. Instead, Quake submitted a copy of Quake's application 11/701,686 ("the '686 application"), filed on February 2, 2007 (Exh. 2004[1]) as the earliest document on which it intends to rely. (Response to Order to Show Cause ("Response"), Paper 275, at 3:8–9.)

In the Decision on Remand, the Board determined that the '686 application is not a constructive reduction to practice of the Count in this Interference. (*See* Decision, Paper 273, at 17:11–21:5.) We denied Quake's request for rehearing of

[1] We note that Quake cites Exhibit 2002, while Quake Exhibit List (Paper 265) identifies the '686 application as Exhibit 2004.

that Decision. (Decision on Request for Rehearing, Paper 277.) The arguments Quake puts forth in its response to the Order to Show Cause are similar to those it raised in its Request for Rehearing. For example, Quake argues that there is testimony in the record showing that methods were well-known at the time the '686 application was filed to utilize sequence/statistical analyses on individually sequenced samples, and that those methods would have been equally applicable to the sequence data obtained in Quake's sequenced mixed sample. (*See* Response, Paper 275, at 4:20–25.) Quake argues that methods were well known in the prior art that could be applied to carry out the method of the Count, along with the disclosures of the '686 application. (*See* Response, Paper 275, at 5:11-13.)

As discussed in the Decision on Request for Rehearing, Quake's arguments do not persuade us that the decision to deny Quake benefit of its '686 application should be modified. (*See* Decision on Request for Rehearing, Paper 277.) Because we determine that the '686 application is not a reduction to practice of the Count, Quake has failed to show why it will prevail over Lo in a priority or derivation phase. Quake does not submit any other evidence of an earlier conception, reduction to practice, or derivation.

Quake also argues that the interference should proceed to a priority phase because of the determination in Interference 105,922 that Quake had an actual reduction to practice of the sequencing embodiment of the Count prior to the filing date accorded to Lo in that proceeding. (Response, Paper 275, at 5:16–19.) The count of Interference 105,922 was different from the current count and the specifications of Quake's currently involved patent and applications are different from the Quake specifications involved in that interference. Accordingly, the

determination of priority in that interference is not dispositive of the issues of this interference.

Because Quake has failed to submit a document on which it can rely to show priority earlier than Lo's accorded priority date and has failed to provide a persuasive reason why this interference should continue to a priority or derivation phase, we enter judgment against Quake as to Count 1, the sole count in the interference.

It is ORDERED that claims 1-4 of Quake's involved patent 8,008,018 be CANCELED 35 U.S.C. § 135(a);

FURTHER ORDERED that a copy of this judgment be entered in the administrative records of the involved 8,008,018 patent and 13/070,275 application.

FURTHER ORDERED that a party seeking judicial review timely serve notice on the Director of the United States Patent and Trademark Office. 37 C.F.R. §§ 90.1 and 104.

FURTHER ORDERED that the parties are directed to 35 U.S.C. § 135(c) and to 37 C.F.R. § 41.205 regarding the filing of settlement agreements.

Interference 105,920

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEPHEN **QUAKE** and HEI-MUN CHRISTINA FAN
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(Patent 8,008,018),

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YUK-MING DENNIS **LO**, ROSSA WAI KWUN CHIU,
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(Application 13/070,275).

Patent Interference No. 105,920 (DK)
(Technology Center 1600)

Decision on Remand

37 C.F.R. § 41.125

Before, RICHARD E. SCHAFER, SALLY GARDNER LANE, and DEBORAH KATZ, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

Interference 105,920

I. *Review of prior history*

Judgement was entered against Quake in Interferences 105,920 based on the decision that the specifications of the 8,008,018 patent ("the '018 patent") does not provide a sufficient written description of Quake's involved claims. (*See* Judgment, Paper 259; *see* Decision on Motion, Paper 258.)

As the assignee of the Quake patents and application, The Board of Trustees of the Leland Stanford Junior University appealed the judgment entered in this interference to the Court of Appeals for the Federal Circuit. (*See The Board of Trustees of the Leland Stanford Junior University v. The Chinese University of Hong Kong*, App. 2015-011 (Fed. Cir. June 27, 2017).) The Federal Circuit vacated the prior decision and remanded the case to the Board, finding error.

The court determined that the Board erred by considering whether the description in the '018 patent *precluded* targeted massively parallel sequencing, instead of considering whether the description *discloses* random massively parallel sequencing. (*See Board of Trustees,* slip op. 18.) The court also determined that the Board improperly relied on portions of Dr. Gabriel's, Lo's expert, testimony regarding a machine mentioned in the '018 patent. (*See Board of Trustees,* slip op. 15-18.)

On remand, the court instructed us to

> examine whether a person of ordinary skill in the art would have known, as of the priority date, that the '018 specification's reference to Illumina products meant random MPS sequencing as recited in the claims, by examining the record evidence as to pre-filing date art-related facts on Illumina products.

(*See Board of Trustees,* slip op. 19.) We should "examine whether a person of ordinary skill would have understood that the '018 patent's specification disclosed random MPS sequencing, as opposed to whether the specification did not preclude targeted MPS sequencing." (*See Board of Trustees,* slip op. 20.)

We find that even though the '018 patent discusses random massively parallel sequencing and mentions identification of chromosomes from random sequence information, it does not do so in the context of Quake's claimed methods. Specifically, we find that the '018 patent does not describe using the data obtained from random massively parallel sequencing and identification of chromosomes to compare the amounts of chromosomes in a mixture of maternal and fetal genomic in order to determine the presence or absence of said fetal aneuploidy, as required in step d. of Quake's claims.

II. *Written Description in the '018 patent*

Quake's claims are directed to methods of determining whether a fetus has the wrong number of chromosomes – a condition called "fetal aneuploidy." In the claimed methods, this determination is made by sampling a maternal tissue, for example blood, that contains both maternal and fetal DNA, instead of a sample of fetal tissue. The claimed methods are less invasive than those currently used to detect fetal aneuploidy, such as amniocentesis. (*See Board of Trustees*, slip op. at 2-3.)

Quake claim 1, the only independent claim in the '018 patent, recites:

> A method for determining presence or absence of fetal aneuploidy in a maternal tissue sample comprising fetal and maternal genomic DNA, wherein the method comprises:

> a. obtaining a mixture of fetal and maternal genomic DNA from said maternal tissue sample;
>
> b. *conducting massively parallel DNA sequencing of DNA fragments randomly selected from the mixture of fetal and maternal genomic DNA of step a) to determine the sequence of said DNA fragments*;
>
> c. identifying chromosomes to which the sequences obtained in step b) belong;
>
> *d. using the data of step c) to compare an amount of at least one first chromosome in said mixture of maternal and fetal genomic DNA to an amount of at least one second chromosome in said mixture of maternal and fetal genomic DNA, wherein said at least one first chromosome is presumed to be euploid in the fetus, wherein said at least one second chromosome is suspected to be aneuploid in the fetus, thereby determining the presence or absence of said fetal aneuploidy*.

(Quake Clean Copy of Claims, Paper 7 (emphasis added).)

A.

We address the court's instruction to examine whether one of skill in the art would have understood that the '018 patent discloses random massively parallel sequencing. (*See Board of Trustees,* slip op. 19.) The '018 patent states, in a portion we refer to as "passage A":

> 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 sq. cm. These templates are sequenced using four-color DNA sequencing-by-synthesis technology. See, products offered by lllumina, 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."

('018 patent, Exh. 1022, at 19:59-20:3.) The parties agree that "products offered by lllumina" were known to be products for massively parallel sequencing at the time of filing. (*See* Lo Motion 1, Paper 54, at Material Fact 44 ('"[P]roducts offered by Illumina' as mention at '018 patent 19:67 includes products for [massively parallel sequencing]."); *see* Quake response ("Admitted.").) Indeed, the passage quoted above expressly discloses massively parallel sequencing.

The passage also includes details of massively parallel sequencing, which the court indicated we failed to explain and compare to the claim limitations in our prior opinion. (*See Board of Trustees*, slip op. at 18-19.) Specifically, as Dr. Detter, Quake's witness, explains, sequencing with Illumina products involves certain steps, which the '018 patent mentions by including the phrases: "using attachment of randomly fragmented genomic DNA," "solid phase amplification," "~1,000 copies of template," and sequencing of templates "using four-color DNA sequencing-by-synthesis technology." (*See* Detter Decl., Exh. 2049, at ¶¶ 39-40, 59-70.) Lo does not dispute that these details are part of massively parallel sequencing with Illumina products. Accordingly, we find that this portion of the '018 patent expressly describes massively parallel sequencing.

Quake's claims require that the massively parallel DNA sequencing be done on "DNA fragments *randomly* selected from the mixture of fetal and maternal genomic DNA . . . ." (*See* Quake Clean Copy of Claims, Paper 7, at A-1 (emphasis added).) Thus, as the court instructed, we consider whether the '018 patent

provides a written description of sequencing randomly selected DNA fragments. (*See Board of Trustees*, slip op. 19.)

The parties agree that the claim limitation of sequencing "DNA fragments randomly selected from the mixture of fetal and maternal genomic DNA" means that the nucleic acid fragments sequenced have not been identified before the sequencing procedure and that sequence-specific primers to target specific gene loci are not required. (*See* '275 appl., Exh. 1023, ¶ 58; *see* Detter Decl. Exh. 2049, at ¶ 91; *see also Board of Trustees*, at slip op. 6.) Lo also agrees that it was known that Illumina products could perform massively parallel sequencing of randomly selected DNA fragments. (*See* Lo Motion 1, Paper 54, at 23:5-7, Material Fact 45 ("Illumina sequencing platforms can perform either random or targeted DNA sequencing, depending on whether predetermined target DNA fragments are specifically identified or targeted prior to sequencing.").)

Passage A of the '018 patent expressly states that a methodology "based on massively parallel sequencing of millions of fragments using attachment of *randomly fragmented* genomic DNA to a planar, optically transparent surface" is useful in the disclosed invention. ('018 patent, Exh. 1022, at 19:59-62 (emphasis added).) We agree with Lo that "randomly fragmented genomic DNA" is not necessarily the same as "DNA fragments randomly selected" from a mixture. (*See* Lo Reply 1, Paper 79, at 7:4-6.) But, we disagree with Lo that this passage necessarily describes target-specific analysis because targeting steps are not specifically recited in the passage. (*See* Lo Motion 1, Paper 54, at 10:9-25.)

Quake argues that passage A does not describe targeted sequencing and therefore must describe random sequencing. (*See* Quake Opp. 1, Paper 73, at 7:5-

14.) Quake attempts to support its argument by citing to Material Fact 87 in Appendix 2 of its Opposition brief and to Dr. Gabriel's testimony. (*See id*., citing p. II-15, Material Fact 87 and Gabriel Decl., Exh. 1021, at ¶ 47.) Material Fact 87 is not helpful to us. Material Fact 87 refers to a document entitled "Technology Spotlight: Illumina® Sequencing," which is provided in Exhibit 2035, but Quake fails to show that it was publically available before the filing date of the application that became the '018 patent, 26 February 2009. We note that Exhibit 2035 has a copyright date of 2010. (*See* Exhibit 2035, at 6.) We need not consider this reference because Quake has not shown that it specifically relates to "Illumina products" existing on the filing date. (*See Board of Trustees*, slip op. at 19-20.)

