IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

Ravgen, Inc., Plaintiff, v. Ariosa Diagnostics, Inc., Roche Sequencing Solutions, Inc., Roche Molecular Systems, Inc., and Foundation Medicine, Inc., Defendants.	Civil Action No. _____ **JURY TRIAL DEMANDED**

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Ravgen, Inc. ("Ravgen"), for its Complaint against Defendants Ariosa Diagnostics, Inc. ("Ariosa"), Roche Sequencing Solutions, Inc. ("RSS"), Roche Molecular Systems, Inc. ("RMS"), and Foundation Medicine, Inc. ("FMI") (collectively "Defendants"), hereby alleges as follows:

NATURE OF THE ACTION

1. This is a civil action for infringement of United States Patent Nos. 7,727,720 (the "'720 Patent") and 7,332,277 (the "'277 Patent") (collectively the "Patents-in-Suit"), arising under the Patent Laws of the United States, 35 U.S.C. §§ 271 *et seq*.

THE PARTIES

2. Plaintiff Ravgen is a Delaware corporation with its principal place of business at 9241 Rumsey Rd., Columbia, MD 21045. Ravgen is a pioneering diagnostics company that focuses on non-invasive prenatal testing. Ravgen has spent millions of dollars researching and developing novel methods for the detection of cell-free DNA to replace conventional, invasive procedures. Ravgen's innovative cell-free DNA technology has various applications, including

non-invasive prenatal and other genetic testing. Those efforts have resulted in the issuance of several patents, including the Patents-in-Suit.

3. Defendant Ariosa is a company organized and existing under the laws of the State of Delaware, with its principal place of business at 5945 Optical Court, San Jose, California 95138. (Ex. 6 (U.S. Security and Exchange Commission webpage for Ariosa) (https://sec.report/CIK/0001493753); Ex. 7 ¶ 8 (*Illumina, Inc. v. Ariosa Diagnostics, Inc*., Case No. 3:18-cv-02847-SI, D.I. 40 (N.D. Cal. Aug. 9, 2018) (Ariosa's Amended Answer to Complaint)).) Ariosa is a wholly owned subsidiary of RMS. (Ex. 7 ¶¶ 8, 10; Ex. 8 at 5 (*Ariosa Diagnostics, Inc. v. Illumina, Inc.*, Case No 2016-2388, D.I. 15 (Fed. Cir. Aug. 12, 2016) (Ariosa's Certificate of Interest)).) Ariosa has appointed the Corporation Trust Company, 1209 Orange St., Wilmington, Delaware 19801 as its agent for service of process. (Ex. 78 (State of Delaware Entity Status for Ariosa Diagnostics, Inc.).)

4. Defendant RSS is a company organized and existing under the laws of the State of Delaware, with its principal place of business at 4300 Hacienda Drive, Pleasanton, California 94588. (Ex. 9 ¶ 9 (*Illumina, Inc. v. Ariosa Diagnostics, Inc*., Case No. 3:18-cv-02847-SI, D.I. 41 (N.D. Cal. Aug. 9, 2018) (RMS's and RSS's Amended Answer to Complaint).) RSS is a wholly owned subsidiary of RMS. (*Id.*) RSS has appointed the Corporation Trust Company, 1209 Orange St., Wilmington, Delaware 19801 as its agent for service of process. (Ex. 79 (State of Delaware Entity Status for Roche Sequencing Solutions, Inc.).)

5. Defendant RMS is a company organized and existing under the laws of the State of Delaware, with its principal place of business at 4300 Hacienda Drive, Pleasanton, California 94588. (Ex. 9 ¶ 10.) RMS has appointed the Corporation Trust Company, 1209 Orange St.,

Wilmington, Delaware 19801 as its agent for service of process. (Ex. 80 (State of Delaware Entity Status for Roche Molecular Systems, Inc.).)

6. Defendant FMI is a company organized and existing under the laws of the State of Delaware, with its principal place of business at 150 Second Street, Cambridge, MA 02141. (Ex. 10 (U.S. Security and Exchange Commission webpage for FMI) (https://sec.report/CIK/0001488613); Ex. 11 (https://www.foundationmedicine.com/contact).) FMI has appointed the Corporation Service Company, 251 Little Falls Drive, Wilmington, Delaware 19808 as its agent for service of process. (Ex. 81 (State of Delaware Entity Status for Foundation Medicine, Inc.).)

7. Defendants, themselves and/or through their subsidiaries and affiliates, make, use, and commercialize genetic tests using cell-free DNA, including non-invasive prenatal tests for the determination of fetal chromosomal abnormalities marketed under the trade name "Harmony." Defendants offer and market these tests throughout the United States, at least through the websites www.harmonytest.com and diagnostics.roche.com. (*See generally* Ex. 12 (https://harmonytest.com/en/expecting-parents.html); Ex. 13 (https://diagnostics.roche.com/us/en/products/other/harmony-expecting-parents.html#product-information).)

8. Defendants, themselves and/or through their subsidiaries and affiliates, make, use, and commercialize genetic tests using cell-free DNA, including genetic diagnostic tests for tumor detection marketed under the trade names "FoundationACT," "Foundation One Liquid," and "FoundationOne Liquid CDx." Defendants offer and market these tests throughout the United States, at least through the websites foundationone.com, foundationmedicine.com, and rochefoundationmedicine.com. (*See generally* Ex. 56 (May 4, 2017 Archive of FMI's Website)

(https://web.archive.org/web/20170501215550/http://foundationone.com/learn.php#4); Ex. 57 (January 22, 2019 Archive of FMI's Website) (https://web.archive.org/web/20190122053016/https://www.foundationmedicine.com/); Ex. 15 (https://www.foundationmedicine.com/test/foundationone-liquid-cdx); Ex. 16 (https://www.rochefoundationmedicine.com/home/services/liquid.html).)

9. Defendants, themselves and/or through their subsidiaries and affiliates also make, use, and commercialize direct-draw tubes for collection, stabilization, and transportation of whole blood specimens, such as the "Roche Cell-Free DNA Collection Tube" and "FoundationOne Liquid CDx cfDNA Blood Collection Tube." Defendants offer the Roche Cell-Free DNA Collection Tube throughout the United States, at least through the website sequencing.roche.com/en.html. (*See generally* Ex. 14 (https://sequencing.roche.com/en/products-solutions/products/sample-collection/cell-free-dna-collection-tube/ordering.html).) Defendants offer the FoundationOne Liquid CDx cfDNA Blood Collection Tube throughout the United States, at least through the website foundationmedicine.com. (Ex. 15 (https://www.foundationmedicine.com/test/foundationone-liquid-cdx); *see also* Ex. 16 (https://www.rochefoundationmedicine.com/home/services/liquid.html).)

JURISDICTION AND VENUE

10. Ravgen incorporates by reference paragraphs 1–9.

11. This action arises under the patent laws of the United States, including 35 U.S.C. §§ 271 *et seq*. The jurisdiction of this Court over the subject matter of this action is proper under 28 U.S.C. §§ 1331 and 1338(a).

12. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391(b), (c), and 1400(b). Defendants are entities organized under the laws of Delaware and reside in Delaware for purposes

of venue under 28 U.S.C. § 1400(b). Defendants conduct business in Delaware, at least by offering for sale and selling products and services through their websites, which are accessible in Delaware. Defendants have also committed and continue to commit acts of infringement in this District.

13. This Court has personal jurisdiction over Defendants because Defendants conduct business in Delaware by at least offering for sale or selling products and services through their websites, which are accessible in Delaware, and because infringement has occurred and continues to occur in Delaware.

14. Personal jurisdiction also exists over Defendants because they are entities organized under the laws of Delaware.

BACKGROUND OF THE INVENTION

15. Dr. Ravinder S. Dhallan is the founder of Ravgen, Inc. and the inventor of several patents in the field of detection of genetic disorders, including chromosomal abnormalities and mutations. Ravgen's mission is to provide state of the art genetic testing that will enrich the lives of its patients. For example, through the use of its novel techniques in non-invasive prenatal diagnostic testing, Ravgen gives patients the knowledge they need to prepare for their pregnancies and treat diseases at an early stage.

16. Prior to founding Ravgen, Dr. Dhallan was a board-certified emergency room physician. Between starting medical school at Johns Hopkins University and shortly after his residency at Mass General (Harvard University School of Medicine), Dr. Dhallan and his wife suffered three miscarriages. At that time, the prenatal diagnostic testing procedures available included (a) non-invasive techniques with low sensitivity and specificity, and (b) tests with higher sensitivity and specificity that were highly invasive and therefore associated with a risk for loss of pregnancy. After discovering the limitations on the available techniques for prenatal testing, Dr.

Dhallan made it his mission to invent an improved prenatal diagnostic exam—one that was both non-invasive and accurate. In September of 2000, Dr. Dhallan founded Ravgen (which stands for "Rapid Analysis of Variations in the GENome") to pursue that goal.

17. Prior to Ravgen's inventions, scientists had recognized the need for a genetic testing technique that used "cell-free" or "free" fetal DNA circulating in maternal blood. A technique that relied on circulating free fetal DNA would require only a simple blood draw from the mother and would therefore be an improvement over invasive diagnostic tests.

18. However, at that time, the use of free fetal DNA for detecting chromosomal abnormalities was limited by the low percentage of free fetal DNA that could be recovered from a sample of maternal blood using existing techniques. (*See, e.g.*, Ex. 17 (Y.M. Dennis Lo et al., *Presence of Fetal DNA in Maternal Plasma and Serum*, 350 THE LANCET 768-75 (1997), https://doi.org/10.1016/S0140-6736(97)02174-0).) Dr. Dhallan recognized that a method that could increase the percentage of free fetal DNA relative to the free maternal DNA in a sample was necessary to the development of an accurate, non-invasive prenatal diagnostic test.

19. After substantial research, Dr. Dhallan conceived that including an agent that impedes cell lysis (disruption of the cell membrane) if cells are present during sample collection, shipping, handling, and processing would permit the recovery of a larger percentage of cell-free fetal DNA (relative to the cell-free maternal DNA in a sample). Dr. Dhallan hypothesized that this new approach would decrease the amount of maternal cell lysis and therefore lower the amount of cell-free maternal DNA in the sample, thereby increasing the percentage of cell-free fetal DNA. He developed a novel method for processing cell-free fetal DNA that involved the addition of an agent that impedes cell lysis—for example, a membrane stabilizer, a cross-linker, and/or a cell lysis inhibitor—to maternal blood samples coupled with careful processing protocols. With that

novel method, Dr. Dhallan was able to increase the relative percentage of cell-free fetal DNA in the processed sample.

20. Having successfully increased the relative percentage of cell-free fetal DNA recovered, Dr. Dhallan next addressed the challenge of distinguishing between the cell-free maternal and cell-free fetal DNA in a sample in order to determine whether a chromosomal abnormality is present in the fetal DNA. Prior to Ravgen's inventions, known methods for detecting fetal chromosomal abnormalities were time-consuming and burdensome. Many required amplification of the entire sequence of a gene, or quantification of the total amount of a particular gene product in a sample. Dr. Dhallan developed an alternate method that greatly increased the efficiency of this process by taking advantage of the variation of base sequences among different individuals (including a mother and fetus) ("alleles") at particular positions ("loci") on chromosomes. The term "allele" refers to an alternate form of a gene, or a non-coding region of DNA that occurs at a particular locus on a chromosome. The alleles present at certain loci on chromosomes (including, for example, "single nucleotide polymorphisms" or "SNPs") vary between different individuals. At such a locus, a fetus may therefore inherit an allele from its father that differs from the alleles present at that locus on its mother's chromosome. Dr. Dhallan developed a novel method for quantifying the allelic ratio at such a locus (or loci) of interest in a sample comprising maternal and fetal cell-free DNA in order to detect whether a fetal chromosomal abnormality was present in the fetal DNA of the sample, without requiring physical separation of the fetal from the maternal cell-free DNA.

