

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

COLD SPRING HARBOR LABORATORY,	)	
	)	
Plaintiff	)	
	)	
v.	)	C.A. No. 25-00263 (JCG)
	)	
GUARDANT HEALTH, INC.,	)	
	)	
Defendant.	)	
	)	

GUARDANT HEALTH, INC.'S INITIAL INVALIDITY CONTENTIONS

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I. INTRODUCTION

Pursuant to the Court's Third Amended Scheduling Order (D.I. 37) and Fourth Amended Scheduling Order (D.I. 43), Defendant Guardant Health, Inc. ("Guardant") hereby provides the following Initial Invalidity Contentions for U.S. Patent Nos. 10,947,589 ("the '589 Patent") and 12,234,510 ("the '510 Patent") (collectively, the "Patents-in-Suit" or "Asserted Patents"), as well as the related invalidating references (e.g., manuals, patents, and publications).

A. Reservation of Rights

Guardant provides these disclosures based on information obtained to date. Guardant's discovery and investigation in connection with this lawsuit are continuing, and Guardant expects that additional evidence and information will become available through discovery. Guardant reserves the right to supplement these invalidity contentions as Guardant's investigation and discovery continue and as appropriate as the case progresses. Guardant further reserves the right to modify, supplement, amend, or otherwise alter these disclosures as discovery progresses, as permitted by the Federal Rules of Civil Procedure, by the Default Standard, or by order of the Court. In particular, Guardant reserves the right to modify, supplement, amend, or otherwise alter these disclosures following an opportunity for expert discovery. These disclosures do not encompass patent unenforceability, which Guardant may allege separately.

The disclosure of a reference as anticipating a claim includes a disclosure of the reference for obviousness purposes should any element of the claim be determined to be absent from the reference. Moreover, Guardant is at the present time unaware of the extent, if any, to which Plaintiff will contend that elements of the claims are not disclosed in references identified by Guardant as anticipatory or obvious. To the extent that Plaintiff makes any such claim with respect to any limitation, Guardant reserves the right to identify other references that may explain the inherency of, or make obvious the addition of, the allegedly missing element.

References disclosed as rendering a claim obvious are representative and are not intended to be exhaustive. Other references disclosing the same or similar elements may be substituted for the cited references. Additional obviousness combinations of the references identified below are possible, and Guardant reserves the right to use any such combination(s) in this litigation. Motivation to combine references can be inferred generally for all references within the fields of art of the Patents-in-Suit. Furthermore, where references refer to or cite one another, motivation to combine may be specifically inferred whether or not called out in a claim chart. Lastly, Guardant's identification of motivation to combine references should not be taken as an admission or a representation that Guardant will not rely upon other tests for obviousness in view of *KSR Int'l. Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). This would include showing any of the following: (1) that the combination of elements was obvious to try; (2) that the combination of elements according to known methods yielded predictable results; (3) that the substitution of one known element for another obtained predictable results; (4) that the application of a known technique to a known device, method, or product ready for improvement yielded predictable results; or (5) that known work in one field of endeavor prompted variations of such work for use in either the same field or a different one based on design incentives or other market forces because the variations are predictable to one of ordinary skill in the art.

The identification of prior art that anticipates and/or renders obvious a particular claim element in these contentions is not an admission that the claim element satisfies the requirements of 35 U.S.C. § 112. Where Guardant asserts that a claim is invalid under 35 U.S.C. § 112 (such as because of a failure to particularly point out and distinctly claim the alleged invention, failure to provide written description support, and/or failure to enable one of ordinary skill in the art to make and use the claimed invention), Guardant has nonetheless provided prior art that anticipates

or renders obvious the claim on the assumption that Plaintiff will contend that those claims are definite, supported by an adequate written description, and adequately enabled.

In addition to the prior art identified in these contentions, and any future supplement to these contentions, Guardant may rely on relevant portions of the Patents-in-Suit, the prosecution histories of the Patents-in-Suit, all references listed in the References Cited portion of the Patents-in-Suit, and fact and expert testimony about the prior art.

Guardant objects to the disclosure of information that is protected by the attorney-client privilege, attorney work-product immunity, the common-interest privilege, or any other applicable privilege or immunity.

Guardant reserves the right to amend and/or supplement these contentions as fact and expert discovery and claim construction proceed.

B. Asserted Claims of Patent-in-Suit

Plaintiff has asserted '589 Patent, Claims 1-3, 6-15, and 17-18 and '510 Patent, Claims 1-12, 15-23, 26-29, 31-34 (the "Asserted Claims"). Guardant's Invalidity Contentions are based in whole or in part on its present understanding of the Asserted Claims and Plaintiff's infringement theories.

II. CLAIM CONSTRUCTION

In the absence of a claim construction order from the Court, Guardant has relied upon ordinary meaning of claim terms and definitions in the patents as well as the meanings evident in the Plaintiff's Infringement Contentions. Guardant expressly reserves the right to propose alternative constructions to those advocated by the Plaintiff. Furthermore, prior art not included in the disclosure, whether or not known to Guardant, may become relevant depending upon the claim constructions that Plaintiff may assert or that the Court may adopt. Guardant's investigation is continuing and is likely to uncover additional art. Guardant will supplement its disclosures at

appropriate times in light of newly discovered art or changes in claim constructions.

III. PRIOR ART

A. Identification of Prior Art References

Subject to the reservation of rights above, Guardant identifies at least the prior art references set forth in Table 1 and any other references or documents identified in any version of Guardant's Invalidity Contentions, which alone or in combination, render the Asserted Claims of the Patents-in-Suit invalid under 35 U.S.C. §§ 102 and § 103. The prior art identified is also relevant in showing obviousness, as demonstrated in the accompanying Invalidity Claim Charts (see Exhibits A1-A16 and B1-B16 as well as for their showing of the state of the art and reasons and motivations for making improvements, additions, and combinations, as described below.) *See* Section V, *infra*. Guardant reserves the right to identify additional prior art references as discovery progresses.

Guardant disputes the Patents-in-Suit are entitled to claim priority to U.S. Provisional Patent Application No. 61/510,579, filed Jul. 22, 2011, U.S. Provisional Patent Application No. 61/406,067, filed Oct. 22, 2010, or any other provision prior to the '589 Patent's filing date. As such, Guardant contends the references listed below constitute prior art to the Asserted Patents.

TABLE 1: Prior Art References		
Prior Art Reference	Year of Issue/ Publication	Short Cite
U.S. Patent Publication 2009/0029377 to Lo et al.	2009	Lo
McCloskey et al., Encoding PCR Products with Batch-Stamps and Barcodes, 45 Biochemical Genetics, 761-767	2007	McCloskey
U.S. Patent 7,537,897 to Brenner et al.	2009	Brenner
U.S. Patent 9,085,798 to Chee et al.	2015 ¹	Chee
U.S. Patent 11,840,730 to Porreca et al.	2023 ²	Porreca
U.S. Patent 8,195,415 to Fan et al.	2012 ³	Quake

¹ Priority to 2010 via Patent Cooperation Treaty Application No. US2010/033064

² Priority to 2010 via Patent Cooperation Treaty Application No. US2010/001293

³ Priority to 2010 via U.S. Patent Publication No. 2010/0138165

TABLE 1: Prior Art References		
U.S. Patent 8,835,385 to Fodor et al.	2014 ⁴	Fodor
Brooks E. Miner et al., "Molecular barcodes detect redundancy and contamination in hairpin-bisulfite PCR," 32 Nucleic Acids Research 1-4	2004	Miner
Certified translation of German Patent DE102008025656 to Björn Rotter	2009	Rotter
German Patent DE102008025656 to Björn Rotter	2009	Rotter Original
U.S. Patent 8,715,967 to Casbon et al.	2013 ⁵	Casbon
Chao Xie and Martti T. Tammi, "CNV-seq, a new method to detect copy number variation using high-throughput sequencing," BMC Bioinformatics 1-9	2009	Xie
Derek Y. Chiang et al., "High-resolution mapping of copy-number alterations with massively parallel sequencing," Nature Methods Vol. 6 No. 1 99-103	2009	Chiang
PCT App No. WO 2010/117620 A2 to Linnarsson titled "Gene Expression Analysis In Single Cells"	2010	Linnarsson
Hug et al., Measurement of Number of Molecules of a Single mRNA Species in a Complex mRNA Preparation, 221 J. Theor. Bio., 615-624	2003	Hug
Rossa W. K. Chiu et al., "Noninvasive prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma," PNAS Vol. 105 No. 51 20458-20463	2008	Chiu
Tian-Li Wang et al., "Digital karyotyping," PNAS Vol. 99 No. 25 16156-16161	2002	Wang
U.S. Patent Publication 2007/0031857 to Makarov et al.	2007	Makarov
Elaine R. Mardis, "Next-Generation DNA Sequencing Methods," Nature Biotechnology 1135-45	2008	Mardis
Elaine R. Mardis, "The Impact of Next-Generation Sequencing Technology on Genetics," Trends in Genetics 133-141	2008	Mardis II
H.C. Yang et al., "A genome-wide study of preferential amplification/hybridization in microarray-based pooled DNA experiments," 34 Nucleic Acids Research 1-11	2006	Yang
Severine A. Degrelle et al., "Amplification bias: possible difference among deviating gene expressions," 9 BMC Genomics 1-15	2008	Degrelle
Gerald Schochetman et al., "Polymerase Chain Reaction," Journal of Infectious Diseases, Vol. 158 No. 6	1988	Schochetman
Andy Itsara et al., "Population Analysis of Large Copy Number Variants and Hotspots of Human Genetic	2009	Itsara

