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In *Stephen Quake et al. v. Yuk Ming Dennis Lo et al.* (July 10), the Federal Circuit affirmed a Board determination that claims to a non-invasive fetal aneuploidy detection method using massively parallel sequencing were unpatentable for lack of adequate written description.[1] The issue was whether inventor Quake's specification disclosed the "random" fragment type of sequencing as opposed to the "targeted" fragment type, but the case turned more fundamentally on the applicable standard of review: substantial evidence.

Technological Issue

Massively parallel sequencing involves breaking sample DNA into a large number of relatively short fragments, determining the sequence of those fragments in parallel, and then analyzing the fragment sequences to "reassemble" the fragments into a representation of the content of the full-length original DNA. In general, sequencing a large number of shorter DNA fragments in parallel is easier, faster, and more accurate then sequencing from one end of a lengthy DNA molecule to the other end.

Massively parallel sequencing can be performed using "random" DNA fragments, which involves sequencing and analyzing all of the fragments of DNA from a sample (oftentimes an entire genome), or with "targeted" DNA fragments, which involves sequencing and analyzing only a subset of fragments from the DNA in a sample, the subset of fragments selected based on a chosen criteria or characteristic (*e.g.,* fragments derived from a specific chromosome or chromosomes). In general, sequencing targeted fragments is easier, faster, and cheaper then sequencing all of the fragments in a sample. For example, if one knows in advance that they need only look at one particular chromosome to find the genetic information one seeks, then one need only sequence fragments from that chromosome rather than the much larger set of fragments spanning the entire genome.

The issue in this case was whether the patent specification provided adequate written description of a fetal aneuploidy detection method using random-fragment massively parallel sequencing – *i.e.,* sequencing all of the DNA fragments in a sample as opposed to a set of targeted fragments.[2] The Board determined that the specification did not adequately describe the random-fragment sequencing method.

Substantial Evidence Standard

Because written description is a fact issue, the standard of review on appeal is "substantial evidence." Under that standard, if a reasonable mind might accept the evidence relied upon by the Board as sufficient to support the Board's determination, then the determination must be affirmed. The Federal Circuit does not re-weigh the evidence; it simply determines what the supporting evidence is and decides whether a reasonable mind might accept that evidence as sufficient.[3]

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[1] The claims relate to a method for determining whether a fetus has an abnormal number of chromosomes (*e.g.,* trisomy associated with Down Syndrome) by analyzing blood drawn from the mother in which cell-free fetal DNA can be detected.

[2] The claims recite "conducting massively parallel DNA sequencing of DNA fragments randomly selected from the mixture of fetal and maternal genomic DNA" in the sample and analyzing the resultant data to determine "the presence or absence of ... fetal aneuploidy." The method relies on the ability to detect a larger-than-expected number of fragments associated with a particular chromosome, which serves as an indicator that the fetus has an extra copy of that chromosome.

[3] *See, e.g., In re Jolley,* 308 F.3d 1317, 1329 (Fed. Cir. 2002): "[W]here two different, inconsistent conclusions may reasonably be drawn from the evidence in record, an agency's decision to favor one conclusion over the other is the epitome of a decision that must be sustained upon review for substantial evidence."

In this case, the Federal Circuit decided that there was substantial evidence to support the Board's determination that the specification did not provide adequate written description of the use of random-fragment massively parallel sequencing.

Decision & Rationale

After noting that Quake had added the random-fragment claims only after learning that others had developed a random fragment aneuploidy detection method,[4] the Federal Circuit determined that there was no *express* description of random-fragment massively-parallel sequencing in the specification. Because *ipsis verbis* description is not required to satisfy the written description requirement, the analysis shifted to the broader issue framed by the legal standard for adequate written description: Whether, despite the absence of express disclosure, the specification nevertheless reasonably conveys to persons of ordinary skill in the art that Quake and the other inventors had possession of a random-fragment massively-parallel sequencing embodiment of the aneuploidy detection method.

The portion of the specification relevant to random-fragment massively-parallel sequencing is very short, only two paragraphs out of a 30 column specification.[5] Quake relied upon two particular passages in those two paragraphs:

> [A] A reference to how one may use "massively parallel sequencing of millions of fragments using attachment of randomly fragmented genomic DNA to a planar, optically transparent surface" (underline added) followed by "four-color DNA sequencing-by-synthesis," citing to a published patent application to Balasubramanian et al.; and
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> [B] A reference to how "[o]nly about 30 bp [base pairs] of random sequence information are needed to identify a sequence as belonging to a specific human chromosome" (underline added).

