IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NATERA, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. _____
	)	
CAREDX, INC.,	)	**JURY TRIAL DEMANDED**
	)	
Defendant.	)	

COMPLAINT

Natera, Inc. ("Natera") submits this Complaint against CareDx, Inc. ("CareDx"). Natera hereby alleges as follows:

NATURE OF THE ACTION

1. Natera brings this claim for patent infringement to compel CareDx to stop infringing Natera's patent and to compensate Natera for CareDx's infringement of Natera's patented technology.

2. Founded in 2004, Natera (f.k.a Gene Security Network) is a pioneering genetics and bioinformatics company with industry-leading diagnostics products. Natera is dedicated to improving disease management for reproductive health, oncology, and organ transplantation. For well over a decade, Natera has been researching, developing, and commercializing non-invasive methods for analyzing DNA in order to help patients and doctors manage diseases. These ongoing efforts have given rise to a number of novel and proprietary genetic testing services to assist with life-saving health management.

3. Natera's pioneering and ongoing innovation is especially evident in the area of cell-free DNA ("cfDNA")-based testing. In the cfDNA field, Natera has developed unique and highly optimized cfDNA-based diagnostic methods that can be used to non-invasively test for a

range of conditions. Natera developed an industry-leading cfDNA test, Panorama, which showcases its mastery of cfDNA in the field of non-invasive prenatal diagnostics. It is considered the industry leading test in this space, with about four million tests performed commercially, and with more than twenty-six peer-reviewed publications. Natera has also applied its cfDNA platform to the challenge of assessing organ transplant rejection. Natera's cfDNA testing methods are simpler and less invasive than traditional biopsy methods used to evaluate transplant health, and also are more sensitive and specific, and less variable, than biomarkers such as serum creatine across all types of kidney transplant rejection. Natera has developed its cfDNA technology for approval in the clinical setting in order to provide patients with tools for early, clinically meaningful rejection assessment. As such, Natera was awarded approval for coverage by Medicare.

4. Natera's cfDNA platform is the product of well over a decade of hard work and investment of, on average, more than fifty million dollars per year in research and development. Natera has expended substantial resources researching and developing its technologies and establishing its reputation among physicians, insurers, and regulators as a company committed to sound science and consistently accurate, reliable results. This research, and the resulting technological innovations therefrom, are protected by a substantial patent portfolio, with over 330 patents issued or pending worldwide.

5. Among these patented inventions is U.S. Patent No. 11,111,544 (the "'544 patent"), which CareDx infringes. In its efforts to improve upon the standard of care in the transplant space, Natera has leveraged its own technologies such as the inventions disclosed and claimed in the '544 patent. By contrast, CareDx has used Natera's patented cfDNA technology without permission and in violation of the patent laws, while asserting only the patents of others

(*e.g.*, Stanford) to create the false impression that it is a true innovator. CareDx must be held accountable for its infringement.

6. Natera is the legal owner by assignment of the ’544 patent, which was duly and legally issued by the United States Patent and Trademark Office (“USPTO”) on September 7, 2021.

7. Natera seeks monetary damages and injunctive relief to address ongoing infringement by CareDx of its valuable patent.

THE PARTIES

8. Natera is a Delaware corporation with its principal place of business at 201 Industrial Road, Suite 410, San Carlos, California 94070.

9. CareDx is a Delaware corporation with its principal place of business at 3260 Bayshore Boulevard, Brisbane, California 94005.

JURISDICTION AND VENUE

10. This is a civil action for patent infringement arising under the patent laws of the United States, 35 U.S.C. § 1 *et seq.*

11. This Court has subject matter jurisdiction over the matters asserted herein under 28 U.S.C. §§ 1331 and 1338(a).

12. CareDx is subject to this Court’s personal jurisdiction at least because CareDx is a Delaware corporation, and because CareDx filed its own actions against Natera, Case Nos. 19-cv-00567-CFC-CJB and 19-cv-00662-CFC-CJB, in this District.

13. In addition, CareDx is subject to this Court’s personal jurisdiction because, on information and belief, CareDx, directly or indirectly, uses, induces others to use, contributes to the use by others, offers for sale, and/or sells the products accused of infringement throughout the United States and within this District. CareDx has infringed and continues to infringe

Natera's patent in this District by, among other things, engaging in infringing conduct within and directed at or from this District and purposely and voluntarily placing its infringing products, including AlloSure, AlloSeq, KidneyCare, HeartCare, and any other CareDx products that use similar technologies (the "Accused Products"), into the stream of commerce with the expectation that the Accused Products will be used in this District.

14. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and 1400(b). As discussed above, CareDx is incorporated in this District and thus resides in this District.

FACTUAL BACKGROUND

Natera's History of Innovation

15. Since 2004, Natera has been a global leader in genetic testing, diagnostics, and DNA testing, including cfDNA testing. Natera's mission is to improve the management of disease worldwide and focuses on reproductive health, oncology, and organ transplantation. To improve the management of these conditions, Natera has developed novel technologies to make significant and accurate clinical assessments from the miniscule amounts of cfDNA present in a single blood sample. These technologies include methods to manipulate cfDNA in unconventional ways in order to capture information about genetic variations ("polymorphisms") in cfDNA and usefully transform that information for noninvasive testing. Natera develops and commercializes its own innovative, non-traditional methods for manipulating, preparing samples of, and analyzing cfDNA, and offers a host of proprietary cfDNA genetic testing services to the public to assist patients and doctors to evaluate and track critical health concerns.

16. Since its founding, Natera has researched, developed, and released ten molecular tests with applications in prenatal diagnostics, cancer, and organ transplants, many of which are available through major health plans, or covered by Medicare or Medicaid, and therefore available to most patients in need of those tests. Natera's tests have helped more than four

million individuals to date. Natera's robust laboratory now processes around 130,000 tests per month from the United States and internationally, improving the ability of physicians to monitor and manage crucial health issues and patients to prosper around the world.

17. Building on these innovations, in 2019, Natera launched its patented next-generation cfDNA diagnostic test for evaluating organ transplant health called "Prospera." Prospera is designed to be the most precise medical testing regime for early, clinically meaningful transplant rejection assessment. Prospera was created to help physicians improve transplant survival by enabling them to optimally suppress immune-system-mediated rejection in transplant recipients while avoiding unnecessary and invasive biopsies of the transplanted organ itself.

18. Prospera's validation led Medicare to issue a draft Local Coverage Determination ("LCD") for Prospera in March 2019. In its draft LCD, Medicare determined that "[t]he evidence is sufficient to support that Prospera provides a non-invasive assessment tool to assess for the presence of active allograft rejection." Furthermore, the LCD established that the "evidence also supports that Prospera identifies both ABMR [antibody-mediated rejection] and TCMR [T-cell mediated rejection], and it is validated to detect subclinical AR [active rejection]." The LCD was finalized after receiving overwhelming public support, with the vast majority of public comments being positive. Natera received nearly four times as many supportive letters than not. In fact, the only three letters submitted which did not support the coverage were submitted either by CareDx itself, by self-identified paid advocates of CareDx or, on information and belief, by known CareDx advisors—all in an attempt by CareDx to interfere with Natera's commercialization efforts.

19. Natera's history of and dedication to innovation in the analysis and testing of cfDNA has resulted in a world-class patent portfolio, with over 133 patents issued to date. Natera has an additional 205 pending patent applications currently under review before various patent offices around the world, and of those 18 have been allowed.

CareDx

20. CareDx is a molecular diagnostics company that develops and commercializes testing products for transplant recipients.

21. CareDx markets and sells its own transplant diagnostic testing products, including the Accused Products.

22. On information and belief, the Accused Products infringe the '544 patent. The '544 patent covers an innovative, unconventional method for preparing preparations of amplified DNA from biological samples and manipulating and measuring DNA from a first individual in a biological sample of a second individual. As set forth below, CareDx's infringing Accused Products incorporate or use technology that is protected by the '544 patent owned by Natera. CareDx has used Natera's patented technology without payment or permission.

