Appeal No. 2018-1779, 2018-1780, 2018-1782

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

STEPHEN QUAKE, HEI-MUN CHRISTINA FAN

Appellants,

v.

YUK-MING DENNIS LO, ROSSA WAI KWUN CHIU, KWAN CHEE CHAN

Appellees.

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. 105,920, 105,923, 105,924, before Admin. Patent Judges Richard E. Schafer, Sally Gardner Lane, and Deborah Katz.

Decided: July 10, 2019

APPELLANTS' PETITION FOR REHEARING EN BANC

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CERTIFICATE OF INTEREST

Counsel for Appellants Stephen Quake, Hei-Mun Christina Fan ("Quake") certify as follows:

1. The full name of every party represented by me is:

   Stephen Quake
   Hei-Mun Christina Fan

2. The name of the real party in interest represented by us is:

   The Board of Trustees of the Leland Stanford Junior University
   Verinata Health, Inc.

3. All parent corporations and any public companies that own 10 percent or more of the stock of the parties represented by us are:

   Illumina, Inc. owns more than 10% of the stock of Verinata Health, Inc

4. The names of all law firms and the partners or associates that appeared for the parties now represented by us in the trial court or are expected to appear in this Court are:

   Edward R. Reines
   Derek C. Walter
   Trevor J. Quist
   Aaron Y. Huang
   Anant N. Pradhan
   Michele A. Gauger

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5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this Court's decision in the pending appeal:

   None

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RULE 35(B) STATEMENT

Based on my professional judgment, I believe that the panel decision is contrary to this Court's precedent as reflected in *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336 (Fed. Cir. 2010) (en banc) and *In Re Global IP Holdings LLC*, 927 F. 3d 1373 (Fed. Cir. 2019) (and cases cited therein).

Dated: August 9, 2019

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ARGUMENT

It is a bedrock principle of patent law that the "level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc); *In Re Global IP Holdings LLC*, 927 F.3d 1373 (Fed. Cir. 2019); *Centrak, Inc. v. Sonitor Technologies, Inc.*, 915 F.3d 1360, 1367-1368 (Fed. Cir. 2019); *Hologic, Inc. v. Smith & Nephew, Inc.*, 884 F.3d 1357, 1361 (Fed. Cir. 2018) ("the field of this invention is a predictable art, such that a lower level of detail is required to satisfy the written description requirement than for unpredictable arts"). In evaluating the adequacy of the disclosure, the decision maker must consider *Ariad's* analysis of predictability in the context of the prior art landscape: "the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, and the predictability of the aspect at issue." *Ariad,* 598 F.3d at 1359 (*quoting Capon v. Eshhar,* 418 F.3d 1349, 1359 (Fed. Cir. 2005) (alterations omitted).

In a dangerous expansion of the written description doctrine, the Panel opinion fails to require the PTAB to consider the predictability of the technology at issue. It also incorrectly states that whether the technology that is supposedly

inadequately disclosed is inventive, as compared to conventional, is "irrelevant." Whether the challenged disclosure involves conventional technology is vital, not irrelevant, to a legally proper written description analysis. Predictability is central to the written description analysis because the legal adequacy of describing an invention ***must*** consider whether the alleged inadequacy relates to the insightful advance at the heart of the invention or, rather, a mundane prior art alternative that can be used with such an advance. If the predictability of the technology is not consistently respected as an important input to the written description analysis, the case outcomes will -- like this one -- diverge unreliably and differ unfortunately from panel to panel and judge to judge in many different tribunals.

Over the last few months, in both *Global IP* and *Centrak*, this Court has had to reverse tribunals for failing to apply the *Ariad* predictability analysis. Now a panel of this Court has done so. The Panel opinion thus unnecessarily destabilizes written description law by demanding undue greater disclosure of a routine prior art alternative as though it were an unpredictable wish or plan. That is dangerous to the law.

A. This Court's Written Description Law Demands The Safeguard Of A "Predictability" Analysis

This Court's leading written description case, *Ariad*, states point blank that the "predictability" of the technology at issue must be considered. That principle is

a key safeguard to prevent written description law from swallowing enablement law and unduly depriving inventors of patent protection for the application of their invention to predictable technology identified in their patent.

Just five days before the Panel opinion, this Court in *Global IP* demonstrated exactly how important "predictability" is to the written description analysis by reversing the PTAB's finding of a written description violation for failing to consider the predictability of the technology at issue. *In Re Global IP Holdings*, 927 F.3d at 1377-1378. Specifically, this Court held that the PTAB legally erred because it stated the patent disclosure was insufficient "regardless of the predictability" of the technology that gave rise to the putative violation. *Id.*

The patentee sought to reissue claims by replacing the claim term "thermoplastic" with simply "plastic" to encompass "thermosetting as well as thermoplastics." *Id*. at 1376. The PTAB held that "regardless of the predictability of results of substituting alternatives, or the actual criticality of thermoplastics in the overall invention, [Global's] Specification, as a whole, indicates to one skilled in the art that the inventors had possession only of the skins and core comprising specifically thermoplastic." *Id.* This Court rejected the Board's analysis because "the predictability of substituting generic plastics for thermoplastics in the skins and cellular cores of vehicle load floors is relevant to the written description inquiry."

Id. at 1377. This Court did so without evaluating the quality of the disclosure of plastics in the specification because the failure to consider predictability is such a fundamental legal failure.

In *Centrak*, this Court reversed the district court for granting summary judgment of invalidity for a written description violation. *Centrak*, 915 F.3d at 1367-68. The district court had failed to properly consider the parties' dispute as to the predictability of the aspect of technology at issue. Because that is so central to the written description analysis, this Court instructed the district court to consider it upon remand. *Id.*

Global IP and *Centrak* are fresh reminders of the importance of the consistent consideration of predictability to written description law as a critical safeguard.

B. The PTAB Failed To Properly Consider "Predictability" When It Invalidated The Quake Patent

The Board found a written description violation because it concluded that Quake's disclosure of "random sequencing" is not good enough. However, the Board acknowledged that Quake did "expressly describe[] random sequencing," as the Panel opinion itself recognized. A12; Appx8 ("the '018 Patent discusses random massively parallel sequencing"); Appx14 ("we find that passage B does expressly describe random sequencing"); Appx15 ("'Massively parallel sequencing' is expressly described, as is random sequencing."). The disclosure of random

sequencing is in the description of the invention as an alternative to other means of molecular counting for use with the invention. Appx90 (19:5-7) ("It should be appreciated that methods involving PCR or other amplification are not the only way to detect or enumerate the molecules…").

Because the panel repeatedly found that random sequencing was disclosed by Quake in his description of the claim steps, how then could it find that the disclosure was not sufficient to meet its understanding of the written description requirement?

This is how: The Board failed to properly consider the predictability of random sequencing as a well-known prior art technique. Without mentioning *Ariad,* and without any evidentiary support, or the required analysis, the Board ultimately found that random sequencing was so new that using it with the Quake invention was supposedly a "mere wish or plan":

> [W]e 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).

Appx21-22 (16:24-17:6).

