IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

FOUNDATION MEDICINE, INC.	)	
Plaintiff,	)	Civil Action No. 2:16-CV-00523-JRG-RSP
v.	)	
GUARDANT HEALTH, INC.	)	
Defendant.	)	

REBUTTAL DECLARATION OF STACEY GABRIEL, PH.D. IN SUPPORT OF FOUNDATION MEDICINE, INC.'S PROPOSED CLAIM CONSTRUCTIONS

I. INTRODUCTION

1. My name is Stacey Gabriel. On March 6, 2017, I submitted an Initial Declaration in Support of Plaintiff Foundation Medicine, Inc.'s ("Foundation Medicine") Proposed Claim Constructions ("Initial Declaration"). I incorporate my Initial Declaration in its entirety herein.

2. I now have been asked by Foundation Medicine to respond to certain points made in the Expert Declaration of John Quackenbush, Ph.D, dated March 6, 2017 ("Dr. Quackenbush's Declaration").

3. My background and qualifications were discussed in my Initial Declaration.

4. Prior to submitting my Initial Expert Declaration, it was unclear to me why Guardant had alleged that the following terms were indefinite: "somatic mutation that appears at a frequency of about 5% or less of the cells from the tumor sample," and "somatic mutation that appears at a frequency of about 10% or higher of the cells from the tumor sample." I understand that Guardant had not provided any reasoning for its position, nor were any bases for the alleged indefiniteness apparent to me, as a person of ordinary skill in the art. Having reviewed Dr. Quackenbush's Declaration, I now understand Guardant's argument, although, for at least the reasons discussed more fully below, I disagree with it. Hence, I take this opportunity to reaffirm my opinions detailed in my Initial Expert Declaration, and to rebut certain arguments and opinions provided by Dr. Quackenbush in his declaration both generally with respect to the technology of the '830 patent and specifically with respect to Guardant's assertion that the above-described claim terms are indefinite.

II. DR. QUACKENBUSH'S STATEMENTS REGARDING THE '830 PATENT AND TECHNOLOGY

5. Dr. Quackenbush devotes a significant portion of his Declaration to providing an "Overview" of the '830 patent and the technology related thereto. For purposes of claim construction, I do not feel that it is necessary to address each of the statements in the Overview section of Dr. Quackenbush's Declaration on a point-by-point basis. That said, I reserve the right to provide my own overview of the relevant technology and/or to address Dr. Quackenbush's statements concerning the technology and the scope of Foundation Medicine's invention to the extent I am asked to do so at any subsequent point in this matter.

6. However, because Dr. Quackenbush makes two broad assertions in the Overview section of his Declaration that purport to provide the basis for his indefiniteness opinion, I address those two assertions below.

7. First, Dr. Quackenbush suggests that the Mutant Allele Fractions ("MAFs") in cell-free DNA ("cfDNA") (also referred to as circulating tumor DNA ("ctDNA")) do not correlate to the MAFs in sample cells taken directly from a tumor. *See, e.g.*, Quackenbush Decl., ¶¶ 52-54. I disagree. In my opinion, those MAFs may be correlated. In fact, contrary to Dr. Quackenbush's assertion, several studies have found a positive correlation coefficient of MAFs taken from plasma samples and those taken from tumor samples. *See, e.g., Murtaza et al.* (Ex. 1) ("Our data, together with recent reports, show that CNAs and somatic mutations identified in ctDNA are widely representative of the tumour genome and provide an alternative method of tumour sampling that can overcome limitations of repeated biopsies.").

8. Dr. Quackenbush's statement that a cancer-related somatic mutation "tends to appear at a much higher frequency in actual tumor cells than it does as a percentage of the patients cfDNA" is simply irrelevant for purposes of the claims of the '830 patent. The '830

patent claims a method for analyzing somatic mutations in tumor nucleic acid molecules – whether that nucleic acid had been sampled directly from the tumor or taken from circulating blood. Indeed, Dr. Quackenbush expressly acknowledges that cfDNA comes from tumor cells: As he states, "tumor cells release small pieces of their DNA into the bloodstream." *See, e.g.,* Quackenbush Decl., ¶ 49.