The '544 Patent

23. The '544 patent, issued on September 7, 2021, is titled "System and Method for Cleaning Noisy Genetic Data and Determining Chromosome Copy Number." Matthew Rabinowitz, Milena Banjevic, Zachary Demko, David Johnson, Dusan Kijacic, Dimitri Petrov, Joshua Sweetkind-Singer, and Jing Xu are the named inventors. Natera is the original and current owner by assignment of the '544 patent. A true and correct copy of the '544 patent is attached hereto as Exhibit B.

24. Claim 1 of the '544 patent recites:

1. A method for determining genetic data for DNA from a first individual in a biological sample of a second individual, the method comprising:

amplifying a plurality of target loci on cell-free DNA extracted from the biological sample to generate amplified products;

sequencing the amplified products by sequencing-by-synthesis to obtain genetic data of the plurality of target loci;

determining the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of target loci.

25. Claim 18 of the ’544 patent recites:

18. A method for determining genetic data for DNA from a first individual in a blood sample of a second individual, the method comprising:

performing targeted PCR to amplify a plurality of SNP loci on cell-free DNA extracted from the blood sample to generate amplified products, wherein the SNP loci are on a plurality of chromosomes;

sequencing the amplified products by sequencing-by-synthesis to obtain genetic data of the plurality of SNP loci, wherein the sequencing-by-synthesis comprises clonal amplification of the amplified products and measurement of sequences of the clonally amplified DNA;

determining the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of SNP loci.

26. Claim 21 of the ’544 patent recites:

21. A method for preparing a preparation of amplified DNA derived from a biological sample of a second individual useful for determining genetic data for DNA from a first individual in the biological sample, the method comprising:

extracting cell-free DNA from the biological sample;

preparing a preparation of amplified DNA by amplifying a plurality of target loci on the cell-free DNA extracted from the biological sample to generate amplified DNA;

analyzing the preparation of amplified DNA by sequencing the amplified DNA using sequencing-by-synthesis to obtain genetic data of the plurality of target loci, and determining the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of target loci.

27. Claim 38 of the ’544 patent recites:

38. A method for preparing a preparation of amplified DNA derived from a biological sample of a second individual useful for determining genetic data for DNA from a first individual in the blood sample, the method comprising:

extracting cell-free DNA from the biological sample;

preparing a preparation of amplified DNA by performing targeted PCR to amplify a plurality of SNP loci on the cell-free DNA extracted from the blood sample to generate amplified DNA, wherein the SNP loci are on a plurality of chromosomes;

analyzing the preparation of amplified DNA by sequencing the amplified DNA using sequencing-by-synthesis to obtain genetic data of the plurality

of SNP loci, wherein the sequencing-by-synthesis comprises clonal amplification of the amplified DNA and measurement of sequences of the clonally amplified DNA, and determining the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of SNP loci.

28. The claims of the ’544 patent are not directed to a natural law or natural phenomenon. Rather, they are directed to preparing preparations of amplified DNA derived from a biological sample and measuring DNA in a biological sample using synthetic pieces of DNA, including amplification products, which are produced using synthetic tools such as primers, to provide a novel and innovative solution to problems peculiar to the particular problem of amplifying and measuring small amounts of DNA from one individual or organism in a biological sample of another individual or organism. The ’544 patent claims are directed to specific, unconventional, non-routine methods for overcoming previously unresolved problems in this area.

CareDx’s Infringing Acts

29. The allegations provided below are exemplary and without prejudice to Natera’s infringement contentions. In providing these allegations, Natera does not convey or imply any particular claim constructions or the precise scope of the claims. Natera’s claim construction contentions regarding the meaning and scope of the claim terms will be provided under the Court’s scheduling order and local rules.

30. The infringing products include, but are not limited to, the Accused Products and any other infringing method, product, device, or test developed by CareDx.

31. As provided in more detail below, each element of at least one claim of the ’544 patent is literally present in the Accused Products or is literally practiced by the processes

through which the Accused Products are practiced. To the extent that any element is not literally present or practiced, each such element is present or practiced under the doctrine of equivalents.

32. On information and belief, CareDx released its AlloSure product for kidney transplant recipients to the public in 2017. On information and belief, CareDx released its AlloSeq product to the public in 2019. On information and belief, CareDx released its KidneyCare and HeartCare products to the public in 2021.

33. Performance of CareDx's Accused Products infringe at least one claim of the '544 patent as set forth in Exhibit A, which is a preliminary and exemplary claim chart detailing CareDx's infringement of the '544 patent. Exhibit A is not intended to limit Natera's right to modify this chart or any other claim chart or allege that other activities of CareDx infringe the identified claims or any other claims of the '544 patent or any other patents.

34. CareDx has made extensive use of Natera's patented technology, including the technology described and claimed in the '544 patent. Natera must defend its proprietary and patented technology, and thus requests that this Court award it damages sufficient to compensate for CareDx's infringement of the '544 patent, find this case exceptional and award Natera its attorneys' fees and costs, and grant an injunction against CareDx to prevent ongoing infringement of the '544 patent.

COUNT I: INFRINGEMENT OF U.S. PATENT NO. 11,111,544

35. Natera incorporates by reference and re-alleges the foregoing paragraphs as if fully set forth herein.

36. On information and belief, CareDx has infringed and continues to infringe the '544 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by making, using, selling, or offering to sell the Accused Products within the United States without authority.

37. Attached as Exhibit A is a preliminary and exemplary claim chart detailing CareDx's infringement of the '544 patent. This chart is not intended to limit Natera's right to modify the chart or allege that other activities of CareDx infringe the identified claims or any other claims of the '544 patent or any other patents. Exhibit A is hereby incorporated by reference in its entirety. Each claim element in Exhibit A that is mapped to the Accused Products is an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

PRAYER FOR RELIEF

WHEREFORE, Natera respectfully requests the following relief:

1. A judgment that CareDx has infringed the '544 patent literally or under the doctrine of equivalents;

2. An order preliminarily and permanently enjoining CareDx and its officers, directors, agents, servants, affiliates, employees, divisions, branches, subsidiaries, parents, and all others acting on behalf of or in active concert or participation therewith, from further infringement of the '544 patent;

3. An award of damages sufficient to compensate Natera for CareDx's infringement under 35 U.S.C. § 284;

4. A determination that this is an exceptional case under 35 U.S.C. § 285 and that Natera be awarded attorneys' fees;

5. Costs and expenses in this action;

6. An award of prejudgment and post-judgment interest; and

7. Such other and further relief as the Court may deem just and proper.

DEMAND FOR JURY TRIAL

Pursuant to Rule 38(b) of the Federal Rules of Civil Procedure, Natera respectfully demands a trial by jury on all triable issues.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Derek J. Fahnestock