This is an upside-down conclusion and, like the trial courts in *Global IP* and *Centrak*, reflects the increasing disregard for the need to evaluate the predictability of the technology at issue to keep the written description doctrine in balance. Both decisions in this Court (*Centocor* and *Regents*) relied upon by the Board to invalidate Quake's patent involve speculative technology far different from the established and predictable sequencing technology at issue in this appeal that is independent of the inventive aspect of the claims.

Centocor and *Regents* involve unknown biomolecules that were a mere "wish" of the inventors, as illustrated by their failure to identify them in their disclosures. In *Centocor*, "it was entirely possible that no fully-human antibody existed that satisfied the claims." 636 F.3d at 1351. In *Regents*, the claimed

biomolecules were a mere "wish" because they included an undefined genus of mammal and vertebrate cDNA supported only by an identification of a specific sequence of rat insulin. *Regents,* 119 F.3d at 1569.

In dramatic contrast to *Centocor* and *Regents*, the disclosure of random massively parallel sequencing for Quake's invention is not some kind of "wish." Rather, the claimed random sequencing was well-established in the prior art. It is undisputed that the reference in the Quake patent to prior art products offered by Illumina for use in the invention refers to off-the-shelf sequencers for performing massively parallel sequencing that are sold for random sequencing. Appx11 ("Lo also agrees that it was known that Illumina products could perform massively parallel sequencing of randomly selected DNA fragments."). Lo himself admitted that massively parallel sequencing was within the basic competency of those of ordinary skill in the art – and was not some kind of unpredictable or unestablished technology. *See* Appx3987 (¶ 42) and Appx6862 (Fact No. 66) (A person of ordinary skill in the art, by definition, "should understand the operation and application of MPS [massively parallel sequencing] platforms and have significant direct experience at performing and applying these techniques").

The inventive aspect of the invalidated claims is the profound insight that fetal DNA does not need to be isolated from maternal DNA to count whether the fetus has too many chromosomes (aneuploidy) causing abnormalities such as Down's Syndrome. A27 ("Quake also points to Dr. Gabriel's testimony [Lo's expert] that the inventive part of the '018 Patent is using a ***mixed*** maternal and fetal DNA sample to determine aneuploidy").[1] Dennis Lo and the scientific community more broadly struggled unsuccessfully for almost a decade to separate the fetal DNA from maternal DNA to try to evaluate if there were excess chromosomes to help diagnose Down's Syndrome. *See* Appx81 ('018 patent (2:7-9)); Appx1686 ("The key will be an antibody or other compound that can more efficiently separate out the fetal cells"). Until Quake's discovery, no one bucked the conventional wisdom and realized you could perform the analysis without separating out the fetal DNA.

Quake's insight revolutionized prenatal testing after nearly a decade of failed attempts. Indeed, Lo's own expert acknowledged it was "an impressive and surprising finding" that fetal DNA did not have to be separate from the maternal DNA to determine whether there were too many chromosomes. Appx2824 (44:6-19).

[1] As explained further below, the Panel opinion wrongly finds this testimony irrelevant.

The Board's decision that the claimed random sequencing was somehow new and its use in the invention a mere wish or plan failed to consider "the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, and the predictability of the aspect at issue." *Ariad*, 598 F.3d at 1351 (internal quotations omitted). It is an intolerable and growing distortion of written description law to fail to consider the predictability of the technology at issue in the context of the prior art, as required by *Ariad*.

C. The Panel Opinion Failed To Require The Board To Analyze The Predictability Of Random Sequencing, Which Is Indispensable To Its Written Description Analysis

Even though Quake's lead argument on this appeal was the failure of the Board to properly apply the predictability analysis required by *Ariad*, the Panel opinion does not acknowledge that legal requirement. *See* Appellants' Opening Br. at 35-36.

Instead, like the Board, the Panel opinion fails to analyze this mandatory aspect of the written description analysis. It fails to acknowledge the sharp distinction between how well-established random sequencing is in this case versus the unrealized molecules wished for in *Centocor* and *Regents* – even though the Board invoked those cases to justify the invalidation of Quake's patent.

The Panel opinion does not attempt to excuse the Board's – or its own -- failure to consider the *Ariad* predictability analysis. Instead, it states that the Board's reference to a "mere wish or a plan" refers to an unclaimed form of sequencing (targeted) that is different from random sequencing. A21 (the Board was referring to "the use of MPS technology for targeted sequencing").

The Panel opinion is off-point in contending that the Board was speaking of targeted sequencing. *See* Appx22 (17:2-6) and the block indent quote on page 7, supra.

First, the Board's opinion refers expressly to "random massively parallel sequencing" when it compares this case to *Centocor* and *Regents*. *Id.* It is unmistakable that the Board is referring to ***random*** sequencing when it speaks of a supposed "new technology." *Id.* The Board finds that ***random*** sequencing is a "mere wish or plan," not targeted sequencing. *Id.* Second, it would make no sense for the Board to characterize ***targeted*** sequencing as a "mere wish or a plan" in finding a written description violation for inadequately disclosing ***random*** sequencing because it is not claimed, not the technology at issue and not the subject of the Board's "mere wish or plan" paragraph.

In addition, the Panel opinion states that the appeal merely challenged whether statistical analysis using random sequencing was predictable and known. That is part of it, but it was never so limited. The appeal centrally challenged the Board's labelling of the use of random sequencing ***generally*** for the invention as a "mere wish or a plan." Appellants' Opening Br. at 36 ("Central to the Board's error is its conclusion that random massively parallel sequencing is so new that the use of that technology with the Quake invention was a 'mere wish or plan'"). There is no showing that ***anything*** about the use of random sequencing for the invention is beyond predictable, known and routine. Yet, neither the Board nor the Panel opinion considered predictability in its analysis.

Moreover, reminiscent of the Board's faulty analysis in *Global IP*, the Panel opinion states that whether a claim step is inventive or conventional is "irrelevant." A27 ("Finally, whether the Step D [of the patent claims at issue] methods were inventive or not is irrelevant to the issue here; they are still part of the claim and need to be adequately described to satisfy §112."). This is a square misstatement of law. Whether the technology that is supposedly described inadequately is inventive or conventional is an indispensable part of the analysis.

In failing to consider the predictability of random sequencing, and by allowing the Board to characterize routine steps as a "mere wish or plan" without performing the required *Ariad* analysis, the Panel opinion creates a fork in written description law that is destabilizing. As illustrated by this Court's recent decisions in *Global IP* and *Centrek*, the written description doctrine is being applied too broadly and without the required attention to the predictability of the technology. This Court should rehear this case en banc to resolve this conflict in the caselaw.

Dated: August 9, 2019

Respectfully submitted,

By: */s/ Edward R. Reines*

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that this brief complies with the type-volume limitations of Fed. R. App. P. 32(a)(7)(B). This brief contains 2,502 words as calculated by the "Word Count" feature of Microsoft Word 2007, the word processing program used to create it.

The undersigned further certifies that this brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2007 in Times New Roman 14 point font.