21. Dr. Dhallan understood that his breakthroughs laid the foundation for the development of accurate non-invasive prenatal diagnostic tests. For example, he published a paper in the *Journal of the American Medical Association* (*JAMA*) in 2004, explaining that "the methods

described herein for increasing the percentage of cell-free fetal DNA provide a solid foundation for the development of a noninvasive prenatal diagnostic test." (Ex. 18 at 1119 (R. Dhallan et al., *Methods to Increase the Percentage of Free Fetal DNA Recovered from the Maternal Circulation*, 291 JAMA 1114–19 (2004), https://doi.org/10.1001/jama.291.9.1114).)

22. *JAMA* also ran an editorial alongside Dr. Dhallan's article in 2004, recognizing the significance of his inventions to applications in prenatal genetic diagnosis and cancer detection and surveillance:

> In this issue of THE JOURNAL, the findings reported in the study by Dhallan and colleagues on enhancing recovery of cell-free DNA in maternal blood have major clinical implications. Developing a reliable, transportable technology for cell-free DNA analysis impacts 2 crucial areas—prenatal genetic diagnosis and cancer detection and surveillance. In prenatal genetic diagnosis, detecting a fetal abnormality without an invasive procedure (or with fewer invasive procedures) is a major advantage. Likewise in cancer surveillance (eg, in patients with leukemia), monitoring treatment without having to perform a bone marrow aspiration for karyotype also would be of great benefit.
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> * * *
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> With prospective studies focusing on clinical applications of these findings, profound clinical implications could emerge for prenatal diagnosis and cancer surveillance.

(Ex. 19 at 1135, 1137 (J.L. Simpson & F. Bischoff, *Cell-Free Fetal DNA in Maternal Blood: Evolving Clinical Applications*, 291 JAMA 1135–37 (2004), https://doi.org/10.1001/jama.291.9.1135).)

23. In 2007, Dr. Dhallan published a second journal article in *The Lancet* that presented a study showcasing Ravgen's ability to use its novel technology to detect Down's syndrome using free fetal DNA in a maternal blood sample. (Ex. 20 (R. Dhallan et al., *A Non-Invasive Test for Prenatal Diagnosis Based on Fetal DNA Present in Maternal Blood: A Preliminary Study*, 369 THE LANCET 474–81 (2007), https://doi.org/10.1016/S0140-6736(07)60115-9).) Dr. Dhallan's

peers at *The Lancet* also recognized that his innovative test "opens a new era in prenatal screening." (*See* Ex. 21 (A. Benachi & J.M. Costa, *Non-Invasive Prenatal Diagnosis of Fetal Aneuploidies*, 369 THE LANCET 440–42 (2007), https://doi.org/10.1016/S0140-6736(07)60116-0).)

24. Dr. Dhallan's publications received worldwide press coverage, from outlets such as CNN, BBC, and Washington Post. (*See* Ex. 22 (L. Palmer, *A Better Prenatal Test?*, CNN MONEY (Sept. 12, 2007), https://money.cnn.com/2007/09/07/smbusiness/amniocentesis.fsb/index.htm); Ex. 23 (*Hope for Safe Prenatal Gene Test*, BBC NEWS, Feb 2, 2007, http://news.bbc.co.uk/2/hi/health/6320273.stm); Ex. 24 (A. Gardner, *Experimental Prenatal Test Helps Spot Birth Defects*, WASH. POST (Feb. 2, 2007), https://www.washingtonpost.com/wp-dyn/content/article/2007/02/02/AR2007020200914.html).)

25. The Patents-in-Suit resulted from Dr. Dhallan's years-long research at Ravgen to develop these innovative new methods for detecting genetic disorders.

PATENTS-IN-SUIT

26. Ravgen incorporates by reference paragraphs 1–25.

27. The '277 Patent, entitled "Methods For Detection Of Genetic Disorders," was duly and legally issued by the United States Patent and Trademark Office on February 19, 2008. The inventor of the patent is Ravinder S. Dhallan, and the patent is assigned to Ravgen. A copy of the '277 Patent is attached hereto as Exhibit 1.

28. Ravgen is the exclusive owner of all rights, title, and interest in the '277 Patent, and has the right to bring this suit to recover damages for any current or past infringement of the '277 Patent. (*See* Ex. 3.)

29. The '720 Patent, entitled "Methods For Detection Of Genetic Disorders," was duly and legally issued by the United States Patent and Trademark Office on June 1, 2010. The inventor

of the patent is Ravinder S. Dhallan, and the patent is assigned to Ravgen. A copy of the '720 Patent is attached hereto as Exhibit 2.

30. Ravgen is the exclusive owner of all rights, title, and interest in the '720 Patent, and has the right to bring this suit to recover damages for any current or past infringement of the '720 Patent. (*See* Ex. 4.)

31. The '277 Patent is directed to, among other things, novel methods used in the detection of genetic disorders. For example, claim 81 of the '277 Patent recites:

> A method for preparing a sample for analysis comprising isolating free fetal nucleic acid from a the sample, wherein said sample comprises an agent that inhibits lysis of cells, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor.

32. The '720 Patent is directed to novel methods for detecting a free nucleic acid in a sample. For example, claim 1 of the '720 Patent recites:

> A method for detecting a free nucleic acid, wherein said method comprises: (a) isolating free nucleic acid from a non-cellular fraction of a sample, wherein said sample comprises an agent that impedes cell lysis, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizer, cross-linker, and cell lysis inhibitor; and (b) detecting the presence or absence of the free nucleic acid.

33. The Patents-in-Suit are directed to unconventional, non-routine techniques for preparing and analyzing extracellular circulatory DNA, including for the detection of genetic disorders. The Patents-in-Suit explain that, *inter alia*, the inventions claimed therein overcame problems in the field—for example, that the low percentage of fetal DNA in maternal plasma makes using the DNA for genotyping the fetus difficult—with a novel and innovative solution—the addition of cell lysis inhibitors, cell membrane stabilizers or cross-linkers to the maternal blood sample, which increase the percentage of cell-free DNA available for detection and analysis:

> The percentage of fetal DNA in maternal plasma is between 0.39-11.9% (Pertl, and Bianchi, *Obstetrics and Gynecology* 98: 483-490 (2001)). **The majority of the DNA in the plasma sample is maternal, which makes using the DNA for genotyping the fetus difficult**. However, methods that increase the percentage of fetal DNA in the maternal plasma allow the sequence of the fetal DNA to be determined, and allow for the detection of genetic disorders including mutations, insertions, deletions, and chromosomal abnormalities. **The addition of cell lysis inhibitors, cell membrane stabilizers or cross-linkers to the maternal blood sample can increase the relative percentage of fetal DNA.** While lysis of both maternal and fetal cells is inhibited, the vast majority of cells are maternal, and thus by reducing the lysis of maternal cells, there is a relative increase in the percentage of free fetal DNA.

(Ex. 1 (’277 Patent) at 32:24–39; Ex. 2 (’720 Patent) at 33:31–46 (emphases added).)

34. The Patents-in-Suit teach that the benefit of Dr. Dhallan’s discovery, an increase in the relative percentage of cell-free DNA, is realized by performance of the claimed method, including through the inclusion of an agent that inhibits the lysis of the cells in a sample:

> An overall increase in fetal DNA was achieved by reducing the maternal cell lysis, and thus, reducing the amount of maternal DNA present in the sample. In this example, formaldehyde was used to prevent lysis of the cells, however any agent that prevents the lysis of cells or increases the structural integrity of the cells can be used. Two or more than two cell lysis inhibitors can be used. The increase in fetal DNA in the maternal plasma allows the sequence of the fetal DNA to be determined, and provides for the rapid detection of abnormal DNA sequences or chromosomal abnormalities including but not limited to point mutation, reading frame shift, transition, transversion, addition, insertion, deletion, addition-deletion, frame-shift, missense, reverse mutation, and microsatellite alteration, trisomy, monosomy, other aneuploidies, amplification, rearrangement, translocation, transversion, deletion, addition, amplification, fragment, translocation, and rearrangement.

(Ex. 1 (’277 Patent) at 91:44–60; Ex. 2 (’720 Patent) at 92:10–26.)

35. For example, during the prosecution of the ’720 Patent at the Patent and Trademark Office, Ravgen explained that the innovative concept of using agents that inhibit cell lysis during

cell-free DNA detection and analysis is recited by the claimed methods of the '720 Patent, including in claim 1:

> Applicant has discovered that the addition of a cell lysis inhibitor to a sample prior to detecting the presence of free nucleic acid can ***significantly and unexpectedly*** increase the proportion of free nucleic acid obtained from the non-cellular fraction of a sample.
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> * * *
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> The methods disclosed in claims 1-8, 21-23, and 26 serve a long-felt need in the medical community, and provide unexpected results, and are therefore non-obvious.

(Ex. 5 ('720 File History, June 2, 2009 Response to Office Action) at 12, 14 (emphasis added).)

36. The inventive concept of the Patents-in-Suit of including an agent that inhibits cell lysis—for example, a membrane stabilizer, a cross-linker, and/or a cell lysis inhibitor—with a sample represented a significant improvement in the preparation of samples used for non-invasive testing, including non-invasive prenatal testing to unmask previously undetectable fetal genetic traits. At the time of the invention, it would not have been routine or conventional to add an agent that inhibits cell lysis to a sample to increase the proportion of free nucleic acid obtained from the non-cellular fraction of a sample. In fact, as described above, that inventive concept was recognized by Dr. Dhallan's peers as "an important step in improving detection of cell-free DNA." (Ex. 19 at 1137.)

37. The '277 Patent is further directed to an unconventional, non-routine method of detecting fetal chromosomal abnormalities which involves "quantitating a ratio of the relative amount of alleles in a mixture of maternal DNA and fetal DNA." (Ex. 25 ('277 File History, May 30, 2007 Response to Office Action) at 30.) For example, claim 1 of the '277 Patent recites:

> A method for detecting the presence or absence of a fetal chromosomal abnormality, said method comprising: quantitating a ratio of the relative amounts of alleles at a heterozygous locus of

> interest in a mixture of template DNA, wherein said mixture comprises maternal DNA and fetal DNA, and wherein said mixture of maternal DNA and fetal DNA has been obtained from a sample from a pregnant female, and further wherein said heterozygous locus of interest has been identified by determining the sequence of alleles at the locus of interest, and wherein said ratio indicates the presence or absence of a fetal chromosomal abnormality.

38. The ’277 Patent explains that this claimed method represented a significant improvement over prior art methods of detecting fetal chromosomal abnormalities, many of which were costly, time-consuming, and burdensome because they either required the amplification of the entire sequence of a gene, or quantification of the total amount of a particular gene product. (Ex. 1 at 66:14-20.) By contrast, the claimed “ratio” method of the ’277 Patent only requires sequencing of discrete “loci of interest” (such as “single nucleotide polymorphisms,” or “SNPs”) from the collected DNA sample. (*Id.* at 34:63-35:37 (“In fact, it is an advantage of the invention that primers that copy an entire gene sequence need not be utilized. . . . There is no advantage to sequencing the entire gene as this can increase cost and delay results. Sequencing only the desired bases or loci of interest maximizes the overall efficiency of the method because it allows for the sequence of the maximum number of loci of interest to be determined in the fastest amount of time and with minimal cost.”); *Id.* at 35:28-37.)