⁴ Priority to 2009 via U.S. Provisional App. No. 61/286,768

⁵ Priority to 2010 via U.S. Provisional App. No. 61/385,001

TABLE 1: Prior Art References		
Disease,” Amer. Soc. of Human Genetics 148-161		
Heather C. Mefford et al., “A method for rapid, targeted CNV genotyping identifies rare variants associated with neurocognitive disease,” Genome Research 1579-85	2009	Mefford
Jay Shendure and Hanlee Ji, “Next-Generation DNA Sequencing,” Nature Biotechnology 1135-45	2008	Shendure
Jonas Binladen et al., “The Use of Coded PCR Primers Enables High Throughput Sequencing of Multiple Homolog Amplification Products by 454 Parallel Sequencing,” 2(2): e197 PLoS ONE 1-9	2007	Binladen
U.S. Patent Publication 2007/0020640, to McCloskey et. al.	2007	McCloskey II
Robert A. Holt and Steven J.M. Jones, “The New Paradigm Of Flow Cell Sequencing,” Cold Spring Harbor Laboratory Press	2008	Holt
Clyde A. Hutchinson III, “DNA Sequencing: Bench to Bedside and Beyond,” Nucleic Acids Research	2007	Hutchinson
David H. Persing, “Polymerase Chain Reaction: Trenches to Benches,” J. of Clin. Microbiology	1991	Persing
U.S. Patent No. 7,794,984 to Kless	2010	Kless
Juliane C. Dohm et al., “Substantial Biases In Ultra-Short Read Data Sets From High-Throughput DNA Sequencing,” Nucleic Acids Research	2008	Dohm
Jingdong Tian et al., “Advancing High-Throughput Gene Synthesis Technology,” Molecular BioSystems	2009	Tian

B. Background of the Prior Art

As shown below, the alleged inventions of the Asserted Claims of the Patents-in-Suit were well-known in the art prior to the date of their alleged invention. Those skilled in the art were aware of all the limitations of the Asserted Claims of the Patents-in-Suit. Accordingly, many prior art patents, prior art publications and combinations thereof, disclose, teach, or embody every limitation of the Asserted Claims, and thus invalidate the Asserted Claims. Examples of these disclosures, teachings, and embodiments are identified in Table 1 and in the attached Invalidity Claim Charts set forth in the attached Invalidity Claim Charts. See Exhibits A1-A16 and B1-B16.

IV. INVALIDITY BASED ON 35 U.S.C. § 112

To the extent the Asserted Claims of the Patents-in-Suit are not obvious, they are invalid based on lack of written description under pre-AIA 35 U.S.C. § 112 ¶ 1 or post-AIA 35 U.S.C. § 112(a) and/or lack of enablement under pre-AIA 35 U.S.C. § 112 ¶ 1 or post-AIA 35 U.S.C. § 112(a). Guardant's contentions that the following claims are invalid under 35 U.S.C. § 112 are made in the alternative, and do not constitute, and should not be interpreted as, admissions regarding the construction or scope of the asserted claims, or that any of the Asserted Claims are not anticipated or rendered obvious by any prior art. Further, the arguments below also apply to the priority documents for the Patent-in-Suit, and as such, they are not entitled to their earliest priority date. Consequently, Guardant reserves the right to rely on any references that predate the filing of the Patent-in-Suit.

Whether the asserted claims of the Patent-In-Suit are invalid for failure to meet the requirements of the first two paragraphs/subsections of 35 U.S.C. § 112, including lack of enablement and/or lack of written support in the specification, will depend in part on the construction of the Asserted Claims. Accordingly, Guardant cannot provide a complete list of all such grounds at this time. Guardant therefore reserves the right to supplement, amend, and/or modify these disclosures.

A. Written Description

To the extent the Asserted Claims are not deemed invalid under 35 U.S.C. §§ 102 and/or 103 for anticipation and/or obviousness, they are necessarily invalid under 35 U.S.C. § 112 for lack of written description. The first paragraph/subsection of 35 U.S.C. § 112 requires a patent specification to contain "a written description of the invention." To satisfy the written description requirement, the description must "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharm., Inc. v. Eli Lilly and Co.*, 598 F.3d

1336, 1351 (Fed. Cir. 2010) (internal citation omitted). “Whether the written description requirement is satisfied is a fact-based inquiry that will depend on the nature of the claimed invention, and the knowledge of one skilled in the art at the time an invention is made and a patent application is filed.” *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008) (internal citation omitted). “Whether the flaw in the specification is regarded as a failure to demonstrate that the patentee possessed the full scope of the invention recited in [the claims] or a failure to enable the full breadth of that claim, the specification provides inadequate support for the claim under section 112, paragraph one.” *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005).

Guardant lists the grounds below upon which it presently contends that certain of the Asserted Claims of the Patents-In-Suit are invalid under pre-AIA 35 U.S.C. § 112 ¶ 1 or post-AIA 35 U.S.C. § 112(a) for failure to provide an adequate written description.

1. The Specifications are Limited to Single Cells

The background of the Asserted Patents shows that the Asserted Patents are directed to determining copy number from samples of single cells. *See* ’589 Patent at 1:51-53 (“Coverage of the genome by sequencing WGA of single cell DNA is limited by the stacking phenomenon.... Thus it is difficult to obtain single cell measurements...”). This focus towards single cell analysis is confirmed throughout the Asserted Patents. *See id.* at 10:37-38 (“In an embodiment of the methods, the tagged nucleic acid molecules are generated from a single cell of each organism”), 12:45-46 (“In an embodiment of the above compositions, the tagged nucleic acid molecules are generated from a single cell.”), 15:34-37 (“In an embodiment, tagged nucleic acid molecules generated from a single cell are pooled with tagged nucleic acid molecules generated from a different single cell.”), 24:47-49 (“The above description is of methodology designed to measure copy number and mutational loads throughout much of the genome in single cells.”). The claims

of the Asserted Patents, however, are directed towards obtaining segments of genomic nucleic acids from any “sample containing the genomic nucleic acids” (’510 Patent at Claim 1) or, even more broadly, from “a sample” (’589 Patent at Claim 1). A review of the specification shows that the inventors were in possession of, at most, a narrow method for the determination of copy number in single-cell samples and did not possess a broader method for the determination of copy number variation in other sample types, such as blood plasma samples, wherein one is seeking to determine copy number variation in the overall genome of a multicellular organism. Certainly, and as explained further below, the inventors were not in possession of a method of inferring copy number variation in a tumor based on a cell-free DNA sample taken from a cancer patient.

2. The Specifications Contains No Disclosure of Cell-free DNA

To the extent that CSHL alleges that the Asserted Patents cover Guardant products that use cell-free DNA as “segments of genomic nucleic acids,” the ’589 Patent specification does not contain any disclosure regarding using cell-free DNA. Cell-free DNA are DNA fragments that exist outside of cells, primarily in blood.

The background section of the Asserted Patents states that “there exists a need for a method that allows for copy number determination free of distortions caused by amplification steps and which allows for accurate and efficient copy number determination of complex samples.” ’589 Patent at 2:33-37. The ’589 Patent provides little explanation about what complex samples means. The ’589 Patent specification states only that “the samples can be individual cells, yielding large numbers of single cell measurements cheaply” and that “[s]amples can be nucleic acids derived from single cells or populations of cells.” ’589 Patent at 30:27-29, 28:67-29:1. Nowhere in the specification is cell-free DNA discussed.

Accordingly, to the extent the Asserted Patents are not invalid as anticipated or obvious, they are invalid for failure of written description to the extent the claims cover the use of cell-free

DNA sample types. As explained above, claim 1 of the '510 Patent only requires “obtaining segments of genomic nucleic acids from a sample containing the genomic nucleic acids” and claim 1 of the '589 Patent only requires “obtaining segments of genomic nucleic acids from a sample.” Similarly claims 17 and 18 of the '589 Patent improperly cover cell-free DNA samples without support in the specification. Claim 17 contains the limitation “wherein the genomic nucleic acids are obtained from blood or other bodily fluids.” Claim 18 contains the limitation “wherein the genomic nucleic acids are obtained from tumor cell DNA in a bodily fluid.” Even within the specification, the description for “tumor cell DNA in a bodily fluid” is limited. The specification only mentions comparing methylated and unmethylated regions to identify tumor cell DNA in bodily fluids but does not explain how the method of claim 1 would use methylation to do so. *See* '589 Patent at 25:55-26:10. Certainly, the specification includes no description of how one would go about inferring copy number variation in a tumor based on a sample of cell-free DNA taken from a cancer patient. Just the opposite, the specification purports to teach two distinct methods of counting nucleic acids to assess the presence of copy number variation, and neither of the disclosed methods teaches how to take into account the background from normal DNA that is present in the patient sample and that would otherwise obscure the informational content from the limited amount of tumor DNA. *See, e.g.,* '589 Patent at 20:1-46. Indeed, such issues are not contemplated in the slightest in the Asserted Patents, confirming that the inventors were not in possession of techniques based on the analysis of cell-free DNA.

