Paper No. ___
Filed: May 28, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FOUNDATION MEDICINE, INC.,
Petitioner,

v.

GUARDANT HEALTH, INC.,
Patent Owner.

Case IPR2019-00636
Patent No. 9,902,992

PATENT OWNER'S PRELIMINARY RESPONSE PURSUANT TO 37 C.F.R. § 42.107

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I. INTRODUCTION

The Board should not institute *inter partes* review of claims 1-11, 13, 15-26 of U.S. Patent No. 9,902,992 ("the '992 patent") because Foundation Medicine, Inc. ("Petitioner") fails to show that it has a reasonable likelihood of prevailing.

The '992 patent is directed to and claims methods for detecting genetic aberrations in cell-free DNA ("cfDNA"). *E.g.*, EX1001, 1:61-2:40, claim 1. Detecting and analyzing cell-free DNA was known to be challenging for a number of reasons, including that it is highly fragmented and present in minute quantities in clinical samples. The '992 patent filled the "need in the art for improved methods and systems for using cell-free DNA to detect and monitor disease" by disclosing methods for high efficiency conversion of cell-free DNA into non-uniquely tagged parent polynucleotides. *E.g.*, *id.*, 1:55-57.

Despite the specific focus of the '992 patent and challenged claims on cell-free DNA, each of the petition's grounds of challenge rely on Schmitt as the primary reference. Schmitt has no applicable teachings for detecting rare mutation in cell-free DNA. Indeed, the petition concedes as much. Pet. 28 ("Schmitt focused on using well-characterized DNA instead of cfDNA from clinical samples."). This defect in Petitioner's primary reference is inescapable. Schmitt does not disclose any of the recited steps directed to cell-free DNA.

The petition is replete with additional defects. For example, the petition repeatedly points to disclosure that simply is not prior art. Furthermore, the petition fails to establish that multiple elements of claim 1 are found in the prior art such as "attaching tags comprising barcodes...to the cfDNA molecules to tag at least 20% of the cfDNA molecules," and detecting "two or more different members selected from the group of members consisting of a single base substitution, a copy number variation (CNV), an insertion or deletion (indel), or a gene fusion." Also lacking from Petitioner's obviousness challenge is any substantiated assertion that a skilled artisan would have been motivated to apply the steps of Schmitt to cell-free DNA or would have had any expectation of success in doing so.

Accordingly, institution of *inter partes* review should be denied.

II. THE CHALLENGED CLAIMS

The petition challenges claims 1-11, 13, and 15-26 as allegedly obvious over Schmitt in view of either Fan or Forshew. Claim 1 is representative and claims a method for detecting two or more genetic aberrations (*e.g.*, single base substitution, a copy number variation, an insertion or deletion (indel), gene fusion) in cell-free DNA obtained from a subject.

1. A method for detecting genetic aberrations in cell-free DNA ("cfDNA") molecules from a subject, comprising:

a) providing cfDNA molecules obtained from a bodily sample of the subject;

b) attaching tags comprising barcodes having a plurality of different barcode sequences to the cfDNA molecules to tag at least 20% of the cfDNA molecules, which attaching comprises ligating adaptors comprising the barcodes to both ends of the cfDNA molecules, wherein ligating comprises using more than 10× molar excess of the adaptors as compared to the cfDNA molecules, thereby generating tagged parent polynucleotides;

c) amplifying the tagged parent polynucleotides to produce amplified tagged progeny polynucleotides;

d) sequencing the amplified tagged progeny polynucleotides to produce a plurality of sequence reads from each of the tagged parent polynucleotides, wherein each sequence read of the plurality of sequence reads comprises a barcode sequence and a sequence derived from a cfDNA molecule of the cfDNA molecules;

e) mapping sequence reads of the plurality of sequence reads to one or more reference sequences from a human genome;

f) grouping the sequence reads mapped in e) into families based at least on barcode sequences of the sequence reads, each of the families comprising sequence reads comprising the same barcode sequence, whereby each of the families comprises sequence reads amplified from the same tagged parent polynucleotide;

g) at each of a plurality of genetic loci in the one or more reference sequences, collapsing sequence reads in each family to yield a base call for each family at the genetic locus; and

h) detecting, at one or more genetic loci, a plurality of genetic aberrations, wherein the plurality of genetic aberrations comprises two or more different members selected from the group of members consisting

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