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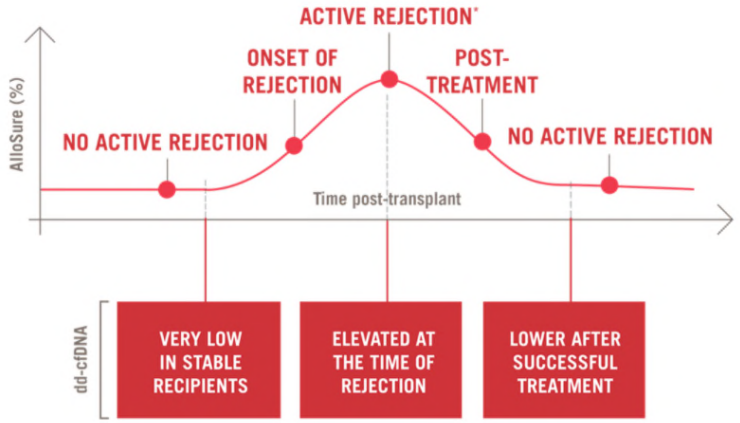
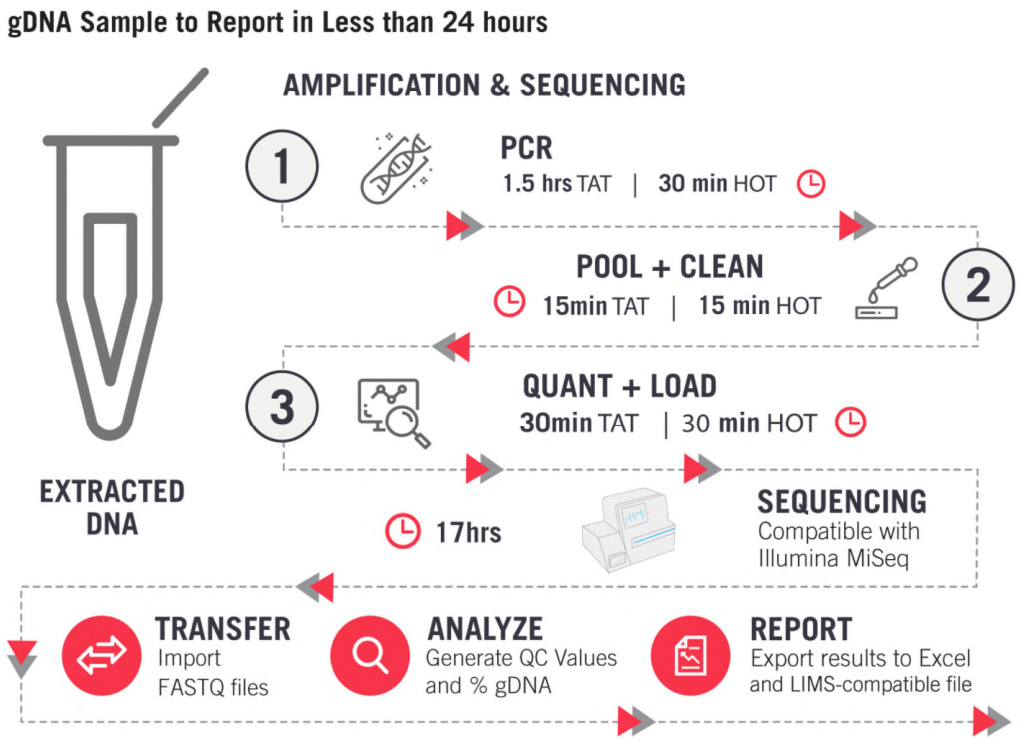
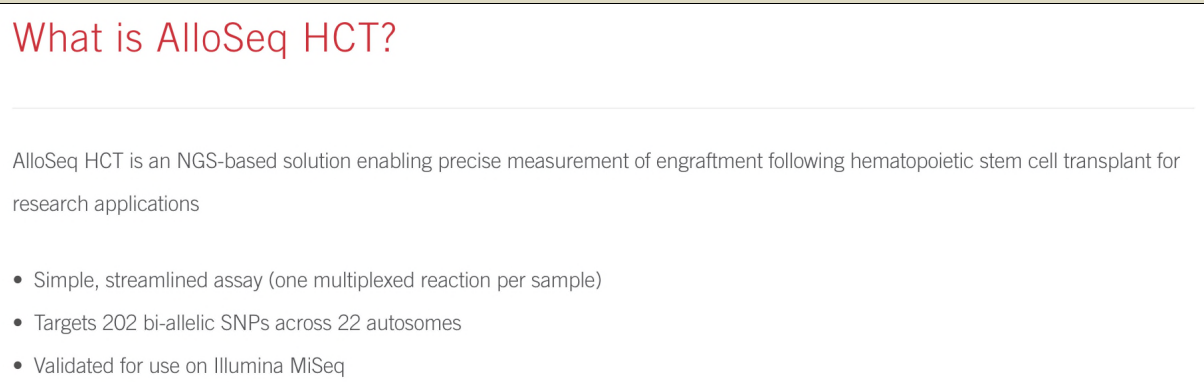
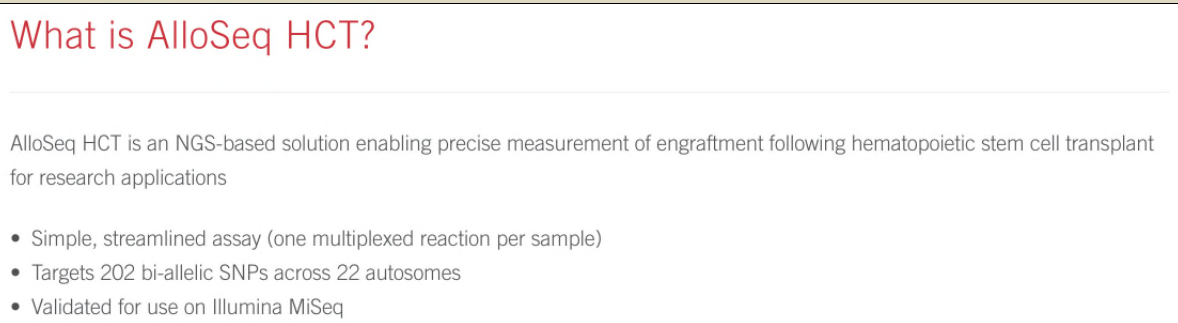
EXHIBIT A

’544 Claim Language	Infringement Support
1[preamble]. A method for determining genetic data for DNA from a first individual in a biological sample of a second individual, the method comprising:	To the extent the preamble is considered a claim limitation, this limitation is met at least by the accused CareDx Products including CareDx’s AlloSure test. The accused CareDx Products include methods for determining genetic data for DNA from a first individual in a biological sample of a second individual. For example, CareDx’s AlloSure website (https://caredx.com/products-and-services/transplant-services/kidney/allosure/), shown in Exhibit C, at 5, describes AlloSure as a “donor derived cell-free DNA (dd-cfDNA) test developed for transplant patients.” The website further shows that the AlloSure test employs a method for determining dd-cfDNA in the blood sample, as results are based on the “% dd-cfDNA” in the sample:  In another example, CareDx’s AlloSeq HCT website (https://caredx.com/products-and-services/transplant-lab-products/post-transplant-surveillance/alloseq-hct/), shown in Exhibit D, at 3,