39. During the prosecution of the ’277 Patent at the Patent and Trademark Office, Ravgen gave the following example of an implementation of the claimed “ratio” method:

> Applicants have invented a method for detecting the presence or absence of a fetal chromosomal abnormality, wherein the method comprises, inter alia, quantitating a ratio of the relative amount of alleles in a mixture of maternal DNA and fetal DNA.
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> ***
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> [R]atios were calculated at both chromosomes 13 and 21 in a heterogeneous mixture of 75% Down syndrome DNA and 25% maternal DNA. Single nucleotide polymorphisms were analyzed

> wherein the maternal genome was homozygous for one allele at a specific genetic site and the Down syndrome DNA was heterozygous at the same genetic site. If at a certain site, the maternal genome contains an adenine at both copies of chromosome 13, and the Down syndrome genome is comprised of one chromosome with an adenine nucleotide and one chromosome with a guanine nucleotide, then the ratio of G:A is 0.60 (0.75 (Down syndrome G allele)/(0.75 Down syndrome A allele + 0.25 + 0.25 maternal A alleles).
>
> On the other hand, if at a certain genetic site on chromosome 21, the maternal genome contains an adenine at both copies of chromosome 21, and the Down syndrome genome is comprised of two chromosome with an adenine nucleotide and one chromosome with a guanine nucleotide, then the ratio of G:A is 0.375 (0.75 (Down syndrome G allele)/(0.75 Down syndrome A allele + 0.75 Down syndrome A allele + 0.25 + 0.25 (maternal A alleles). Thus, the methods described in the present application detect chromosomal abnormalities using a method that comprises, inter alia, quantitating a ratio of alleles in a heterogeneous mixture of DNA, wherein the ratio represents alleles from more than one individual.

(Ex. 25 at 30.)

RELATIONSHIP BETWEEN THE DEFENDANTS

40. Ravgen incorporates by reference paragraphs 1-39.

41. Roche Holding Ltd. ("Roche") is a Swiss multinational healthcare company and the ultimate parent company of RMS, RSS, Ariosa, and FMI. (Ex. 26 (Roche Finance Report 2020).) On December 2, 2014, Roche announced its acquisition of Ariosa. (Ex. 27 (Roche Press Release) (https://www.roche.com/media/releases/med-cor-2014-12-02.htm#:~:text=Media-,Roche%20acquires%20Ariosa%20Diagnostics%20and%20enters%20the%20non%2Dinvasive%20prenatal,free%20DNA%20testing%20services%20markets&text=Roche%20(SIX%3A%20RO%2C%20ROG,San%20Jose%2C%20California%2C%20USA).) After the acquisition, Ariosa became a wholly-owned subsidiary of RMS. (Ex. 7 ¶ 8, 10 (*Illumina, Inc. v. Ariosa Diagnostics, Inc.*, Case No. 3:18-cv-02847-SI, D.I. 40 (N.D. Cal. Aug. 9, 2018) (Ariosa's Amended Answer to

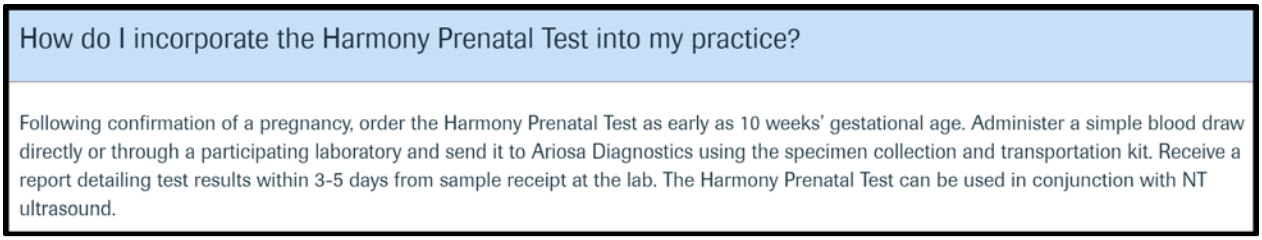
Complaint)); Ex. 8 at 5 (*Ariosa Diagnostics, Inc. v. Illumina, Inc.*, Case No. 2016-2388, D.I. 15 (Fed. Cir. Aug. 12, 2016) (Ariosa's Certificate of Interest)).)

42. RMS and RSS exercise control over Ariosa and hold out Ariosa as part of their own business such that Ariosa is an agent and/or alter ego of RMS and RSS.

43. On information and belief, RMS and RSS control the activities of Ariosa. On information and belief, Ariosa employees are RSS employees. (*See* Ex. 7 ¶ 18 (*Illumina, Inc. v. Ariosa Diagnostics, Inc.*, Case No. 3:18-cv-02847-SI, D.I. 40 (N.D. Cal. Aug. 9, 2018) (Ariosa's Amended Answer to Complaint)).)

44. On April 25, 2014, Illumina, Inc. sued Ariosa for patent infringement of U.S. Patent No. 7,955,794. (Ex. 28 (*Illumina, Inc. v. Ariosa Diagnostics, Inc.*, Case No. 3:14-cv-01921, D.I. 1 (N.D. Cal. Apr. 25, 2014)).) RMS filed a petition for *inter partes review* of U.S. Patent No. 7,955,794. (Ex. 29 (*Roche Molecular Systems, Inc. v. Illumina, Inc.*, IPR2015-01091, Paper No. 3 (PTAB April 24, 2015)).) In that petition, RMS identified both itself and Ariosa as real parties-in-interest. (*Id.* at 1.) RMS also identified itself as a real party-in-interest in an updated mandatory notice in IPR2014-01093, an earlier *inter partes review* petition filed by Ariosa against U.S. Patent No. 7,955,794. (Ex. 30 (*Ariosa Diagnostics, Inc. v. Illumina, Inc.*, IPR2014-01093, Paper No. 36 (PTAB May 1, 2014)).)

45. Roche's U.S. websites, which market and offer for sale the Harmony Prenatal Test, instruct clinicians interested in incorporating the Harmony Prenatal Test into their practice to send samples to Ariosa using a specimen collection and transportation kit provided by Defendants.


How do I incorporate the Harmony Prenatal Test into my practice?

Following confirmation of a pregnancy, order the Harmony Prenatal Test as early as 10 weeks' gestational age. Administer a simple blood draw directly or through a participating laboratory and send it to Ariosa Diagnostics using the specimen collection and transportation kit. Receive a report detailing test results within 3-5 days from sample receipt at the lab. The Harmony Prenatal Test can be used in conjunction with NT ultrasound.

(Ex. 31 (https://diagnostics.roche.com/us/en/products/other/harmony-clinicians.html#faq).) Ariosa's webpage (https://www.harmonytest.com) states that "The Harmony prenatal test is a Roche offering." (Ex. 32 (https://harmonytest.com/en/about-harmony.html).)

46. RSS develops, markets, and sells the Harmony Prenatal Test in conjunction with Ariosa. (Ex. 33 (Roche expands Harmony Prenatal Test to include 22q11.2 deletion testing) (https://sequencing.roche.com/en/news-overview/2017/roche-expands-harmony-prenatal-test-to-include-22q112-deletion-testing.html) (listing Elizabeth Baxter of RSS as a contact for further information).)

47. RSS's websites market and offer for sale the Harmony Prenatal Test. (Ex. 34 (https://sequencing.roche.com/en/products-solutions/by-application/clinical/nipt.html).)

48. Attempts to contact Ariosa through its website (https://harmonytest.com/en/contact-us.html) are directed to a "roche.com" email address: "sjc.clientservices@roche.com."

49. On information and belief, RSS and RMS participate in marketing activity related to the Harmony Prenatal Test, the distribution of the Harmony Prenatal Test to customers, and the maintenance of infrastructure for performing the Harmony Prenatal Test.

50. The foregoing facts confirm that RSS and RMS exercise control over Ariosa, that Ariosa is RSS's and RMS's alter ego and/or agent, and that RSS and RMS hold out Ariosa as part of their own businesses.

51. On June 19, 2018, Roche announced its acquisition of FMI. (Ex. 35 (https://www.roche.com/media/releases/med-cor-2018-06-19.htm).) FMI is a wholly owned subsidiary of Roche. (Ex. 26 (Roche Finance Report 2020).)

DEFENDANTS' INFRINGING ACTIVITIES

52. Ravgen incorporates by reference paragraphs 1–51.

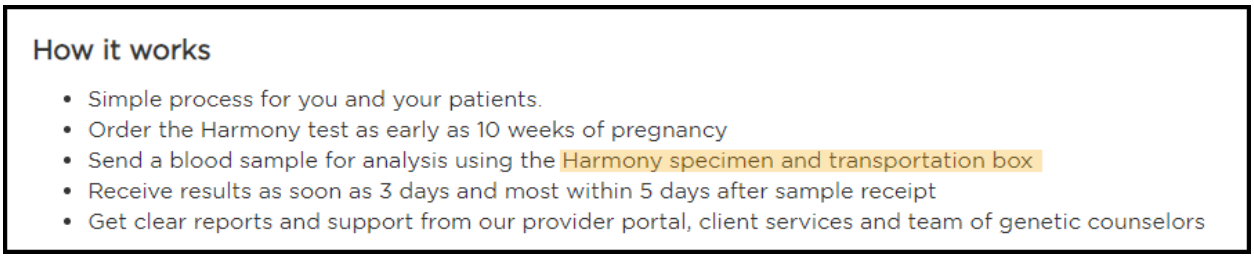
A. The Accused Harmony Prenatal Test

53. In 2012, Ariosa launched the Harmony Prenatal Test, a cell-free DNA-based non-invasive prenatal test. (Ex. 32 (https://harmonytest.com/en/about-harmony.html) ("Ariosa Diagnostics, Inc., the creator of the Harmony test, started offering the test in 2012"); Ex. 36 (Ariosa Diagnostics 2012 Press Release) (https://www.prnewswire.com/news-releases/ariosa-diagnostics-announces-nationwide-launch-of-the-harmony-prenatal-test-through-labcorp-150414545.html).) After Roche's acquisition of Ariosa in 2014, Ariosa continued to offer the Harmony Prenatal Test as a "Roche offering" that is "supported by Roche's strong technical support and responsible marketing." (Ex. 32 (https://harmonytest.com/en/about-harmony.html).) Defendants have continued to make, use, sell, and offer for sale the Harmony Prenatal Test since that acquisition.

54. Defendants sell the Harmony Prenatal Test on their websites. (Ex. 37 (Ariosa's Website) (https://harmonytest.com/en/clinicians.html#getharmonytest); Ex. 38 (RSS's Website) (https://sequencing.roche.com/en/products-solutions/by-application/clinical/nipt/get-harmony.html); Ex. 31 (Roche's Website) (https://diagnostics.roche.com/us/en/products/other/harmony-clinicians.html#faq).)

55. Defendants sell Cell-Free DNA Collection Tubes, a "direct-draw tube for the collection, stabilization and transportation of whole blood specimens" on their websites. (Ex. 39 (Cell-Free DNA Collection Tube Overview) (https://sequencing.roche.com/en-us/products-solutions/by-category/sample-collection/cell-free-dna-collection-tube.html).) For example, RSS sells the Cell-Free DNA Collection Tubes on its website. (Ex. 40 (https://sequencing.roche.com/en/products-solutions/products/sample-collection/cell-free-dna-

collection-tube/ordering.html).) On information and belief, Defendants also sell the Cell-Free DNA Collection Tubes as a part of specimen collection and transportation kits, including the "Harmony specimen and transportation box."