Dated: August 9, 2019

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ADDENDUM

United States Court of Appeals for the Federal Circuit

STEPHEN QUAKE, HEI-MUN CHRISTINA FAN,
Appellants

v.

YUK-MING DENNIS LO, ROSSA WAI KWUN CHIU, KWAN CHEE CHAN,
Appellees

2018-1779, 2018-1780, 2018-1782

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. 105,920, 105,923, 105,924.

Decided: July 10, 2019

EDWARD R. REINES, Weil, Gotshal & Manges LLP, Redwood Shores, CA, argued for appellants. Also represented by DEREK C. WALTER.

CHARLES E. LIPSEY, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, Reston, VA, argued for appellees. Also represented by STEVEN O'CONNOR; JEFFREY DANIEL SMYTH, Palo Alto, CA; MICHELE C. BOSCH, Washington, DC.

Before REYNA, CHEN, and HUGHES, *Circuit Judges.*

CHEN, *Circuit Judge*.

This appeal arises from a decision of the U.S. Patent and Trademark Office Patent Trial and Appeal Board (Board) finding the four claims of Dr. Stephen Quake and Dr. Christina Fan's (collectively, Quake) U.S. Patent No. 8,008,018 and Claim 25 of their U.S. Patent Application No. 12/393,833 unpatentable for lack of written description under 35 U.S.C. § 112 as part of three interference proceedings.

The claims cover a method of determining the presence of a chromosomal abnormality (called aneuploidy) in fetuses by using massively parallel sequencing (MPS) technology to sequence deoxyribonucleic acid (DNA) fragments from a sample of the mother's blood that contains both maternal and fetal DNA, identifying what chromosomes those DNA fragments come from based on their sequences, and determining if the test chromosome is over- or under-represented in the sample as compared to a reference chromosome. The claims recite a random MPS method for the detection step, meaning that all of the DNA in the sample is sequenced, as opposed to sequencing specific, targeted sequences. Quake's specification (shared by the '018 patent and the '833 application), however, only expressly describes detection of *target* sequences in its thirty-plus column specification.

The Board issued a first decision in 2015, finding the random MPS claims at issue invalid for lack of written description. That decision was appealed to this court. This court remanded to the Board to correct three errors and redo its § 112 analysis. On remand, the Board found that a citation to a reference and a single sentence in Quake's specification support random sequencing, but that the two, on their own, are insufficient to describe the claimed method of determining fetal aneuploidy through random MPS. The Board also found that the specification did not

describe the final claimed comparison step in terms that would be applicable to random MPS, namely adjusting/normalizing for chromosome size before assessing the over- or under-representation of a chromosome. In this fact-specific case, substantial evidence supports the Board's findings on lack of adequate written description. The Board also did not reopen the record to admit expert testimony from another proceeding, and we find that the Board did not abuse its discretion in not doing so. Accordingly, we affirm.

BACKGROUND

The primary issue on appeal is whether the patent specification shared by the '018 patent and the '833 application sufficiently describes using random MPS to determine fetal aneuploidy, such that it meets the requirements of § 112.

A. Technology and Patents

Humans are normally born with twenty-three pairs of chromosomes. Chromosomal aneuploidy describes the condition where a fetus is born with either an abnormally high or low number of chromosomes. For example, Down syndrome is the presence of an extra chromosome 21. Historically, testing for fetal aneuploidy required invasive and risky procedures. One such procedure, amniocentesis, involves sampling amniotic fluid from the womb with a needle. Alternative non-invasive methods existed, but their accuracy was suboptimal.

The two competing inventors in the underlying interferences on appeal—Stanford Professor Quake and Chinese University of Hong Kong Professor Dennis Lo—both developed methods for diagnosing aneuploidies using cell-free fetal DNA (cff-DNA) from maternal blood samples. In 1997, Lo and a colleague discovered that cff-DNA circulates in maternal blood in small amounts. This discovery made possible new prenatal screening techniques for chromosomal and other abnormalities, but researchers developing

techniques for assaying cff-DNA had to overcome interference from maternal DNA in the maternal blood sample.

Both Quake's and Lo's inventions, which are at the center of the interferences here, involve successful use of *mixed* maternal and fetal DNA samples to determine fetal aneuploidy. Assuming the mother does not have aneuploidy, aneuploidy in the fetus would affect the mother's blood sample such that the ratio between the amount of any given normal chromosome to the abnormal chromosome would no longer be 1:1.

Additionally, both inventions incorporate MPS technology, which allows for sequencing of large amounts of DNA samples simultaneously. When a sequence is long enough, it can be uniquely identified as originating from a certain chromosome. Counting how many sequences come from various chromosomes is useful for determining over- or under-representation of a chromosome, thereby determining the presence of fetal aneuploidy. MPS can be performed by "random" or "targeted" methods. In the random format, all DNA in a sample is amplified, then sequenced. In the targeted format, only the target sequence(s) are amplified, then sequenced.

Quake is the named inventor of the '018 patent. The patent's "Brief Summary of the Invention" states that the "present invention is directed to a method of differential detection of *target* sequences in a mixture of maternal and fetal genetic material." '018 patent, col. 4 ll. 43–45 (emphasis added). The '018 patent specification outlines four steps in the method: (1) obtaining a maternal tissue sample, preferably blood; (2) distributing single DNA molecules from this sample to a number of discrete reaction samples; (3) "[d]etecting the presence of the *target* in the DNA in a large number of reaction samples"; and (4) performing "[q]uantitative analysis of the detection of the maternal and fetal *target* sequences." *Id.* at col. 8 l. 35–col. 9 l. 6

(emphasis added); *see also id.* at col. 4 l. 39–col. 6 l. 60 ("Brief Summary of Invention").

The '018 patent specification consistently focuses on detection of targeted sequences, using the term "target" more than sixty times throughout the patent. *See, e.g.*, *id.* at col. 7 l. 62–col. 8 l. 17 (In Fig. 1A, "[s]hown in the wells are *targets* representing chromosome 21 and 22," "no *target* DNA is found" in well 2A, "[a] single run will have numerous random variations, such as wells that have no *target* sequence," "samples with no *target* will clearly result in no peak at all," and "wells with two or more *targets*[] will give peaks significantly higher.") (emphases added); col. 8 l. 35–col. 9 l. 6 ("[T]he number of reaction samples is selected to give a statistically significant result for the number of copies of a *target* in the DNA molecules;" "[d]etecting the presence of the *target* in the DNA in a large number of reaction samples;" "[q]uantitative analysis of the detection of the maternal and fetal *target* sequences," which in "some case cases . . . may include *targets* to different regions, such as probes to a *target* on a chromosome suspected of being present in an abnormal copy number (trisonomy) compared to a normal diploid chromosome, which is used as a control.") (emphases added); col. 11 ll. 40–43 (For digital PCR, "[a] reaction sample in general will contain a single template molecule (haplotype), two *target* molecules (diploid) or three *target* molecules (trisomy).") (emphases added); col. 14 ll. 27–28 (describing detection through digital PCR via "probes[] which become fluorescent on binding to the *target* sequence(s)") (emphasis added); col. 12 ll. 28–30, col. 19 ll. 10–12, 51–52 (describing detection by sequencing, including MPS, as "carried out by directly sequencing a region of interest to determine if it is the *target* sequence of interest," "sequenc[ing] the *target* sequence in the reaction sample directly," "sequenc[ing] . . . by labeled probes to detect a *target specific* sequence," and "[l]onger sequences [being able to] uniquely identify more particular *targets*") (emphases added); col. 21 ll. 8–12 (explaining the quantitative