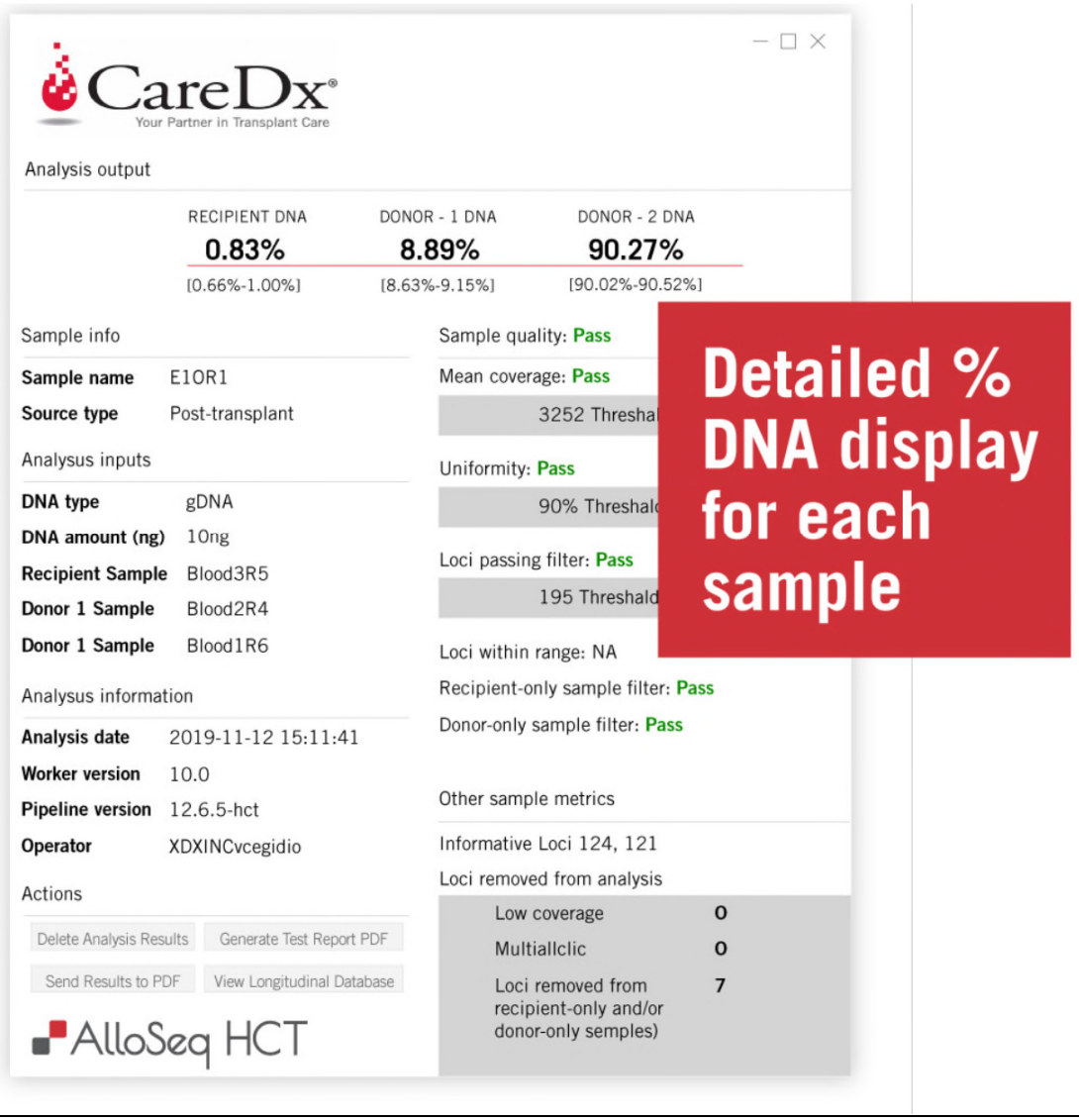
’544 Claim Language	Infringement Support
	describes AlloSeq as a method for measuring the percent recipient and donor DNA in post-transplant samples: How does AlloSeq HCT work? The AlloSeq HCT assay enables the amplification and sequencing of 202 single nucleotide polymorphisms (SNPs) across all autosomal chromosomes. The AlloSeq HCT software automatically calculates % recipient and donor DNA in post-transplant samples.
1[a]. amplifying a plurality of target loci on cell-free DNA extracted from the biological sample to generate amplified products;	The accused CareDx Products meet this limitation. For example, AlloSure involves amplifying a plurality of polymorphic loci on cell-free DNA extracted from the biological sample to generate amplified products. CareDx’s AlloSure Kidney Laboratory Services Guide brochure, Exhibit E, at 2, states that according to the Principle of the [AlloSure] Test: Donor-derived cell-free DNA is measured via targeted amplification and sequencing of a set of carefully selected and validated single nucleotide polymorphisms (SNPs) specifically chosen to discriminate among individuals based on genetic sequence (genotype). The AlloSeq HCT website, Exhibit D, at 3-4, also shows a workflow of the accused AlloSeq product that includes amplifying cell-free DNA extracted from the biological sample to generate amplified products:

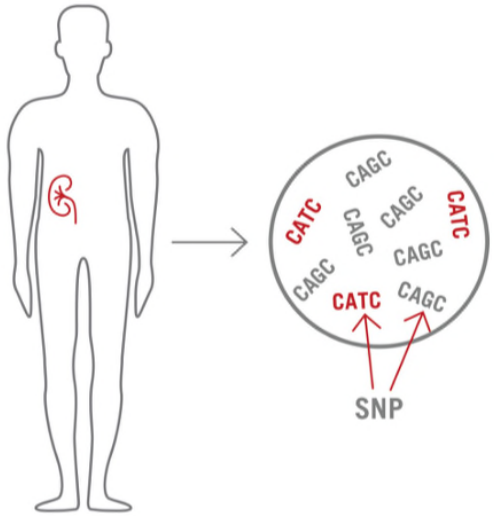
’544 Claim Language	Infringement Support
	Rapid workflow with automated analysis  In another example, CareDx’s AlloSeq website, Exhibit D, at 2, states that AlloSeq performs targeted amplification of a plurality of 202 bi-allelic SNPs:

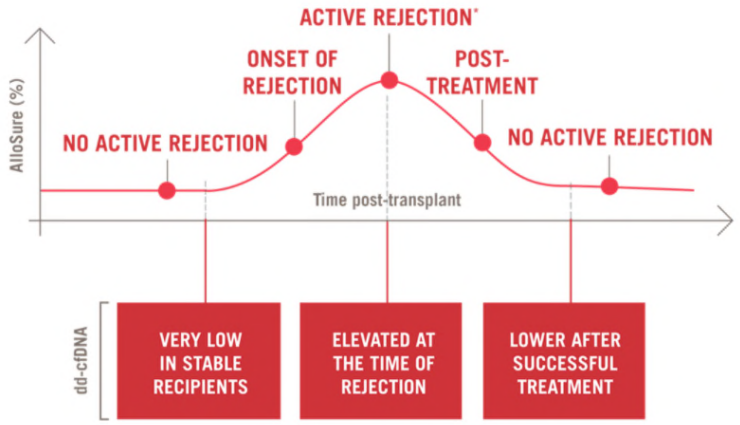
’544 Claim Language	Infringement Support
	
1[b]. sequencing the amplified products by sequencing-by-synthesis to obtain genetic data at the plurality of target loci;	The accused CareDx Products meet this limitation. For example, AlloSure involves sequencing the amplified products by sequencing-by-synthesis to obtain genetic data at the plurality of target loci. CareDx’s AlloSure Test Results Interpretation guide, Exhibit F, at 1, states that AlloSure uses next generation sequencing to measure SNPs to quantify donor-derived DNA: **TEST DESCRIPTION** The AlloSure test is a clinical-grade, targeted, next generation sequencing (NGS) assay that measures single-nucleotide polymorphisms (SNPs) to accurately quantify donor-derived cell-free DNA (dd-cfDNA) in renal transplant recipients without separate genotyping of either the donor or the recipient. The assay quantifies the fraction of dd-cfDNA in both unrelated and related donor-recipient pairs. CareDx’s AlloSeq website, Exhibit D, at 2, further shows that AlloSeq involves sequencing the amplified products by sequencing-by-synthesis to obtain genetic data at the plurality of target loci using the Illumina MiSeq for measurement of engraftment following hematopoeitic stem cell transplant:

’544 Claim Language	Infringement Support
	
1[c]. determining the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of target loci.	The accused CareDx Products meet this limitation. For example, AlloSure determines the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of target loci. CareDx’s AlloSure Kidney Laboratory Services Guide brochure describes measuring the amount of DNA from the transplant donor present in the biological sample based on allele frequency. *See* Exhibit E, at 2 (“Donor-derived cell-free DNA is measured via targeted amplification and sequencing of a set of carefully selected and validated single nucleotide polymorphisms (SNPs) specifically chosen to discriminate among individuals based on genetic sequence (genotype). The AlloSure bioinformatics software calculates the percent dd-cfDNA in the sample tested and applies the QC criteria.”). Results are then obtained “[b]ased on a proprietary algorithm that uses the known population frequencies of the SNPs sequenced and expected distribution of alleles….” *Id*. at 3. The AlloSure Test Results Interpretation guide, Exhibit F, at 3, further states that the DNA from the donor is measured using an expected quantity of each allele at the SNP loci for different DNA fractions:

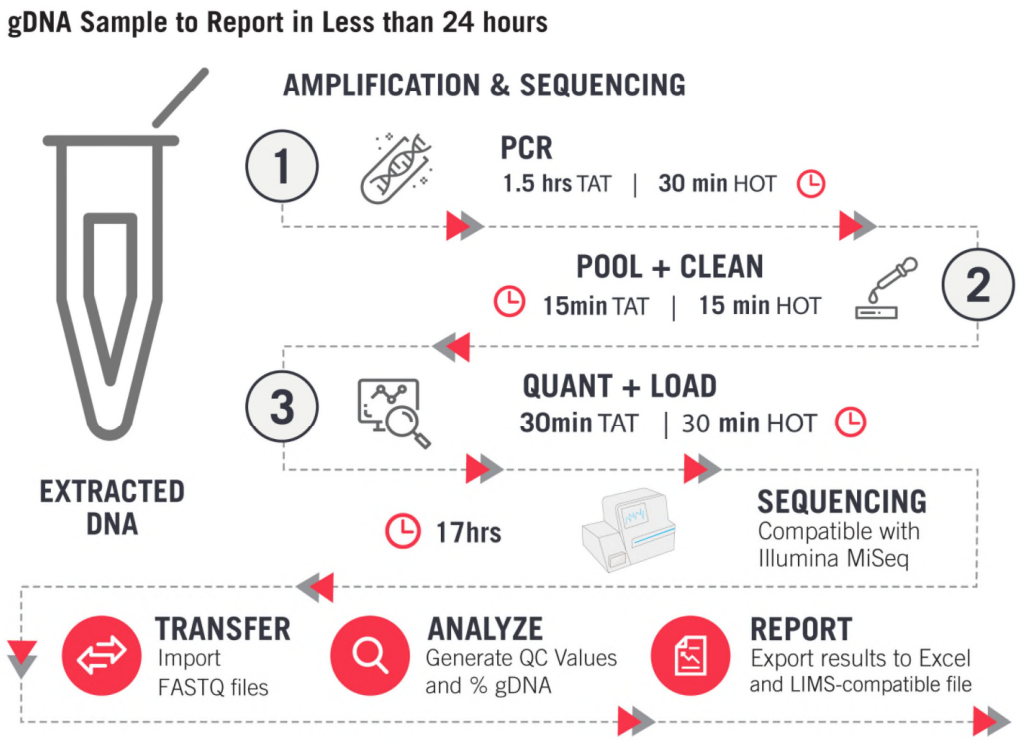
’544 Claim Language	Infringement Support
	INTERPRETATION OF ALLOSURE TEST RESULTS • **>1% dd-cfDNA is associated with active rejection (Ref 2)** dd-cfDNA level greater than 1% indicate a probability of active rejection (antibody-mediated rejection or T cell-mediated rejection). dd-cfDNA levels 1% and below reflect absence of active rejection. For dd-cfDNA greater than 1%, there is a positive predictive value (PPV) of 61% and a negative predictive value (NPV) of 84% for active rejection. The positive and negative predictive values for antibody-mediated rejection at a threshold of 1.0% dd-cfDNA are 44% and 96%, respectively. The reference standard for rejection diagnosis was histological evidence from renal allograft biopsies performed for clinical suspicion. • **0.21% dd-cfDNA is the median observed in a reference population of stable recipients (Ref 3)** dd-cfDNA values greater than 1% were above the 96th percentile of all values in a study of stable kidney transplant recipients i.e. outside the normal range for this population. 75% of stable recipients had an AlloSure result below 0.40% dd-cfDNA. • **>61% increase in dd-cfDNA from a prior sample exceeds the biological and analytical variability observed in the reference population (Ref 3)** An increase of greater than 61% in consecutive dd-cfDNA results in an individual is greater than the change that may be attributable to normal biological and analytical variation. In addition, CareDx’s AlloSeq website, Exhibit D, at 4, shows that AlloSeq determines the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of target loci:

’544 Claim Language	Infringement Support
	

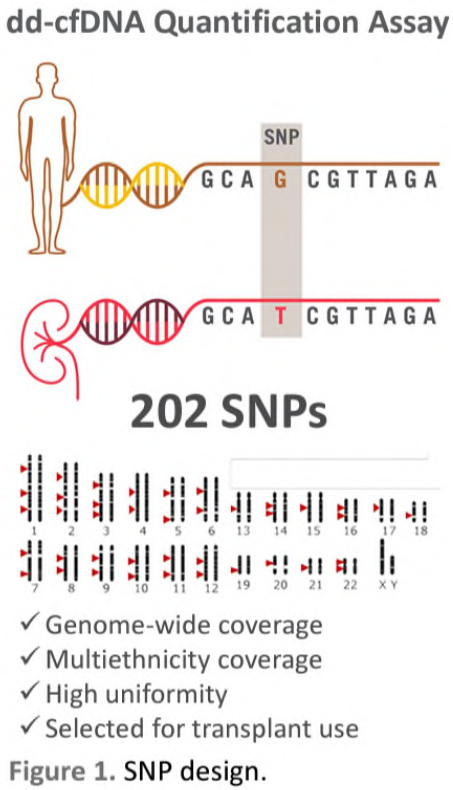
’544 Claim Language	Infringement Support
	A poster describing AlloSeq that is linked on CareDx’s website, Exhibit G, further shows that AlloSeq determines the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of target loci:  Figure 2. Relative quantification of dd-cfDNA (in red), based on SNP sequence.
18[preamble]. A method for determining genetic data for DNA from a first individual in a blood sample of a second individual, the method comprising:	To the extent the preamble is considered a claim limitation, this limitation is met at least by the accused CareDx Products including CareDx’s AlloSure test. The accused CareDx Products include methods for determining genetic data for DNA from a first individual in a biological sample of a second individual. For example, CareDx’s AlloSure website (https://caredx.com/products-and-services/transplant-

’544 Claim Language	Infringement Support
	services/kidney/allosure/), shown in Exhibit C, at 5, describes AlloSure as a “donor derived cell-free DNA (dd-cfDNA) test developed for transplant patients.” The website further shows that the AlloSure test employs a method for determining dd-cfDNA in the blood sample, as results are based on the “% dd-cfDNA” in the sample:  In another example, CareDx’s AlloSeq HCT website (https://caredx.com/products-and-services/transplant-lab-products/post-transplant-surveillance/alloseq-hct/), shown in Exhibit D, at 3, describes AlloSeq as a method for measuring the percent recipient and donor DNA in post-transplant samples: How does AlloSeq HCT work? The AlloSeq HCT assay enables the amplification and sequencing of 202 single nucleotide polymorphisms (SNPs) across all autosomal chromosomes. The AlloSeq HCT software automatically calculates % recipient and donor DNA in post-transplant samples.