How it works

- Simple process for you and your patients.
- Order the Harmony test as early as 10 weeks of pregnancy
- Send a blood sample for analysis using the Harmony specimen and transportation box
- Receive results as soon as 3 days and most within 5 days after sample receipt
- Get clear reports and support from our provider portal, client services and team of genetic counselors

(Ex. 41 (https://harmonytest.com/en/clinicians.html#).)

56. The Harmony Prenatal Test "evaluates the probability of trisomies (trisomy 21, 18 and 13) and additional menu options, including sex chromosome aneuploidies and 22q11.2 microdeletion by analyzing cell-free DNA (cfDNA) in maternal blood." (Ex. 42 at 1 (https://harmonytest.com/content/dam/rochesequence/harmony/Worldwide/resources/Harmony-Abstract-Booklet-English-Letter-v20_PRINT.pdf).)

57. On information and belief, Defendants' offers for sale and sales of the Harmony Prenatal Test comprise the obligation to perform the steps of the infringing methods. For example, when a patient is referred by her healthcare provider to use the Harmony Prenatal Test, and she agrees to pay (or for her insurer to pay) in exchange for the Harmony Prenatal Test, on information and belief, Defendants provide instructions to the patient's healthcare provider directing them to use collection tubes specifically tailored for isolating cell-free DNA using at least an agent that inhibits cell lysis, such as Defendants' Cell-Free DNA Collection Tubes or Streck Cell-Free DNA BCT Tubes ("Streck BCT Tubes").

SPECIMEN COLLECTION, TRANSPORT, STORAGE, AND PREPARATION

1. It is recommended that two (2) tubes of maternal whole blood* are collected by venipuncture using the Roche Cell-Free DNA Collection tube (P/N 07832389001 or equivalent), according to the manufacturer's instructions. Transport and store the whole blood specimen according to the cfDNA-compatible blood collection tube manufacturer's instructions.

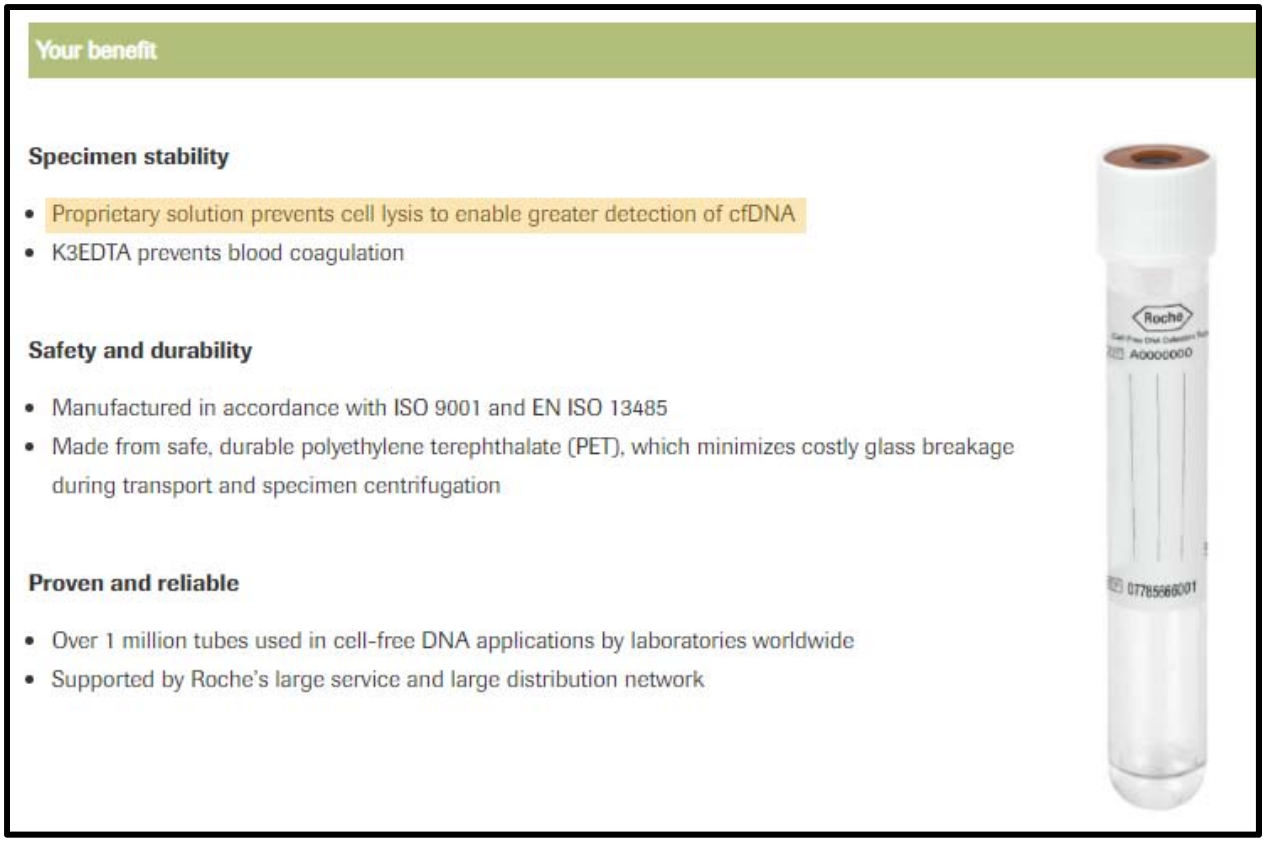
(Ex. 43 at 3, 12 (Harmony IVD Kit Instructions for Use) ("The Harmony test ***requires*** cfDNA that has been isolated using a commercially available cfDNA extraction kit from approximately 4mL of plasma collected using a ***cell-free DNA collection tube*** (Roche PN 07785666001 or equivalent).") (emphases added).)

58. Roche and Ariosa-funded scientific articles analyzing or involving the Harmony Prenatal Test confirm the use of collection tubes specifically tailored for isolating cell-free DNA using at least an agent that inhibits cell lysis, such as a Roche Cell-Free DNA Collection Tube or Streck BCT Tube, to collect samples for the Harmony Prenatal Test. (*See, e.g.*, Ex. 44 at 185 (Renee Stokowski, *et al.*, *Hemolysis and Fetal Fraction in Cell-Free DNA Blood Collection Tubes for Noninvasive Prenatal Testing*, 24 MOLECULAR DIAGNOSIS & THERAPY 185, 185 (2020) ("[B]lood from pregnant women was collected into three Roche Cell-Free DNA Collection Tubes. . . . The specimens were then processed with the Harmony[] prenatal test to measure fetal fraction using polymorphic digital analysis of selected regions (DANSR) assays.")); Ex. 45 at 814 (M. Schmid, *et al.*, *Accuracy and reproducibility of fetal-fraction measurement using relative quantitation at polymorphic loci with microarray*, 51 ULTRASOUND OBSTETRICS & GYNECOLOGY 813, 814 (2018) ("Sample preparation and analysis for the Harmony prenatal test were performed as described previously[]. In brief, blood samples were collected in either cfDNA BCT tubes (Streck, Omaha, NE, USA) or cfD tubes (Roche, Pleasanton, CA, USA) and processed to yield cell-free plasma within 7 days of collection."); Ex. 46 at 1590 (Mary E. Norton, *et al.*, *Cell-free DNA Analysis for Noninvasive Examination of Trisomy*, 372 NEW ENG. J. MED. 1589, 1590 (2015) ("Peripheral blood was collected into two Cell-free DNA BCT tubes (Streck) that were labeled

with a unique patient identifier. Samples were sent to the Ariosa clinical laboratory . . . without further processing.")).)

59. The Harmony Prenatal Test requires samples containing an agent that inhibits cell lysis. (Ex. 43 at 3, 12 (Harmony IVD Kit Instructions for Use) ("The Harmony test ***requires*** cfDNA that has been isolated using a commercially available cfDNA extraction kit from approximately 4mL of plasma collected using a ***cell-free DNA collection tube*** (Roche PN 07785666001 or equivalent).") (emphases added).) In addition, documentation published by Defendants list, as one of the "limitations" of the product, that the Harmony Prenatal Test has been specifically validated for use on specimens collected using the Roche Cell-Free DNA Collection Tube. (*Id.* at 24.) The documentation also notes that "[r]eliable results are dependent on appropriate specimen collection, transport, storage, and processing." (*Id.*).

60. The Roche Cell-Free DNA Collection Tubes include proprietary solutions that "***prevent[] cell lysis and preserve[] nucleated cells*** to enable efficient analysis of cell-free DNA (cfDNA)." (Ex. 39 (Cell-Free DNA Collection Tube Overview) (https://sequencing.roche.com/en-us/products-solutions/by-category/sample-collection/cell-free-dna-collection-tube.html) (emphasis added).) The Roche Cell-Free DNA Collection Tubes contain an agent that inhibits cell lysis.

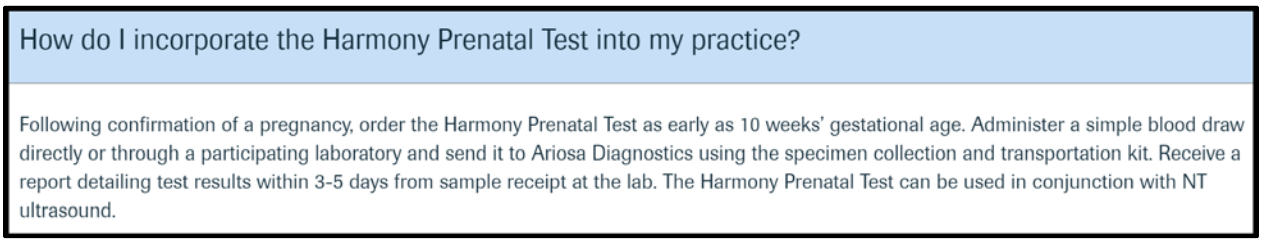


(Ex. 47 (http://roche-html5.coservice.ch/app/webroot/book/en/cell-free-dna-collection-tube.html); Ex. 48 at 1 (https://sequencing.roche.com/content/dam/rochesequence/worldwide/resources/Cell-Free-DNA-Collection-Tube-CE-IVD-SS-SEQ100087.pdf) ("Preservation of cfDNA with a specially formulated solution that prevents cell lysis").)

61. The Streck BCT Tube also includes an agent that inhibits cell lysis. A Streck BCT Tube "stabilizes nucleated blood cells. The unique preservative limits the release of genomic DNA, allowing isolation of high-quality cell-free DNA. Cell-Free DNA BCT has also been demonstrated to minimize the degradation of circulating tumor cells (CTCs). By limiting cell lysis, the specialized chemistry provides sample integrity during storage, shipping and handling of blood samples. Cell-free DNA and gDNA are stable for up to 14 days at 6 °C to 37 °C. CTCs are

stable for up to 7 days at 15 °C to 30 °C." (Ex. 49 at 2 (https://www.streck.com/products/stabilization/cell-free-dna-bct/#resources).)

62. Ariosa receives Harmony Prenatal Test samples from health care providers.


How do I incorporate the Harmony Prenatal Test into my practice?