analysis step as follows: "[i]f chromosome A is euploid and represents an internal control, and chromosome B is aneuploid and is the *target* to be measured, then one can amplify representative segments from both chromosomes via digital PCR" and "the number of *target* sequences needed for statistical[ly significant] sequences may be reduced by using controls sequences") (emphases added); col. 22 ll. 26 (providing "[e]xamples of diseases where the *target* sequence may exist" in one copy in the maternal DNA, but with two copies in the fetal DNA) (emphasis added); col. 25 ll. 49–col. 28 ll. 43 (describing an exemplary detection method with two target sequences: amyloid for test chromosome 21 and GAPDH for control chromosome 12).

The specification states that the digital polymerase chain reaction (PCR) technique is the preferred embodiment for amplifying and detecting target sequences. *See id.* at col. 12 ll. 18–20. In digital PCR, a mixed maternal and fetal DNA sample is distributed amongst thousands of reaction wells. Known target DNA sequences—usually one sequence from a reference chromosome and one sequence from the chromosome being tested for aneuploidy—are amplified by target-specific primers located in those wells. If either target sequence is present in any particular individual reaction well, it will be amplified by PCR (positive result); if no target sequence is present in the reaction well, no sequence will be amplified (negative result). *Id.* at col. 8 ll. 52–56. The reaction wells are then tested for the presence of the target sequences. *Id.* at col. 7 l. 62–col. 8 l. 9.

The specification also identifies some alternative detection methods to digital PCR, one of which is MPS. *Id.* at col. 19 ll. 5–12. Only two paragraphs in the thirty-plus columns in the specification relate to MPS. *Id.* at col 19 l. 48–col. 20 l. 20. This appeal focuses on the content of those two paragraphs; the relevant text is reproduced in the discussion below.

Either technique, digital PCR or MPS, can be used to count the number of chromosomes containing the targeted sequence versus the number of chromosomes containing the reference chromosome sequence in the sample. The '018 patent specification describes using this molecular counting data to run statistical analysis. *Id.* at col. 21 ll. 1–45. The number of positive results from each target sequence leads to a ratio of the reference and test chromosomes. *Id.* If the ratio of the two chromosomes is not 1:1 and the deviation is statistically significant, the fetus is determined to have aneuploidy. *See, e.g.*, *id.* at col. 28 ll. 5–25 (Table 1). The specification describes running a "Student's T-test" and z-test/chi-squared test to analyze the statistical significance of a deviation from the expected 1:1 ratio. *Id.* at col. 5 l. 64–col. 6 l. 3, col. 28 ll. 5–34.

Quake claimed his method of determining fetal aneuploidy by detecting target sequences in an application filed on February 2, 2007, and filed a continuation as Application No. 12/393,803 in February 2009. The original claims of Quake's '803 application explicitly recited methods that required the detection of "target sequences." In 2011, Quake split the '803 application into multiple applications. In the application which later issued as the '018 patent, Quake canceled all pending claims and added new claims covering the use of random MPS to determine fetal aneuploidy. J.A. 4134–42. Representative issued claim 1 recites:

> 1. 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.

'018 patent, col. 33 ll. 48–67. Claim 25 of Application No. 12/393,833, another application that continued from the '803 application, also recites using random MPS to determine fetal aneuploidy.

Also in 2007, Lo, along with Rossa Wai Kwun Chu and Kwan Chee Chan (collectively, Lo), filed a patent application that undisputedly describes and claims a method of using "random" MPS to determine fetal aneuploidy. The application was published in 2009. Lo's application is devoted to, and describes in considerable detail, randomly sequencing the entire sample via MPS after fragmentation and division. *See* J.A. 4159–60; *see also, e.g.*, J.A. 4154–59 ¶¶ 14, 21, 48, 55, 58, 67, 70–71 (repeatedly stating that "a fraction of the [whole] genome" in the sample is sequenced). The sequencing data is mapped, based on known sequences of the human genome, to determine which chromosome each sequenced fragment is from. However, since some chromosomes are longer and would contribute more fragments to the random sample, Lo's application explains that

a skilled artisan would need to adjust for chromosome size, i.e., normalize the data by the length of each chromosome, before being able to accurately determine the presence of fetal aneuploidy. *See* J.A. 4158 ¶¶ 69–70. Lo filed U.S. Provisional Application No. 60/951,438 describing this method on July 23, 2007, and subsequently filed U.S. Patent Application Nos. 13/070,275, 12/178,181, 13/070,240, 12/614,350, 13/070,251, and 13/417,119 on the same invention.

B. Procedural History

Both Quake and Lo requested interferences to determine who first invented the random MPS method and when the method was invented. In early 2013, the Board declared three interferences between Quake's patent and application and Lo's applications.[1] In each proceeding, Lo attacked the claims of Quake's '018 patent or '833 application as unpatentable for lack of written description. Although the '018 patent specification is over thirty columns, MPS is discussed in just two paragraphs at columns 19 to 20. In Quake's view, these two paragraphs not only teach MPS as a sequencing tool, but also describe a second detection methodology—i.e., random sequencing—distinct from targeted sequencing. The Board, however, disagreed with Quake and granted Lo's written description motions in all three interferences and, in 2015, found Quake's claims unpatentable for lack of written description.

Quake appealed the Board's decisions to the U.S. District Court for the Northern District of California under 35

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[1] Interference No. 105,920 involved Lo Application No. 13/070,275 and the '018 patent. Interference No. 105,923 involved Lo Application Nos. 12/178,181, 13/070,240, 12/614,350, and 13/070,251 and Quake's '833 application. Interference No. 105,924 involved Lo Application No. 13/417,119 and Quake's '833 application.

U.S.C. § 146. Some expert discovery took place before the case was removed to this court once the law mandated that the district court lacked jurisdiction to review the Board's interference decisions. *See Biogen MA, Inc. v. Japanese Found. for Cancer Research*, 785 F.3d 648 (Fed. Cir. 2015) (holding that this court has exclusive appellate jurisdiction over Board decisions), *cert. denied*, 136 S. Ct. 1450 (2016).

In 2017, this court vacated the Board's 2015 decisions and remanded with instructions for the Board: (1) to consider whether the patent's written description at columns 19 to 20 discloses random MPS, as opposed to the Board's 2015 finding that the description in those columns "does not preclude targeted MPS"; (2) to explain the meaning of various phrases in that portion of the patent specification, including "using attachment of randomly fragmented genomic DNA," "solid phase amplification," "~1,000 copies of template," "templates," and "[t]hese templates are sequenced using four-color DNA sequencing-by-synthesis technology"; and (3) to examine whether a skilled artisan would have known, as of the priority date, that the specification's reference to Illumina products meant random MPS sequencing based on record evidence describing Illumina products or any other random MPS products existing as of the filing date. *Bd. of Trs. of Leland Stanford Junior Univ. v. Chinese Univ. of Hong Kong*, 860 F.3d 1367, 1377–79 (Fed. Cir. 2017).