3. The Specification Describes Only “Substantially Unique” Tagging

As the specification makes clear, the use of a sufficiently large number of tags is central to the alleged invention. *See, e.g.,* '589 Patent at 19:47-49 (“Within a pool of tagged nucleic acid molecules, each tagged nucleic acid molecule is likely unique in the pool when a sufficiently large number of distinct tags is used.”); *id.* at 23:21-25 (“But if the set of tags are sufficiently large, the

tagged nucleic acid molecules will generally differ at more than one nucleotide, and so tagged nucleic acid molecules that differ by a single nucleotide can (optionally) be ignored when counting.”). As to what is a “sufficiently large” number of tags, the specification contemplates only one thing, which is tags that are “substantially unique,” defined in the specification to mean “tags in a plurality of tags, wherein at least 50% of the tags of the plurality are unique to the plurality of tags. Preferably, substantially unique tags will be at least 60%, 70%, 80%, 90%, or 100% unique tags.” *Id.* at 16:43-47; *see also id.* at 16:38-42 (defining “substantially unique primers” in terms of tag uniqueness).

Indeed, the specification describes throughout nothing other than the use of such “substantially unique” tags or primers. *See, e.g., id.* at Abstract (“A method for obtaining from genomic material genomic copy number information unaffected by amplification distortion, comprising obtaining segments of the genomic material, tagging the segments with substantially unique tags to generate tagged nucleic acid molecules....”); *id.* at 2:47 (“tagging the segments with substantially unique tags”); *id.* at 3:45 (reciting the use of “substantially unique primers”); *id.* at 4:49, 5:6, 5:42, 5:48-50, 8:25, 9:26, 10:48, 11:13, 11:38, 12:6, 12:45-46 (same); *id.* at 6:50 (“tagging the segments with substantially unique tags”); *id.* at 13:3-4 (“In an embodiment of the above kits, the substantially unique tags comprise the sample tags”); *id.* at 19:36-38 (“Input nucleic acid molecules (0-th order derivatives), or first round copies of them (1-st order derivatives), present in the sample, can be randomly tagged using a large choice of distinct tags.”); *id.* at 19:47-49 (“Within a pool of tagged nucleic acid molecules, each tagged nucleic acid molecule is likely unique in the pool when a sufficiently large number of distinct tags is used.”); *id.* at 23:12-15 (“The ligated molecules now are essentially unique, the ligated molecules each being the combination of a substantially unique tag and DNA sequence to which they were ligated.”).

To the extent the claims are deemed to encompass approaches that use anything other than unique or substantially unique tagging, they are invalid for failure of written description. For instance, to the extent the claims are deemed to encompass approaches based on the use of smaller tag sets wherein the number of sample molecules is far in excess of the number of tags, the Asserted Patents provide no written description support for such an approach, which is nowhere contemplated in the patent. Indeed, the Asserted Patents warn against such an approach, stating, for instance, that “[i]f the number of molecules at a location on a genome or cDNA library exceeds the number of tags, and tagging is too efficient, copy number information can not be recovered.” *Id.* at 20:35-37. Nowhere does the specification include any discussion of how to address the complexities that may arise when the number of sample molecules is far in excess of the number of tags. The specification, for instance, never includes any discussion of the diversity of molecules that may be present in a sample and how one might use start and stop positions for sequence reads to distinguish among molecules and the number of tags one might need. Instead, the specification assumes that one needs to have a sufficiently large number of tags that are, as defined, in the specification “sufficiently unique.” To the extent the claims cover anything more than this, they are invalid for failure of written description.

4. The Inventors Were Not In Possession Of The Claimed “Sequencing”

The claims of the Asserted Patents all require the use of “sequencing,” and are generic with respect to the type of sequencing that may supposedly be used. The inventors, however, were not in possession of an approach that could be used with generic sequencing approaches. Rather, the only sequencing techniques disclosed in the patent are so-called high-throughput sequencing approaches based on the use of Solexa, Illumina, or Roche sequencing platforms. *See, e.g.*, ’589 Patent at 17:30-35, 17:64, 18:21-25, 18:29-31, 18:62, 25:55-59, 26:15-19, 26:36-38, 28:20-24, Fig. 7a. To the extent the claims are deemed to encompass alternative approaches to sequencing, they

are invalid for failure of written description.

5. The Inventors Were Not In Possession Of Approaches Based On The Use Of Ligation

To the extent the Asserted Patents are deemed to cover the use of ligation for attaching tags, they are invalid for failure of written description. Indeed, the Asserted Patents criticize ligation as an unworkable approach. As the patent states, for instance, “Miner et al. and U.S. Pat. No. 7,537,897 both describe labeling of input nucleic acid molecules by ligation, which has been found to be an inefficient reaction.” ’589 Patent at 2: 20-22. To the extent the Asserted Patents purport to subsequently contemplate the use of ligation, no working examples are provided that teach how to overcome the alleged inefficiency of the ligation process.

B. Enablement

To satisfy the enablement requirement of pre-AIA 35 U.S.C. § 112 ¶ 1 or post-AIA 35 U.S.C. § 112(a), the disclosure “must teach those skilled in the art how to make and use the full scope of the claimed invention without ‘undue experimentation.’” *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). “If a patent claims an entire class of processes, machines, manufacture, or compositions of matter, the patent’s specification must enable a person skilled in the art to make and use the entire class.... In other words, the specification must enable the full scope of the invention as defined by its claims. The more one claims, the more one must enable.” *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023). The Federal Circuit has enumerated several factors to consider in determining whether a disclosure would require “undue experimentation”: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737

(Fed. Cir. 1988). To the extent the Asserted Claims are not invalid under 35 U.S.C. § 102 and/or § 103 as being anticipated and/or obvious, Guardant lists the grounds below upon which it presently contends that certain of the asserted claims of the Patent In-Suit are invalid under 35 U.S.C. § 112 for failure to provide an enabling disclosure. And, to the extent that Plaintiff argues that the enabling disclosure that is missing in the Patent-In-Suit or the priority application thereto may be found in patents or other documents that are incorporated by reference into the Patents-In-Suit or the priority applications thereto, Guardant argues that such incorporations by reference are improper or otherwise fail to provide the missing enabling disclosure for the claims.

As explained above, the Asserted Patents describe a narrow method of nucleic acid counting directed to single cells to determine relative copy number information in the sample. The specification describes only the use of “substantially unique” tags, teaches against the use of ligation, and contemplates only the use of high-throughput sequencing.

The scope of the claims, however, covers any sample type, including complex samples, any type of sequencing, and conceivably other approaches to tagging that do not use “substantially unique” tags. According to CSHL’s infringement contentions, the claims allegedly cover Guardant’s testing products which use cell-free DNA samples and predicting absolute copy number in tumor DNA. Furthermore, the specifications of the Asserted Patents emphasize the advantages the invention provides by tagging nucleic acid molecules using the enzyme terminal transferase “which is a robust enzyme from which high efficiency is expected” in contrast with tagging by ligation which the specification characterizes as an “inefficient reaction.” ’589 Patent at 22:7-8, 22:6. However, the claims of the Asserted Patents do not even discuss terminal transferase and claim 10 of the ’589 Patent claims tagging by ligation.

Similarly, the claims of the Asserted Patents are not limited by sequencing approach, type

of copy number information, mapping method, or construction of nucleic acid tags. However, the specification does not contain support for complex sample types, multiple sequencing approaches, diverse copy number information, or mapping approaches and discloses only a limited set of nucleic acid tags.

Thus, there is a mismatch between the disclosure in the specification and what is claimed. As documented below by evaluation of the *Wands* factors, the Asserted Patents are invalid under 35 U.S.C. § 112 ¶ 1 for failure to provide enabling disclosure which would allow a skilled artisan to practice the full scope of the claimed invention without undue experimentation.

1. Quantity of Experimentation

It would take an undue amount of experimentation to practice the full scope of the claimed methods because the specification provides little to no guidance on using multiple sequencing approaches, mapping sequence reads, constructing nucleic acid tags, calculating copy number information, and analyzing complex sample types, including by using tag sets that are not “substantially unique.” For example, the specification states that tags “may be designed such that the variable portion has a random sequence,” but does not provide guidance on how to generate tags with random sequences. ’589 Patent at 21:33-35. Reading the specifications of the Asserted Patents alone, a skilled artisan would require substantial experimentation to generate tags with random sequences and ensure that the resulting tagged nucleic acid molecules are “unique tagged nucleic acid molecules” as required by step [b] of claim 1 of the two Asserted Patents.