Following confirmation of a pregnancy, order the Harmony Prenatal Test as early as 10 weeks' gestational age. Administer a simple blood draw directly or through a participating laboratory and send it to Ariosa Diagnostics using the specimen collection and transportation kit. Receive a report detailing test results within 3-5 days from sample receipt at the lab. The Harmony Prenatal Test can be used in conjunction with NT ultrasound.

(Ex. 31 (https://diagnostics.roche.com/us/en/products/other/harmony-clinicians.html#faq).)

63. In processing Harmony Prenatal Tests, Defendants isolate cell-free DNA from a sample of maternal blood collected in a Cell-Free DNA Collection Tube and then analyze the isolated fetal cell-free DNA to detect chromosomal abnormalities. (Ex. 43 at 3 (Harmony IVD Kit Instructions for Use) ("The Harmony prenatal test . . . utilizes a target amplification technology termed DANSR (Digital ANalysis of Selected Regions) and an analysis algorithm termed FORTE to analyze selected regions of the genome in cfDNA from pregnant women to aid in the detection of fetal chromosomal abnormalities."); *Id.* at 12 ("Separate maternal plasma by centrifuging the whole blood specimen . . . and remove the top plasma layer . . . taking care to avoid the opaque buffy coat layer which contains the maternal blood cells."); *Id.* ("Isolate cfDNA from approximately 4mL maternal plasma using a commercially available DNA isolation kit or established in-house procedure . . . . The QiaSymphony SP/AS nucleic acid extraction platform, MagnaPure 24 platform, and MagnaPure 26 platform have been validated for use with the Harmony test . . . .").) On information and belief, Defendants then process and analyze isolated fetal cell-free DNA to detect chromosomal abnormalities. (*See, e.g.*, Ex. 50 at 301 (Maximilian Schmid, *et al.*, *Prenatal Screening for 22q11.2 Deletion Using a Targeted Microarray-Based Cell-Free DNA Test*, 44 FETAL DIAGNOSIS AND THERAPY 299, 301 (2018) ("These samples were

submitted to Ariosa Diagnostics CLIA laboratory for clinical cfDNA testing for fetal trisomy using the Harmony Prenatal Test.") (funded by Roche)); Ex. 51 at 5 (Kypros H. Nicolaides, *et al.*, *Assessment of Fetal Sex Chromosome Aneuploidy Using Directed Cell-Free DNA Analysis*, 35 FETAL DIAGNOSIS AND THERAPY 1, 5 (2014) ("Analysis of samples [to detect fetal sex chromosome aneuploidies] was performed at their own expense by Ariosa Diagnostics.")); Ex. 52 at 1244 (Renee Stokowski, *et al.*, *Clinical performance of non-invasive prenatal testing (NIPT) using targeted cell-free DNA analysis in maternal plasma with microarrays or next generation sequencing (NGS) is consistent across multiple controlled clinical studies*, 35 PRENATAL DIAGNOSTICS 1243, 1244 (2015) ("Nonpolymorphic DANSR assays on chromosomes 13, 18, and 21 were used to assess relative chromosome representation, while 576 single-nucleotide polymorphic (SNP) DANSR assays were used to estimate fetal fraction.")).)

64. Ariosa operates as RMS's and RSS's laboratory and carries out RMS's and RSS's business when it processes Harmony Prenatal Test samples.

B. <u>The Accused Foundation Liquid Biopsy Product</u>

65. On May 3, 2016, FMI announced the commercial launch of FoundationACT (Assay for Circulating Tumor DNA), an "analytically validated and accurate blood-based circulating tumor DNA (ctDNA) assay . . . ." (Ex. 53 (https://www.foundationmedicine.com/press-releases/07936a8f-b1e6-4fb5-a4a8-26c909f684c5).) The FoundationACT product provides "comprehensive genomic profiling when a tissue biopsy is not feasible." (*Id.*)

66. On September 24, 2018, FMI announced the commercial launch of FoundationOne Liquid, a "next-generation liquid biopsy test" that "expands upon the previous versions of [FMI's] liquid biopsy test, FoundationACT." (Ex. 54 (https://www.foundationmedicine.com/press-

releases/d67a6b76-e9a9-4f5f-9a0a-c47831980163).) "Using a blood sample, FoundationOne Liquid analyzes 70 genes known to drive cancer growth . . . ." (*Id.*)

67. On August 26, 2020, FMI announced that its newest liquid biopsy product, FoundationOne Liquid CDx, had been approved by the FDA and would be commercially available on August 28, 2020. (Ex. 55 (https://www.foundationmedicine.com/press-releases/445c1f9e-6cbb-488b-84ad-5f133612b721).) The FoundationOne Liquid CDx incorporates the "genomic biomarker blood tumor mutational burden (bTMB)" in the FoundationOne Liquid product, allowing the FoundationOne Liquid product to incorporate "multiple companion diagnostics (CDx)." (Ex. 54 (https://www.foundationmedicine.com/press-releases/d67a6b76-e9a9-4f5f-9a0a-c47831980163).)

68. Defendants have offered and sold FoundationACT, Foundation One Liquid, and FoundationOne Liquid CDx (collectively, the "Foundation Liquid Biopsy Tests") for sale in the United States, including through their websites accessible throughout the United States. FMI has sold FoundationACT on its website. (Ex. 56 (May 4, 2017 Archive of FMI's Website) (https://web.archive.org/web/20170501215550/http://foundationone.com/learn.php#4).)

69. FMI has sold FoundationOne Liquid on its website.

(Ex. 57 (January 22, 2019 Archive of FMI's Website) (https://web.archive.org/web/20190122053016/https://www.foundationmedicine.com/).)

70. FMI sells FoundationOne Liquid CDx on its website. (Ex. 15 (https://www.foundationmedicine.com/test/foundationone-liquid-cdx).) FoundationOne Liquid CDx is also sold on Roche websites. (Ex. 16 (https://www.rochefoundationmedicine.com/home/services/liquid.html).)

71. The Foundation Liquid Biopsy Tests are sold and distributed with sample shipping kits that include materials for collecting and shipping blood samples for testing. For example, the FoundationOne Liquid CDX tests are sold and distributed with two FoundationOne Liquid CDx cfDNA Blood Collection Tubes.

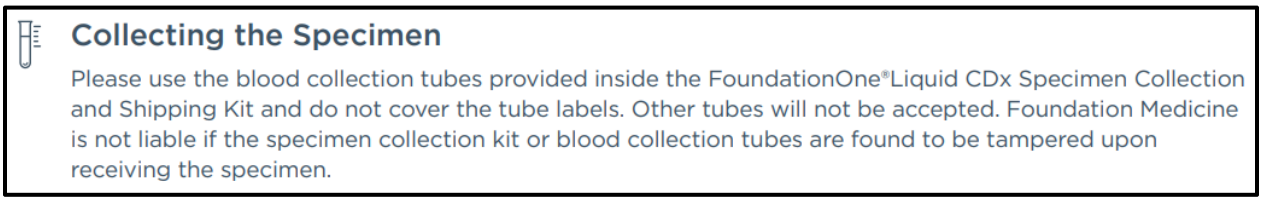
6 FoundationOne Liquid CDx cfDNA Blood Specimen Collection Kit Contents

Test Kit Contents
The test includes a sample shipping kit, which is sent to ordering laboratories. The shipping kit contains the following components:

- Specimen preparation and shipping instructions
- Two FoundationOne Liquid CDx cfDNA blood collection tubes (8.5 mL nominal fill volume per tube)
- Return shipping label

(Ex. 58 at 7 (FoundationOne Liquid CDx Technical Information) (https://assets.ctfassets.net/w98cd481qyp0/3a8jFw3KUjIU3RWPdcT9Ax/137cd6a35520ea2eaa6428131524f064/FoundationOne_Liquid_CDx_Label_Technical_Info.pdf).)

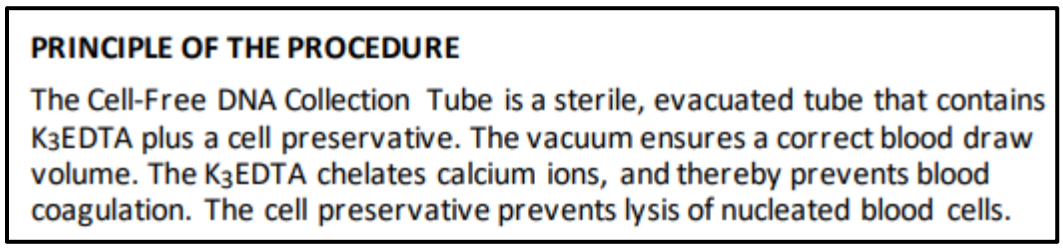
72. On information and belief, FMI's offers for sale and sales of the Foundation Liquid Biopsy Tests comprise the obligation to perform the steps of the infringing methods. For example, when a patient was referred by her healthcare provider to use the Foundation Liquid Biopsy Tests and she agrees to pay (or for her insurer to pay) in exchange for the Foundation Liquid Biopsy Tests, on information and belief, FMI provides instructions to the patient's healthcare provider directing them to use collection tubes specifically tailored for isolating cell-free DNA using at least an agent that inhibits cell lysis, such as FMI's FoundationOne Liquid CDx cfDNA Blood Collection Tubes.



(Ex. 59 (FoundationOne Liquid CDx Specimen Instructions) (https://assets.ctfassets.net/w98cd481qyp0/2LUvDQvycj0iiF0BXCjZh5/9729216855dbc1ee4382b7495873233c/FoundationOne_Liquid_CDx_Specimen_Instructions.pdf).)

73. FMI's FoundationOne Liquid CDx cfDNA Blood Collection Tubes were required by the FDA to demonstrate "suppression of white blood cell lysis." (Ex. 60 (https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190032A.pdf) ("FMI must provide robust and high confidence data . . . which demonstrates acceptable stability of whole blood collected . . . and stored in the FoundationOne Liquid CDx cfDNA Blood Collection tubes . . . confirm[ing] the suppression of white blood cell lysis across multiple lots.").) On information and belief, the

FoundationOne Liquid CDx cfDNA Blood Collection Tubes contain an agent that inhibits cell lysis, described in product documentation as "a cell preservative."



PRINCIPLE OF THE PROCEDURE

The Cell-Free DNA Collection Tube is a sterile, evacuated tube that contains K_3EDTA plus a cell preservative. The vacuum ensures a correct blood draw volume. The K_3EDTA chelates calcium ions, and thereby prevents blood coagulation. The cell preservative prevents lysis of nucleated blood cells.

(Ex. 61 (FMI Instruction for Use).) On information and belief, the blood collection tubes sold and distributed with FoundationACT similarly use sample collection tubes containing an agent that inhibits cell lysis. (Ex. 62 at 26 (FMI 2017 Form 10K) ("For FoundationACT, blood samples are submitted in blood collection tubes containing ***a preservative that helps stabilize nucleated cells to minimize cell lysis*** during normal shipping conditions.") (emphasis added).)

74. In processing the Foundation Liquid Biopsy Test, FMI isolates cell-free DNA from a sample of blood collected in a blood collection tube that inhibits cell lysis and then analyzes the isolated cell-free DNA to detect over 300 genes, blood tumor mutational burden (bTMB), and microsatellite instability (MSI). (Ex. 15 (https://www.foundationmedicine.com/test/foundationone-liquid-cdx); Ex. 58 at 2 (FoundationOne Liquid CDx Technical Information) (https://assets.ctfassets.net/w98cd481qyp0/3a8jFw3KUjIU3RWPdcT9Ax/137cd6a35520ea2eaa6428131524f064/FoundationOne_Liquid_CDx_Label_Technical_Info.pdf) ("FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma . . . .").); *id.* at 4 ("The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes.").)