On remand, the Board held a conference call with the parties and issued an order declining to reopen the record, in relevant part denying Quake's request for admission of testimony by Lo's expert from the terminated district court proceedings. J.A. 7576–620; Interference No. 105,920, Order–New Briefing and Evidence 37 C.F.R. § 41.104(a) (December 12, 2017). The Board issued its remand decisions on December 20, 2017. J.A. 6, 31, 53. The Board's analysis was substantively identical in each interference, so for purposes of this appeal, we refer primarily to the Board's

findings as to the '018 patent and treat them as representative of the Board's findings as to the '833 application.

In its decisions, the Board first followed this court's instructions. It focused on whether the '018 patent describes random MPS, rather than on whether its written description does not preclude targeted MPS. The Board explained the various phrases in the two MPS-related paragraphs at columns 19 to 20 in the specification as describing MPS generally, without reference to targeted versus random MPS. The Board also credited an admission from Lo that "Illumina sequencing platforms [referenced in column 19 of the '018 patent specification] can perform either random or targeted DNA sequencing, depending on whether predetermined target DNA fragments are specifically identified or targeted prior to sequencing," but found no record evidence of the Illumina products' capabilities as of the date of invention. J.A. 11.

The Board then looked elsewhere in the two MPS paragraphs of the '018 patent specification for evidence of written description of the '018 claims:

> [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 Illumina, 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."*
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> [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. illustrative of software methods that can be used to identify a sequence in comparison to the known genome sequence. See, also Zhu et al., describing a single-molecule-based technology for studying mRNA.

J.A. 9–10, 14 (quoting '018 patent, col. 19 l. 59–col. 20 l. 20 and referring to the first paragraph as Passage A and the second paragraph as Passage B) (emphases added).

The Board found that the citation to Balasubramanian in Passage A "provides some[] disclosure of massively parallel sequencing of DNA fragments selected randomly" based on the testimony of Lo's expert, Dr. Gabriel. J.A. 13 (citing J.A. 2828 (Gabriel Depo. at 60:18–22)). The Board then found that Passage B "expressly describe[s] random sequencing" because it uses the phrase "random sequence information" in the sentence "about 30 bp of random sequence information are needed to identify a sequence as belonging to a specific human chromosome." '018 patent, col. 20 ll. 7–9.

But the Board subsequently found that Balasubramanian and the "30 bp of random sequence information are needed to identify a sequence" sentence are not sufficient to meet the requirements of § 112. The Board characterized passages A and B as providing "*some* express description of individual elements recited in Quake's claims," but found these disclosures "[in]sufficient to have demonstrated [to a skilled artisan] that the inventors were in possession of a method of determining fetal aneuploidy with

random massively parallel sequencing as claimed by Quake." J.A. 15 (emphasis added).

Specifically, the Board found that although the "the express language describes some of the elements of the claimed method, . . . it is not sufficient to provide a written description under 35 U.S.C. § 112" because the '018 patent (1) "does not tie these elements together into a complete method" and (2) "does not explain how to use the data from random massively parallel sequencing of a mixture of genomic DNA to determine fetal aneuploidy." *Id.* First, the Board contrasted the scant information in the '018 patent regarding random MPS to the thirty columns of detailed, step-by-step description of targeted detection and targeted MPS, tying the steps together into a complete method. J.A. 15–17. Second, the Board explained that nothing in the '018 patent suggests to a skilled artisan to adjust for chromosome size when doing the comparison claimed in step D—a statistical normalization step necessary when using random MPS data to determine the presence or absence of aneuploidy, as disclosed in Lo's applications and explained above. J.A. 17–22. Quake argued that a skilled artisan would have known *how* to do so, but the Board found that "Quake did not direct [it] to a portion of the '018 patent that describes the *need* to do so," and therefore, a skilled artisan "would not have considered that the inventors of the '018 patent contemplated a method requiring" normalizing for chromosome size. J.A. 21 (emphasis added).

As in its 2015 decision, the Board again granted Lo's written description motions and found Quake's claims unpatentable.

Quake appeals both the Board's written description findings and its decision not to admit testimony from the

district court proceedings. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(4)(A).[2]

DISCUSSION

I.

Compliance with the written description requirement of § 112 is a question of fact, judged from the perspective of a skilled artisan as of the patent's filing date. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1355 (Fed. Cir. 2010) (en banc). Accordingly, in an appeal from the Board, this court examines whether the Board's decision is supported by substantial evidence. *Harari v. Lee*, 656 F.3d 1331, 1341 (Fed. Cir. 2011). "A finding is supported by substantial evidence if a reasonable mind might accept the evidence to support the finding." *Redline Detection, LLC v. Star Envirotech, Inc.*, 811 F.3d 435, 449 (Fed. Cir. 2015) (citation omitted).

"The essence of the written description requirement is that a patent applicant, as part of the bargain with the public, must describe his or her invention so that the public will know what it is and that he or she has truly made the claimed invention." *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1298 (Fed. Cir. 2014). The written description requirement is satisfied if the inventor "convey[s] with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention,' and demonstrate[s] that by disclosure in the specification of the patent." *Centocor*

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[2] This court has exclusive jurisdiction over an appeal from a decision of the Board in an interference declared after September 15, 2012 pursuant to the version of 28 U.S.C. § 1295(a)(4)(A) as it existed on September 15, 2012. *Biogen*, 785 F.3d at 654; Technical Corrections—Leahy-Smith America Invents Act, Pub. L. 112-274, 126 Stat. 2456 § 1(k)(3).

Ortho Biotech, Inc. v. Abbott Labs., 636 F.3d 1341, 1348 (Fed. Cir. 2011) (quoting *Carnegie Mellon Univ. v. Hoffmann–La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008)).

"[T]he purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not," and the requirement is particularly important when, as here, claims are added later during prosecution in response to development by others. *Agilent Techs., Inc. v. Affymetrix, Inc.*, 567 F.3d 1366, 1383 (Fed. Cir. 2009). Here, the first time Quake tried to cover random MPS with this specification was after the publication of Lo's patent application directed to random MPS: Quake then canceled all his pending claims and replaced them with claims covering random MPS, creating a mismatch between the claims and the originally filed specification.

An invention is usually expressly described in the specification; there is no reasonable argument for that being the case here. Though the Board found some express disclosure of two elements of the claimed invention in Passages A and B, the term "random MPS" is never mentioned in the '018 patent, the process of amplifying all the DNA in a sample before sequencing is never described, and Quake admits that there is no embodiment describing the statistical analysis needed to determine fetal aneuploidy from data generated by random MPS. Oral Arg. at 9:39–53. The method as a whole is not expressly described.