As another example, while the specification describes sequencing with high-throughput, next-generation sequencing methods, step [d] of claim 1 of the Asserted Patents is directed to any sequencing method. The specification describes using “high throughput single molecule sequencing by either the Illumina or Roche 454 methods.” *Id.* at 25:53-54. A skilled artisan would require substantial experimentation to use the claimed methods of the Asserted Patents with other

sequencing technologies, if practicing the methods using other sequencing technologies is even possible.

A skilled artisan would also require substantial experimentation to determine copy number information, especially from complex sample types. Absent guidance from the specification of the Asserted Patents, a skilled artisan would require undue experimentation to apply the claimed methods to determining copy number information of cancer cells in complex samples, such as cell-free DNA samples. Certainly, the specification includes no description of how one would go about inferring copy number variation in a tumor based on a sample of cell-free DNA taken from a cancer patient. Just the opposite, the specification purports to teach two distinct methods of counting nucleic acids to assess the presence of copy number variation, and neither of the disclosed methods teaches how to take into account the background from normal DNA that is present in the patient sample and that would otherwise obscure the informational content from the limited amount of tumor DNA. *See, e.g.*, '589 Patent at 20:1-46. Indeed, such issues are not contemplated in the slightest in the Asserted Patents, confirming that the specification does not enable techniques based on the analysis of cell-free DNA.

As another example, a skilled artisan would require undue experimentation to map sequence reads as required by step [e] of claim 1 of the two Asserted Patents. The specification does not explain or give examples of any mapping algorithms. The specification also states that “an additional degree of freedom, which our algorithms do not yet incorporate, is selecting the ‘boundary’ of the bins.” *Id.* at 19:20-22. This statement requires the skilled artisan to experiment to determine the best bin size to use for mapping.

As yet another example, the specification is clear that the use of a sufficiently large number of tags is central to the alleged invention. *See, e.g.*, '589 Patent at 19:47-49 (“Within a pool of

tagged nucleic acid molecules, each tagged nucleic acid molecule is likely unique in the pool when a sufficiently large number of distinct tags is used.”); *id.* at 23:21-25 (“But if the set of tags are sufficiently large, the tagged nucleic acid molecules will generally differ at more than one nucleotide, and so tagged nucleic acid molecules that differ by a single nucleotide can (optionally) be ignored when counting.”). As to what is a “sufficiently large” number of tags, the specification contemplates only one thing, which is tags that “substantially unique,” defined in the specification to mean “tags in a plurality of tags, wherein at least 50% of the tags of the plurality are unique to the plurality of tags. Preferably, substantially unique tags will be at least 60%, 70%, 80%, 90%, or 100% unique tags.” *Id.* at 16:43-47; *see also id.* at 16:38-42 (defining “substantially unique primers” in terms of tag uniqueness). To the extent the claims are deemed to encompass approaches that use anything other than unique or substantially unique tagging, they fail they enablement requirement. For instance, to the extent the claims are deemed to encompass approaches based on the use of smaller tag sets wherein the number of sample molecules is far in excess of the number of tags, the Asserted Patents provide no guidance for such an approach. Just the opposite, the Asserted Patents warn against such an approach, stating, for instance, that “[i]f the number of molecules at a location on a genome or cDNA library exceeds the number of tags, and tagging is too efficient, copy number information can not be recovered.” *Id.* at 20:35-37. Nowhere does the specification include any discussion of how to address the complexities that may arise when the number of sample molecules is far in excess of the number of tags. The specification, for instance, never includes any discussion of the diversity of molecules that may be present in a sample and how one might use start and stop positions for sequence reads to distinguish among molecules and the number of tags one might need. Instead, the specification assumes that one needs to have a sufficiently large number of tags that are, as defined, in the specification

“sufficiently unique.”

Accordingly, consideration of the quantity of experimentation necessary to practice the full scope of the invention shows that the claims are not enabled for their full scope.

2. Guidance in the Specification

The specification provides little to no guidance on how to practice the claimed inventions, especially to the extent the claims cover multiple sequencing approaches, tag construction, tag numerosities, complex samples, mapping of sequence reads, and techniques for calculating copy number information.

As an example, the specification provides no guidance regarding using complex samples or calculating copy number information beyond a basic counting approach. As discussed above, cell-free DNA samples are mixtures containing DNA fragments from both healthy cells and cells of interest, such as tumor cells, with nearly identical genomic sequences. The Asserted Patents do not enable obtaining copy number information from such samples because the specification of the Asserted Patents contains no discussion of using a mixed initial sample or differentiating counts obtained from a mixed sample. Instead, the specification only provides a brief description of using counts across multiple locations to obtain copy number information:

Step (b) of the above embodiment may further comprise

- i) summing the counts obtained in step (f) for locations on the genome which comprise a third region of the genome, wherein the third region is comprised of a number of locations which is comparable to the number of locations of the first region; and
- ii) ***obtaining an average of the sum of the counts*** obtained in step (f) for locations which comprise the second region and the sum of the counts obtained in step (f) for locations which comprise the third region.

Id. at 7:27-37 (emphasis added). However, this disclosure fails to enable obtaining copy number information for all cells within a mixed cell-free DNA sample—using pure molecule counts or an average of counts at different locations may assist in obtaining copy number information in a

homogenous sample, but neither calculation enables determining copy number information for cells within a mixed sample containing cell-free DNA. This is especially true where the genomes of the two cell populations are nearly identical, and where the cell type of interest makes up only a small fraction of the initial sample. The specification purports to teach two distinct methods of counting nucleic acids to assess the presence of copy number variation, and neither of the disclosed methods teaches how to take into account the background from normal DNA that is present in the patient sample and that would otherwise obscure the informational content from the limited amount of tumor DNA. *See, e.g.,* '589 Patent at 20:1-46. Indeed, such issues are not contemplated in the slightest in the Asserted Patents, confirming that the specification does not enable techniques based on the analysis of cell-free DNA.

As an additional example, the Asserted Claims cover all sequencing approaches, but the specification of the Asserted Patents only describes using “high throughput single molecule sequencing by either the Illumina or Roche 454 methods.” *Id.* at 25:53-54. No guidance is provided for other sequencing approaches, such as Sanger sequencing.

As yet another example, claim 1 of the '510 Patent covers “randomly tagging the segments of genomic nucleic acids with different nucleic acid tags,” and claim 1 of the '589 Patent covers “tagging the segments with nucleic acid tags, thereby generating a plurality of unique tagged nucleic acid molecules.” However, the specification contains limited information about creating these nucleic acid tags. The specification states only that tags “may be designed such that the variable portion has a random sequence” and that “each tagged nucleic acid molecule is likely unique in the pool when a sufficiently large number of distinct tags is used.” *Id.* at 25:53-54, 20:47-49.

The specification provides limited guidance regarding mapping sequence reads to locations

on the genome for counting. The specification defines “mapping” but states only that “[m]apping algorithms then align each sequence read with a high quality score (with a read length in excess of 35 bp) and an unambiguous sample tag to a specific location on the DpnII restriction map of the human genome.” *Id.* at 8-12. The specification does not explain or give examples of any mapping algorithms. The lack of guidance found in the specification is exemplified by the specification’s statement that “an additional degree of freedom, which our algorithms do not yet incorporate, is selecting the ‘boundary’ of the bins.” *Id.* at 19:20-22.

The specification also provides limited guidance regarding calculating different types of copy number information, including deletions and duplications. Figure 4 of the specification of the Asserted Patents analyzes “raw ratio data for...one lane of Solexa sequencing reads” but fails to explain how to use that data to generate relative copy number. *Id.* at 26:37-38, Figure 4. The specification discusses analyzing known cancer cell lines to identify existing deletions but does not provide guidance to discover new deletions, especially if the sample contains heterozygous deletions. *See id.* at 27:39-56.

In sum, consideration of the amount of guidance provided in the specification confirms the failure of enablement.

3. Working Examples

The specifications of the Asserted Patents provides a single working example for a sample with a previously determined copy number. The specification states that “[w]e have previously obtained copy number profiles of SKBR3 genomic DNA from a million cell library, by sequencing and sequence counting” and references Figure 11 to demonstrate calculations of copy number information. *See id.* at 28:29-31, Figure 11. However, Figure 11 provides little detail regarding the copy number calculations. Nor does the specification point to specific locations where a relative copy number was determined. The specification states that data analysis “for the

procedure described above employed a modification of the ‘bin-counting’ method because the NlaIII restriction sites are not distributed evenly in the genome.” *See id.* at 28:40-43. Without further guidance, a skilled artisan would not be able to practice the claimed methods of the Asserted Patents.