C. Defendants' Knowledge Of The Ravgen Patents

75. The Patents-in-Suit claim advancements in the genetic testing industry in which Defendants actively participate and are widely acclaimed as breakthroughs in genetic testing. On information and belief, Defendants have been aware of the Patents-in-Suit and the fact that performance of the Defendants' cell-free DNA tests, including the Harmony Prenatal Test and the Foundation Liquid Biopsy Tests, practice the claimed inventions of those patents since at least the launch date of the infringing products.

76. Defendants have been and are assignees of a number of patents and patent applications that are related to subject matter similar to the Patents-in-Suit and that were filed after the Patents-in-Suit were published. On information and belief, in researching the patentability of their own patents, Defendants did, or at a minimum should have, become aware of the Patents-in-Suit.

77. The Patents-in-Suit and their corresponding patent application publications were cited, either by Defendants or by an examiner, during prosecution of Defendants' own patent applications at the United States Patent and Trademark Office.

78. Ravgen's '277 Patent or the application that matured into Ravgen's '277 Patent (U.S. Patent Application Publication No. 2004/0137470) was cited during the prosecution of Defendants' U.S. Patent Nos. 8,700,338; 8,712,697; 8,756,020; 9,206,417; 9,567,639; 9,624,490; 9,890,421; 9,994,897; 10,131,937; 10,131,947; 10,131,951; 10,167,508; 10,233,496; 10,289,800; 10,308,981; 10,533,223; 10,718,019; and 10,718,024.

79. Ravgen's '277 Patent or the application that matured into Ravgen's '277 Patent (U.S. Patent Application Publication No. 2004/0137470) was cited during the prosecution of Defendants' U.S. Patent Application Publication Nos. 2016/0002729 and 2018/0346986.

80. Ravgen's '720 Patent or the application that matured into Ravgen's '720 Patent (U.S. Patent Application Publication No. 2006/0121452) was cited during the prosecution of Defendants' U.S. Patent Nos. 8,700,338; 8,712,697; 8,756,020; 9,206,417; 9,567,639; 9,624,490; 9,890,421; 9,994,897; 10,131,937; 10,131,947; 10,131,951; 10,167,508; 10,233,496; 10,289,800; 10,308,981; 10,533,223; 10,718,019; and 10,718,024.

81. Ravgen's '720 Patent or the application that matured into Ravgen's '720 Patent (U.S. Patent Application Publication No. 2006/0121452) was cited during the prosecution of Defendants' U.S. Patent Application Publication Nos. 2016/0002729 and 2018/0346986.

82. Defendants were also aware of the Patents-in-Suit through *inter partes* review proceedings at the Patent Trial and Appeal Board (PTAB).

83. Ariosa and RMS initiated and were parties in Case Nos. IPR2013-00276 and IPR2013-00277 at the PTAB.

84. The petitions in each of Case Nos. IPR2013-00276 and IPR2013-00277 included grounds asserting Ravgen's '277 Patent as prior art against certain challenged claims. (*See generally* Ex. 63 (Petition in IPR2013-00276); Ex. 64 (Petition in IPR2013-00277).) The petitions were filed by Ariosa and RMS on May 10, 2013. (Ex. 63 (Petition in IPR2013-00276) at 57; Ex. 64 (Petition in IPR2013-00277) at 55.)

85. Ariosa and RMS advanced substantive arguments regarding Ravgen's '277 patent during Case Nos. IPR2013-00276 and IPR2013-00277 at the PTAB. Ariosa and RMS also advanced substantive arguments regarding Ravgen's '277 patent during related appeals at the Federal Circuit in Case Nos. 2015-1215 and 2015-1226.

86. Ariosa initiated and was a party in Case No. IPR2013-00308.

87. The petition in Case No. IPR2013-00308 included grounds asserting Ravgen's '277 Patent as prior art against certain challenged claims. (*See generally* Ex. 65 (Petition in IPR2013-00308).) The petition was filed by Ariosa on May 24, 2013. (*Id.* at 60.)

88. Ariosa advanced substantive arguments regarding Ravgen's '277 patent during Case No. IPR2019-00308 at the PTAB.

89. Defendants were also aware of the Patents-in-Suit through reexamination proceedings at the United States Patent and Trademark Office.

90. Ariosa filed a request for reexamination in Reexamination No. 90/013,678 (the "'678 Reexamination") on January 8, 2016. (*See* Ex. 66 (Request for Reexamination).) The request asserted Ravgen's '277 Patent and the application that matured into Ravgen's '720 Patent (U.S. Patent Application Publication No. 2006/0121452) as prior art to certain challenged claims. (*See id.* at 8.) Ariosa advanced substantive arguments regarding Ravgen's '277 Patent and the application that matured into Ravgen's '720 Patent (U.S. Patent Application Publication No. 2006/0121452) in the reexamination request.

91. Defendants were also aware of the Patents-in-Suit through communication with Dr. Dhallan and Ravgen regarding Ravgen's technology and patent portfolio.

92. On July 8, 2009, Ken Song from Venrock, a venture capital firm, contacted Dr. Dhallan regarding Ravgen and its prenatal diagnostic technology. (Ex. 67 (Song email dated July 8, 2009).) Dr. Song indicated he "ha[d] been evaluating various technologies in the prenatal diagnostics space and came across Ravgen." (*Id.*) Dr. Song requested a chance to discuss Ravgen and its technology and indicated he was looking to invest in prenatal technologies. (*Id.*)

93. On July 22, 2011, Dr. Song emailed certain contacts, including Dr. Dhallan, to inform them of his new contact information. (Ex. 68 (Song email dated July 22, 2011).) Dr. Song's new contact information indicated he had become CEO of Tandem Diagnostics. (*Id.*)

94. On December 6, 2011, Dr. Song again emailed certain contacts, including Dr. Dhallan, to inform them that Tandem Diagnostics had changed its name to Aria Diagnostics, Inc. (Ex. 69 (Song email dated December 6, 2011).) Dr. Song was the CEO of Aria Diagnostics at that time. Dr. Song indicated Aria was "committed to developing highly accurate, safe, and affordable molecular tests with an initial focus on prenatal testing." (*Id.*)

95. On January 14, 2012, Dr. Song contacted Dr. Dhallan again to discuss Ravgen and its technology. (Ex. 70 (Song emails dated January 14, 2012 through January 30, 2012).) Dr. Song indicated he was leading Aria's efforts "to develop a non-invasive prenatal test for fetal genetic conditions" and requested an in-person meeting with Dr. Dhallan. (*Id.* at 3.) Dr. Song and Dr. Dhallan met in person at Ravgen on or around February 1, 2012, to discuss Ravgen and its technology. (*Id.* at 1-2.) John Stuelpnagel, executive chair at Aria, joined Dr. Song at that in-person meeting. (*Id.* at 1.)

96. On information and belief, Aria changed its name to Ariosa Diagnostics in or around March 2012. On information and belief, Dr. Song was the CEO of Ariosa Diagnostics following the name change.

97. Following their first in-person meeting at Ravgen, Dr. Song and Mr. Stuelpnagel followed up with Dr. Dhallan and invited him to another in-person meeting at Ariosa's facilities in California to continue their discussions. (Ex. 71 (Song emails dated March 8, 2012 through March 24, 2012).) Dr. Dhallan travelled to California for an all-day meeting in person with Dr.

Song, Mr. Stuelpnagel, and other employees of Ariosa on or around April 9, 2012 to continue discussing Ravgen and its technology. (*Id.* at 1-2.)

98. On October 30, 2012, Dr. Song followed up with Dr. Dhallan to arrange another phone call with Dr. Dhallan and Mr. Stuelpnagel to continue their discussions of Ravgen and its technology. (Ex. 72 (Song email dated October 30, 2012).) On information and belief, that phone call occurred on November 2, 2012. (Ex. 73 (Song meeting invite for November 2, 2012).)

99. Dr. Song and Mr. Stuelpnagel are named inventors on multiple patents and patent applications filed by Defendants that cite the Patents-in-Suit, including certain patents and patent applications cited above. *See supra* ¶¶ 78-81.

100. After Roche acquired Ariosa, Roche employees continued to monitor Ravgen and to discuss Ravgen's technology and patent portfolio with Dr. Dhallan and other employees and consultants for Ravgen.

101. On March 2, 2016, Dr. Dhallan was introduced to Luba Greenwood, VP of Global Business Development and Mergers & Acquisitions for Roche Diagnostics, via email. (Ex. 74 (Greenwood emails dated March 2, 2016 through March 6, 2016).) Dr. Dhallan and Ms. Greenwood spoke by telephone on March 28, 2016 to discuss Ravgen and its technologies. (Ex. 75 (Greenwood emails dated March 6, 2016 through April 6, 2016) at 2-3.)

102. Following their phone conversation, Dr. Dhallan and Ms. Greenwood discussed meeting in person at Roche's facilities in Boston, MA. (*Id.* at 1.) Dr. Dhallan indicated the meeting would involve discussion of Ravgen's patents and that "[i]t would be ideal to block out a few hours in order to go over how our patents can help you in the short term with your litigation battle with Illumina." (*Id.*) In a later email regarding a potential in-person meeting, Ms.

Greenwood requested a background slide deck on Ravgen. (Ex. 76 (Greenwood emails dated March 6, 2016 through April 8, 2016) at 1.)

103. On May 9, 2016, Frank Garofalo contacted Ms. Greenwood to discuss Ravgen's technology and patent portfolio. (Ex. 77 (Garofalo Emails dated May 9, 2016 through June 17, 2016) at 4-5.) Mr. Garofalo provided a summary of Ravgen's patent portfolio. (*Id.* at 4-5.) The Ravgen patent portfolio—both at that time and today—is composed of seven issued U.S. patents, including the two Patents-in-Suit.

104. On May 31, 2016, Mr. Garofalo and Ms. Greenwood spoke by telephone to discuss Ravgen. (*Id.* at 1-2.) Mr. Garofalo followed up by email after that phone call to continue the conversation on June 1, 2016. (*Id.*) Mr. Garofalo followed up with Ms. Greenwood again on June 17 to continue discussion of Ravgen and its patent portfolio. (*Id.* at 1.) Mr. Garofalo noted that Ms. Greenwood previously mentioned a review of Ravgen's technology by Roche's patent attorneys and offered to make Ravgen's lead patent attorney available to Roche to assist in that review. (*Id.* at 1.)

105. Additionally, to the extent RMS and RSS were not aware of the Patents-in-Suit prior to December 2014, RMS and RSS became aware of the Patents-in-Suit by at least December 2014 when Roche announced its acquisition of Ariosa.

106. Additionally, to the extent FMI was not aware of the Patents-in-Suit prior to June 2018, FMI became aware of the Patents-In-Suit by at least June 2018 when Roche announced its acquisition of FMI.

107. Despite their knowledge of the Patents-in-Suit and of their infringement of those patents, Defendants have continued to willfully infringe the Patents-in-Suit so as to obtain the significant benefits of Ravgen's innovations without paying compensation to Ravgen. For

example, Defendants have continued to use the claimed methods in their Harmony Prenatal Test and the Foundation Liquid Biopsy Tests without a license, and, on information and belief, have generated hundreds of millions of dollars in revenue from their infringement. Additionally, after becoming aware of the Patents-in-Suit, Defendants proceeded to commercialize the Harmony Prenatal Test and the Foundation Liquid Biopsy Tests built on and including the claimed inventions of the Patents-in-Suit without entering into a license to the Patents-in-Suit.