Even if we consider the content of Material Fact 87 and the document it cites, we would be unpersuaded by Quake's argument. The summary of Exhibit 2035 provided in Material Fact 87 highlights the use of non-specific primers in the Illumina platform, but this aspect is not expressly stated in the '018 patent. Similarly, although Dr. Detter's testimony is cited in Material Fact 87 (*see* Detter Decl., Exh. 2049, at ¶ 146), it is virtually identical with the Material Fact and fails to explain how the express disclosure of the '018 patent describes what is taught in Exhibit 2035. For example, Quake highlights the portion of the summary in Material Fact 87 that refers to using primers that are not specific for a target sequence, but this direction is not stated in the '018 patent itself. Quake does not direct us to a discussion of non-specific primers or a citation to Exhibit 2035 in the '018 patent. Accordingly, we do not find that Material Fact 87 supports an express description of the claimed methods.

Quake also argues that the Balasubramanian patent application cited in passage A "supports random massively parallel sequencing." (Quake Opp. 1, Paper 73, at 4:20-23.) The four lines of Dr. Gabriel's deposition transcript that Quake cites support Quake's argument because on cross-examination Dr. Gabriel agreed with this statement. (*See* Gabriel Depo., Exh. 2078, at 60:18-22.) Thus, we find that Balasubramanian provides some of disclosure of massively parallel sequencing of DNA fragments selected randomly.

In contrast, we not persuaded by Quake's argument that random massively parallel sequencing is supported by the Braslavsky article, which is disclosed elsewhere in the '018 patent. (Quake Opp. 1, Paper 73, at 4:23-27; *see* '018 patent, Exh. 1022, at 2:23-29 and 19:14-22.) According to Quake, Dr. Gabriel's testimony supports this argument because the Braslavsky article was "the concept behind the Helicos sequencer, which could be used for random sequencing." (Quake Opp. 1, Paper 73, at 4:24-25, citing Gabriel Depo., Exh. 2078, at 92:6-94:2.) Because Quake does not direct us to discussion of the Helicos sequencer in the '018 patent, we are not persuaded by this argument. (*See Board of Trustees*, slip op. at 17 ("All of the published references on which the Board relies focus on the Roche 454 platform, not the Illumina platform actually referenced in the specification.")

Accordingly, we find that passage A of the '018 patent expressly describes massively parallel sequencing. The only portion, though, of passage A that ties this sequencing to the random sequence information mentioned in passage B is the citation to Balusubramanian, as characterized by four lines of Dr. Gabriel's testimony.

B.

Immediately following passage A, the '018 patent also states, in a portion we refer to as "passage B":

> Sequencing may be combined with amplification-based methods in a microfluidic chip having reaction chambers for both PCR and microscopic template-based sequencing. 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. An algorithm for designing unique sequences is described in Yamada. et al. [Exhibit 1016] illustrative of software methods that can be used to identify a sequence in comparison to the known genome sequence. See, also Zhu et al., [Exhibit 1017] describing a single-molecule-based technology for studying mRNA.

('018 patent, Exh. 1022, at 20:4-20.) Lo argues that, based on the citations to Yamada and Zhu, passage B refers to designing primers for the targeted digital PCR analysis described in the rest of the '018 patent, not to random massively parallel sequencing. (*See* Lo Motion 1, Paper 54, at 12:6-13:5.) Quake opposes Lo's argument by arguing that this passage refers to alignment of the sequence reads produced from random sequencing. (Quake Opp. 1, Paper 73, at 9:24-10:10.)

Passage B expressly recites "random sequence information." Accordingly, even if the Yamada and Zhu references that follow are not relevant to random sequence information, we find that passage B does expressly describe random sequencing.

C.

We find that passage A and passage B of the '018 patent provide some express description of individual elements recited in Quake's claims. "Massively parallel sequencing" is expressly described, as is random sequencing. These activities are linked in the Balasubramanian reference.

Our task is to determine whether these disclosures are sufficient to have demonstrated one of ordinary skill in the art that the inventors were in possession of a method of determining fetal aneuploidy with random massively parallel sequencing as claimed by Quake. Although the express language describes some of the elements of the claimed method, we find that it is not sufficient to provide a written description under 35 U.S.C. § 112, first paragraph, because the '018 patent does not tie these elements together into a complete method and does not explain how to use the data from random massively parallel sequencing of a mixture of genomic DNA to determine fetal aneuploidy.

D.

The insufficiency of the description of random massively parallel sequencing in the '018 patent is apparent when it is compared to the description of a different method, called digital analysis, in that patent. The parties agree that the '018 patent sufficiently describes the digital analysis method of determining fetal aneuploidy from a mixed sample. (*See* Lo Motion 1, Paper 54, at 19:16-17, Material Fact 7 ("The '018 Patent discloses 'digital analysis' method for detecting fetal aneuploidy.") and Quake Opp. 1, Paper 73, at II-2 (admitting Lo Material Fact 7).) Specifically, the '018 patent recites, in part:

> Thus, the present method [of digital analysis] comprises generally the following steps:
> 1. Obtaining a tissue containing DNA from a pregnant subject, ...

> 2. Distributing single DNA molecules from this sample to a number of discrete reaction samples, where the number of reaction samples is selected to give a statistically significant result for the number of copies of a target in the DNA molecules. . . .
> 3. Detecting the presence of the target in the DNA in a large number of reaction samples, preferably with a sequence specific technique such as highly multiplexed short read sequencing or a PCR reaction wherein the PCR product is labeled to give a convenient quantitative read out . . . . and
> 4. Quantitative analysis of the detection of the maternal and fetal target sequences.

('018 patent, Exh. 1022, at 8:33-9:6.) Thus, the '018 patent outlines the specific steps one would take to perform digital analysis with a sequence specific technique such as sequencing or a PCR reaction.

In contrast, the disclosures in the '018 patent that relate to a method of random massively parallel sequencing are the mention of massively parallel sequencing of randomly fragmented DNA, "products offered by Illumina," citation to Balasubramanian, and a sentence about the number of base pairs needed to identify the chromosomal origin of a sequence. The '018 patent does not recite specific series of steps one would take to determine whether fetal aneuploidy exists using random massively parallel sequencing.

We find that the '018 patent fails to provide *express* "blazemarks" of a method of massively parallel sequencing of DNA fragments randomly selected from a mixture to determine fetal aneuploidy. *See In re Ruschig*, 379 F.2d 990, 994–95 (C.C.P.A. 1967) (analogizing, where the disclosure recited a list of possible reactants, but failed to highlight the necessary one, that "[i]t is an old custom in the woods to mark trails by making blaze marks on the trees. It is no

help in finding a trail or in finding one's way through the woods where the trails have disappeared— or have not yet been made, which is more like the case here— to be confronted simply by a large number of unmarked trees.")

E.

In the absence of an express written description, the '018 patent could still provide a sufficient description of the claimed methods if one of ordinary skill in the art would have understood from what was expressly described that the inventors were in possession of the inventions. *See Fujikawa v*. *Wattanasin*, 93 F.3d 1559, 1570 (Fed. Cir. 1996) ("As the Board recognized, however, *ipsis verbis* disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question."). Thus, we look to how one of ordinary skill in the art would have understood the claims as a whole. We find that the '018 patent does not describe how to analyze the data that would be obtained from massively parallel sequencing to determine if fetal aneuploidy is present and that, thus, one of ordinary skill in the art would not know that the inventors possessed a method of determining fetal aneuploidy.

Quake's claims require step d: using the data from the identified chromosomes to compare an amount of a first chromosome (presumed to be euploid[1] in the fetus) and to an amount of a second chromosome (suspected of being aneuploid in the fetus) to determine the presence or absence of aneuploidy. (Quake Clean Copy of Claims, Paper 7.) Lo argues that because the '018 patent focuses on detecting aneuploidy based on a 1:1 ratio between predetermined

sequences from two chromosomes, which is appropriate for digital analysis (*see* '018 patent, Exh. 1022, at 21:1-45), it does not describe the considerations that must be made when comparing data from massively parallel sequencing of DNA fragments randomly selected. (Lo Motion 1, Paper 54, at 17:20-18:20, citing Gabriel Decl., Exh. 1021, at ¶¶ 87-89; *see also* Lo Reply 1, Paper 79, at 8:26-9:2.)

Lo bases its argument on Dr. Gabriel's testimony that because human chromosomes are not all the same size, randomly selected fragments are more likely to be identified from larger chromosomes than from smaller chromosomes. (Gabriel Decl., Exh. 1021, at ¶ 88.) According to Dr. Gabriel, given an equal number of all chromosomes, there is a greater chance that a random fragment will be from a larger chromosome than a smaller one. A method relying on random massively parallel sequencing cannot rely on a 1:1 ratio of sequences because even in the absence of aneuploidy, the number of random sequence reads aligning to a larger chromosome versus those aligning to a smaller chromosome will always result in a ratio greater than 1:1. (Gabriel Decl., Exh. 1021, at ¶ 88.) Dr. Gabriel explains that instead of focusing on deviations from a 1:1 ratio, methods that use massively parallel sequencing of randomly selected fragments must take into consideration the size of the chromosomes before determining a ratio that represents a normal number of chromosomes. (*See* Gabriel Decl., Exh. 1021, at ¶ 89.)

Quake does not dispute that a random massively parallel sequencing method for determining fetal aneuploidy would need to take into account the length of the chromosomes being analyzed and could not be based on deviations from a 1:1

[1] The term "euploid" means the state of having normal sets of chromosomes.

ratio. Instead, Quake argues that Dr. Gabriel admitted that statistical tests reportedly disclosed in the '018 patent specification could be used to determine aneuploidy. (Quake Opp. 1, Paper 73, at 10:12-25, citing Gabriel Depo., Exh. 2078, at 51:2-53:16 and 73:22-74:18; *see* Detter Decl., Exh. 2082, at ¶ 29.) We do not find that the cited cross-examination refers to disclosures in the '018 patent specification. Instead, Dr. Gabriel testifies about statistical methods, such as the "T-test" and the "Z-test," and how they could be used in general. (*See* Gabriel Depo., Exh. 2078, at 51:2-53:16 and 73:22-74:18.) Quake also argues that Dr. Gabriel testified that the fraction of a sample comprising a given chromosome is consistent from individual to individual in the absence of aneuploidy. (*See* Quake Opp. 1, Paper 73, at 10:18-21, citing Gabriel Depo, Exh. 2078, at 54:1-56:2.) We do not find that the testimony Quake cites addresses the statistical analysis needed when using sequences from chromosomes of differing lengths. None of the testimony is evidence that Dr. Gabriel admitted statistical methods relying on the different lengths of identified chromosomes were described in the '018 patent specification.