Furthermore, the example provided by the specification in Figure 11 analyzed a collection of single cells, not a complex sample, such as a sample containing cell-free DNA.

Given that there is only a single poorly, documented example in the specification, consideration of the working examples confirms lack of enablement.

4. Nature of the Invention

The alleged invention pertains to the determination of copy number using tagging and sequencing. To the extent the claims are not invalid as obvious, the nature of the invention confirms lack of enablement. As set forth in the specification, the invention is supposedly performed using new techniques for high-throughput sequencing and a new method of tagging using terminal transferase. *See id.* at 26:11-12, 22:4-8. The ’589 Patent states that tagging by ligation is an “inefficient reaction” and hence purports to offer new methods. *See id.* at Claim 10, 2:22. As to the counting process, the specification purports to use next generation sequencing in a new way, stating that “[h]igh throughput sequencers are in effect single molecule sequencers. Because the human genome is sequenced and assembled, a single molecule sequencer is also a single molecule identifier. Therefore, sequencing is also counting....” *Id.* at 17:6-9. Thus, the patent purports to offer new uses of instruments that were, at the time, relatively new. To the extent such assertions are true, the nascent nature of the invention weighs against enablement. Additionally, the invention claims counting the number of unique tagged nucleic acid molecules to calculate copy number information. However, as described above, the specification lacks details about working examples of determining copy number that would provide guidance to and allow a

skilled artisan to practice the claimed invention.

5. State of the Prior Art

To the extent that the Asserted Patents are not invalid under 35 U.S.C. §§ 102 and/or 103 as anticipated and/or obvious in view of the prior art, the state of the prior art would have required undue experimentation in light of the specification. For example, to the extent the claims are not invalid in view of prior art, then in the relevant time frame, methods involving cell-free DNA, bin-sizing for sequence read mapping, tag construction, tagging, algorithms to calculate copy number information, and sequencing methods were still new and developing. Without further guidance from the specification, it would have taken a skilled artisan undue experimentation to practice the claimed invention.

6. Relative Skill of Those in the Art

The skill of those in the art in the relevant time around 2010 would have familiarity with standard laboratory techniques, including sample preparation, tagging polynucleotides, PCR, sequencing, and reference genome mapping. Given familiarity with such a wide variety techniques and methods, without further guidance from the specification, a skilled artisan would have needed to engage in undue experimentation to practice the claimed invention.

7. Predictability or Unpredictability of the Art

As noted above, the prior art disclosed a wide variety of methods and techniques for nucleic acid analysis, molecular tagging, amplification, reference genome mapping, and sequencing. As such, determining a particular methodology to successfully calculate copy number information from cell-free DNA samples without further guidance from the specification would have required undue experimentation due to the unpredictable nature of cell-free DNA experimentation.

8. Breadth of the Claims

As explained above, the full scope of the Asserted Claims is very broad in view of the

specifications of the Asserted Patents. The Asserted Claims cover the broad areas of multiple sequencing approaches, tag construction, complex samples, mapping sequence reads, and calculating multiple varieties of copy number information. However, the specifications of the Asserted Patents provide little to no discussion on these topics, preventing a skilled artisan from practicing the full scope of the Asserted Claims without undue experimentation.

V. INVALIDITY BASED ON OBVIOUSNESS AND ANTICIPATION

As set forth below and in the accompanying claim charts, the Asserted Claims are invalid over at least the cited prior art listed pursuant to 35 U.S.C. §§ 102 and/or 103. Guardant identifies below prior art that it contends anticipates and/or renders obvious one or more of the Asserted Claims. To the extent a reference below is not cited against a particular Asserted Claim, Guardant nonetheless may rely on the reference as relevant background art in demonstrating that the Asserted Claim is obvious. References to patents shall be taken to include all related U.S. and foreign patents and/or publications. Guardant may also rely on additional prior art references, alone or in combination with any of the references set forth in Table 1 or the accompanying charts, to further demonstrate that the Asserted Claims are anticipated and/or obvious. Guardant may also rely on expert testimony to explain how the Asserted Claims are anticipated and/or obvious in light of the prior art.

The citations to the prior art and the combinations of prior art references corresponding to the claim limitations in the claim charts are merely exemplary and are not intended to be exhaustive. Some of the citations and those in the corresponding claim charts involve prior art references that have corresponding related, U.S., foreign, and/or PCT counterpart publications. In such cases, it is to be understood that the corresponding disclosures from the counterpart patent and publications (which are largely substantively the same) are implicitly incorporated by reference in the alternative to avoid needless repetition. For the claim charts, Guardant identifies

disclosures in the prior art concerning the preamble without regard to whether the preamble is a claim limitation. Terms in the preamble may not be claim limitations.

Specific combinations of prior art, by way of example, are provided below. The use of a prior art reference in an obviousness combination, however, does not preclude the use of the reference as an anticipatory reference. In addition, Guardant incorporates by reference each and every prior art reference of record in the prosecution of the Patents-in-Suit and related applications, including the statements made therein by the applicant, as well as the prior art discussed in the specification.

A. Inter Partes Review

In IPR2025-01353 and IPR2025-01355, Guardant argues that Lo in view the knowledge of a POSA as reflected in McCloskey, Brenner, Chee, and Porreca rendered obvious the Asserted Claims of the '589 Patent and '510 Patent. Guardant also argues that Quake in view of the knowledge of a POSA as reflected in McCloskey, Brenner, Chee, and Porreca rendered obvious claims 4-5 of the '589 Patent. Guardant incorporates in full all invalidity arguments made in IPR2025-01353 and IPR2025-01355. The same prior art and combinations thereof before the Patent Trial and Appeal Board renders the Asserted Claims of the Patents-in-Suit invalid here.

B. Anticipation

Under 35 U.S.C. § 102(a) an applicant is not entitled to a patent, “if the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.” A patent claim is anticipated by “a prior art reference which expressly or inherently contains each and every limitation of the claimed subject matter.” *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003). The party asserting invalidity bears the burden of proving it by clear and convincing evidence. Even if the prior art relied on was previously considered by the Patent Office, that

burden remains constant. *Sciele Pharma, Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012). A prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is inherent in the single anticipating reference. *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 471 F.3d 1363, 1368 (Fed. Cir. 2006) (quoting *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003)); see *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005). A prior art reference must be enabling to constitute an anticipation. *In re Elsner*, 381 F.3d 1125, 1128 (Fed. Cir. 2004). “When an accused infringer asserts that a prior art patent anticipates specific patent claims, the infringer enjoys a presumption that the anticipating disclosure also enables the claimed invention.” *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 545 F.3d 1312, 1316 (Fed. Cir. 2008).

To the extent the Asserted Claims are not deemed invalid under 35 U.S.C. § 112 for lack of written description, enablement, or indefiniteness, Guardant contends that certain Asserted Claims of the ’589 Patent are anticipated by Rotter (2009) alone, to the extent any of Guardant’s commercial products are deemed to infringe the Patents-in-Suit. *See* Exhibit A14.

To the extent the Asserted Claims are not deemed invalid under 35 U.S.C. § 112 for lack of written description, enablement, or indefiniteness, Guardant contends that certain Asserted Claims of the ’510 Patent are anticipated by Rotter (2009) alone, to the extent any of Guardant’s commercial products are deemed to infringe the Patents-in-Suit. *See* Exhibit B14.

C. Obviousness

To the extent the Asserted Claims are not deemed invalid under 35 U.S.C. § 112 for lack of written description, enablement, or indefiniteness, Guardant contends that the prior art listed in Table 1, whether alone or in combination with each other, renders the Asserted Claims of the Patents-in-Suit obvious under 35 U.S.C. § 103, as set forth in the claim charts.

In particular, each prior art reference may be combined with: (1) information known to

persons skilled in the art at the time of the alleged invention; (2) any other prior art references listed in Table 1; (3) any additional prior art Guardant may identify; and (4) any additional prior art identified or to be identified in prosecution of the Patents-in-Suit or their related patent applications. The citations to the prior art corresponding to the claim limitations in the claim charts are merely exemplary and are not intended to be exhaustive.

Additionally, while the burden of proof is on the Plaintiff to show any objective indicia of non-obviousness, Guardant reserves the right to respond to any objective indicia raised by the Plaintiff.

1. State of the Art Before the Priority Date of the Patents-in-Suit

The Asserted Claims of the Asserted Patents are generally made up of a set of discrete concepts. As explained in the table below, claim 1 of the '589 Patent is composed of the following discrete concepts.