COUNT I

(Infringement Of The '277 Patent)

108. Ravgen incorporates by reference paragraphs 1–107.

109. The '277 Patent is valid and enforceable.

110. Ariosa, RMS, and RSS have infringed, and continue to infringe, one or more claims of the '277 Patent under 35 U.S.C. § 271, either literally and/or under the doctrine of equivalents, by making, using, selling, and/or offering for sale in the United States, and/or importing into the United States, products and/or methods encompassed by those claims, including the Harmony Prenatal Test.

111. As one example, Ariosa, RMS, and RSS infringe at least exemplary claim 81 of the '277 Patent by using the Harmony Prenatal Test. For example, use of the Harmony Prenatal Test requires using a method for preparing a sample for analysis, wherein said method comprises:

a. isolating free fetal nucleic acid (such as cell-free fetal DNA) from a sample (such as a maternal blood sample) (*see, e.g.*, Ex. 43 at 3 (Harmony IVD Kit Instructions for Use) ("The Harmony test is intended for use in analysis of cfDNA samples isolated from plasma from pregnant women . . . ."); *Id.* at 12 ("Separate maternal plasma by centrifuging the whole blood specimen . . . and remove the top plasma

layer . . . taking care to avoid the opaque buffy coat layer which contains the maternal blood cells."); *Id.* ("Isolate cfDNA from approximately 4mL maternal plasma using a commercially available DNA isolation kit or established in-houes procedure . . . . The QiaSymphony SP/AS nucleic acid extraction platform, MagnaPure 24 platform, and MagnaPure 26 platform have been validated for use with the Harmony test . . . .")),

b. wherein said sample comprises an agent that inhibits lysis of cells, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizers, cross-linkers, and cell lysis inhibitor (such as Roche's Cell-Free DNA Collection Tubes or Streck BCT Tubes containing maternal blood) (*see id.* at 3 ("The Harmony test ***requires*** cfDNA that has been isolated using a commercially available cfDNA extraction kit from approximately 4mL of plasma collected using a cell-free DNA collection tube (Roche PN 07785666001 or equivalent).") (emphasis added); Ex. 45 at 814 (M. Schmid, *et al.*, *Accuracy and reproducibility of fetal-fraction measurement using relative quantitation at polymorphic loci with microarray*, 51 ULTRASOUND OBSTETRICS & GYNECOLOGY 813, 814 (2018) ("Sample preparation and analysis for the Harmony prenatal test were performed as described previously[]. In brief, blood samples were collected in either cfDNA BCT tubes (Streck, Omaha, NE, USA) or cfD tubes (Roche, Pleasanton, CA, USA) and processed to yield cell-free plasma within 7 days of collection."); Ex. 46 at 1590 (Mary E. Norton, *Cell-free DNA Analysis for Noninvasive Examination of Trisomy*, 372 NEW ENG. J. MED. 1589, 1590 (2015) ("Peripheral blood was collected into two Cell-free DNA BCT tubes (Streck) that

were labeled with a unique patient identifier. Samples were sent to the Ariosa clinical laboratory . . . without further processing.")); Ex. 48 at 1 (https://sequencing.roche.com/content/dam/rochesequence/worldwide/resources/Cell-Free-DNA-Collection-Tube-CE-IVD-SS-SEQ100087.pdf) ("**Benefits:** . . . Preservation of cfDNA with a specially formulated solution that prevents cell lysis"); Ex. 49 at 2 (https://www.streck.com/products/stabilization/cell-free-dna-bct/#resources) (describing Streck cell-free DNA BCTs as containing a "unique preservative [which] limits the release of genomic DNA, allowing isolation of high-quality cell-free DNA" and "specialized chemistry" that "limit[s] cell lysis")).

112. Ariosa has infringed, and continues to infringe, one or more claims of the '277 Patent under 35 U.S.C. § 271(a), either literally and/or under the doctrine of equivalents, by using the Harmony Prenatal Test either itself and/or by directing and/or controlling the performance of the claimed steps by third-party laboratories performing the Harmony Prenatal Test. For example, Ariosa uses the Harmony Prenatal Test by collecting and analyzing samples sent to Ariosa's laboratories for processing. (*See* Ex. 31 (https://diagnostics.roche.com/us/en/products/other/harmony-clinicians.html#faq) ("Administer a simple blood draw directly or through a participating laboratory and send it to Ariosa Diagnostics using the specimen collection and transportation kit.").)

113. RMS and RSS have infringed, and continue to infringe, one or more claims of the '277 Patent under 35 U.S.C. § 271(a), either literally and/or under the doctrine of equivalents, by using the Harmony Prenatal Test either themselves, as Ariosa's alter ego, through Ariosa as their agent, and/or by directing and/or controlling the performance of the claimed steps by Ariosa and/or

third-party laboratories. On information and belief, RMS and RSS have the right and the ability to direct and control the activities of Ariosa in several ways, including through RMS's 100% ownership of Ariosa, through instituting programs and measures (such as policies or protocols) at Ariosa, and through interim instructions via at least RMS's and RSS's employees and/or officers who hold leadership roles at Ariosa. Further, Ariosa acts on behalf of RMS and RSS, including when Ariosa performs tests on RMS's and RSS's behalf for RMS's and RSS's patients, or provides test results to health care providers and/or patients on RMS's and RSS's behalf.

114. In addition or in the alternative, Ariosa, RMS, and RSS have also induced infringement, and continue to induce infringement, of one or more claims of the '277 Patent under 35 U.S.C. § 271(b). Ariosa, RMS, and RSS actively, knowingly, and intentionally induce infringement of the '277 Patent by selling or otherwise supplying the Harmony Prenatal Test with the knowledge and intent that their customers, subsidiaries, intermediaries, or agents, including at least Ariosa, will use the Harmony Prenatal Test to infringe the '277 Patent. Ariosa, RMS, and RSS act with the knowledge and intent to encourage and facilitate third-party infringement through the dissemination of the Harmony Prenatal Test and/or the creation and dissemination of supporting materials, instructions, product manuals, technical information, and or licenses related to the Harmony Prenatal Test. At a minimum, RMS and RSS have induced and continue to induce infringement by, without limitation, encouraging Ariosa to perform the Harmony Prenatal Test.

115. Ariosa, RMS, and RSS specifically intend and are aware that the ordinary and customary use of the Harmony Prenatal Test would infringe the '277 Patent. For example, Ariosa, RMS, and RSS sell and provide the Harmony Prenatal Test, which when used in its ordinary and customary manner intended and instructed by Ariosa, RMS, and RSS, infringe one or more claims of the '277 Patent, including at least exemplary claim 81. On information and belief, Ariosa, RMS,

and RSS further provide product manuals and other instructional materials that cause customers, subsidiaries, intermediaries, or agents to operate the Harmony Prenatal Test for their ordinary and customary use. (*See, e.g.*, Ex. 43 (Harmony IVD Kit Instructions for Use).) Ariosa, RMS, and RSS accordingly induce their customers, subsidiaries, intermediaries, or agents to use the Harmony Prenatal Test in its ordinary and customary way to infringe the '277 Patent, knowing, or at least being willfully blind to the fact, that such use constitutes infringement of the '277 Patent.

116. In addition or in the alternative, Ariosa, RMS, and RSS contribute to the infringement by third parties, such as health care providers or laboratories, of one or more claims of the '277 Patent under 35 U.S.C. § 271(c), by making, selling and/or offering for sale in the United States, and/or importing into the United States, the Harmony Prenatal Test, knowing that the product constitutes a material part of the inventions of the '277 Patent, knowing that the product is especially made or adapted to infringe the '277 Patent, and knowing that the product is not a staple article of commerce suitable for substantial non-infringing use.

117. Ariosa, RMS, and RSS have had knowledge of and notice of the '277 Patent and their infringement since at least the launch date of the infringing products.

118. Ariosa, RMS, and RSS's infringement of the '277 Patent has been, and continues to be, willful and deliberate since at least the launch date of the infringing products.

119. Ravgen has been and continues to be damaged by Ariosa, RMS, and RSS's infringement of the '277 Patent, and will suffer irreparable injury unless the infringement is enjoined by this Court.

120. Ariosa, RMS, and RSS's conduct in infringing the '277 Patent renders this case exceptional within the meaning of 35 U.S.C. § 285.

COUNT II

Infringement Of The '720 Patent

121. Ravgen incorporates by reference paragraphs 1–120.

122. The '720 Patent is valid and enforceable.

123. For example, Ariosa, RMS, and RSS infringe at least exemplary claim 1 of the '720 patent by using the Harmony Prenatal Test. For example, use of the Harmony Prenatal Test requires using a method for detecting a free nucleic acid, wherein said method comprises:

a. isolating free nucleic acid (such as cell-free DNA) from a non-cellular fraction of a sample (such as a maternal blood sample) (*see, e.g.*, Ex. 43 at 3 (Harmony IVD Kit Instructions for Use) ("The Harmony test is intended for use in analysis of cfDNA samples isolated from plasma from pregnant women . . . ."); *Id.* at 12 ("Separate maternal plasma by centrifuging the whole blood specimen . . . and remove the top plasma layer . . . taking care to avoid the opaque buffy coat layer which contains the maternal blood cells."); *Id.* ("Isolate cfDNA from approximately 4mL maternal plasma using a commercially available DNA isolation kit or established in-house procedure . . . . The QiaSymphony SP/AS nucleic acid extraction platform, MagnaPure 24 platform, and MagnaPure 26 platform have been validated for use with the Harmony test . . . .")),

b. wherein said sample comprises an agent that impedes cell lysis, if cells are present, and wherein said agent is selected from the group consisting of membrane stabilizers, cross-linkers, and cell lysis inhibitor (such as Roche's Cell-Free DNA Collection Tubes or Streck BCT Tubes containing maternal blood) (*see id.* at 3 ("The Harmony test ***requires*** cfDNA that has been isolated using a

commercially available cfDNA extraction kit from approximately 4mL of plasma collected using a cell-free DNA collection tube (Roche PN 07785666001 or equivalent).") (emphasis added); Ex. 45 at 814 (M. Schmid, et al., *Accuracy and reproducibility of fetal-fraction measurement using relative quantitation at polymorphic loci with microarray*, 51 ULTRASOUND OBSTETRICS & GYNECOLOGY 813, 814 (2018) ("Sample preparation and analysis for the Harmony prenatal test were performed as described previously[]. In brief, blood samples were collected in either cfDNA BCT tubes (Streck, Omaha, NE, USA) or cfD tubes (Roche, Pleasanton, CA, USA) and processed to yield cell-free plasma within 7 days of collection."); Ex. 46 at 1590 (Mary E. Norton, *Cell-free DNA Analysis for Noninvasive Examination of Trisomy*, 372 NEW ENG. J. MED. 1589, 1590 (2015) ("Peripheral blood was collected into two Cell-free DNA BCT tubes (Streck) that were labeled with a unique patient identifier. Samples were sent to the Ariosa clinical laboratory . . . without further processing.")); Ex. 48 at 1 (https://sequencing.roche.com/content/dam/rochesequence/worldwide/resources/Cell-Free-DNA-Collection-Tube-CE-IVD-SS-SEQ100087.pdf) ("**Benefits:** . . . Preservation of cfDNA with a specially formulated solution that prevents cell lysis"); Ex. 49 at 2 (https://www.streck.com/products/stabilization/cell-free-dna-bct/#resources) (describing Streck cell-free DNA BCTs as containing a "unique preservative [which] limits the release of genomic DNA, allowing isolation of high-quality cell-free DNA" and "specialized chemistry" that "limit[s] cell lysis")),

c. detecting the presence or absence of the free nucleic acid (Ex. 43 at 3 (Harmony

IVD Kit Instructions for Use) ("The Harmony prenatal test . . . utilizes a targeted amplification technology termed DANSR . . . and an analysis algorithm termed FORTE to analyze selected regions of the genome in cfDNA from pregnant women to aid in the detection of fetal chromosomal conditions.")).