9. Second, Dr. Quackenbush contends that to perform the methods claimed in the '830 patent, a POSITA would "first have to determine in advance the frequencies at which each of the mutations would be expected to appear in the cells of the sample." Quackenbush Decl., ¶ 60. Again, I disagree. In my opinion, a POSITA would readily understand that, to practice the claims of the '830 patent, he or she has to employ a method capable of detecting somatic mutations that appear at certain frequencies, and that these frequencies may be low (i.e., <5%). A POSITA would also understand that there is no way to know in advance what the exact frequency of any mutation will be in any given sample. That is, based on his or her knowledge of cancer biology, a POSITA would understand that the '830 patent claims methods of using bait sets capable of detecting somatic mutations within a subgenomic interval at the desired mutant allele frequencies.

10. Contrary to Dr. Quackenbush's assertion in Paragraph 60 of his Declaration, there is nothing in claim 1 or 65 of the '830 patent that requires targeting of any "specific" mutation. Rather, claims 1 and 65 of the '830 patent are directed to detecting *any* somatic mutation in targets of interest that "appears at a frequency of about 5% or less" – *i.e.*, any such mutation in a given sample.

III. PROFESSOR QUACKENBUSH'S INDEFINITENESS ANALYSIS

A. The terms "somatic mutation that appears at a frequency of about 5% or less of the cells from the tumor sample" and "somatic mutation that appears at a frequency of about 10% or higher of the cells from the tumor sample" do not require a precise prediction of the frequencies of somatic mutations in a particular tumor sample.

11. In my opinion, Dr. Quackenbush's indefiniteness analysis is flawed for several reasons. The most obvious flaw in his declaration is that, without providing any support, he simply assumes an interpretation of these terms, and then argues that the terms, *as interpreted by him*, fail to reasonably inform one skilled in the art about the scope of the claim. For example, Dr. Quackenbush spends much of his declaration arguing that the terms are indefinite because it would be impossible to "predict" the frequencies of specific mutations in advance; but, he never explains why these claim terms would be interpreted by a POSITA to require detection of "predicted" frequencies of somatic mutations in the first place. *See* Quackenbush Decl., ¶¶ 71, 72, 73, 78, 82. It seems that his interpretation is at least partly based on his incorrect understanding of Foundation Medicine's position on the disputed terms. He notes incorrectly that Foundation Medicine proposed the following construction of these terms: "a somatic mutation that is ***predicted to appear*** at a frequency of 5% or less (10% or higher) of the nucleic acid molecules obtained from malignant or premalignant cells." Quackenbush Decl., ¶¶ 66-67 (emphasis added). However, it is my understanding that, in fact, Foundation Medicine did not propose a construction for these terms. Likewise, nowhere in my Initial Expert Declaration explaining the meaning of these terms did I suggest that these terms refer to detecting a somatic mutation that is predicted to appear at a particular frequency in a given sample.

12. Regardless, I disagree with Dr. Quackenbush's contention that a person skilled in the art would read the claim terms to require detecting a somatic mutation that is "predicted" to appear at a frequency of 5% or less (10% or higher). Quackenbush Decl., ¶¶ 66-67. First, such an interpretation needlessly reads the phrase "predicted to appear" into the claim language, without any support from the '830 patent, its file history, or any extrinsic evidence. In fact, Dr. Quackenbush appears to admit the lack of disclosure supporting this construction. Quackenbush Decl., ¶ 71 ("The patent does not contain any disclosure or description of predicting the frequency at which a mutation will appear prior to performing the claimed method."). Second, Dr. Quackenbush is correct that one cannot know in advance the frequency of a particular mutation in a tumor sample. *See* Quackenbush Decl., ¶¶ 71, 72, 73, 78, 81, 82. As a result, contrary to Dr. Quackenbush's assertion, a person of skill in the art would not interpret these terms to require predicting the frequency of mutations in a particular tumor sample ahead of time.