'589 Patent Claim Language	Concept(s)
[1A] 1. A method comprising: a) obtaining segments of genomic nucleic acids from a sample	Sample preparation
[1B] b) tagging the segments with nucleic acid tags, thereby generating a plurality of unique tagged nucleic acid molecules, such that each of the unique tagged nucleic acid molecules comprises a segment of the segments of the genomic nucleic acids from step (a) and a nucleic acid tag of the nucleic acid tags;	Tagging of nucleic acid molecules
[1C] c) subjecting the plurality of the unique tagged nucleic acid molecules to a polymerase chain reaction (PCR), thereby generating amplified tagged nucleic acid molecules;	Amplification
[1D] d) generating tag associated sequence reads by sequencing the amplified tagged nucleic acid molecules of step (c);	Sequencing

[1E] e) assigning each of the amplified tagged nucleic acid molecules to a location on a reference genome from the same species from which the sample has been obtained by mapping each of the tag associated sequence read of step (d) to a location of the reference genome; and	Mapping sequences to a reference genome
[1F] f) at a plurality of locations on the reference genome, counting the number of unique tagged nucleic acid molecules that have been assigned to the same location on the reference genome based on the mapping step to obtain a count for each location of the plurality of locations on the reference genome, thereby obtaining copy number information from genomic nucleic acids in the sample	Counting; Copy Number Variation

Claim 1 of the '510 Patent is contains similar claim language and is composed of the same discrete concepts.

'510 Patent Claim Language	Concept(s)
[1A] A method comprising: a) obtaining segments of genomic nucleic acids from a sample containing the genomic nucleic acids;	Sample preparation
[1B] b) randomly tagging the segments of genomic nucleic acids with different nucleic acid tags, thereby generating unique tagged nucleic acid molecules from the segments of genomic nucleic acids, such that each of the unique tagged nucleic acid molecules comprises a segment of the segments of the genomic nucleic acids from step (a) and a nucleic acid tag of the nucleic acid tags;	Tagging of nucleic acid molecules
[1C] c) subjecting the unique tagged nucleic acid molecules to a polymerase chain reaction (PCR), thereby generating copies of the unique tagged nucleic acid molecules;	Amplification
[1D] d) generating tag associated sequence reads by sequencing the copies of the unique tagged nucleic acid molecules of step (c);	Sequencing

[1E] e) assigning each of the unique tagged nucleic acid molecules to a location on a genome by mapping each of the tag associated sequence reads of step (d) to a location in the genome; and	Mapping sequences to a reference genome
[1F] f) in a plurality of locations in the genome, obtaining relative copy number information of the genomic nucleic acids from the sample based on the number of unique tagged nucleic acid molecules that have been assigned to each of the plurality of locations in the genome.	Counting; Copy Number Information

The claims of the Asserted Patents consist of similar combinations of these general concepts. Groups of prior art references disclosing these and related concepts are set forth below:

- Prior art teaching the use of molecular tags to identify and track nucleic acid molecules includes, for instance and without limitation: McCloskey, Brenner, Chee, Porreca, Miner, Fodor, Rotter, Casbon, Linnarsson, Hug, Binladen, McCloskey II (the “**Tagging Art**”)
- Prior art teaching the use of amplification of nucleic acid molecules includes, for instance and without limitation: Lo, Quake, McCloskey, Brenner, Chee, Porreca, Miner, Fodor, Rotter, Casbon, Linnarsson, Hug, Degrelle, Yang, Schochetman, Binladen, McCloskey II, Persing (the “**Amplification Art**”)
- Prior art teaching sequencing nucleic acids to collect sequence information includes, for instance and without limitation: Lo, Quake, McCloskey, Brenner, Chee, Porreca, Miner, Fodor, Rotter, Casbon, Xie, Linnarsson, Hug, Chiu, Wang, Chiang, Mardis, Mardis II, Binladen, McCloskey II, Holt, Hutchinson, Dohm, Tian (the “**Sequencing Art**”)
- Prior art teaching mapping of nucleic acid sequences to a reference genome

includes, for instance and without limitation: Lo, Quake, Xie, Fodor, Rotter, Chiu, Wang, Chiang, Itsara, Mefford, Binladen (the “**Mapping Art**”)

- Prior art teaching counting molecules by sequencing includes, for instance and without limitation: Lo, Quake, McCloskey, Brenner, Chee, Porreca, Miner, Fodor, Rotter, Casbon, Xie, Linnarsson, Hug, Chiu, Wang, Chiang, McCloskey II (the “**Counting Art**”)
- Prior art teaching methods of obtaining copy number information includes, for instance and without limitation: Lo, Quake, Brenner, Porreca, Fodor, Rotter, Xie, Chiu, Wang, Chiang, Itsara, Mefford (the “**Copy Number Information Art**”)
- Prior art teaching the preparation of nucleic acid samples includes, for instance and without limitation: Lo, Quake, McCloskey, Brenner, Chee, Porreca, Miner, Fodor, Rotter, Casbon, Xie, Linnarsson, Hug, Chiu, Wang, Chiang, Makarov, Binladen, McCloskey II (the “**Sample Preparation Art**”)

For the reasons stated below, the Asserted Claims would have been obvious in view of the numerous prior art references that were available before the priority dates of the Patents-in-Suit. In particular, the Asserted Claims would have been rendered obvious in view of the combinations of groups of prior art describe above. These prior art combinations are not exhaustive—they are illustrative examples of prior art combinations based on the following categories of art and specific references within these categories of art and the art listed above.

2. The Asserted Claims Would Have Been Obvious in View of the Prior Art References

To the extent the Asserted Claims are not invalid under 35 U.S.C. § 112 for lack of written description, enablement, or indefiniteness, the following combinations of art render the claims obvious. Examples are set forth in the claim charts in the attached exhibits. The combinations

below are merely exemplary and are not intended to be exhaustive:

- The Asserted Claims are rendered obvious by any reference of the Tagging Art, alone or in combination, with any reference of the Mapping Art.
- The Asserted Claims are rendered obvious by any reference of the Copy Number Information Art, alone or in combination, with any reference of the Tagging Art.

3. Motivation to Combine

A person of skill in the art would have been motivated to combine the preceding references. Teachings, suggestions, motivations, and or reasons to modify any of the references and/or to combine any two or more of the references can come from many sources, including the prior art (specific and as a whole), common knowledge, common sense, predictability, expectations, industry trends, design incentives or need, market demand or pressure, market forces, obviousness to try, the nature of the problem faced, and/or knowledge possessed by a person of ordinary skill.

Although a patent claim may be invalidated based on a teaching-suggestion-motivation (“TSM”) rationale-i.e., that some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference to combine prior art reference teachings to arrive at the claimed invention-the Supreme Court identified additional rationales in *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007). The following of these rationales apply here:

- a) The Asserted Claims combine prior art elements, such as tagging, amplification, sequencing, mapping, and counting, according to known methods to yield predictable results;
- b) The Asserted Claims involve the simple substitution of one known element for another to obtain predictable results;
- c) The Asserted Claims involve the use of a known technique to improve similar devices

- (methods or products) in the same way;
- d) The Asserted Claims apply a known technique to a known device (method or product) ready for improvement to yield predictable results;
 - e) The Asserted Claims involve combinations of prior art references that would have been “obvious to try”—a person of ordinary skill in the art could have reached the Asserted Claims by choosing from a finite number of identified, predictable solutions with a reasonable expectation of success;
 - f) The Asserted Claims are simply variations of work from one field of endeavor or a different one that would have been prompted based on design incentives or other market forces because the variations were predictable to one of ordinary skill in the art.

KSR, 550 U.S. at 414-18 (rejecting the Federal Circuit’s “rigid” application of the teaching, suggestion, or motivation to combine test, and instead espousing an “expansive and flexible” approach); *see also* Department of Commerce, Patent and Trademark Office, *Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57526 (Oct. 10, 2007). Indeed, the Supreme Court held that a person of ordinary skill in the art is “a person of ordinary creativity, not an automaton” and “in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle.” *KSR*, 550 U.S. at 420-21.

Thus, even in the absence of a specific teaching, suggestion, or motivation to combine references, the Asserted Claims here are obvious and therefore invalid. Each of the cited references is in the same field, making it obvious for someone of ordinary skill in the art to identify and combine elements from these references. One of skill in the art would have recognized that improvements could be achieved by combining or modifying prior art references that described

such improvements. Each of the above prior-art references describes methods that were known to offer such improvements, and, accordingly, one of skill in the art would have been motivated to combine or modify the references as identified in each of the combinations above.

The '589 Patent and '510 Patent recite the analysis of genomic nucleic acid molecules by applying the prior art techniques of tagging, amplification, sequencing, mapping, and counting towards obtaining copy number information. The nucleic acid tags can be used to identify unique copies of molecules that exist in the sample prior to amplification and sequencing. By mapping the nucleic acid sequences to a reference genome, copy number information can be generated by counting the number of starting molecules in the sample. Each step of the claimed inventions and the concepts they correspond to were well known in the art before the filing of the Asserted Claims, as set forth in the accompanying claim charts.

To the extent the Asserted Claims are understood to require obtaining copy number information, this concept was well known before the Patents-in-Suit were filed. *See, e.g.*, the Copy Number Information Art; Lo ¶¶ 14, 60; Quake at 3:47-56; Xie at 2; Chiang at Abstract, 99.