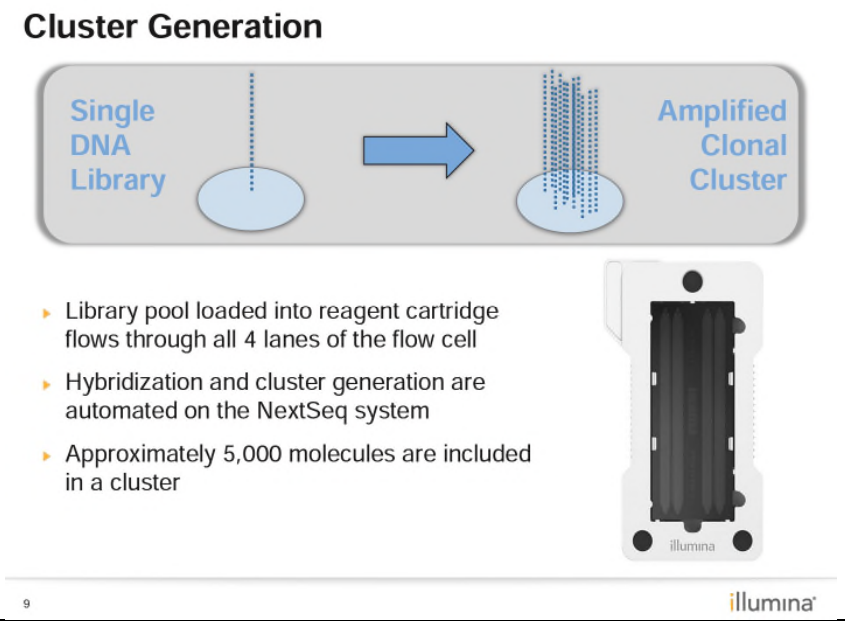
’544 Claim Language	Infringement Support
18[a]. performing targeted PCR to amplify a plurality of SNP loci on cell-free DNA extracted from the blood sample to generate amplified products, wherein the SNP loci are on a plurality of chromosomes;	The accused CareDx Products meet this limitation. For example, AlloSure involves performing targeted PCR to amplify a plurality of SNP loci on cell-free DNA extracted from the blood sample to generate amplified products. CareDx’s AlloSure Kidney Laboratory Services Guide brochure, Exhibit E, at 2, states that according to the Principle of the [AlloSure] Test: Donor-derived cell-free DNA is measured via targeted amplification and sequencing of a set of carefully selected and validated single nucleotide polymorphisms (SNPs) specifically chosen to discriminate among individuals based on genetic sequence (genotype). The AlloSeq HCT website, Exhibit D, at 3-4, also shows a workflow of the accused AlloSeq product that includes performing targeted PCR to amplify a plurality of SNP loci on cell-free DNA extracted from the blood sample to generate amplified products:

’544 Claim Language	Infringement Support
	Rapid workflow with automated analysis  In another example, CareDx’s AlloSeq website, Exhibit D, at 2, states that AlloSeq performs targeted PCR to amplify a plurality of SNP loci on cell-free DNA extracted from the blood sample to generate amplified products:

’544 Claim Language	Infringement Support
	What is AlloSeq HCT? AlloSeq HCT is an NGS-based solution enabling precise measurement of engraftment following hematopoietic stem cell transplant for research applications • Simple, streamlined assay (one multiplexed reaction per sample) • Targets 202 bi-allelic SNPs across 22 autosomes • Validated for use on Illumina MiSeq In addition, the SNP loci amplified in AlloSure are on a plurality of chromosomes. For example, CareDx’s AlloSure website, Exhibit C, at 5, states that AlloSure targets SNPs across “all somatic chromosomes”: What is AlloSure? **A Surveillance Solution** The first analytically and clinically validated donor derived cell-free DNA (dd-cfDNA) test developed for transplant patients with a targeted SNP assay across all somatic chromosomes. Similarly, the SNP loci amplified in AlloSeq are on a plurality of chromosomes. In addition, a

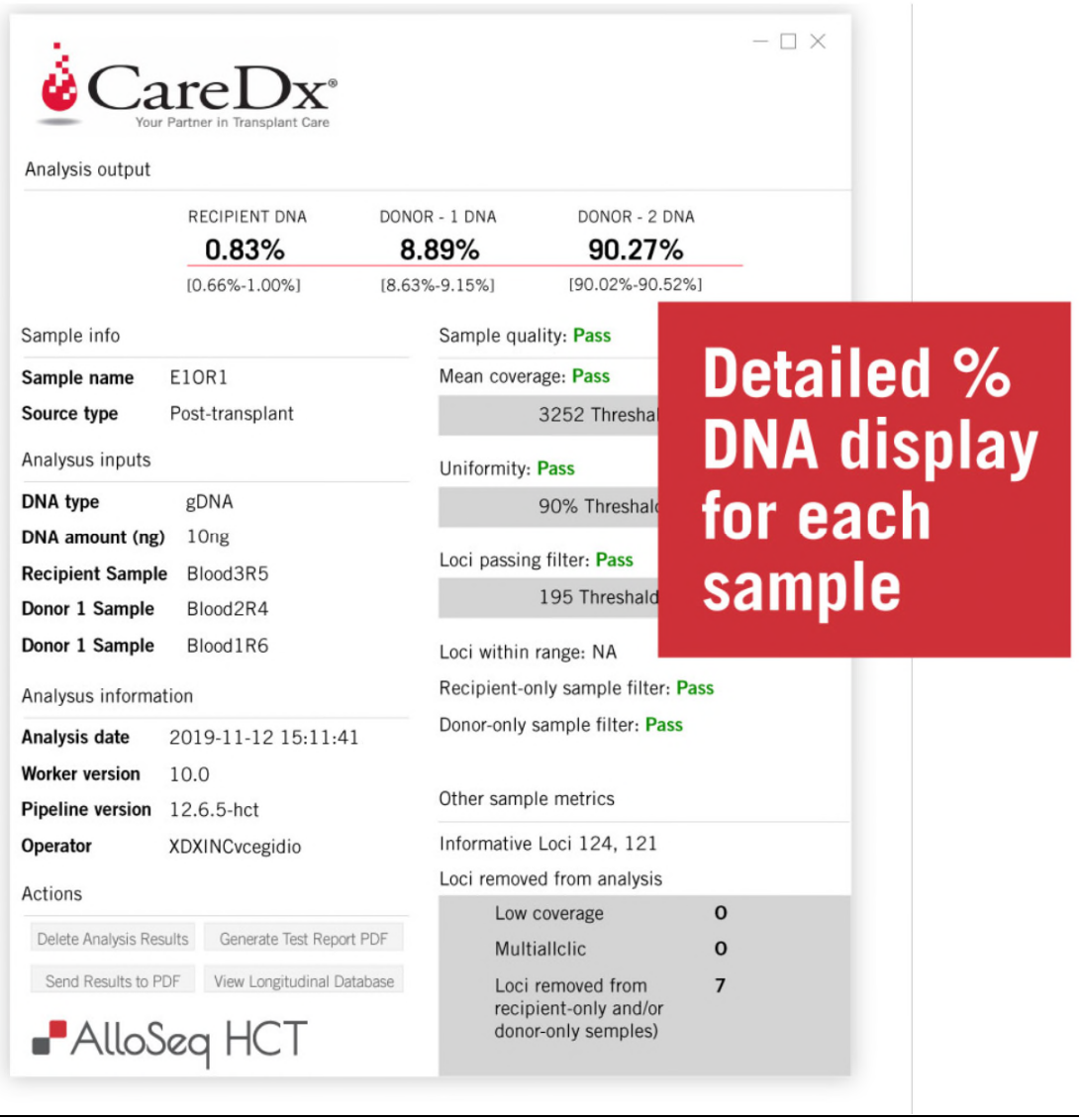
’544 Claim Language	Infringement Support
	poster describing AlloSeq that is linked on CareDx’s website at https://stage.caredx.com/wp-content/uploads/2020/10/P198-Poster-AQ-cfDNA-1.pdf, Exhibit G, includes a figure showing that AlloSeq targets SNP loci on chromosomes 1 through 22:  Figure 1. SNP design.
18[b]. sequencing the amplified products by sequencing-by-synthesis to obtain genetic data of the plurality of SNP loci, wherein	The accused CareDx Products meet this limitation. For example, AlloSure involves sequencing the amplified products by sequencing-by-synthesis to obtain genetic data at the plurality of target loci.