Quake also argues that the evidence Lo submitted with its Priority Statement (*see* Paper 52; Ex. 2074) and Lo's provisional application (Exh. 2010) contain less disclosure than the Quake '018 patent about the statistical analysis used to assess fetal aneuploidy. (Quake Opp. 1, Paper 73, at 4:3-10, citing Gabriel Depo., Exh. 2078, at 33:11-34:4 and 38:5-12.) Presumably Quake's argument is that a description of the statistical analysis is not necessary because it not present in Lo's other documents. This argument is not persuasive because written description

support is evaluated on what is described in specification at issue. Whether or not Lo's other documents provide sufficient written description is not at issue.

Quake argues further that Dr. Detter explained how the '018 patent discloses a method that "intrinsically corrects for biases due to chromosome size by comparing results from a test sample to normal samples using statistical methods, such as a Student's T-test." (*See* Quake Opp. 1, Paper 73, at 3:3:3-6, citing Detter Decl., Exh. 2082, at ¶¶ 13 and 29, and '018 patent, Exh. 1022, at 5:64-6:3 and 28:5-34.) This argument is not supported by the cited portions of the '018 patent. Paragraphs 13 and 29 of Dr. Detter's declaration address Dr. Gabriel's cross-examination testimony about what was known in the art of normalized frequencies, chromosome size, and generalized statistical analyses. (*See* Lo Reply, Paper 79, at 9:8-24.) This testimony does not explain anything about the specification of the '018 patent. Similarly, the portions of the '018 patent that Quake cites do not mention chromosome size and do not discuss any "intrinsic correction." The portions refer only to statistical significance in general (*see* '018 patent, Exh. 1022, at 5:64-6:3) and to analysis based on a 1:1 ratio (*see id*. at 23:5-34).

Quake argues further that those of skill in the art would have known how to correct for chromosome size in February 2007, relying on Dr. Gabriel's testimony. (*See* Quake Opp. 1, Paper 73, at 3:11-15; citing Detter Decl., Exh. 2082, at ¶ 13, and Gabriel Depo., Exh. 2078, at 34:13-35:9.) In the portion of her testimony cited by Quake, Dr. Gabriel testifies that it was well known at the time how to create a "normalized frequency," but her testimony is about the disclosure of Lo's priority statement (Exhibit 2074), not the '018 patent. (*See* Gabriel Depo., Exh. 2078, at

34:13-35:9.) Specifically, Dr. Gabriel addresses Example 3 of Exhibit 2074, which provides for random sequencing and states:

> By taking into account of the relative size of chromosome 21 compared with the other chromosome, one could obtain a normalized frequency, within a reference range, of chromosome 21-specific sequences from such a sequencing exercise. If the fetus has trisomy 21, then the normalized frequency of chromosome 21-derived sequences from such a sequencing exercise will increase, thus allow the detection of trisomy 21.

(Exh. 2074, at 11, *see* Gabriel Depo., Exh. 2078, at 34:17-19 (referring to Example 3 of Exh. 2074 "It actually says you've got to take into account the chromosome size of things you're comparing.").) Quake does not direct us to similar discussion of "normalized frequency" in the '018 patent.

Quake's argument is that those of skill in the art would have known *how* to normalize the frequency of sequence reads by the size of the chromosome, but Quake does not direct us to a portion of the '018 patent that describes the need to do so. Accordingly, we are persuaded that one of ordinary skill in the art would not have considered that the inventors of the '018 patent contemplated a method requiring this statistical analysis.

The '018 patent specification does not provide a description of an analysis that compares the amounts of the identified chromosomes determined from random massively parallel sequencing data and determines the presence or absence of fetal aneuploidy. In the absence of a description of such analysis, we are persuaded that the express teachings in the specification about equipment useful for random massively parallel sequencing and techniques for determining sequences are not sufficient to demonstrate possession of the claimed method for "determining

presence or absence of fetal aneuploidy in a maternal tissue sample comprising fetal and maternal genomic DNA." Instead, the description in the '018 patent indicates that the inventors had only "a mere wish or plan" to use this new technology in their invention. *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1351 (Fed. Cir. 2011); *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997).

In light of the Federal Circuit's remand, we are persuaded that the '018 patent fails to describe the methods claimed by Quake as required under 35 U.S.C. § 112. Accordingly, after considering the Federal Circuit's remand, we grant Lo Motion 1.

III. Benefit of Quake's earlier filing dates

After review of the record on remand, it is apparent that the issue of written description support for Quake's claims is not a threshold issue in this interference. (*Contra* Decision on Motions, Paper 258, at 2.) In this interference, Quake is patentee and Lo substantially copied its claims from Quake's patent. (*See* Amendment in Appl. 13/070,275, filed 12 April 2012, at 4) ("Claims 24-27 have been substantially copied from U.S. Patent 8,008,018 issue August 31, 2011. . . . A request for interference pursuant to 37 C.F.R. § 41.202 will be filed at an appropriate time.").) Whether Lo is entitled to the claims presented in this interference as the first to invent under 35 U.S.C. § 102(g) has not been determined. *See* Guinn v. Kopf, 96 F.3d 1419, 1421–22 (Fed. Cir. 1996) ("Section 135 provides the basis for the Commissioner to declare an interference. Guinn does not dispute that Interference 103,096 was properly declared by the Commissioner. Section 135 also states that the Board 'shall determine questions of priority' after

the declaration of an interference. Guinn asserts that his unilateral act of disclaiming [the only patent claim corresponding to the count] can divest the Board of its responsibility to determine the priority question in the interference. The statute does not provide for any such divestment of jurisdiction.")

To address the issue of priority, we first decide Quake Motion 1 for benefit of the filing date of its prior application 11/701,686 ("the '686 application"), and provisional application 60/764,420 ("the '420 provisional application"). (*See* Quake Motion 1, Paper 69.) To be accorded benefit, Quake must show that both applications meet the written description and enablement requirements of 35 U.S.C. § 112 for one embodiment within the scope of the Count. *See Hunt v. Treppschuh*, 523 F.2d 1386, 1389 (C.C.P.A. 1975). The Count in this interference is claim 24 of Lo's involved application 13/070,275, which recites

> A method for determining presence or absence of fetal aneuploidy in a maternal biological sample comprising fetal and maternal genomic DNA, wherein the method comprises:
> a. obtaining a mixture of fetal and maternal genomic DNA from said maternal biological sample;
> b. conducting massively parallel DNA sequencing of DNA fragments randomly selected from the mixture of fetal and maternal genomic DNA of step a) to determine the sequence of said DNA fragments;
> c. identifying chromosomes to which the sequences obtained in step b) belong;
> d. using data of step c) to compare an amount of at least one first chromosome in said mixture of maternal and fetal genomic DNA to an amount of at least one second chromosome in said mixture of maternal and fetal genomic DNA, wherein said at least one first chromosome is presumed to be euploid in the fetus, wherein said at least one second chromosome is suspected to be aneuploid in the

> fetus, thereby determining the presence or absence of said fetal aneuploidy.

(Decl., Paper 1, at 4.) The Count is almost identical to claim 1 of Quake's '018 patent, including the limitation to "conducting massively parallel DNA sequencing of DNA fragments randomly selected from a mixture of fetal and maternal genomic DNA" to compare amounts of two chromosomes and determine the presence or absence of fetal aneuploidy.

Quake argues that step d. of the Count, using the data from chromosomes identified in random massively parallel sequencing to compare an amount of at least a first and second chromosome to determine fetal aneuploidy, is supported by paragraphs 27, 59, 95, 99, 104, and 141-149 of the '686 application (Exh. 2004) and paragraphs 21, 37, 50-52, 81, and 89-90 of the '420 provisional application (Exh. 2005). (Quake Motion 1, Paper 69, at 7:4-12, citing Detter Decl., Exh. 2049, at ¶ 100.) Quake cites to the testimony of Dr. Detter in support of its argument, but neither Quake nor Dr. Detter explain how these paragraphs support the element of the Count.

Lo argues that the cited paragraphs of the '686 application and '420 provisional application do not support an embodiment of the Count because they disclose a statistical method for detecting aneuploidy based on a 1:1 ratio between predetermined target sequences on two chromosomes. (*See* Lo Opp. 1. Paper 71, at 18:2-5.) Similar to its argument that the '018 patent lacks written description for Quake's claims, Lo argues that the random sequencing and alignment method of the Count does not require deviation from a 1:1 ratio to detect aneuploidy. (*See* Lo Opp. 1. Paper 71, at 18:14-16.) Lo argues that the data analysis used in the

example at paragraphs 141-149 of the '686 application relies on detecting variation from a 1:1 ratio between predetermined sequences, which would not work for a random sequencing and alignment method of the Count. (Lo Opp. 1, Paper 71, at 18:24-27, *see* Gabriel Decl, Exh. 1021, at ¶¶ 88 and 89 (cited in Lo Material Fact 117).)

As explained above, we are persuaded by Dr. Gabriel's testimony that deviations from a 1:1 ratio of identified sequences is not an appropriate analysis for a method of detecting aneuploidy using random sequencing of a mixture of maternal and fetal genomic DNA because the sequence reads must be normalized to chromosome size. Although Quake argues that its prior applications describe the use of a t statistic in its analysis to measure statistical significance (*see* Quake Reply 1, Paper 81, at 4:11-18[2]), we are not persuaded that this aspect of statistical analysis describes an analysis other than reliance on deviations from a 1:1 ratio and normalization to chromosome size. Instead, we are persuaded that the statistical analysis described in the prior applications does not recognize the need to normalize the number of sequence reads to the size of the chromosomes from which they are derived.

Accordingly, we are not persuaded that the '686 application and '420 provisional application present written description of an embodiment of the Count.

[2] Quake cites to the Board's Decision to Institute in IPR2013-00390 in support of its argument. (*See* Quake Reply 1, Paper 81, at 4:11-18, citing Ex. 2094 at 20:3-13.) IPR2013-00390 addressed the patentability of Patent 8,195,415, which was filed later than and does not share a specification with Quake's '686 application. Quake does not sufficiently explain how decisions or findings of fact made in IPR2013-00390 are specifically relevant to the issues of this interference.

To be a constructive reduction to practice of a count, an application must be a described and enabled anticipation under 35 U.S.C. 102(g)(1) of the subject matter of a count. *See* 37 C.F.R. § 41.201. Thus, neither the '686 application nor the '420 provisional application is a constructive reduction to practice of the Count. Accordingly, we deny Quake Motion 1 as to both of these prior applications.

IV. Conclusion

We grant Lo Motion 1, determining that Quake's involved claims are not patentable. Quake's claims will be canceled when judgment is entered in this proceeding.

We deny Quake Motion 1 to be accorded the benefit of the filing dates of its earlier applications as constructive reductions to practice of the Count.

An Order to Show Cause is issued separately regarding continuation of the interference to a priority phase. (*See* Paper 274.)

Any request for rehearing of our decisions filed 18 January 2018 will be considered timely. 37 C.F.R. § 41.104(b).

Interference 105,920

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Filed: December 20, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

YUK-MING DENNIS **LO**, ROSSA WAI KWUN CHIU, and KWAN CHEE CHAN
Junior Party
(Application 12/178,181; 13/070,240; 12/614,350; and 13/070,251),

v.