To the extent the Asserted Claims are understood to require tagging nucleic acid molecules, including tagging with random tags and tags with unknown sequences, this concept was well known before the Patents-in-Suit were filed. *See, e.g.*, Tagging Art; McCloskey at 762, 764; Brenner at Abstract, 3:15-24, 5:16-23; Chee at 2:21-30, 11:14-25; Porreca at 5:1-8, 29:28-33; Rotter ¶¶ 13, 18; Fodor at 3:58-4:2; Miner at 1; Casbon at Abstract, 2:10-27; Hug at 618; or Linnarsson at ¶¶ 18-19. Indeed, the specification of the Patents-in-Suit admit as much. *See* '589 Patent at 2:1-28.

To the extent Plaintiff contends that the Mapping Art and Copy Number Information Art does not disclose the use of tagging to mitigate the amplification distortion of PCR, it would have

been obvious to one having ordinary skill in the art to combine the teaching of those references with any one or more of the methods taught in the Tagging Art, for example Miner at 1, McCloskey at 762, Chee at 10:42-46, Brenner at 3:15-24, Porreca at 58:43-49, Rotter ¶¶ 10-13, and Fodor at 23:32-35, for at least the following reasons.

First, the method of tagging prior to amplification and counting was well-known and was part of the standard tool kit of the skilled artisan, since it offered a known solution to a known problem: the need to improve the accuracy of counting molecules, particularly in situations where there were few sample DNA molecules and/or it is important to be more accurate in counting.

Second, the Mapping Art and Copy Number Information Art teach approaches based on counting, and a POSA would desire to count as accurately as possible. Using tagging as described in the Tagging Art in combination with the Mapping Art and Copy Number Information Art would enable one to subsequently use amplification unaffected by amplification bias. The ability to use amplification would allow one to ensure that one better captures the full range of molecules from the chromosome or chromosome region of interest, which would further improve the overall counting accuracy.

Third, several Tagging Art references expressly contemplate using the tagging method specifically to determine copy number information. For example, Brenner discusses using tagging and subsequent amplification to for the “measurement of genetic copy number variation.” Brenner at 4:6-7. Porreca discloses a method for “detecting nucleic acid deletions or insertions in regions containing nucleic acid sequence repeats” for cancer detection “which has been associated with micro satellite instability (MSI) involving an increase or decrease in the genomic copy number of nucleic acid repeats at one or more microsatellite loci.” Porreca at 55:48-51, 56:54-58; *see also*, *e.g.*, Casbon at 18:30-49, Rotter ¶ 2, Fodor at 1:59-62, 2:53-56.

Fourth, the addition of the tagging features described in the Tagging Art would help to solve the signal-to-noise challenge described in several of the Mapping Art and Copy Number Information Art references. For example, Lo explains that “fetal DNA is present in low absolute concentration” in maternal plasma, creating a low signal problem. Lo ¶ 13. Lo emphasized that it was “desirable to have methods that allow the noninvasive detection of fetal chromosomal aneuploidy by maximizing the amount of genetic information that could be inferred from the limited amount of fetal nucleic acids which exist as a minor population in a biological sample containing maternal background nucleic acids.” *Id.* Chiu states that “the fact that fetal DNA represents only a minor fraction of total DNA in maternal plasma, with the majority being contributed by the pregnant woman herself, has offered considerable challenge.” Chiu at 1; *see also* Quake at 27:59-61, 4:12-16. A POSA would understand that amplification could be used to increase the measured signal and that tagging could be used to preserve the original ratio of nucleic acids measured.

Furthermore, a POSA would have reasonable expectation of success because the tagging and counting techniques described were well-known in the art and because the Tagging Art provided a predictable solution to a known problem. Tagging was well-known in the art before the filing of the Asserted Patents as described in each of the Tagging Art references and was frequently used in combination with PCR amplification. ’589 Patent at 2:10-28; *see also* the Amplification Art. The Tagging Art references recognize the problem of amplification bias and provide a predictable solution. For example, in Miner, each “genomic fragment is marked prior to amplification, allowing us to...quantify accurately the proportion of cells carrying a particular sequence variant by counting only distinctly tagged sequences. This highly sensitive method offers confirmation of the independent genomic origin of all sequences in final data sets derived

from PCR amplification.” Miner at 1. The specification of the ’589 Patent highlights the problem of “amplification distortion” but admits that tagging was a known solution. ’589 Patent at 2:10-28. Indeed, the specification points to Miner, Brenner, and McCloskey as describing methods using random tags to accurately count starting molecules after amplification. *Id.*

To the extent Plaintiff contends that the Tagging Art and Counting Art does not disclose mapping sequence reads to genomic regions or estimating copy number, it would have been obvious to one having ordinary skill in the art to combine the teaching of those references with any one or more of the methods taught in the Mapping Art and Copy Number Information Art, for example Lo ¶ 70, Quake at 3:47-56, Rotter ¶ 137, Wang at 16:157, Chiu at 20:459, and Chiang at 99-101, for at least the following reasons.

First, both the Counting Art and Copy Number Information Art as sequencing and counting-based methods. Indeed, as mentioned above, the several references in the Tagging Art and Counting Art explicitly contemplated applying the sequencing and counting techniques to copy number information. *See, e.g.*, Brenner at 4:6-7; Porreca at 55:48-51, 56:54-58; Casbon at 18:30-49, Rotter ¶ 2, Fodor at 1:59-62, 2:53-56.

Second, the genomic mapping techniques described in the Mapping Art were well-known techniques to apply molecular counting to genomic copy number. *See, e.g.*, Chiu at 20:459 (“One end of the clonally expanded copies of each plasma DNA fragment was sequenced and processed by standard postsequencing bioinformatics alignment analysis for the Illumina Genome Analyzer, which uses the Efficient Large-Scale Alignment of Nucleotide Databases (ELAND) software.”); Rotter ¶ 137 (“Using a BLAST search with the RAT-TAG construct in GenBank, the individual TAGs could be assigned to a specific human gene”); Lo ¶ 93 (“All reads were then aligned to the repeat-masked reference human genomic sequence, NCBI 36 assembly (GenBank accession

numbers: NC_000001 to NC_000024), using the Eland application.”). It was commonplace to use existing software like ELAND and BLAST and to map genomic sequence reads to locations on the genome. Copy number information relates to the number of copies of a specific gene, chromosomal region, or chromosome, and the Mapping Art facilitates counting by describing techniques that allow mapping of genomic sequences to specific locations in the genome. It would have been obvious to a person of skill in the art to using mapping techniques to apply molecular counting techniques to copy number information.

To the extent the Counting Art, Mapping Art, and/or Copy Number Information Art do not disclose estimating copy number at multiple locations, comparing the count from step (f) between the target sample and a reference sample, and estimating copy number using sums of counts at multiple locations (e.g. claims 2, 3, and 6 of the ’589 Patent), using such counting methods would have been obvious to the skilled artisan based on disclosures of mapping and counting in the prior art and because using multiple locations would improve accuracy. *See generally* the Mapping Art and the Copy Number Variation Art; *see also, e.g.*, Lo ¶¶ 14, 44, 67, 71, 99, 108; Wang at 16159-60; Chiu at 20459, Figure 1.

To the extent the Tagging Art, Counting Art, Mapping Art, and/or Copy Number Information Art do not disclose using more than one tag, sample tagging and sample pooling (e.g. claims 11, 12, 14, and 15 of the ’589 Patent and claims 5, 6, and 7 of the ’510 Patent), using sample tags and pooling samples would have been obvious to the skilled artisan based on disclosures of sample tagging in the prior art and because the technique was commonplace. *See generally* the Tagging Art; *see also, e.g.*, Brenner at 21:29-32, McCloskey at 763-764, Porreca at 21:4-6.

To the extent the Tagging Art, Counting Art, Mapping Art, and/or Copy Number Information Art do not disclose hybrid capture (e.g. claims 7 and 8 of the ’589 Patent and claims

9 of the '510 Patent), including hybrid capture methods would have been obvious to the skilled artisan based on disclosures of hybrid capture in the prior art and because the technique was commonplace. *See generally* the Sample Preparation Art; *see also, e.g.*, Lo ¶ 77, Brenner at 43:26-31, Chee at 15:34-43, Porreca at 64:59-64, Rotter ¶ 37.

To the extent the Tagging Art, Counting Art, Mapping Art, and/or Copy Number Information Art do not disclose using blood or tumor samples (e.g. claims 17 and 18 of the '589 Patent and claim 11 of the '510 Patent), using such samples would have been obvious to the skilled artisan based on disclosures of blood and tumor samples in the prior art and because using such samples was commonplace. *See generally* the Sample Preparation Art; *see also, e.g.*, Lo ¶¶ 52, 92; Quake at 3:35-39; Brenner at 27:10-15; Porreca at 13:56-60; Chiu at 20462-63.