However, "*ipsis verbis* disclosure is not necessary to satisfy the written description requirement of section 112." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570 (Fed. Cir. 1996). "[T]he disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question." *Id.* This court has analogized such a disclosure as "mark[ing] trails by making blaze marks on . . . trees" to "find[] one's way through the woods" of a specification such that a skilled artisan would

be able to follow that trail and understand what the inventors had invented. *In re Ruschig*, 379 F.2d 990, 994–95 (CCPA 1967). The Board made such an inquiry here.

We address the Board's findings as to the Balasubramanian citation in Passage A and the single sentence in Passage B, and then its treatment of the chromosome size adjustment necessary for claimed step D.

We find that there is substantial evidence for the Board's finding that Balasubramanian supports random MPS and clarify that the record indicates that Balasubramanian also supports targeted MPS.

Balasubramanian is directed to a method of MPS that involves immobilizing polynucleotides (e.g., DNA) to an array and sequencing the polynucleotides to detect differences between sequences. U.S. Patent Publication No. 2003/0022207 A1 at Abstract. In particular, the publication focuses on finding single polynucleotide polymorphisms (SNPs). *See, e.g.*, *id.* at ¶¶ [0006], [0034], [0069], [0070]. SNPs tend to occur at unique locations, so identifying them in DNA samples can indicate which chromosome the polynucleotide belongs to. Significantly, the amplification step that differentiates targeted and random MPS[3] is a preparatory step in the Illumina methods that comes before any of the steps disclosed in Balasubramanian. J.A. 5763. Consequently, as Lo's expert Dr. Gabriel explains, the teachings of Balasubramanian could be used in either random or targeted MPS, depending on the nature of the preceding amplification step. *Id.*

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[3] As explained above and in our previous opinion, the main difference between random and targeted MPS is that in targeted MPS, the target sequence(s) are specifically amplified before sequencing, whereas in random MPS, all DNA in the sample is amplified. *Stanford*, 860 F.3d at 1370.

So, while we agree with Quake and the Board that Dr. Gabriel admitted that Balasubramanian "supports randomly massively parallel sequencing," J.A. 2828, record evidence cited by the Board establishes that Balasubramanian supports targeted sequencing as well. Dr. Gabriel stated that "Balasubramanian discloses *both* targeted and random sequencing approaches." J.A. 5763 (emphasis added). The Board previously credited this testimony when discussing Illumina products based on the Balasubramanian technology.[4] *Stanford*, 860 F.3d at 1372–73 (noting that the Board relied on "Dr. Gabriel's statement that the Illumina platform referenced in the specification could be used for both random and targeted sequencing"). The Board also cited to this fact in the decisions now on appeal. J.A. 11, 36, 58 (citing a "Material Fact" in Lo's motions that "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" (emphasis added)).[5] Further, as Lo points out, the Balasubramanian reference is cited in the '018 patent specification for "sequenc[ing] using four-color DNA sequencing-by-synthesis technology," a statement applicable to sequencing generally, rather than random versus targeted sequencing. '018 patent, col. 19 l. 65–col. 20 l. 3; Oral Arg. at 22:04–22.

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[4] The '833 application notes that "the assignee of the Balasubramanian PG Publication, Solexa, was acquired by Illumina," and that Balasubramanian's teachings form a partial basis of Illumina's commercial sequencing system described in the Quake's specification. J.A. 4330 n.2.

[5] There is no evidence in the record that skilled artisans disputed that MPS could be used in either random or targeted sequencing approaches at the time of filing of Quake's patent application.

In sum, we agree with the Board that the citation to Balasubramanian in Passage A "provides some . . . disclosure of massively parallel sequencing of DNA fragments selected randomly," J.A. 13, but note, in line with the Board's other findings, that skilled artisans would have understood the specification to support targeted MPS as well, *see* J.A. 11–12 (Board rejecting Quake's argument that "passage A does not describe targeted sequencing and therefore must describe random sequencing"). Our previous decision did not reject a finding that Quake's specification supports targeted sequencing; rather we explained that Quake's description "might be able to disclose both random and targeted sequencing" and therefore directed the Board on remand to "examine whether a [skilled artisan] 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." *Stanford*, 860 F.3d at 1378, 1379. That a skilled artisan would understand Balasubramanian to support targeted sequencing as well makes the Quake specification's citation to Balasubramanian consistent with the rest of its discussion of *detecting* target sequences.

As for the disclosure of Passage B, the Board does not cite to any record evidence that a skilled artisan would understand the sentence—"about 30 bp of random sequence information are needed to identify a sequence as belonging to a specific human chromosome"—as referring to random MPS. First, the Board found elsewhere that simply using the word "random" is not enough to indicate random MPS. *See* J.A. 11 (finding that the phrase "randomly fragmented genomic DNA" from Passage A is "not necessarily the same" as the phrase referring to random MPS in the claims). Second, the 30 bp statement precedes the sentence, "Longer sequences can uniquely identify more particular *targets*," indicating that the 30 bp language covers identifying the chromosomes of origin for DNA fragments generated through *targeted* MPS. '018 patent, col. 20 ll. 9–

10 (emphasis added); J.A. 4755, ¶ 80 (Lo's expert stating the 30 bp "statement refers to the minimum size of a unique target sequence in the genome for use in amplification, particularly given the statements in the following sentence[]"). But the passage could also cover identifying the chromosomes of origin for DNA fragments generated through *random* MPS. We agree with the Board that the 30 bp sentence is more generally "about the number of base pairs needed to identify the chromosomal origin of a sequence." J.A. 16. There is no indication in the record that the length of a sequence needed to identify the chromosome of origin is any different for DNA fragments sequenced via random and targeted MPS.

However, given the specification's repeated discussion of targeted sequencing, a bare citation to Balasubramanian and use of the phrase "about 30 bp of random sequence information are needed to identify a sequence" in the context of this patent would be a highly elliptical, cryptic way to communicate possession of a second method of sequencing to determine fetal aneuploidy. An alternative explanation consistent with the entire patent specification is that Quake invented using targeted MPS for determining fetal aneuploidy and wrote the '018 patent specification to describe targeted MPS, among other ways of performing targeted detection such as digital PCR. Balasubramanian was cited in Passage A to support a sentence describing detection via sequencing with four-color DNA sequencing-by-synthesis technology. That method of detection would result in a ratio of two targeted sequences that would be analyzed, as described in the specification, for statistically significant deviations from a 1:1 ratio to determine fetal aneuploidy. '018 patent, col. 21 ll. 1–45, col. 28 ll. 5–34.

In light of the limited disclosure value of the single Balasubramanian citation and the "about 30 bp of random sequence information are needed to identify a sequence" sentence, substantial evidence supports the Board's finding that those two items together are not adequate to

convey using random MPS to determine fetal aneuploidy as claimed. In terms of *Ruschig*'s analogy of the written description requirement being akin to creating a trail through the woods, the two are (at most) faint "blaze marks" for determining fetal aneuploidy by random MPS, while the rest of the specification marks a clear trail to targeted MPS. *Ruschig*, 379 F.2d at 994–95.