STEPHEN **QUAKE** and HEI-MUN CHRISTINA FAN
Senior Party
(Application 12/393,833).

Patent Interference No. 105,923 (DK)
(Technology Center 1600)

Judgment

37 C.F.R. § 41.127

Before, RICHARD E. SCHAFER, SALLY GARDNER LANE, and DEBORAH KATZ, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

Interference 105,923

Following remand from the Federal Circuit (*see The Board of Trustees of the Leland Stanford Junior University v. The Chinese University of Hong Kong*, App. 2015-011 (Fed. Cir. June 27, 2017)), we determine that application 12/393,833 fails to provide written description of Quake's involved, copied claims as required by 35 U.S.C. § 112. (*See* Decision on Motions, Paper 247.) Accordingly, we grant Lo Motion 1. We need not determine whether the benefit accorded to Quake upon declaration should be changed, as argued in Lo Motion 5 and Quake Motion 1.

ORDERED that judgment be entered against Quake for Count 1 (*see* Paper 1);

FURTHER ORDERED that claims 25, 29, 32, 40, 42, 78, 79, 86, 87, 90, 91, 93, 95, 97, and 98-101 of Quake's involved application 12/393,833 be FINALLY REFUSED 35 U.S.C. 135(a);

FURTHER ORDERED that a copy of this judgment be entered in the administrative records of the involved 12/393,833 application and Lo applications 12/178,181, 13/070,240, 12/614,350, and 13/070,251.

FURTHER ORDERED that a party seeking judicial review timely serve notice on the Director of the United States Patent and Trademark Office. 37 C.F.R. §§ 90.1 and 104.2.

FURTHER ORDERED that the parties are directed to 35 U.S.C. § 135(c) and to 37 C.F.R. § 41.205 regarding the filing of settlement agreements.

Interference 105,923

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Filed: December 20, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

YUK-MING DENNIS **LO**, ROSSA WAI KWUN CHIU, and KWAN CHEE CHAN
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(Application 12/178,181; 13/070,240; 12/614,350; and 13/070,251),

v.

STEPHEN **QUAKE** and HEI-MUN CHRISTINA FAN
Senior Party
(Application 12/393,833).

Patent Interference No. 105,923 (DK)
(Technology Center 1600)

Decision on Remand

37 C.F.R. § 41.125

Before, RICHARD E. SCHAFER, SALLY GARDNER LANE, and DEBORAH KATZ, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

Interference 105,923

I. *Review of prior history*

Judgement was entered against Quake in Interference 105,923 based on the decision that the specification of the application 12/393,833 ("the '833 application") does not provide a sufficient written description of Quake's involved claims. (*See* Judgment, Paper 233; *see* Decision on Motion, Paper 232.)

As the assignee of the Quake patents and application, The Board of Trustees of the Leland Stanford Junior University appealed the judgment entered in this interference to the Court of Appeals for the Federal Circuit. (*See The Board of Trustees of the Leland Stanford Junior University v. The Chinese University of Hong Kong*, App. 2015-011 (Fed. Cir. June 27, 2017).) The Federal Circuit vacated the prior decision and remanded the case to the Board, finding error. The court's decision refers to the issue of written description in patent 8,008,018, which is involved in Interference 105,920, but the court noted that its decision applies to the Board's findings in the instant interference as well. (*See Board of Trustees*, slip. op. 2, n.1.) The specifications of the '833 application and the '018 patent are substantially the same.

The court determined that the Board erred by considering whether the description in the '018 patent *precluded* targeted massively parallel sequencing, instead of considering whether the description *discloses* random massively parallel sequencing. (*See Board of Trustees,* slip op. 18.) The court also determined that the Board improperly relied on portions of Dr. Gabriel's, Lo's expert, testimony regarding a machine mentioned in the '018 patent. (*See Board of Trustees,* slip op. 15-18.)

On remand, the court instructed us to

> examine whether a person of ordinary skill in the art would have known, as of the priority date, that the '018 specification's reference to Illumina products meant random MPS sequencing as recited in the claims, by examining the record evidence as to pre-filing date art-related facts on Illumina products.

(*See Board of Trustees,* slip op. 19.) We should "examine whether a person of ordinary skill would have understood that the '018 patent's specification disclosed random MPS sequencing, as opposed to whether the specification did not preclude targeted MPS sequencing." (*See Board of Trustees,* slip op. 20.)

We find that even though the '833 application discusses random massively parallel sequencing and mentions identification of chromosomes from random sequence information, it does not do so in the context of Quake's claimed methods. Specifically, we find that the '833 application does not describe using the data obtained from random massively parallel sequencing and identification of chromosomes to compare the amounts of chromosomes in a mixture of maternal and fetal genomic in order to determine the presence or absence of said fetal aneuploidy, as required in step d. of Quake's claims.

II. *Written Description*

Quake's claims are directed to methods of determining whether a fetus has the wrong number of chromosomes – a condition called "fetal aneuploidy." In the claimed methods, this determination is made by sampling a maternal tissue, for example blood, that contains both maternal and fetal DNA, instead of a sample of fetal tissue. The claimed methods are less invasive than those currently used to detect fetal aneuploidy, such as amniocentesis. (*See Board of Trustees*, slip op. at 2-3.)

Claim 25 of the ’833 application recites:

> A method for performing prenatal diagnosis of a fetal chromosomal aneuploidy from a plasma or serum sample of a female subject pregnant with at least one fetus, wherein the plasma or serum sample includes cell-free genomic DNA molecules from the female subject and from the at least one fetus, the method comprising:
>
> *massively parallel sequencing cell-free genomic DNA molecules contained in the plasma or serum sample to obtain random nucleic acid sequences from the genomic DNA molecules of the female subject and of the at least one fetus*;
>
> identifying at least a portion of the nucleic acid sequences as belonging to a first specific human chromosome and at least one second specific human chromosome;
>
> determining a first amount of the nucleic acid sequences identified as being uniquely present on the first specific human chromosome; and
>
> determining a second amount of the nucleic acid sequences identified as being uniquely present on the at least one second specific human chromosome;
>
> *determining a ratio based on the first amount and the second amount, thereby determining a ratio of the amount of the nucleic acid sequences identified as being uniquely present on the first specific human chromosome to the amount of the nucleic acids being uniquely present on the at least one second specific chromosome*;
>
> determining whether the ratio is statistically significant; and
>
> correlating a statistically significant result with the presence of a fetal chromosomal aneuploidy on the first chromosome.

(Quake Clean Copy of Claims, Paper 11 (emphasis added).) The other independent claims in the ’833 application each include a limitation to massively parallel sequencing to obtain random nucleic acid sequences from genomic DNA of a female subject and a fetus and a limitation to determining a ratio of the amount a first specific chromosome and of a second specific chromosome identified in the sample. (*See id*.)

A.

We address the court's instruction to examine whether one of skill in the art would have understood that the specification of the '833 application discloses random massively parallel sequencing. (*See Board of Trustees,* slip op. 19.) The '833 application states, in a portion we refer to as "passage A":

> 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 sq. cm. These templates are sequenced using four-color DNA sequencing-by-synthesis technology. See, products offered by lllumina, Inc., San Diego California. Also. see US 2003/0022207 to Balasubramanian, et al., published January 30, 2003, entitled "Arrayed polynucleotides and their use in genome analysis."

('833 application, Exh. 1050, at ¶ 98.) Lo admits that "products offered by lllumina" were known to be products for massively parallel sequencing at the time of filing. (*See* Lo Motion 1, Paper 26, at Material Fact 49 ("'[P]roducts offered by Illumina' as mention at '833 application includes products for [massively parallel sequencing].").) Indeed, the passage quoted above expressly discloses massively parallel sequencing.

The passage also includes details of massively parallel sequencing, which the court indicated we failed to explain and compare to the claim limitations in our prior opinion. (*See Board of Trustees*, slip op. at 18-19.) Specifically, as Dr. Detter, Quake's witness, explains, sequencing with Illumina products involves certain steps, which the '833 application mentions by including the phrases: "using

attachment of randomly fragmented genomic DNA," "solid phase amplification," "~1,000 copies of template," and sequencing of templates "using four-color DNA sequencing-by-synthesis technology." (*See* Detter Decl., Exh. 2049, at ¶¶ 39-40, 59-70.) Lo does not dispute that these details are part of massively parallel sequencing with Illumina products. Accordingly, we find that this portion of the '833 application expressly describes massively parallel sequencing.

Quake's claims require that the massively parallel DNA sequencing be done "to obtain *random* nucleic acid sequences from the genomic DNA molecules of the female subject and of the at least one fetus . . . ." (*See* Quake Clean Copy of Claims, Paper 11, at 1 (emphasis added); *see also id*. at 2-6 (independent claims 42, 91, 95, reciting similar language regarding random nucleic acid sequences).) Thus, as the court instructed, we consider whether the '833 application provides a written description of sequencing randomly selected DNA fragments. (*See Board of Trustees*, slip op. 19.)

The parties agree that the claim limitation of obtaining "random nucleic acid sequences" means that the nucleic acid fragments have not been identified before the sequencing procedure and that sequence-specific primers to target specific gene loci are not required. (*See* Lo appl. 13/070,275, Exh. 1023, at ¶ 58; *see* Detter Decl. Exh. 2049, at ¶ 91; *see also Board of Trustees*, at slip op. 6.) Lo also agrees that it was known that Illumina products could perform massively parallel sequencing of randomly selected DNA fragments. (*See* Lo Motion 1, Paper 26, at 23:17-19, Material Fact 50 ("Illumina sequencing platforms can perform either random or targeted DNA sequencing, depending on whether predetermined target DNA fragments are specifically identified or targeted prior to sequencing.").)

Passage A of the '833 application expressly states that a methodology "based on massively parallel sequencing of millions of fragments using attachment of *randomly fragmented* genomic DNA to a planar, optically transparent surface" is useful in the disclosed invention. ('833 application, Exh. 1050, at ¶ 98 (emphasis added).) We agree with Lo that "randomly fragmented genomic DNA" is not necessarily the same as "DNA fragments randomly selected" from a mixture. (*See* Lo Reply 1, Paper 54, at 7:1-2.) But, we disagree with Lo that this passage necessarily describes target-specific analysis because targeting steps are not specifically recited in the passage. (*See* Lo Motion 1, Paper 26, at 9:25-10:13.)

Quake argues that passage A does not describe targeted sequencing and therefore must describe random sequencing. (*See* Quake Opp. 1, Paper 47, at 7:8-18.) Quake attempts to support its argument by citing to Material Fact 92 in Appendix 2 of its Opposition brief and to Dr. Gabriel's testimony. (*See id*., citing p. II-18, Material Fact 92 and Gabriel Decl., Exh. 1021, at ¶ 47.) Material Fact 92 is not helpful to us. Material Fact 92 refers to a document entitled "Technology Spotlight: Illumina® Sequencing," which is provided in Exhibit 2035, but Quake fails to show that it was publically available before the filing date of the '833 application, 26 February 2009. We note that Exhibit 2035 has a copyright date of 2010. (*See* Exhibit 2035, at 6.) We need not consider this reference because Quake has not shown that it specifically relates to "Illumina products" existing on the filing date. (*See Board of Trustees*, slip op. at 19-20.)