As to passage [A], the Federal Circuit found that the Balasubramanian patent application describes a sequencing method that is applicable to *both* random-fragment sequencing and targeted-fragment sequencing – *i.e.,* Balasubramanian describes a sequencing method performed on whatever DNA fragments are fed into it, be they random genome-wide fragments or targeted fragments. Thus, while it does provide disclosure that is relevant to random-fragment sequencing, passage [A] does not necessarily describe an aneuploidy detection method that uses random-fragment sequencing or otherwise indicate that random-fragment sequencing can or should be used in the aneuploidy detection method. Passage [A] therefore supports the Board's determination at least as much as it does Quake's position, rendering it ineffective for reversing the Board under the substantial evidence standard.

As to passage [B], the Federal Circuit found that the reference to "30 bp of random sequence information" relates to "the number of base pairs needed to identify the chromosomal origin of a sequence" (*i.e.*, the amount of information needed to determine if a fragment corresponds to a particular chromosome), which applies equally to random-fragment and targeted-fragment sequencing. In addition, the Federal Circuit explained that the use of passage [B] would be "a highly elliptical, cryptic way to communicate possession

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[4] "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 mis-match between the claims and the originally filed specification." Adding claims to cover a competitor's technology or product is perfectly legitimate but also heightens the risk (and suspicion) of over-stepping the disclosure of the specification.

[5] Most of the specification is devoted to the use of digital PCR as the analytic process. In digital PCR, a mixture of maternal and fetal DNA is distributed across thousands of reaction wells, with the goal of distributing one DNA fragment to each well. Target-specific primers are then used to perform PCR in each of the wells in parallel, the target DNA being sequences of the chromosomes being looked at – one control chromosome of which two copies are expected to be present and a test chromosome of which an extra copy may be present. Each well provides a binary (*i.e.,* digital) "yes/no" result regarding the presence of DNA from each chromosome. Counting the wells giving "yes" results allows determination of whether the test chromosome is present at a higher-than-expected copy number. Massively parallel sequencing is described as an alternative analytic process.

of a second method of sequencing to determine fetal aneuploidy," and that it was more likely that Quake invented a targeted aneuploidy detection method and used the two paragraphs, including passage [B], to describe a *targeted* sequencing embodiment as an alternative to the digital PCR method that is described in the bulk of the rest of the 30 column specification. Passage [B] therefore supports the Board's determination more so than it does Quake's position, rendering it ineffective for reversing the Board under the substantial evidence standard.

The Federal Circuit concluded that passages [A] and [B] are "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 [massively parallel sequencing]."

There was also a technology issue that supported the Board's determination. Quake's opponent, Lo, presented evidence that using a random-fragment sequencing method requires adjusting for chromosome size in the analysis before being able to detect fetal aneuploidy. This is because longer chromosomes are broken down into a larger number of fragments, leading to over-representation of longer chromosomes in fragment counts in random sequencing. In contrast, targeted-fragment sequencing looks at only specific, pre-selected fragments from the chromosomes at issue, which avoids the over-representation issue since chromosome length does not affect the number of fragments of the specific, targeted portion of the chromosome. The Quake specification contained no disclosure of adjusting or normalizing for chromosome size. This omission was relevant not because such disclosure was necessarily required, but rather because *had the specification included such disclosure*, then passages [A] and [B] would have had a different context that would have more strongly supported Quake's position. Thus, the Federal Circuit agreed 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."

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Concluding thoughts:

- The Quake specification was light on description of the massively parallel sequencing embodiment, be it targeted or random. It is not clear why that was so, since at the time of drafting the specification the technology was available and gaining significant traction in the marketplace. Although digital PCR may have been perceived as a better analytic process and the most likely commercial embodiment, the specification could have and should have been drafted to include more disclosure about sequencing alternatives, including both random-fragment and targeted-fragment types.
- It's hard to fault Quake for taking a shot-on-goal to cover random-fragment massively parallel sequencing with this patent family, but to the extent that he could have marshalled more evidence (*e.g.,* expert testimony, etc.) and refined arguments to support his position he certainly should have because the result in this case – exclusion of random-fragment sequencing as not adequately described – is potentially *res judicata* as to claims broad enough to cover random-fragment sequencing in the several other issued patents and applications in this family.