124. Ariosa has infringed, and continues to infringe, one or more claims of the '720 Patent under 35 U.S.C. § 271(a), either literally and/or under the doctrine of equivalents, by using the Harmony Prenatal Test either itself and/or by directing and/or controlling the performance of the claimed steps by third-party laboratories performing the Harmony Prenatal Test. For example, Ariosa uses the Harmony Prenatal Test by collecting and analyzing samples sent to Ariosa's laboratories for processing. (*See* Ex. 31 (https://diagnostics.roche.com/us/en/products/other/harmony-clinicians.html#faq) ("Administer a simple blood draw directly or through a participating laboratory and send it to Ariosa Diagnostics using the specimen collection and transportation kit.").)

125. RMS and RSS have infringed, and continue to infringe, one or more claims of the '720 Patent under 35 U.S.C. § 271(a), either literally and/or under the doctrine of equivalents, by using the Harmony Prenatal Test either themselves, as Ariosa's alter ego, through Ariosa as their agent, and/or by directing and/or controlling the performance of the claimed steps by Ariosa and/or third-party laboratories. On information and belief, RMS and RSS have the right and the ability to direct and control the activities of Ariosa in several ways, including through RMS's 100% ownership of Ariosa, through instituting programs and measures (such as policies or protocols) at Ariosa, and through interim instructions via at least RMS's and RSS's employees and/or officers who hold leadership roles at Ariosa. Further, Ariosa acts on behalf of RMS and RSS, including

when Ariosa performs tests on RMS's and RSS's behalf for RMS's and RSS's patients, or provides test results to health care providers and/or patients on RMS's and RSS's behalf. (*Id.*)

126. In addition or in the alternative, Ariosa, RMS, and RSS have also induced infringement, and continue to induce infringement, of one or more claims of the '720 Patent under 35 U.S.C. § 271(b). Ariosa, RMS, and RSS actively, knowingly, and intentionally induce infringement of the '720 Patent by selling or otherwise supplying the Harmony Prenatal Test with the knowledge and intent that their customers, subsidiaries, intermediaries, or agents, including at least Ariosa, will use the Harmony Prenatal Test supplied by Ariosa, RMS, and RSS to infringe the '720 Patent. Ariosa, RMS, and RSS act with the knowledge and intent to encourage and facilitate third-party infringement through the dissemination of the Harmony Prenatal Test and/or the creation and dissemination of supporting materials, instructions, product manuals, technical information, and or licenses related to the Harmony Prenatal Test. At a minimum, RMS and RSS has induced and continues to induce infringement by, without limitation, encouraging Ariosa to perform the Harmony Prenatal Test.

127. Ariosa, RMS, and RSS specifically intend and are aware that the ordinary and customary use of the Harmony Prenatal Test would infringe the '720 Patent. For example, Ariosa, RMS, and RSS sell and provide the Harmony Prenatal Test, which when used in its ordinary and customary manner intended and instructed by Ariosa, RMS, and RSS, infringe one or more claims of the '720 Patent, including at least exemplary claim 1. On information and belief, Ariosa, RMS, and RSS further provide product manuals and other instructional materials that cause customers, subsidiaries, intermediaries, or agents to operate the Harmony Prenatal Test for their ordinary and customary use. (Ex. 43 (Harmony IVD Kit Instructions for Use).) Ariosa, RMS, and RSS accordingly induce their customers, subsidiaries, intermediaries, or agents to use the Harmony

Prenatal Test in its ordinary and customary way to infringe the ’720 Patent, knowing, or at least being willfully blind to the fact, that such use constitutes infringement of the ’720 Patent.

128. In addition or in the alternative, Ariosa, RMS, and RSS contribute to the infringement by third parties, such as health care providers or laboratories, of one or more claims of the ’720 Patent under 35 U.S.C. § 271(c), by making, selling and/or offering for sale in the United States, and/or importing into the United States, the Harmony Prenatal Test, knowing that the product constitutes a material part of the inventions of the ’720 Patent, knowing that the product is especially made or adapted to infringe the ’720 Patent, and knowing that the product is not a staple article of commerce suitable for substantial non-infringing use.

129. As another example, FMI, RMS, and RSS infringe at least exemplary claim 1 of the ’720 Patent by using the Foundation Liquid Biopsy Tests. For example, use of the Foundation Liquid Biopsy Tests requires using a method for preparing a sample for analysis, wherein said method comprises:

a. isolating free nucleic acid (such as cell-free DNA) from a sample (such as a blood sample) (*see*, *e.g.*, Ex. 58 at 2 (FoundationOne Liquid CDx Technical Information) (https://assets.ctfassets.net/w98cd481qyp0/3a8jFw3KUjIU3RWPdcT9Ax/137cd6a35520ea2eaa6428131524f064/FoundationOne_Liquid_CDx_Label_Technical_Info.pdf) (“FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma . . . .”).); *id.* at 4 (“The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood.”).)

b. wherein said sample comprises an agent that impedes cell lysis, if cells are present, and wherein said agent is selected from the group consisting of

membrane stabilizers, cross-linkers, and cell lysis inhibitor (Ex. 60 at 6 (https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190032A.pdf) ("FMI must provide robust and high confidence data . . . which demonstrates acceptable stability of whole blood collected . . . and stored in the FoundationOne Liquid CDx cfDNA Blood Collection tubes . . . confirm[ing] the suppression of white blood cell lysis across multiple lots."); Ex. 62 at 26 (FMI 2017 Form 10K) ("For FoundationACT, blood samples are submitted in blood collection tubes containing ***a preservative that helps stabilize nucleated cells to minimize cell lysis*** during normal shipping conditions.") (emphasis added)),

c. detecting the presence or absence of the free nucleic acid (Ex. 15 (https://www.foundationmedicine.com/test/foundationone-liquid-cdx); Ex. 58 at 4 (FoundationOne Liquid CDx Technical Information) (https://assets.ctfassets.net/w98cd481qyp0/3a8jFw3KUjIU3RWPdcT9Ax/137cd6a35520ea2eaa6428131524f064/FoundationOne_Liquid_CDx_Label_Technical_Info.pdf) ("Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes.")).

130. FMI, RSS, and RMS have infringed, and continue to infringe, one or more claims of the '720 Patent under 35 U.S.C. § 271(a), either literally and/or under the doctrine of equivalents, by using the Foundation Liquid Biopsy Tests either themselves and/or by directing and/or controlling the performance of the claimed steps by third-party laboratories. For example, FMI, RSS, and RMS use the Foundation Liquid Biopsy Tests by collecting and analyzing samples sent to their laboratories for processing. (Ex. 59 (FoundationOne Liquid CDx Specimen Instructions)

(https://assets.ctfassets.net/w98cd481qyp0/2LUvDQvycj0iiF0BXCjZh5/9729216855dbc1ee4382b7495873233c/FoundationOne_Liquid_CDx_Specimen_Instructions.pdf) (instructing the customer to ship the sample to FMI).)

131. In addition or in the alternative, FMI, RSS, and RMS have also induced infringement, and continue to induce infringement, of one or more claims of the '720 Patent under 35 U.S.C. § 271(b). FMI, RSS, and RMS actively, knowingly, and intentionally induce infringement of the '720 Patent by selling or otherwise supplying the Foundation Liquid Biopsy Tests with the knowledge and intent that their customers, subsidiaries, intermediaries, or agents will use the Foundation Liquid Biopsy Tests supplied by FMI, RSS, and RMS to infringe the '720 Patent. FMI, RSS, and RMS act with the knowledge and intent to encourage and facilitate third-party infringement through the dissemination of the Foundation Liquid Biopsy Tests and/or the creation and dissemination of supporting materials, instructions, product manuals, technical information, and or licenses related to the Foundation Liquid Biopsy Tests.

132. FMI, RSS, and RMS specifically intend and are aware that the ordinary and customary use of the Foundation Liquid Biopsy Tests would infringe the '720 Patent. For example, FMI, RSS, and RMS sell and provide the Foundation Liquid Biopsy Tests, which when used in their ordinary and customary manner intended and instructed by FMI, RSS, and RMS, infringe one or more claims of the '720 Patent, including at least exemplary claim 1. On information and belief, FMI, RSS, and RMS further provide product manuals and other instructional materials that cause customers, subsidiaries, intermediaries, or agents to operate the Foundation Liquid Biopsy Tests for their ordinary and customary use. (*See, e.g.*, Ex. 58 (FoundationOne Liquid CDx Technical Information) (https://assets.ctfassets.net/w98cd481qyp0/3a8jFw3KUjIU3RWPdcT9Ax/137cd6a35520ea2eaa6

428131524f064/FoundationOne_Liquid_CDx_Label_Technical_Info.pdf).) FMI, RSS, and RMS accordingly induce their customers, subsidiaries, intermediaries, or agents to use the Foundation Liquid Biopsy Tests in their ordinary and customary way to infringe the '720 Patent, knowing, or at least being willfully blind to the fact, that such use constitutes infringement of the '720 Patent.

133. In addition or in the alternative, FMI, RSS, and RMS contribute to the infringement by third parties, such as health care providers or laboratories, of one or more claims of the '720 Patent under 35 U.S.C. § 271(c), by making, selling and/or offering for sale in the United States, and/or importing into the United States, the Foundation Liquid Biopsy Tests, knowing that those products constitute a material part of the inventions of the '720 Patent, knowing that those products are especially made or adapted to infringe the '720 Patent, and knowing that those products are not staple articles of commerce suitable for substantial non-infringing use.

134. Defendants have had knowledge of and notice of the '720 Patent and their infringement since at least the launch date of the infringing products.

135. Defendants' infringement of the '720 Patent has been, and continues to be, willful and deliberate since at least the launch date of the infringing products.

136. Ravgen has been and continues to be damaged by Defendants' infringement of the '720 Patent, and will suffer irreparable injury unless the infringement is enjoined by this Court.

137. Defendants' conduct in infringing the '720 Patent renders this case exceptional within the meaning of 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Ravgen prays for judgment as follows:

A. That Defendants have infringed each of the Patents-in-Suit;

B. That Defendants' infringement of each of the Patents-in-Suit has been willful;

C. That Ravgen be awarded all damages adequate to compensate it for Defendants' past infringement and any continuing or future infringement of the Patents-in-Suit up until the date such judgment is entered, including pre- and post-judgment interest, costs, and disbursements as justified under 35 U.S.C. § 284;

D. That any award of damages be enhanced under 35 U.S.C. § 284 as result of Defendants' willful infringement;

E. That this case by declared an exceptional case within the meaning of 35 U.S.C. § 285 and that Ravgen be awarded the attorney fees, costs, and expenses incurred in connection with this action;

F. That Ravgen be awarded either a permanent injunction, or, at least, a compulsory ongoing licensing fee; and

F. That Ravgen be awarded such other and further relief at law or equity as this Court deems just and proper.

DEMAND FOR JURY TRIAL

Plaintiff Ravgen hereby demands a trial by jury on all issues so triable.

Dated: December 3, 2020

Respectfully submitted,

FARNAN LLP

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