13. Instead, as explained in my Initial Expert Declaration, a person skilled in the art would understand that these terms refer to those somatic mutations that appear at a frequency of 5% or less (or 10% or higher) at a subgenomic interval in the tested nucleic acid population. Gabriel Initial Decl., ¶¶ 54, 55. In the context of the claims, these terms clearly define for a POSITA the first and second bait sets of claims 1 and 65 (claim elements 1(i) and (ii), and 65(i) and (ii)):

> (i) **a first bait set** that selects a high-level target chosen from one or more tumor nucleic acid molecules that comprise a subgenomic interval comprising **a somatic mutation that appears at a frequency of about 5% or less of the cells from the tumor sample**;
>
> (ii) **a second bait set** that selects a mid-level target chosen from one or more tumor nucleic acid molecules that comprise a subgenomic interval comprising **a somatic mutation that appears at a frequency of about 10% or higher of the cells from the tumor sample**;

Claims 1, 65 (emphasis added). Thus, for a POSITA, the first bait set refers to a bait set that is designed to detect those somatic mutations that appear at a frequency of 5% or less in the tested nucleic acid population, while the second bait set refers to a bait set that is designed to detect those somatic mutations that appear at a frequency of 10% or more in the tested nucleic acid population. In other words, the mutation frequency in these terms refers to the ability to detect those somatic mutations that appear at certain frequencies, rather than the actual mutation frequency in a tested tumor sample.

14. One skilled in the art would understand that the claimed invention involves designing bait sets tailored towards detecting those mutations within a target (e.g., a subgenomic interval) that appear at certain frequencies. For example, the first bait set is designed to detect mutations present at levels of 5% or less in a tumor sample. This understanding by a POSITA is consistent with the teachings of the '830 patent, and the file history. The '830 patent teaches: "The bait sets can be designed from reference sequences, such that the baits are optimal for selecting targets of the reference sequences." '830 patent, Col. 55: 35-37. It also provides examples showing how bait tiling densities may be adjusted to detect mutations that are difficult to capture. *See, eg.*, '830 patent, Col. 202: 53-56 ("low tiling densities may make capturing of alleles with in/dels more difficult. Therefore, bait sets were designed for MAP3K1 with the different tiling."). Similarly, Doron Lipson, one of the inventors of the patent, in a declaration submitted to the U.S.P.T.O., explained that mutations corresponding to bait sets (i) and (ii) could be detected by designing bait sets "with a high-density representation of relatively shorter exonic sequences." Declaration of Doron Lipson (dated Dec. 15, 2015), pg. 5.

15. While having some idea of the likelihood of a mutation occurring in a particular type of cancer is helpful when designing bait sets, a prior knowledge of the frequency of a particular mutation in a tumor sample from a particular patient is neither possible nor necessary. For example, the '830 patent teaches "that judicious incorporation of prior expectations around tumor type specific mutation spectra can be beneficial in translation of NGS-based tumor genome analysis …" '830 patent, Col. 200: 20-22. As I explained in my Initial Expert Declaration, if a POSITA expects certain mutations to occur at low frequencies, the assay can be improved by designing bait sets with increased coverage depth for these mutations. Initial Expert Decl., ¶ 57. The prior probability of a mutation at a particular site may also be used to improve variant calling methods. *See also* '830 patent, col. 119:4-col.120:44; Table 6. The '830 patent teaches that probabilities of specific mutations can be obtained from public databases, listing, for example, the frequencies of known mutations in epithelial cancers in Table 9. *See also* '830 patent, col. 119:4-col.120:44; Table 6. However, prior knowledge of the frequency of a particular mutation in a given sample is neither possible nor necessary to perform the claimed method of the '830 patent.

16. Dr. Quackenbush states that a person of skill in the art would not know if he or she is practicing the invention because of the uncertainty about predicted mutation frequencies. *See* Quackenbush Decl., ¶¶ 74, 75. However, the inability to accurately predict the mutation frequencies in a sample does not mean that one would not know whether he or she is practicing a method capable of detecting mutations that may occur at a certain frequency in the tested sample. For example, Guardant itself claims that "Guardant360 accurately calls SNVs, Indels, Fusions and CNVs **at <0.1%** and as low as 2.12 gene copies." *See* Guardant360: Sensitivity Matters (Ex. 2) (emphasis added). If foreknowledge of exact mutation frequency was a

necessity, certainly Guardant could not have made this claim. Since people skilled in the art would know the mutation frequencies their practiced method is capable of detecting, they can readily determine whether they are practicing the invention.