To the extent the Tagging Art, Counting Art, Mapping Art, and/or Copy Number Information Art do not disclose using genomic nucleic acids from a single species, single cell, two or more organisms, two or more species, or from a population of microbes (e.g. claim 10 of the '510 Patent), using such samples would have been obvious to the skilled artisan based on disclosures in the prior art and because using such samples was commonplace. *See generally* the Sample Preparation Art; *see also, e.g.*, Lo ¶¶ 6, 92; Quake at 3:43-45; Brenner at 21:29-32; Porreca at 13:56-60; Chiu at 20458.

To the extent the Tagging Art, Counting Art, Mapping Art, and/or Copy Number Information Art do not disclose using mechanical shearing or sonicating (e.g. claim 4 of the '510 Patent), using such techniques would have been obvious to the skilled artisan based on disclosures of mechanical shearing and sonicating in the prior art and because those techniques were commonplace. *See generally* the Sample Preparation Art; *see also, e.g.*, Brenner at 18:33-34, Porreca at 71:16-19, Rotter ¶ 113.

To the extent the Tagging Art, Counting Art, Mapping Art, and/or Copy Number Information Art do not disclose using region-specific PCR primers (e.g. claim 2 of the '510 Patent), using such primers would have been obvious to the skilled artisan based on disclosures of region-specific primers in the prior art and because using such primers was commonplace. *See generally* the Amplification Art; *see also, e.g.*, McCloskey at 762, Chee at 17:48-50, Brenner at 38:58-60, Porreca at 39:19-24, Rotter ¶ 17.

To the extent the Tagging Art, Counting Art, Mapping Art, and/or Copy Number Information Art do not disclose using tags that are sufficiently large in number or differ at more than one molecule (e.g. claim 9 of the '589 Patent and claims 3 and 22 of the '510 Patent), using such tags would have been obvious to the skilled artisan based on disclosures of tagging in the prior art and because using such tags mitigated the known problem of sequencing errors. *See generally* the Tagging Art; *see also, e.g.*, McCloskey at 762, 764; Chee at 11:18-22; Brenner at 21:14-18, 37:48-55; Porreca at 73:10-38; Rotter ¶¶ 18, 39.

To the extent the Tagging Art, Counting Art, Mapping Art, and/or Copy Number Information Art do not disclose tagged molecules which are unique based on a combination of sequence information in the tags and genomic nucleic acids (e.g. claims 12 and 23 of the '510 Patent), determining uniqueness in that way would have been obvious to the skilled artisan based on disclosures of tagging in the prior art and because the standard counting mechanism counted unique sequence reads. *See generally* the Tagging Art; *see also, e.g.*, Chee at 5:27-29, 9:54-60, Brenner at 5:17-21, 18:2-4, Porreca at 5:41-43, 29:13-14, 72:67-73:2, Rotter ¶¶ 39-40.

To the extent the Tagging Art, Counting Art, Mapping Art, and/or Copy Number Information Art do not disclose using tags with constant and variable portions with same and different lengths (e.g. claims 15, 16, 17, 26, 27, and 28 of the '510 Patent), using such tags would

have been obvious to the skilled artisan based on disclosures of tagging in the prior art and because using such tags was commonplace and efficient for combining tagging with preparation for sequencing. *See generally* the Tagging Art; *see also, e.g.*, McCloskey at 762; Chee at 2:65-67; Brenner at 8:31-33, 43:45-53, 14:30-33; Porreca at 31:21-27, Rotter ¶¶ 16, 18, 34, 39, 113, 128.

To the extent the Tagging Art, Counting Art, Mapping Art, and/or Copy Number Information Art do not disclose using double-stranded tags (e.g. claim 8 of the '510 Patent), using such tags would have been obvious to the skilled artisan based on disclosures of double-stranded tagging in the prior art and because using such tags was commonplace. *See generally* the Tagging Art; *see also, e.g.*, McCloskey at 764; Brenner at 28:37-39; Porreca at FIG. 4C; Rotter ¶¶ 19, 130.

To the extent the Tagging Art, Counting Art, Mapping Art, and/or Copy Number Information Art do not disclose using ligation to tag nucleic acid molecules (e.g. claim 10 of the '589 Patent), using ligation to attach nucleic acid tags would have been obvious to the skilled artisan based on disclosures of ligation-based tagging in the prior art and because using ligation was commonplace. *See generally* the Tagging Art; *see also, e.g.*, Chee at 11:18-20, 23:28-35; Brenner at 17:60-64; Porreca at 31:10-21; Rotter ¶¶ 37, 47-48.

To the extent the Tagging Art, Counting Art, Mapping Art, and/or Copy Number Information Art do not disclose using only two or three species of nucleic acid in the variable portions of nucleic acid tags (e.g. claims 18, 19, 20, 21, 29, 30, 31, and 32 of the '510 Patent), using such tags would have been obvious to the skilled artisan based on disclosures in the prior art and because using such tags could assist in identifying sequencing errors. *See generally* the Tagging Art; *see also, e.g.*, Casbon at 15:24-41, Table 1; Kless at 2:61-3:44; Tian at 715-17.

To the extent the Tagging Art, Counting Art, Mapping Art, and/or Copy Number Information Art do not disclose ignoring tagged nucleic acid molecules that differ by a single

nucleotide (e.g. claim 13 of the '589 Patent), ignoring such similar sequencing reads during counting would have been obvious to the skilled artisan based on disclosures in the prior art and because ignoring such reads would improve counting accuracy. *See generally* the Tagging Art; *see also, e.g.*, Chee at 23:19-25; Porreca at 65:62-66:2, 78:1-8.

For all possible combinations, a skilled artisan would have had a reasonable likelihood of success because, as made clear by the extensive list of prior art in Section V.C.1, the Tagging Art, Counting Art, Mapping Art, and Copy Number Information Art all describe techniques that were well known as of the earliest priority dates of the Asserted Patents.

VI. INVALIDITY BASED ON 35 U.S.C. § 101

35 U.S.C. § 101 precludes the patenting of mental processes and abstract ideas. *See Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012). The Supreme Court has established a framework for distinguishing patents that claim laws of nature, natural phenomenon, and abstract ideas from those that claim patent-eligible applications of those concepts. *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2350 (2014). First, the court determines whether the claim is directed to a law of nature, natural phenomenon, or an abstract idea. *Id.* at 2355. If so, the court then proceeds to step two and considers the elements of the claim “both individually and ‘as an ordered combination’ to determine whether the additional elements ‘transform the nature of the claim’ into a patent-eligible application.” *Id.* Absent such an “inventive concept,” a patent directed to abstract ideas is not patent eligible. *Id.*

The Asserted Claims of the Asserted Patents are directed to non-statutory subject matter under 35 U.S.C. § 101 because the claims are directed to an abstract idea – namely, tagging, copying, and counting nucleic acid molecules. Tagging is a patent ineligible idea and has long been used to record the source of items that are labeled, making this the practice of an abstract idea. *See Gonzalez v. Infostream Grp., Inc.*, No. 2:14-cv-906-JRG, 2016 WL 1643313, at *4 (E.D.

Tex. Apr. 25, 2016) (“The claims themselves offer nothing more than taking the well-known concept of labeling and applying it to the internet.”). The idea of counting molecules is similarly abstract. The Federal Circuit has even found more complex algorithms directed to genetic information to be ineligible subject matter. *See In re Bd. of Trustees of Leland Stanford Junior Univ.*, 991 F.3d 1245, 1246 (Fed. Cir. 2021) (affirming the Patent Trial and Appeal Board’s decision holding an algorithm to determine genetic haplotype phasing to be subject matter ineligible). Nor does limiting the abstract idea of tagging to a particular technological context does not make it patent eligible. *See Alice*, 134 S. Ct. at 2358 (“the prohibition against patenting abstract ideas cannot be circumvented by attempting to limit the use of [the idea] to a particular technological environment”).

Furthermore, there is no inventive concept claimed by the Asserted Patents beyond tagging and counting DNA fragments. *See generally* D.I. 15. The background of the invention admits that tagging, copying, and counting DNA were previously described and conventional. D.I. 15, Ex. 1 at 2:12-28. The dependent claims of the Asserted Patent add no additional inventive elements that would preserve eligibility—the dependent claims recite well-known sample manipulation techniques and further abstract ideas like the idea of using a second tag for labeling different sample sources or using a diverse set of tags where each tag is hard to confuse with any other tag. *See, e.g.* D.I. 15, Ex. 1 at Claims 7-14. Thus, the claims of the Asserted Patents do not include additional elements that are sufficient to overcome the judicial exception of unpatentability under 35 U.S.C. § 101.

VII. CONCLUSION

Precise identification of all of the bases upon which the Asserted Claims are invalid and/or unenforceable are likely to be revealed only after further developments in the case, including claim construction and fact and expert discovery. Guardant reserves the right to amend or supplement

these Invalidity Contentions to address any additional invalidity arguments that become apparent in view of any relevant facts and information revealed during discovery.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on September 19, 2025, true and correct copies of the foregoing document were caused to be served on the following counsel of record as indicated:

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