Even if we consider the content of Material Fact 92 and the document it cites, we would be unpersuaded by Quake's argument. The summary of Exhibit 2035 provided in Material Fact 92 highlights the use of non-specific primers in the

Illumina platform, but this aspect is not expressly stated in the '833 application. Similarly, although Dr. Detter's testimony is cited in Material Fact 92 (*see* Detter Decl., Exh. 2049, at ¶ 146), it is virtually identical with the Material Fact and fails to explain how the express disclosure of the '833 application describes what is taught in Exhibit 2035. For example, Quake highlights the portion of the summary in Material Fact 92 that refers to using primers that are not specific for a target sequence, but this direction is not stated in the '833 application itself. Quake does not direct us to a discussion of non-specific primers or a citation to Exhibit 2035 in the '833 application. Accordingly, we do not find that Material Fact 92 supports an express description of the claimed methods.

Quake also argues that the Balasubramanian patent application cited in passage A "supports random massively parallel sequencing." (Quake Opp. 1, Paper 47, at 4:23-25.) The four lines of Dr. Gabriel's deposition transcript that Quake cites support Quake's argument because on cross-examination Dr. Gabriel agreed with this statement. (*See* Gabriel Depo., Exh. 2078, at 60:18-22.) Thus, we find that Balasubramanian provides some of disclosure of massively parallel sequencing of DNA fragments selected randomly.

In contrast, we not persuaded by Quake's argument that random massively parallel sequencing is supported by the Braslavsky article, which is disclosed elsewhere in the '833 application. (Quake Opp. 1, Paper 47, at 4:25-5:2; *see* '833 appl., Exh. 1050, at ¶¶ 10 and 96.) According to Quake, Dr. Gabriel's testimony supports this argument because the Braslavsky article was "the concept behind the Helicos sequencer, which could be used for random sequencing." (Quake Opp. 1, Paper 47, at 4:26-27, citing Gabriel Depo., Exh. 2078, at 92:6-94:2.) Because

Quake does not direct us to discussion of the Helicos sequencer in the '833 application, we are not persuaded by this argument. (*See Board of Trustees*, slip op. at 17 ("All of the published references on which the Board relies focus on the Roche 454 platform, not the Illumina platform actually referenced in the specification.")

Accordingly, we find that passage A of the '833 application expressly describes massively parallel sequencing. The only portion, though, of passage A that ties this sequencing to the random sequence information mentioned in passage B is the citation to Balusubramanian, as characterized by four lines of Dr. Gabriel's testimony.

B.

Immediately following passage A, the '833 application also states, in a portion we refer to as "passage B":

> Sequencing may be combined with amplification-based methods in a microfluidic chip having reaction chambers for both PCR and microscopic template-based sequencing. 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. An algorithm for designing unique sequences is described in Yamada. et al. [Exhibit 1016] illustrative of software methods that can be used to identify a sequence in comparison to the known genome sequence. See, also Zhu et al., [Exhibit 1017] describing a single-molecule-based technology for studying mRNA.

('833 application, at ¶ 99.) Lo argues that, based on the citations to Yamada and Zhu, passage B refers to designing primers for the targeted digital PCR analysis

described in the rest of the '833 application, not to random massively parallel sequencing. (*See* Lo Motion 1, Paper 26, at 11:21-12:19.) Quake opposes Lo's argument by arguing that this passage refers to alignment of the sequence reads produced from random sequencing. (Quake Opp. 1, Paper 47, at 9:22-10:9.)

Passage B expressly recites "random sequence information." Accordingly, even if the Yamada and Zhu references that follow are not relevant to random sequence information, we find that passage B does expressly describe random sequencing.

C.

We find that passage A and passage B of the '833 application provide some express description of individual elements recited in Quake's claims. "Massively parallel sequencing" is expressly described, as is random sequencing. These activities are linked in the Balasubramanian reference.

Our task is to determine whether these disclosures are sufficient to have demonstrated one of ordinary skill in the art that the inventors were in possession of a method of determining fetal aneuploidy with random massively parallel sequencing as claimed by Quake. Although the express language describes some of the elements of the claimed method, we find that it is not sufficient to provide a written description under 35 U.S.C. § 112, first paragraph, because the '833 application does not tie these elements together into a complete method and does not explain how to use the data from random massively parallel sequencing of a mixture of genomic DNA to determine fetal aneuploidy.

D.

The insufficiency of the description of random massively parallel sequencing in the '833 application is apparent when it is compared to the description of a different method, called digital analysis, in that patent. The parties agree that the '833 application sufficiently describes the digital analysis method of determining fetal aneuploidy from a mixed sample. (*See* Lo Motion 1, Paper 26, at 20:1-2, Material Fact 11 ("The '833 Application discloses 'digital analysis' method for detecting fetal aneuploidy.") and Quake Opp. 1, Paper 47, at II-3 (admitting Lo Material Fact 11).) Specifically, the '833 application recites, in part:

> Thus, the present method [of digital analysis] comprises generally the following steps:
> 1. Obtaining a tissue containing DNA from a pregnant subject, ...
> 2. Distributing single DNA molecules from this sample to a number of discrete reaction samples, where the number of reaction samples is selected to give a statistically significant result for the number of copies of a target in the DNA molecules. . . .
> 3. Detecting the presence of the target in the DNA in a large number of reaction samples, preferably with a sequence specific technique such as highly multiplexed short read sequencing or a PCR reaction wherein the PCR product is labeled to give a convenient quantitative read out . . . . and
> 4. Quantitative analysis of the detection of the maternal and fetal target sequences.

('833 appl., Exh. 1050, at ¶ 41.) Thus, the '833 application outlines the specific steps one would take to perform digital analysis with a sequence specific technique such as sequencing or a PCR reaction.

In contrast, the disclosures in the '833 application that relate to a method of random massively parallel sequencing are the mention of massively parallel

sequencing of randomly fragmented DNA, "products offered by Illumina," citation to Balasubramanian, and a sentence about the number of base pairs needed to identify the chromosomal origin of a sequence. The '833 application does not recite specific series of steps one would take to determine whether fetal aneuploidy exists using random massively parallel sequencing.

We find that the '833 application fails to provide *express* "blazemarks" of a method of massively parallel sequencing of DNA fragments randomly selected from a mixture to determine fetal aneuploidy. *See In re Ruschig*, 379 F.2d 990, 994–95 (C.C.P.A. 1967) (analogizing, where the disclosure recited a list of possible reactants, but failed to highlight the necessary one, that "[i]t is an old custom in the woods to mark trails by making blaze marks on the trees. It is no help in finding a trail or in finding one's way through the woods where the trails have disappeared— or have not yet been made, which is more like the case here— to be confronted simply by a large number of unmarked trees.")

E.

In the absence of an express written description, the '833 application could still provide a sufficient description of the claimed methods if one of ordinary skill in the art would have understood from what was expressly described that the inventors were in possession of the inventions. *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570 (Fed. Cir. 1996) ("As the Board recognized, however, *ipsis verbis* disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question."). Thus, we look to how one of ordinary skill in the art would have understood the claims as a

whole. We find that the '833 application does not describe how to analyze the data that would be obtained from massively parallel sequencing to determine if fetal aneuploidy is present and that, thus, one of ordinary skill in the art would not know that the inventors possessed a method of determining fetal aneuploidy.

Quake's claims require that after determining the amounts of nucleic acid sequences for a first and a second human chromosome, "a ratio based on the first amount and the second amount" is determined and used to correlate with or identify fetal aneuploidy. (Quake Clean Copy of Claims, Paper 11.) Lo argues that because the '833 application focuses on detecting aneuploidy based on a 1:1 ratio between predetermined sequences from two chromosomes, which is appropriate for digital analysis (*see* '833 appl., Exh. 1050, at ¶¶104-106), it does not describe the considerations that must be made when comparing data from massively parallel sequencing of DNA fragments randomly selected. (Lo Motion 1, Paper 26, at 17:1-18:21, citing Gabriel Decl., Exh. 1049, at ¶¶ 109-110; *see also* Lo Reply 1, Paper 54, at 8:23-9:5.)

Lo bases its argument on Dr. Gabriel's testimony that because human chromosomes are not all the same size, randomly selected fragments are more likely to be identified from larger chromosomes than from smaller chromosomes. (Gabriel Decl., Exh. 1049, at ¶ 109.) According to Dr. Gabriel, given an equal number of all chromosomes, there is a greater chance that a random fragment will be from a larger chromosome than a smaller one. A method relying on random massively parallel sequencing cannot rely on a 1:1 ratio of sequences because even in the absence of aneuploidy, the number of random sequence reads aligning to a larger chromosome versus those aligning to a smaller chromosome will always

result in a ratio greater than 1:1. (Gabriel Decl., Exh. 1049, at ¶ 109.) Dr. Gabriel explains that instead of focusing on deviations from a 1:1 ratio, methods that use massively parallel sequencing of randomly selected fragments must take into consideration the size of the chromosomes before determining a ratio that represents a normal number of chromosomes. (*See* Gabriel Decl., Exh. 1049, at ¶ 110.)

Quake does not dispute that a random massively parallel sequencing method for determining fetal aneuploidy would need to take into account the length of the chromosomes being analyzed and could not be based on deviations from a 1:1 ratio. Instead, Quake argues that Dr. Gabriel admitted that statistical tests reportedly disclosed in the '833 application could be used to determine aneuploidy. (Quake Opp. 1, Paper 47, at 10:11-25, citing Gabriel Depo., Exh. 2078, at 51:2-53:16 and 73:22-74:18; *see* Detter Decl., Exh. 2082, at ¶ 29.) We do not find that the cited cross-examination refers to disclosures in the '833 application specification. Instead, Dr. Gabriel testifies about statistical methods, such as the "T-test" and the "Z-test," and how they could be used in general. (*See* Gabriel Depo., Exh. 2078, at 51:2-53:16 and 73:22-74:18.) Quake also argues that Dr. Gabriel testified that the fraction of a sample comprising a given chromosome is consistent from individual to individual in the absence of aneuploidy. (*See* Quake Opp. 1, Paper 47, at 10:18-20, citing Gabriel Depo, Exh. 2078, at 54:1-56:2.) We do not find that the testimony Quake cites addresses the statistical analysis needed when using sequences from chromosomes of differing lengths. None of the testimony is evidence that Dr. Gabriel admitted statistical methods relying on the

different lengths of identified chromosomes were described in the '833 application specification.

Quake also argues that the evidence Lo submitted with its Priority Statement (*see* Paper 24; Ex. 2074) and Lo's provisional application (Exh. 2010) contain less disclosure than the Quake '833 application about the statistical analysis used to assess fetal aneuploidy. (Quake Opp. 1, Paper 47, at 4:4-12, citing Gabriel Depo., Exh. 2078, at 33:11-34:4 and 38:5-12.) Presumably Quake's argument is that a description of the statistical analysis is not necessary because it not present in Lo's other documents. This argument is not persuasive because written description support is evaluated on what is described in specification at issue. Whether or not Lo's other documents provide sufficient written description is not at issue.