As for claim step D, as the Board recognized, if the '018 patent had contained some description of adjusting for chromosome size when comparing the data resulting from the MPS step, then a skilled artisan may have had an indirect, but clear indication that the inventor contemplated a method of using random MPS to determine fetal aneuploidy. But the '018 patent only describes statistical analyses, such as a "Student's T-test" and z-test/chi-squared test, in the context of assessing divergence from a 1:1 ratio between a targeted sequence and a sequence from a reference chromosome. '018 patent, col. 5 l. 64–col. 6 l. 3, col. 28 ll. 5–34. There is no discussion of adjusting for chromosome size before performing those statistical analyses. We agree with the Board that "[i]n the absence of a description of such analysis, [the] teachings in the specification about [the Balasubramanian] equipment *useful* for random massively parallel sequencing and techniques for determining sequences are not sufficient to demonstrate possession of the claimed method." J.A. 21 (emphasis added).

On appeal, Quake incorrectly characterizes the Board's decision as finding that all but the normalization for chromosome size in claim step D are disclosed in the '018 patent and then focuses solely on why the Board's step D finding should be reversed. Lo counters, and we agree, that the Board's findings did not go so far. The Board found no express description or sufficient blazemarks of the claimed method as a whole and also relied on the chromosome size adjustment issue as a key missing disclosure that could have cured Quake's written description problem. Under

this understanding of the Board's decision, we reject each of Quake's six specific arguments.

First, Quake argues that conducting statistical analysis on random MPS data was known and predictable, and not a "mere wish or plan" as in *Centocor Ortho Biotech*, 636 F.3d 1341, 1351 and *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997). The Board cites to these two decisions when concluding that "the inventors had only 'a mere wish or plan' to use this new technology in their invention." J.A. 22. We understand this statement as characterizing the two-paragraph, very-brief suggestion of using MPS (as an alternative to digital PCR) in the '018 patent as a "mere wish or plan" to use MPS in its method of detecting *targeted* sequences, such that the details could be filled in by a skilled artisan. But that view as to the use of MPS technology for targeted sequencing is consistent with the Board's core finding that the patent fails to reasonably convey using MPS to detect the chromosomal origin of "DNA fragments *randomly selected* from the mixture of fetal and maternal genomic DNA" to determine the presence or absence of fetal aneuploidy, as claimed. '018 patent, col. 33 ll. 48–67.

Second, Quake argues that the normalization (chromosome size adjustment) details necessarily required for using random MPS data to perform the comparison step claimed in step D are unclaimed limitations and thus did not need to be described to satisfy § 112. The language of claim step D requires using the data from random MPS (recited in claim steps B and 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*." '018 patent, col. 33 ll. 59–67 (emphases

added). Quake argues that the claim language only requires a comparison of two chromosome amounts to determine aneuploidy and cites three passages from the specification as disclosing how to conduct such a comparison:

> Quantitative analysis of the detection of the maternal and fetal *target sequences*. In some cases this may include *targets* to different regions, such as probes to a *target* on a chromosome suspected of being present in an abnormal copy number (trisonomy) compared to a normal diploid chromosome, which is used as a control.

Id. at col. 9 ll. 1–6 (emphases added).

> A control sequence is used to distinguish an abnormal increase in the *target sequence*, e.g., a trisonomy. Thus there is a differential detection of *target sequences*, one of which is chosen to represent a normal genotype present in both mother and offspring, and one of which is chosen for detection of an abnormal genotype in the offspring, where the *target sequence* in the offspring will be different from that of the mother, e.g. in trisomy.

Id. at col. 7 ll. 54–61 (emphases added).

> The presence or absence of different *target sequences* in the discrete samples is detected; and the results are analyzed whereby the number of results from the discrete samples will provide data sufficient to obtain results distinguishing different *target sequences*. In one aspect, the method involves an analysis of a trisomy. In this method, one of the different *target sequences* (e.g. chromosome 21) is diploid in maternal genetic material and aneuploid in fetal genetic material and another of the different target sequences (e.g. chromosome 12) is diploid in both maternal and fetal genetic material.

Id. at col. 5 ll. 21–31 (emphases added). These passages specifically recite comparison of "target sequences," which cannot be random MPS. And we disagree with Quake's understanding that the Board required disclosure of the normalization step to show written description of the claimed method. Rather, the Board found that to establish possession of random MPS for determining fetal aneuploidy, such a disclosure would have helped communicate possession of the claimed subject matter, given that the specification lacks an express disclosure of the random sequencing-based invention. J.A. 17. This is because the normalization step is relevant for data generated from random sequencing and not targeted sequencing. J.A. 17–18.

Third, Quake argues that because the claim language does not require normalizing for chromosome size, the alleged lack of disclosure is more of an enablement issue than a written description issue. But the Board cited the lack of disclosure not because normalization is required by the claim language of step D, but because disclosure of normalization would have conveyed to a skilled artisan reading the specification that the inventor contemplated a comparison step for a random sequencing method, in addition to the specification's very clear disclosure of a comparison step for a targeted sequencing method. This missing description could have provided a supporting blazemark, but without it, there is no description of "using the data of step c)" obtained by random MPS to compare chromosomal amounts and "determin[e] the presence or absence of . . . fetal aneuploidy." '018 patent, col. 33 ll. 59–67 (claim 1, step D).

Fourth, Quake argues that the need to normalize random MPS results was known to a skilled artisan in 2007 and therefore not necessary to describe in the specification. Appellants' Op. Br. 38, 43–44 (characterizing it as an implementation detail that did not need to be described); Appellants' Reply Br. 8, 10 (same); Oral Arg. at 7:01–03 (same). Quake argues that MPS (generally) was known in

the art, that a skilled artisan would recognize that the 1:1 ratio analysis detailed in the specification would not work for random sequencing without modification due to differences in chromosome sizes, and that a skilled artisan would resort to their knowledge of normalization to fill in the details. Appellants' Op. Br. 44. The Board agreed that a skilled artisan would have known how to normalize the random sequence data to account for chromosome size *if the artisan understood that there was a need to do so*—i.e., if the artisan understood that using random MPS to determine fetal aneuploidy was being described by the rest of the written description. J.A. 21. As explained above, the Board reasonably found that the Balasubramanian citation and the "about 30 bp of random sequence information are needed to identify a sequence" sentence are not adequate to do so.

Fifth, Quake argues that the statistical steps described in the '018 patent are sufficient to describe step D. The disclosure explains, in the context of a simplified digital PCR example, that one expects to find an increased number of amplified DNA fragments corresponding to an abnormal chromosome compared to a normal chromosome. '018 patent, col. 21 ll. 4–21. Quake argues that a skilled artisan would have understood this passage to describe the concept of using molecular counting and basic statistical analysis to assess over- or under-representation of the test chromosome in the DNA, indicating aneuploidy. However, there is no explicit discussion of normalizing the molecular counting data, i.e., adjusting the statistical analysis for chromosome size. J.A. 20–21. And the issue of whether a skilled artisan would have thought to do so turns on the strength of the blazemarks disclosing random MPS in Passages A and B, which we explain above are insufficient for a skilled artisan to recognize.