17. Unlike Dr. Quackenbush, I see no reason why someone of skill in the art would be confused about satisfying the first bait set limitation versus the second bait set limitation. *See* Quackenbush Decl., ¶¶ 78-80. One skilled in the art would understand that if the practiced method includes a bait set capable of detecting somatic mutations at a frequency of 5% or less of the tested nucleic acid population, it satisfies the first bait set. Similarly, if the practiced method includes a bait set capable of detecting a somatic mutation at a frequency of 10% or higher of the tested nucleic acid population, it satisfies the second bait set. The actual frequency of any particular mutation in a particular tested sample would not matter. It is clear from the claim language that practicing the claimed method is not dependent on the presence of certain mutations in a sample, but rather on the capability of detecting them if they are present in a sample. A contrary interpretation would lead to bizarre results because then an entity could conduct the same test, with the same bait sets, on different tumor samples, and infringement would vary depending on whether a mutation is present in a tumor samples, and the frequency of that mutation. For this additional reason, in my opinion a POSITA would not interpret these claim terms in the manner suggested by Dr. Quackenbush.

18. In short, there is no uncertainty regarding the scope of these terms because a person of skill in the art would not understand the terms at issue to require detecting somatic mutations that are predicted to occur at 5% or less (or 10% or higher).

B. Foreknowledge of mutation frequency in a sample is not necessary to preselect efficiency of bait sets.

19. Dr. Quackenbush further argues that it would be impossible to "preselect" a bait set's "efficiency for selection for its target" because of the uncertainty about the mutation frequency in a sample. Quackenbush Decl., ¶¶ 82-84. The relevance of this argument to the indefiniteness of the terms "somatic mutation that appears at a frequency of about 5% or less (or 10% or higher) of the cells from the tumor sample," is unclear to me. Regardless, I disagree with Dr. Quackenbush that it would be impossible to preselect the efficiency of selection of the bait sets.

20. As I have explained already, designing the claimed bait sets does not require prior knowledge of the actual mutation frequency in a tumor sample. Designing bait sets with desired efficiencies for selecting their targets likewise does not require prior knowledge of the actual mutation frequency in a given tumor sample.

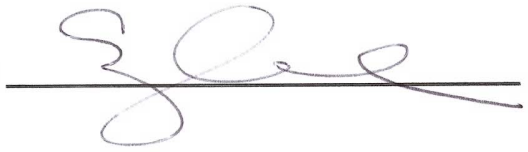
21. One skilled in the art would understand from reading the '830 patent that efficiency of bait sets can be "preselected" by designing the bait sets with the goal to achieve a desired depth of coverage of their targets. This is consistent with the teaching of the '830 patent, which teaches that different depths of coverages may be appropriate for detecting different types of genetic alterations. Col. 14:17-62; *see also* Figure 2. The '830 patent further teaches that the efficiency of selection can be modified, for example, by "differential representation of different bait sets, differential overlap of bait subsets, differential bait parameters, mixing of different bait sets, and/or using different types of bait sets." '830 patent, col. 14:64-67; see also col. 15:1- col. 17:21; claim 2.

22. As is the case when designing bait sets, having some idea about the probability of the mutation would be helpful, but not necessary, in preselecting the efficiencies of the bait

sets. For example, if one expects a mutation to occur at a low frequency, one may design bait sets with greater coverage depth, thereby increasing the selection efficiency. However, knowledge of the frequency at which a particular mutation occurs in a sample is certainly not required to preselect the desired efficiency of selection of the bait sets. In my opinion, nothing in the '830 patent suggests that knowledge of the frequency at which a particular mutation occurs is required prior to performing the method.

IV. DECLARATION

I declare that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true.

Executed: 

By: Stacey Gabriel, Ph.D.

Date: March 17, 2017