Quake argues further that Dr. Detter explained how the '833 application discloses a method that "intrinsically corrects for biases due to chromosome size by comparing results from a test sample to normal samples using statistical methods, such as a Student's T-test." (*See* Quake Opp. 1, Paper 47, at 3:4-19), citing Detter Decl., Exh. 2082, at ¶¶ 13 and 29, and '018 patent, Exh. 1022, at 5:64-6:3 and 28:5-34 (which correspond to '833 appl., Exh. 1050, at ¶¶ 27 and 148, Table 1.) This argument is not supported by the cited portions of the '833 application. Paragraphs 13 and 29 of Dr. Detter's declaration address Dr. Gabriel's cross-examination testimony about what was known in the art of normalized frequencies, chromosome size, and generalized statistical analyses. (*See* Lo Reply, Paper 54, at 9:11-19.) This testimony does not explain anything about the specification of the '833 application. Similarly, the portions of the '833 application that Quake cites do not mention chromosome size and do not discuss

any "intrinsic correction." The portions refer only to statistical significance in general (*see* '833 appl., Exh. 1050, at ¶ 27) and to analysis based on a 1:1 ratio (*see id*. at ¶ 148, Table 1).

Quake argues further that those of skill in the art would have known how to correct for chromosome size in February 2007, relying on Dr. Gabriel's testimony. (*See* Quake Opp. 1, Paper 47, at 3:14-18; citing Detter Decl., Exh. 2082, at ¶ 13, and Gabriel Depo., Exh. 2078, at 34:13-35:9.) In the portion of her testimony cited by Quake, Dr. Gabriel testifies that it was well known at the time how to create a "normalized frequency," but her testimony is about the disclosure of Lo's priority statement (Exhibit 2074), not the '018 patent. (*See* Gabriel Depo., Exh. 2078, at 34:13-35:9.) Specifically, Dr. Gabriel addresses Example 3 of Exhibit 2074, which provides for random sequencing and states:

> By taking into account of the relative size of chromosome 21 compared with the other chromosome, one could obtain a normalized frequency, within a reference range, of chromosome 21-specific sequences from such a sequencing exercise. If the fetus has trisomy 21, then the normalized frequency of chromosome 21-derived sequences from such a sequencing exercise will increase, thus allow the detection of trisomy 21.

(Exh. 2074, at 11, *see* Gabriel Depo., Exh. 2078, at 34:17-19 (referring to Example 3 of Exh. 2074 "It actually says you've got to take into account the chromosome size of things you're comparing.").) Quake does not direct us to similar discussion of "normalized frequency" in the '833 application.

Quake's argument is that those of skill in the art would have known *how* to normalize the frequency of sequence reads by the size of the chromosome, but Quake does not direct us to a portion of the '833 application that describes the need

to do so. Accordingly, we are persuaded that one of ordinary skill in the art would not have considered that the inventors of the '833 application contemplated a method requiring this statistical analysis.

The '833 application specification does not provide a description of an analysis that compares the amounts of the identified chromosomes determined from random massively parallel sequencing data and determines the presence or absence of fetal aneuploidy. In the absence of a description of such analysis, we are persuaded that the express teachings in the specification about equipment useful for random massively parallel sequencing and techniques for determining sequences are not sufficient to demonstrate possession of the claimed method for "determining presence or absence of fetal aneuploidy in a maternal tissue sample comprising fetal and maternal genomic DNA." Instead, the description in the '833 application indicates that the inventors had only "a mere wish or plan" to use this new technology in their invention. *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1351 (Fed. Cir. 2011); *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997).

In light of the Federal Circuit's remand, we are persuaded that the '833 application fails to describe the methods claimed by Quake as required under 35 U.S.C. § 112. Accordingly, we grant Lo Motion 1.

III. *Conclusion*

During prosecution of the '833 application, Quake stated numerous times that the pending claims were amended and new claims were added to "track" the amendments and new claims made in Lo application 12/178,181 ("the '181 application"). Lo's '181 application was published on 29 January 2009, as U.S.

Patent Application Publication 2009/0029377, before Quake's '833 application was filed on 26 February 2009. Quake stated that it filed and amended the claims of the '833 application to anticipate or render obvious Lo's '181 application claims. (*See* Amendment in the '833 appl., filed 6 June 2011 at 12-13; *see also* Amendments in the '833 appl., filed 29 January 2010, 12 October 2011, 27 January 2012.)

Because Quake's involved application does not provide a sufficient written description to support the claims that "tracked" Lo's claims, Quake's claims are unpatentable to Quake and Quake should not have been able to challenge Lo's claims with them. Accordingly, Quake does not have standing in this proceeding and we determine that the written description of Quake's claims is a threshold issue. (*See* 37 C.F.R. § 41.201 (defining "threshold issue" as one which, if resolved in favor of the movant, would deprive the opponent of standing in the interference, for example, unpatentability for lack of written description under 35 U.S.C. § 112 of an involved application where the applicant's claims were first made after the publication of a movant's application and the applicant could have suggested an interference).)

Accordingly, we need not decide Quake Motion 1 (Paper 43) or Lo Motion 5 (Paper 27). We enter judgment, in a separate paper, against Quake.

Interference 105,923

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Filed: December 20, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

YUK-MING DENNIS **LO**, ROSSA WAI KWUN CHIU, and KWAN CHEE CHAN
Junior Party
(Application 13/417,119),

v.

STEPHEN **QUAKE** and HEI-MUN CHRISTINA FAN
Senior Party
(Application 12/393,833).

Patent Interference No. 105,924 (DK)
(Technology Center 1600)

Judgment

37 C.F.R. § 41.127

Before, RICHARD E. SCHAFER, SALLY GARDNER LANE, and DEBORAH KATZ, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

Interference 105,924

Following remand from the Federal Circuit (*see The Board of Trustees of the Leland Stanford Junior University v. The Chinese University of Hong Kong*, App. 2015-011 (Fed. Cir. June 27, 2017)), we determine that application 12/393,833 fails to provide written description of Quake's involved, copied claims as required by 35 U.S.C. § 112. (*See* Decision on Motions, Paper 245.) Accordingly, we grant Lo Motion 1. We need not determine whether the benefit accorded to Quake upon declaration should be changed, as argued in Lo Motion 5 and Quake Motion 1.

ORDERED that judgment be entered against Quake for Count 1 (*see* Paper 1);

FURTHER ORDERED that claims 25, 29, 32, 40, 42, 78, 79, 86, 87, 90, 91, 93, 95, 97, and 98-101 of Quake's involved application 12/393,833 be FINALLY REFUSED 35 U.S.C. 135(a);

FURTHER ORDERED that a copy of this judgment be entered in the administrative records of the involved 12/393,833 application and Lo application 13/417,119.

FURTHER ORDERED that a party seeking judicial review timely serve notice on the Director of the United States Patent and Trademark Office. 37 C.F.R. §§ 90.1 and 104.2.

FURTHER ORDERED that the parties are directed to 35 U.S.C. § 135(c) and to 37 C.F.R. § 41.205 regarding the filing of settlement agreements.

Interference 105,924

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Filed: December 20, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

YUK-MING DENNIS **LO**, ROSSA WAI KWUN CHIU, and KWAN CHEE CHAN
Junior Party
(Application 13/417,119),

v.

STEPHEN **QUAKE** and HEI-MUN CHRISTINA FAN
Senior Party
(Application 12/393,833).

Patent Interference No. 105,924 (DK)
(Technology Center 1600)

Decision on Remand

37 C.F.R. § 41.125

Before, RICHARD E. SCHAFER, SALLY GARDNER LANE, and DEBORAH KATZ, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

Interference 105,924

I. *Review of prior history*

Judgement was entered against Quake in Interference 105,924 based on the decision that the specification of the application 12/393,833 ("the '833 application") does not provide a sufficient written description of Quake's involved claims. (*See* Judgment, Paper 231; *see* Decision on Motion, Paper 230.)

As the assignee of the Quake patents and application, The Board of Trustees of the Leland Stanford Junior University appealed the judgment entered in this interference to the Court of Appeals for the Federal Circuit. (*See The Board of Trustees of the Leland Stanford Junior University v. The Chinese University of Hong Kong*, App. 2015-011 (Fed. Cir. June 27, 2017).) The Federal Circuit vacated the prior decision and remanded the case to the Board, finding error. The court's decision refers to the issue of written description in patent 8,008,018, which is involved in Interference 105,920, but the court noted that its decision applies to the Board's findings in the instant interference as well. (*See Board of Trustees*, slip. op. 2, n.1.) The specifications of the '833 application and the '018 patent are substantially the same.

The court determined that the Board erred by considering whether the description in the '018 patent *precluded* targeted massively parallel sequencing, instead of considering whether the description *discloses* random massively parallel sequencing. (*See Board of Trustees,* slip op. 18.) The court also determined that the Board improperly relied on portions of Dr. Gabriel's, Lo's expert, testimony regarding a machine mentioned in the '018 patent. (*See Board of Trustees,* slip op. 15-18.)

On remand, the court instructed us to

> examine whether a person of ordinary skill in the art would have known, as of the priority date, that the '018 specification's reference to Illumina products meant random MPS sequencing as recited in the claims, by examining the record evidence as to pre-filing date art-related facts on Illumina products.

(*See Board of Trustees,* slip op. 19.) We should "examine whether a person of ordinary skill would have understood that the '018 patent's specification disclosed random MPS sequencing, as opposed to whether the specification did not preclude targeted MPS sequencing." (*See Board of Trustees,* slip op. 20.)

We find that even though the '833 application discusses random massively parallel sequencing and mentions identification of chromosomes from random sequence information, it does not do so in the context of Quake's claimed methods. Specifically, we find that the '833 application does not describe using the data obtained from random massively parallel sequencing and identification of chromosomes to compare the amounts of chromosomes in a mixture of maternal and fetal genomic in order to determine the presence or absence of said fetal aneuploidy, as required in step d. of Quake's claims.

II. *Written Description*

Quake's claims are directed to methods of determining whether a fetus has the wrong number of chromosomes – a condition called "fetal aneuploidy." In the claimed methods, this determination is made by sampling a maternal tissue, for example blood, that contains both maternal and fetal DNA, instead of a sample of fetal tissue. The claimed methods are less invasive than those currently used to detect fetal aneuploidy, such as amniocentesis. (*See Board of Trustees*, slip op. at 2-3.)