Finally, Quake argues that the Board erroneously shifted the burden of proof from Lo to Quake by "not identifying any evidence submitted by Lo, or otherwise present

in the record, that a person of ordinary skill in the art would have been unable to recognize promptly the need for this basic [chromosome size adjustment/normalization] step to be performed." Appellants' Op. Br. 46. The Board noted in its 2015 decisions that "[t]o prevail, Lo must provide sufficient evidence to persuade us that the Quake '018 patent is so lacking of written description that one of skill in the art at the time would not have recognized the invention Quake claims." J.A. 1007, 1034, 1063. On remand, the Board determined that step D of Quake's claims was not supported by the '018 patent specification based on Lo's arguments and expert testimony explaining that random MPS requires normalization for chromosome size and explaining why the '018 patent does not describe such analysis. J.A. 17–22. We do not find that the Board erroneously shifted the burden of proof here.

II.

Quake also argues that the Board erred by refusing to admit expert testimony from the terminated district court proceedings into the record. According to Quake, Dr. Gabriel (Lo's expert) made key admissions on the issue of whether there was adequate description of claim step D.[6]

This court already characterized the district proceeding as a "nullity" and declined to consider evidence from it in the previous appeal. *Stanford*, 860 F.3d at 1374–75. We did however leave it "up to the Board to decide whether it wishes to reopen the record" on remand if it believed that

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[6] Lo argues that we should reject this argument because Quake did not present it to the Board. Appellee's Br. 54. But Quake raised the issue both in a conference call with the Board after this court's remand and in its rehearing request. Interference No. 105,920, Order–New Briefing and Evidence 37 C.F.R. § 41.104(a) (December 12, 2017); J.A. 7741–42. We do not find waiver of this issue.

"new evidence may have been developed in the district proceedings," and specifically "express[ed] no opinion on whether it should do so." *Id.* at 1375.

On remand, the Board considered and then decided not to reopen the record. We review that Board decision regarding management of its permissive rules governing trial proceedings for abuse of discretion. *Redline Detection, LLC v. Star Envirotech, Inc.*, 811 F.3d 435, 442 (Fed. Cir. 2015). Quake argues that this case is like *Ultratec*, where we found such abuse when (1) the proffered testimony was inconsistent with the same witness's testimony already in the record (both for substantive and credibility purposes); (2) there was no reviewable transcript of a conference call during which the Board discussed the issue with the parties; and (3) the Board provided no written, reviewable reasoning for why it did not allow the evidence into the record. *Ultratec, Inc. v. CaptionCall, LLC*, 872 F.3d 1267, 1272–1275 (Fed. Cir. 2017). None of these issues are present here.

First, the testimony that Quake argues should have been considered is not inconsistent to the extent it would bear on the substance of Dr. Gabriel's reasoning or her credibility. One excerpt reads:

> Q. So the written description issue you have with Step D of Claim 1 relates to the fact that the data comes from Step C, not anything else in Step D, right?
>
> A. Step B and C.
>
> Q. Step B and C, okay. But nothing else in Step D. It's not the comparison in Step D that's the problem, right? Because that's described throughout the patent specification.
>
> A. Yes.

J.A. 12835. This testimony is consistent with what Dr. Gabriel and Lo have been arguing all along and what the Board found: the written description issue with step D results from the recitation of random MPS data in preceding steps B and C. "[N]othing else . . . in Step D [is] the problem" in that step D is adequately described for analyzing data resulting from methods such as digital PCR or targeted MPS and would be adequately described for analyzing data from random MPS, if obtaining data via random MPS (Steps B and C) was expressly described in the specification.

Quake also points to Dr. Gabriel's testimony that the inventive part of the '018 patent is using a *mixed* maternal and fetal DNA sample to determine aneuploidy, while admitting that the "digital analysis techniques discussed in the '018 patent" were known. J.A. 12838–39. Quake argues that this would explain "why a skilled artisan would understand the invention is possessed by Quake even if unclaimed details of embodiments of the invention were not expressly spelled out for known sequencing methods." Appellants' Op. Br. 53. As an initial matter, as Lo points out, this excerpted testimony refers expressly to using "digital analysis techniques" and "digital analytic methods" to conduct aneuploidy detection, which is digital PCR, not random MPS. Appellees' Br. 58–59. Further, this testimony is not inconsistent; it is inapposite. An admission that MPS was generally known does not address whether the '018 specification describes using random MPS to determine fetal aneuploidy. Finally, whether the step D methods were inventive or not is irrelevant to the issue here; they are still part of the claim and need to be adequately described to satisfy § 112.

Second, there is a transcript of the conference call between the Board and parties here, J.A. 7576–620, and the Board provided written reasoning for its decision. The Board issued an Order explaining in detail why it would not reopen the record, pointing out that (1) "[n]either party

argued . . . that it lacked an opportunity to present evidence during the interference"; (2) Quake did not provide a "sufficient reason to give either party a second chance to present evidence on the same issues that were originally before the Board"; (3) "Quake did not provide a persuasive reason why the arguments and evidence it made in opposition to Lo's original motions were not complete during the interference"; and (4) "Quake did not explain how allowing additional evidence at this point in the proceeding will lead to a more 'just, speedy, and inexpensive' resolution of the proceeding." J.A. 7574. Quake did not seek rehearing of the Board's decision in the Order. J.A. 7741.

Third, the Board again wrote out its reasoning for why it did not admit the testimony in denying Quake's requests for rehearing of the final written decisions now on appeal. J.A.7740–42. In those requests, Quake asked the Board to reopen the record to add a specific part of Dr. Gabriel's district court testimony regarding *Lo*'s statistical analysis disclosure and argued that it would be a denial of due process not to do so. The Board denied that request because it found the testimony irrelevant to *Quake*'s written description. J.A. 7741–42. The Board also found that "[b]ecause Quake has failed to show why it did not have a full and fair opportunity to present evidence and argument with its original briefs, including from the cross-examination of Dr. Gabriel conducted during the interference, it is not clear what due process was denied." *Id.*

In sum, we find that the Board was within its discretion to not reopen the record for the admission of the testimony at issue.

CONCLUSION

Because the shared specification of Quake's '018 patent and '833 application does not disclose a method of using random MPS to determine fetal aneuploidy, substantial evidence supports the Board's grant of Lo's motions finding the four claims of the '018 patent and claim 25 of the '833

application unpatentable for lack of written description under § 112. We also find that the Board did not abuse its discretion in not admitting Dr. Gabriel's testimony from the district court proceedings. Accordingly, the Board's three interference decisions are

AFFIRMED

CERTIFICATE OF SERVICE

I hereby certify that on August 9, 2019, I filed or caused to be filed copies of the foregoing with the Clerk of the United States Court of Appeals for the Federal Circuit via the CM/ECF system and served or caused to be served a copy on all counsel of record by the CM/ECF system.

Dated: August 9, 2019

/s/ *Edward R. Reines*

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