Claim 25 of the '833 application recites:

> A method for performing prenatal diagnosis of a fetal chromosomal aneuploidy from a plasma or serum sample of a female subject pregnant with at least one fetus, wherein the plasma or serum sample includes cell-free genomic DNA molecules from the female subject and from the at least one fetus, the method comprising:
>
> *massively parallel sequencing cell-free genomic DNA molecules contained in the plasma or serum sample to obtain random nucleic acid sequences from the genomic DNA molecules of the female subject and of the at least one fetus*;
>
> identifying at least a portion of the nucleic acid sequences as belonging to a first specific human chromosome and at least one second specific human chromosome;
>
> determining a first amount of the nucleic acid sequences identified as being uniquely present on the first specific human chromosome; and
>
> determining a second amount of the nucleic acid sequences identified as being uniquely present on the at least one second specific human chromosome;
>
> *determining a ratio based on the first amount and the second amount, thereby determining a ratio of the amount of the nucleic acid sequences identified as being uniquely present on the first specific human chromosome to the amount of the nucleic acids being uniquely present on the at least one second specific chromosome*;
>
> determining whether the ratio is statistically significant; and
>
> correlating a statistically significant result with the presence of a fetal chromosomal aneuploidy on the first chromosome.

(Quake Clean Copy of Claims, Paper 11 (emphasis added).) The other independent claims in the '833 application each include a limitation to massively parallel sequencing to obtain random nucleic acid sequences from genomic DNA of a female subject and a fetus and a limitation to determining a ratio of the amount a first specific chromosome and of a second specific chromosome identified in the sample. (*See id*.)

A.

We address the court's instruction to examine whether one of skill in the art would have understood that the specification of the '833 application discloses random massively parallel sequencing. (*See Board of Trustees,* slip op. 19.) The '833 application states, in a portion we refer to as "passage A":

> 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 sq. cm. These templates are sequenced using four-color DNA sequencing-by-synthesis technology. See, products offered by lllumina, Inc., San Diego California Also. see US 2003/0022207 to Balasubramanian, et al., published January 30, 2003, entitled "Arrayed polynucleotides and their use in genome analysis."

('833 application, Exh. 1050, at ¶ 98.) Lo admits that "products offered by lllumina" were known to be products for massively parallel sequencing at the time of filing. (*See* Lo Motion 1, Paper 26, at Material Fact 49 ("'[P]roducts offered by Illumina' as mention at '833 application includes products for [massively parallel sequencing]."); *see* Quake response ("Admitted.").) Indeed, the passage quoted above expressly discloses massively parallel sequencing.

The passage also includes details of massively parallel sequencing, which the court indicated we failed to explain and compare to the claim limitations in our prior opinion. (*See Board of Trustees*, slip op. at 18-19.) Specifically, as Dr. Detter, Quake's witness, explains, sequencing with Illumina products involves certain steps, which the '833 application mentions by including the phrases: "using

attachment of randomly fragmented genomic DNA," "solid phase amplification," "~1,000 copies of template," and sequencing of templates "using four-color DNA sequencing-by-synthesis technology." (*See* Detter Decl., Exh. 2049, at ¶¶ 39-40, 59-70.) Lo does not dispute that these details are part of massively parallel sequencing with Illumina products. Accordingly, we find that this portion of the '833 application expressly describes massively parallel sequencing.

Quake's claims require that the massively parallel DNA sequencing be done "to obtain *random* nucleic acid sequences from the genomic DNA molecules of the female subject and of the at least one fetus . . . ." (*See* Quake Clean Copy of Claims, Paper 11, at 1 (emphasis added); *see also id*. at 2-6 (independent claims 42, 91, 95, reciting similar language regarding random nucleic acid sequences).) Thus, as the court instructed, we consider whether the '833 application provides a written description of sequencing randomly selected DNA fragments. (*See Board of Trustees*, slip op. 19.)

The parties agree that the claim limitation of obtaining "random nucleic acid sequences" means that the nucleic acid fragments have not been identified before the sequencing procedure and that sequence-specific primers to target specific gene loci are not required. (*See* Lo appl. 13/070,275, Exh. 1023, ¶ 58; *see* Detter Decl. Exh. 2049, at ¶ 91; *see also Board of Trustees*, at slip op. 6.) Lo also agrees that it was known that Illumina products could perform massively parallel sequencing of randomly selected DNA fragments. (*See* Lo Motion 1, Paper 26, at 23:17-19, Material Fact 50 ("Illumina sequencing platforms can perform either random or targeted DNA sequencing, depending on whether predetermined target DNA fragments are specifically identified or targeted prior to sequencing.").)

Passage A of the '833 application expressly states that a methodology "based on massively parallel sequencing of millions of fragments using attachment of *randomly fragmented* genomic DNA to a planar, optically transparent surface" is useful in the disclosed invention. ('833 application, Exh. 1050, at ¶ 98 (emphasis added).) We agree with Lo that "randomly fragmented genomic DNA" is not necessarily the same as "DNA fragments randomly selected" from a mixture. (*See* Lo Reply 1, Paper 53, at 7:1-2.) But, we disagree with Lo that this passage necessarily describes target-specific analysis because targeting steps are not specifically recited in the passage. (*See* Lo Motion 1, Paper 26, at 9:24-10:12.)

Quake argues that passage A does not describe targeted sequencing and therefore must describe random sequencing. (*See* Quake Opp. 1, Paper 47, at 7:7-17.) Quake attempts to support its argument by citing to Material Fact 92 in Appendix 2 of its Opposition brief and to Dr. Gabriel's testimony. (*See id*., citing p. II-16, Material Fact 92 and Gabriel Decl., Exh. 1021, at ¶ 47.) Material Fact 92 is not helpful to us. Material Fact 92 refers to a document entitled "Technology Spotlight: Illumina® Sequencing," which is provided in Exhibit 2035, but Quake fails to show that it was publically available before the filing date of the '833 application, 26 February 2009. We note that Exhibit 2035 has a copyright date of 2010. (*See* Exhibit 2035, at 6.) We need not consider this reference because Quake has not shown that it specifically relates to "Illumina products" existing on the filing date. (*See Board of Trustees*, slip op. at 19-20.)

Even if we consider the content of Material Fact 92 and the document it cites, we would be unpersuaded by Quake's argument. The summary of Exhibit 2035 provided in Material Fact 92 highlights the use of non-specific primers in the

Illumina platform, but this aspect is not expressly stated in the '833 application. Similarly, although Dr. Detter's testimony is cited in Material Fact 92 (*see* Detter Decl., Exh. 2049, at ¶ 146), it is virtually identical with the Material Fact and fails to explain how the express disclosure of the '833 application describes what is taught in Exhibit 2035. For example, Quake highlights the portion of the summary in Material Fact 92 that refers to using primers that are not specific for a target sequence, but this direction is not stated in the '833 application itself. Quake does not direct us to a discussion of non-specific primers or a citation to Exhibit 2035 in the '833 application. Accordingly, we do not find that Material Fact 92 supports an express description of the claimed methods.

Quake also argues that the Balasubramanian patent application cited in passage A "supports random massively parallel sequencing." (Quake Opp. 1, Paper 47, at 4:22-24.) The four lines of Dr. Gabriel's deposition transcript that Quake cites support Quake's argument because on cross-examination Dr. Gabriel agreed with this statement. (*See* Gabriel Depo., Exh. 2078, at 60:18-22.) Thus, we find that Balasubramanian provides some of disclosure of massively parallel sequencing of DNA fragments selected randomly.

In contrast, we not persuaded by Quake's argument that random massively parallel sequencing is supported by the Braslavsky article, which is disclosed elsewhere in the '833 application. (Quake Opp. 1, Paper 47, at 4:24-5:1; *see* '833 appl., Exh. 1050, at ¶¶ 10 and 96.) According to Quake, Dr. Gabriel's testimony supports this argument because the Braslavsky article was "the concept behind the Helicos sequencer, which could be used for random sequencing." (Quake Opp. 1, Paper 47, at 4:25-26, citing Gabriel Depo., Exh. 2078, at 92:6-94:2.) Because

Quake does not direct us to discussion of the Helicos sequencer in the '833 application, we are not persuaded by this argument. (*See Board of Trustees*, slip op. at 17 ("All of the published references on which the Board relies focus on the Roche 454 platform, not the Illumina platform actually referenced in the specification.")

Accordingly, we find that passage A of the '833 application expressly describes massively parallel sequencing. The only portion, though, of passage A that ties this sequencing to the random sequence information mentioned in passage B is the citation to Balusubramanian, as characterized by four lines of Dr. Gabriel's testimony.

B.

Immediately following passage A, the '833 application also states, in a portion we refer to as "passage B":

> Sequencing may be combined with amplification-based methods in a microfluidic chip having reaction chambers for both PCR and microscopic template-based sequencing. 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. An algorithm for designing unique sequences is described in Yamada. et al. [Exhibit 1016] illustrative of software methods that can be used to identify a sequence in comparison to the known genome sequence. See, also Zhu et al., [Exhibit 1017] describing a single-molecule-based technology for studying mRNA.

('833 application, at ¶ 99.) Lo argues that, based on the citations to Yamada and Zhu, passage B refers to designing primers for the targeted digital PCR analysis

described in the rest of the '833 application, not to random massively parallel sequencing. (*See* Lo Motion 1, Paper 26, at 11:28-12:17.) Quake opposes Lo's argument by arguing that this passage refers to alignment of the sequence reads produced from random sequencing. (Quake Opp. 1, Paper 47, at 9:21-10:8.)

Passage B expressly recites "random sequence information." Accordingly, even if the Yamada and Zhu references that follow are not relevant to random sequence information, we find that passage B does expressly describe random sequencing.

C.

We find that passage A and passage B of the '833 application provide some express description of individual elements recited in Quake's claims. "Massively parallel sequencing" is expressly described, as is random sequencing. These activities are linked in the Balasubramanian reference.

Our task is to determine whether these disclosures are sufficient to have demonstrated one of ordinary skill in the art that the inventors were in possession of a method of determining fetal aneuploidy with random massively parallel sequencing as claimed by Quake. Although the express language describes some of the elements of the claimed method, we find that it is not sufficient to provide a written description under 35 U.S.C. § 112, first paragraph, because the '833 application does not tie these elements together into a complete method and does not explain how to use the data from random massively parallel sequencing of a mixture of genomic DNA to determine fetal aneuploidy.

D.

The insufficiency of the description of random massively parallel sequencing in the '833 application is apparent when it is compared to the description of a different method, called digital analysis, in that patent. The parties agree that the '833 application sufficiently describes the digital analysis method of determining fetal aneuploidy from a mixed sample. (*See* Lo Motion 1, Paper 26, at 20:1-2, Material Fact 11 ("The '833 Application discloses 'digital analysis' method for detecting fetal aneuploidy.") and Quake Opp. 1, Paper 47, at II-3 (admitting Lo Material Fact 11).) Specifically, the '833 application recites, in part:

> Thus, the present method [of digital analysis] comprises generally the following steps:
> 1. Obtaining a tissue containing DNA from a pregnant subject, ...
> 2. Distributing single DNA molecules from this sample to a number of discrete reaction samples, where the number of reaction samples is selected to give a statistically significant result for the number of copies of a target in the DNA molecules. . . .
> 3. Detecting the presence of the target in the DNA in a large number of reaction samples, preferably with a sequence specific technique such as highly multiplexed short read sequencing or a PCR reaction wherein the PCR product is labeled to give a convenient quantitative read out . . . . and
> 4. Quantitative analysis of the detection of the maternal and fetal target sequences.

('833 appl., Exh. 1050, at ¶ 41.) Thus, the '833 application outlines the specific steps one would take to perform digital analysis with a sequence specific technique such as sequencing or a PCR reaction.

In contrast, the disclosures in the '833 application that relate to a method of random massively parallel sequencing are the mention of massively parallel

sequencing of randomly fragmented DNA, "products offered by Illumina," citation to Balasubramanian, and a sentence about the number of base pairs needed to identify the chromosomal origin of a sequence. The '833 application does not recite specific series of steps one would take to determine whether fetal aneuploidy exists using random massively parallel sequencing.

We find that the '833 application fails to provide *express* "blazemarks" of a method of massively parallel sequencing of DNA fragments randomly selected from a mixture to determine fetal aneuploidy. *See In re Ruschig*, 379 F.2d 990, 994–95 (C.C.P.A. 1967) (analogizing, where the disclosure recited a list of possible reactants, but failed to highlight the necessary one, that "[i]t is an old custom in the woods to mark trails by making blaze marks on the trees. It is no help in finding a trail or in finding one's way through the woods where the trails have disappeared— or have not yet been made, which is more like the case here— to be confronted simply by a large number of unmarked trees.")

E.

In the absence of an express written description, the '833 application could still provide a sufficient description of the claimed methods if one of ordinary skill in the art would have understood from what was expressly described that the inventors were in possession of the inventions. *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570 (Fed. Cir. 1996) ("As the Board recognized, however, *ipsis verbis* disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question."). Thus, we look to how one of ordinary skill in the art would have understood the claims as a

whole. We find that the '833 application does not describe how to analyze the data that would be obtained from massively parallel sequencing to determine if fetal aneuploidy is present and that, thus, one of ordinary skill in the art would not know that the inventors possessed a method of determining fetal aneuploidy.

Quake's claims require that after determining the amounts of nucleic acid sequences for a first and a second human chromosome, "a ratio based on the first amount and the second amount" is determined and used to correlate with or identify fetal aneuploidy. (Quake Clean Copy of Claims, Paper 11.) Lo argues that because the '833 application focuses on detecting aneuploidy based on a 1:1 ratio between predetermined sequences from two chromosomes, which is appropriate for digital analysis (*see* '833 appl., Exh. 1050, at ¶¶104-106), it does not describe the considerations that must be made when comparing data from massively parallel sequencing of DNA fragments randomly selected. (Lo Motion 1, Paper 26, at 17:1-18:21, citing Gabriel Decl., Exh. 1049, at ¶¶ 109-110; *see also* Lo Reply 1, Paper 53, at 8:23-9:5.)

Lo bases its argument on Dr. Gabriel's testimony that because human chromosomes are not all the same size, randomly selected fragments are more likely to be identified from larger chromosomes than from smaller chromosomes. (Gabriel Decl., Exh. 1049, at ¶ 109.) According to Dr. Gabriel, given an equal number of all chromosomes, there is a greater chance that a random fragment will be from a larger chromosome than a smaller one. A method relying on random massively parallel sequencing cannot rely on a 1:1 ratio of sequences because even in the absence of aneuploidy, the number of random sequence reads aligning to a larger chromosome versus those aligning to a smaller chromosome will always

result in a ratio greater than 1:1. (Gabriel Decl., Exh. 1049, at ¶ 109.) Dr. Gabriel explains that instead of focusing on deviations from a 1:1 ratio, methods that use massively parallel sequencing of randomly selected fragments must take into consideration the size of the chromosomes before determining a ratio that represents a normal number of chromosomes. (*See* Gabriel Decl., Exh. 1049, at ¶ 110.)

Quake does not dispute that a random massively parallel sequencing method for determining fetal aneuploidy would need to take into account the length of the chromosomes being analyzed and could not be based on deviations from a 1:1 ratio. Instead, Quake argues that Dr. Gabriel admitted that statistical tests reportedly disclosed in the '833 application could be used to determine aneuploidy. (Quake Opp. 1, Paper 47, at 10:10-24, citing Gabriel Depo., Exh. 2078, at 51:2-53:16 and 73:22-74:18; *see* Detter Decl., Exh. 2082, at ¶ 29.) We do not find that the cited cross-examination refers to disclosures in the '833 application specification. Instead, Dr. Gabriel testifies about statistical methods, such as the "T-test" and the "Z-test," and how they could be used in general. (*See* Gabriel Depo., Exh. 2078, at 51:2-53:16 and 73:22-74:18.) Quake also argues that Dr. Gabriel testified that the fraction of a sample comprising a given chromosome is consistent from individual to individual in the absence of aneuploidy. (*See* Quake Opp. 1, Paper 47, at 10:17-19, citing Gabriel Depo, Exh. 2078, at 54:1-56:2.) We do not find that the testimony Quake cites addresses the statistical analysis needed when using sequences from chromosomes of differing lengths. None of the testimony is evidence that Dr. Gabriel admitted statistical methods relying on the

different lengths of identified chromosomes were described in the '833 application specification.

Quake also argues that the evidence Lo submitted with its Priority Statement (*see* Paper 24; Ex. 2074) and Lo's provisional application (Exh. 2010) contain less disclosure than the Quake '833 application about the statistical analysis used to assess fetal aneuploidy. (Quake Opp. 1, Paper 47, at 4:3-11, citing Gabriel Depo., Exh. 2078, at 33:11-34:4 and 38:5-12.) Presumably Quake's argument is that a description of the statistical analysis is not necessary because it not present in Lo's other documents. This argument is not persuasive because written description support is evaluated on what is described in specification at issue. Whether or not Lo's other documents provide sufficient written description is not at issue.

Quake argues further that Dr. Detter explained how the '833 application discloses a method that "intrinsically corrects for biases due to chromosome size by comparing results from a test sample to normal samples using statistical methods, such as a Student's T-test." (*See* Quake Opp. 1, Paper 47, at 3:4-19), citing Detter Decl., Exh. 2082, at ¶¶ 13 and 29, and '018 patent, Exh. 1022, at 5:64-6:3 and 28:5-34 (which correspond to '833 appl., Exh. 1050, at ¶¶ 27 and 148, Table 1.) This argument is not supported by the cited portions of the '833 application. Paragraphs 13 and 29 of Dr. Detter's declaration address Dr. Gabriel's cross-examination testimony about what was known in the art of normalized frequencies, chromosome size, and generalized statistical analyses. (*See* Lo Reply, Paper 53, at 9:11-19.) This testimony does not explain anything about the specification of the '833 application. Similarly, the portions of the '833 application that Quake cites do not mention chromosome size and do not discuss

any "intrinsic correction." The portions refer only to statistical significance in general (*see* '833 appl., Exh. 1050, at ¶ 27) and to analysis based on a 1:1 ratio (*see id*. at ¶ 148, Table 1).

Quake argues further that those of skill in the art would have known how to correct for chromosome size in February 2007, relying on Dr. Gabriel's testimony. (*See* Quake Opp. 1, Paper 47, at 3:14-18; citing Detter Decl., Exh. 2082, at ¶ 13, and Gabriel Depo., Exh. 2078, at 34:13-35:9.) In the portion of her testimony cited by Quake, Dr. Gabriel testifies that it was well known at the time how to create a "normalized frequency," but her testimony is about the disclosure of Lo's priority statement (Exhibit 2074), not the '018 patent. (*See* Gabriel Depo., Exh. 2078, at 34:13-35:9.) Specifically, Dr. Gabriel addresses Example 3 of Exhibit 2074, which provides for random sequencing and states:

> By taking into account of the relative size of chromosome 21 compared with the other chromosome, one could obtain a normalized frequency, within a reference range, of chromosome 21-specific sequences from such a sequencing exercise. If the fetus has trisomy 21, then the normalized frequency of chromosome 21-derived sequences from such a sequencing exercise will increase, thus allow the detection of trisomy 21.

(Exh. 2074, at 11, *see* Gabriel Depo., Exh. 2078, at 34:17-19 (referring to Example 3 of Exh. 2074 "It actually says you've got to take into account the chromosome size of things you're comparing.").) Quake does not direct us to similar discussion of "normalized frequency" in the '833 application.

Quake's argument is that those of skill in the art would have known *how* to normalize the frequency of sequence reads by the size of the chromosome, but Quake does not direct us to a portion of the '833 application that describes the need

to do so. Accordingly, we are persuaded that one of ordinary skill in the art would not have considered that the inventors of the '833 application contemplated a method requiring this statistical analysis.

The '833 application specification does not provide a description of an analysis that compares the amounts of the identified chromosomes determined from random massively parallel sequencing data and determines the presence or absence of fetal aneuploidy. In the absence of a description of such analysis, we are persuaded that the express teachings in the specification about equipment useful for random massively parallel sequencing and techniques for determining sequences are not sufficient to demonstrate possession of the claimed method for "determining presence or absence of fetal aneuploidy in a maternal tissue sample comprising fetal and maternal genomic DNA." Instead, the description in the '833 application indicates that the inventors had only "a mere wish or plan" to use this new technology in their invention. *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1351 (Fed. Cir. 2011); *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997).

In light of the Federal Circuit's remand, we are persuaded that the '833 application fails to describe the methods claimed by Quake as required under 35 U.S.C. § 112. Accordingly, we grant Lo Motion 1.

III. *Conclusion*

During prosecution of the '833 application, Quake stated numerous times that the pending claims were amended and new claims were added to "track" the amendments and new claims made in Lo application 12/178,181 ("the '181 application"). The '181 application is not involved in this interference, but is

involved in related interference 105,923, in which Quake's '833 application is also involved. Lo's '181 application was published on 29 January 2009, as U.S. Patent Application Publication 2009/0029377, before Quake's '833 application was filed on 26 February 2009. Quake stated that it filed and amended the claims of the '833 application to anticipate or render obvious Lo's '181 application claims. (*See* Amendment in the '833 appl., filed 6 June 2011 at 12-13; *see also* Amendments in the '833 appl., filed 29 January 2010, 12 October 2011, 27 January 2012.)

Because Quake's involved application does not provide a sufficient written description to support the claims that "tracked" Lo's claims, Quake's claims are unpatentable to Quake and Quake should not have been able to challenge Lo's claims with them. We make this determination even though Lo's application involved in this interference was published on 16 August 2012, after Quake's claims were filed on 26 February 2009, because Quake's claims are directed to the same subject matter as Lo's claims involved in the 105,923 interference.[1] Accordingly, Quake does not have standing in this proceeding and we determine that the written description of Quake's claims to be a threshold issue. . (*See* 37 C.F.R. § 41.201 (defining "threshold issue" as one which, if resolved in favor of the movant, would deprive the opponent of standing in the interference, for example, unpatentability for lack of written description under 35 U.S.C. § 112 of an involved application where the applicant's claims were first made after the publication of a movant's application and the applicant could have suggested an interference).)

[1] The counts in both this interference and the '105,923 interference include Quake '833 application claim 25, as well as Lo claims involved in each interference.

Accordingly, we need not decide Quake Motion 1 (Paper 43) or Lo Motion 5 (Paper 27). We enter judgment, in a separate paper, against Quake.

cc (via electronic delivery):

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