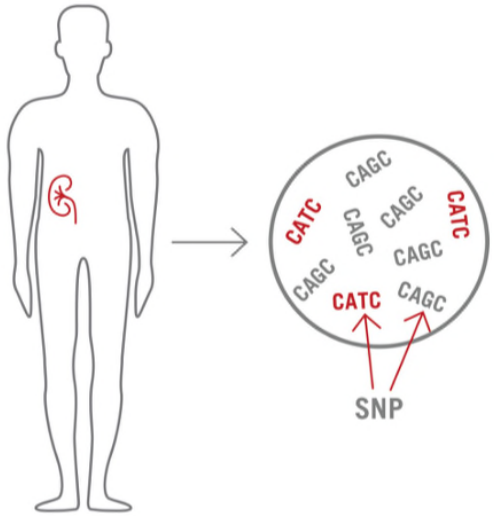
’544 Claim Language	Infringement Support
the sequencing-by-synthesis comprises clonal amplification of the amplified products and measurement of sequences of the clonally amplified DNA;	CareDx’s AlloSure Test Results Interpretation guide, Exhibit F, at 1, states that AlloSure uses next generation sequencing to measure SNPs to quantify donor-derived DNA: **TEST DESCRIPTION** The AlloSure test is a clinical-grade, targeted, next generation sequencing (NGS) assay that measures single-nucleotide polymorphisms (SNPs) to accurately quantify donor-derived cell-free DNA (dd-cfDNA) in renal transplant recipients without separate genotyping of either the donor or the recipient. The assay quantifies the fraction of dd-cfDNA in both unrelated and related donor-recipient pairs. CareDx’s AlloSeq website, Exhibit D, at 2, further shows that AlloSeq involves sequencing the amplified products by sequencing-by-synthesis to obtain genetic data at the plurality of target loci using the Illumina MiSeq for measurement of engraftment following hematopoeitic stem cell transplant: What is AlloSeq HCT? AlloSeq HCT is an NGS-based solution enabling precise measurement of engraftment following hematopoietic stem cell transplant for research applications • Simple, streamlined assay (one multiplexed reaction per sample) • Targets 202 bi-allelic SNPs across 22 autosomes • Validated for use on Illumina MiSeq The sequencing-by-synthesis performed in AlloSure further comprises clonal amplification of the amplified products. For example, CareDx’s Wong publication, Wong, *et al.*, *J. Med. Diagn. Methods* (2020) 9:302 (“Wong”) states that “[t]he assay is run on the Illumina NextSeq 550 using either mid- or high-output flow cells.” Wong, Exhibit H, at 2. Illumina’s website states that “[t]he NextSeq 550 System harnesses proven Illumina sequencing by synthesis (SBS) technology to deliver highly accurate data and robust performance for multiple applications.”

’544 Claim Language	Infringement Support
	Exhibit I, https://www.illumina.com/systems/sequencing-platforms/nextseq/specifications.html#:~:text=Sequencing%20by%20Synthesis,-%26amp%3Bamp&text=The%20NextSeq%20550%20System%20leverages,that%20sets%20Illumina%20systems%20apart. Illumina discloses in the MiSeq Application Note: DNA Analysis for MiSeq that its MiSeq System comprises clonal amplification of the amplified products. *See* Application Note: DNA Analysis, Exhibit J, at 1 (“The MiSeq system features enhanced fluidics architecture, enabling a five-fold decrease in chemistry cycle time to provide results in hours, rather than the weeks required by CE. Preparing a sequencing library takes just 90 minutes, with clonal amplification and sequencing completed within as little as 4.5 hours.”). Illumina also discloses in a teaching presentation that the NextSeq products use clonal amplification and sequence clonally amplified DNA: 

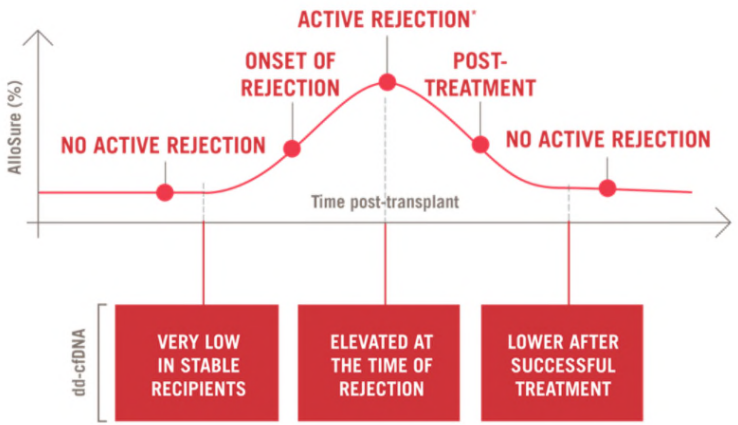
’544 Claim Language	Infringement Support
	See Illumina publication “Introduction to the NextSeq System,” Exhibit K, at slide 9.
18[c]. determining the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of SNP loci.	The accused CareDx Products meet this limitation. For example, AlloSure determines the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of SNP loci. CareDx’s AlloSure Kidney Laboratory Services Guide brochure describes measuring the amount of DNA from the transplant donor present in the biological sample based on allele frequency. *See* Exhibit E, at 2 (“Donor-derived cell-free DNA is measured via targeted amplification and sequencing of a set of carefully selected and validated single nucleotide polymorphisms (SNPs) specifically chosen to discriminate among individuals based on genetic sequence (genotype). The AlloSure bioinformatics software calculates the percent dd-cfDNA in the sample tested and applies the QC criteria.”). Results are then obtained “based on a proprietary algorithm that uses the known population frequencies of the SNPs sequenced and expected distribution of alleles.” *Id*. at 3. The AlloSure Test Results Interpretation guide, Exhibit G at 3, further states that the DNA from the donor is measured using an expected quantity of each allele at the SNP loci for different DNA fractions:

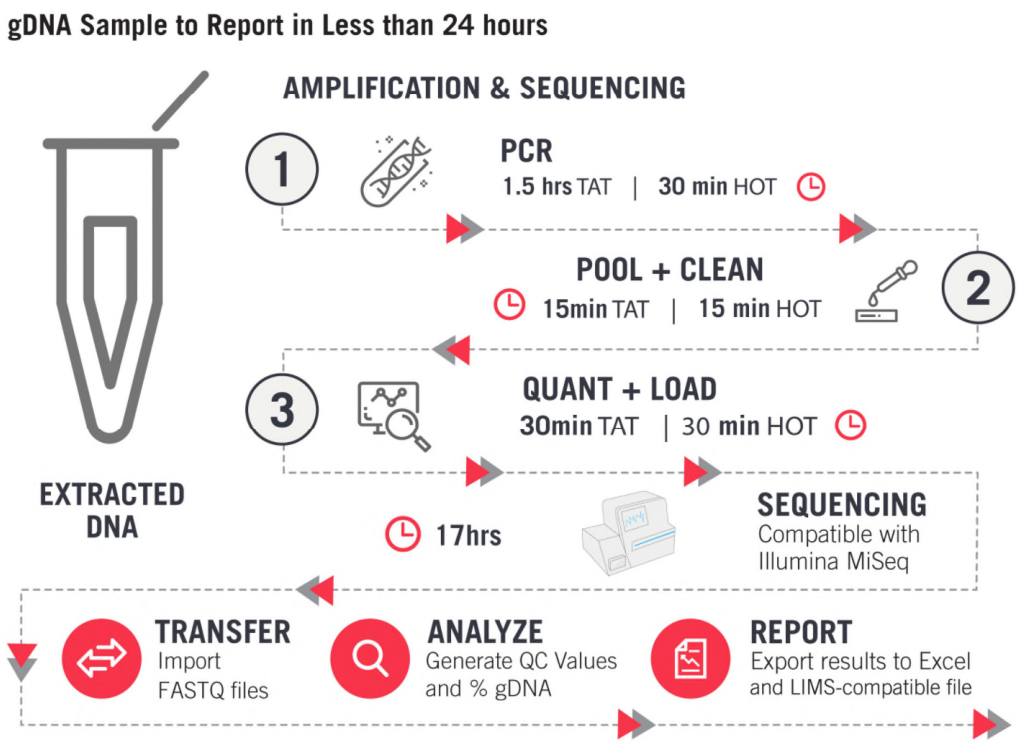
’544 Claim Language	Infringement Support
	INTERPRETATION OF ALLOSURE TEST RESULTS • **>1% dd-cfDNA is associated with active rejection (Ref 2)** dd-cfDNA level greater than 1% indicate a probability of active rejection (antibody-mediated rejection or T cell-mediated rejection). dd-cfDNA levels 1% and below reflect absence of active rejection. For dd-cfDNA greater than 1%, there is a positive predictive value (PPV) of 61% and a negative predictive value (NPV) of 84% for active rejection. The positive and negative predictive values for antibody-mediated rejection at a threshold of 1.0% dd-cfDNA are 44% and 96%, respectively. The reference standard for rejection diagnosis was histological evidence from renal allograft biopsies performed for clinical suspicion. • **0.21% dd-cfDNA is the median observed in a reference population of stable recipients (Ref 3)** dd-cfDNA values greater than 1% were above the 96th percentile of all values in a study of stable kidney transplant recipients i.e. outside the normal range for this population. 75% of stable recipients had an AlloSure result below 0.40% dd-cfDNA. • **>61% increase in dd-cfDNA from a prior sample exceeds the biological and analytical variability observed in the reference population (Ref 3)** An increase of greater than 61% in consecutive dd-cfDNA results in an individual is greater than the change that may be attributable to normal biological and analytical variation. In addition, CareDx’s AlloSeq website, Exhibit D, at 4, shows that AlloSeq determines the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of SNP loci:

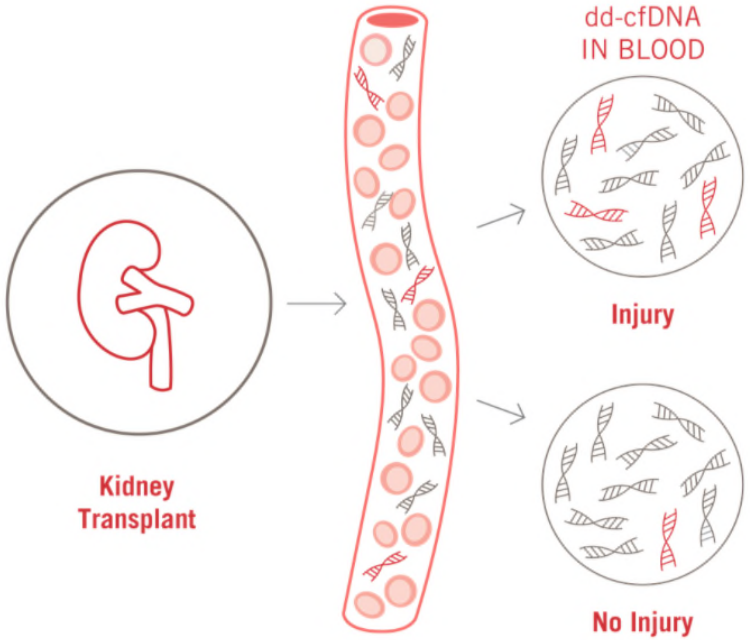
’544 Claim Language	Infringement Support
	

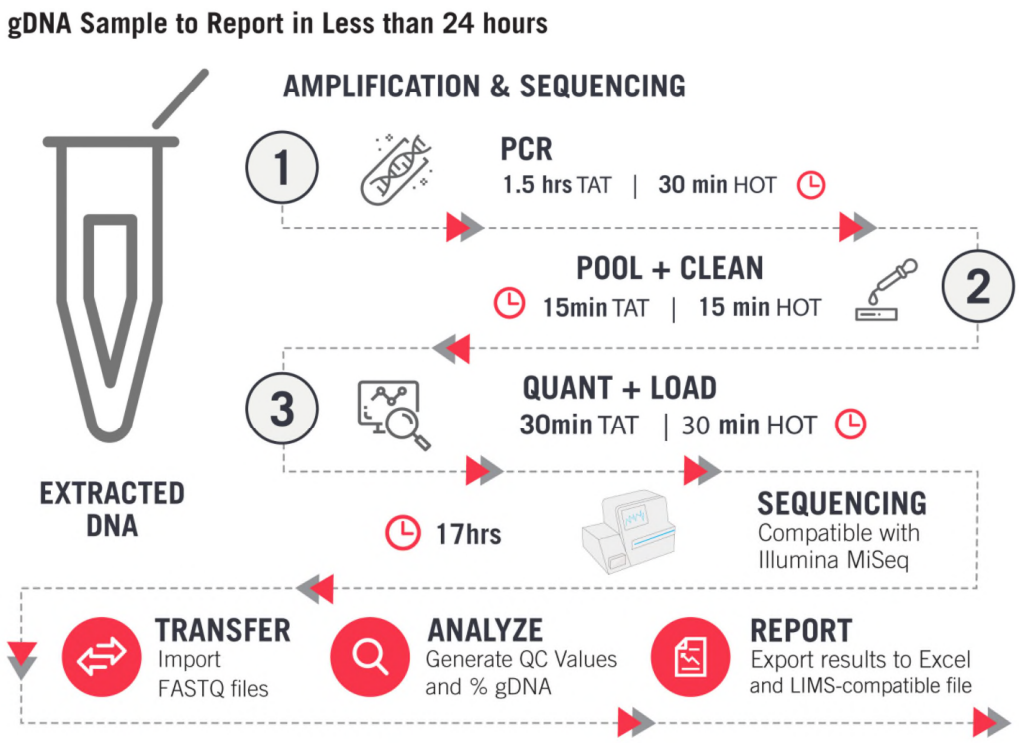
’544 Claim Language	Infringement Support
	A poster describing AlloSeq that is linked on CareDx’s website, Exhibit G, further shows that AlloSeq determines the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of SNP loci:  Figure 2. Relative quantification of dd-cfDNA (in red), based on SNP sequence.
21[preamble]. A method for preparing a preparation of amplified DNA derived from a biological sample of a second individual useful for determining genetic data for DNA from a first individual	To the extent the preamble is considered a claim limitation, this limitation is met at least by the accused CareDx Products including CareDx’s AlloSure and AlloSeq tests. The accused CareDx Products include methods for preparing a preparation of amplified DNA derived from a biological sample of a second individual useful for determining genetic data for DNA from a first individual in a biological sample.

’544 Claim Language	Infringement Support
in the biological sample, the method comprising:	For example, CareDx’s Wong publication describes preparing a preparation of amplified DNA in AlloSure “using PCR conditions optimized for multiplexing.” Wong, Exhibit H, at 2. Wong further explains that for the preparation: > The components of the multiplex master mix were based on the preamplification conditions used for the original AlloSure assay []. The components were optimized for the AlloSure application, including magnesium chloride concentration, enzyme concentration, dNTP concentration, PCR enhancers, DMSO, and primer concentration. The final conditions and chemistry for the library preparation amplification increased hybridization specificity and melting temperature, resulting in improved assay performance. *Id.* CareDx’s AlloSure website (https://caredx.com/products-and-services/transplant-services/kidney/allosure/), shown in Exhibit C, at 5, also describes AlloSure as a “donor derived cell-free DNA (dd-cfDNA) test developed for transplant patients.” The website further shows that the AlloSure test employs a method for determining dd-cfDNA in the blood sample, as results are based on the “% dd-cfDNA” in the sample:

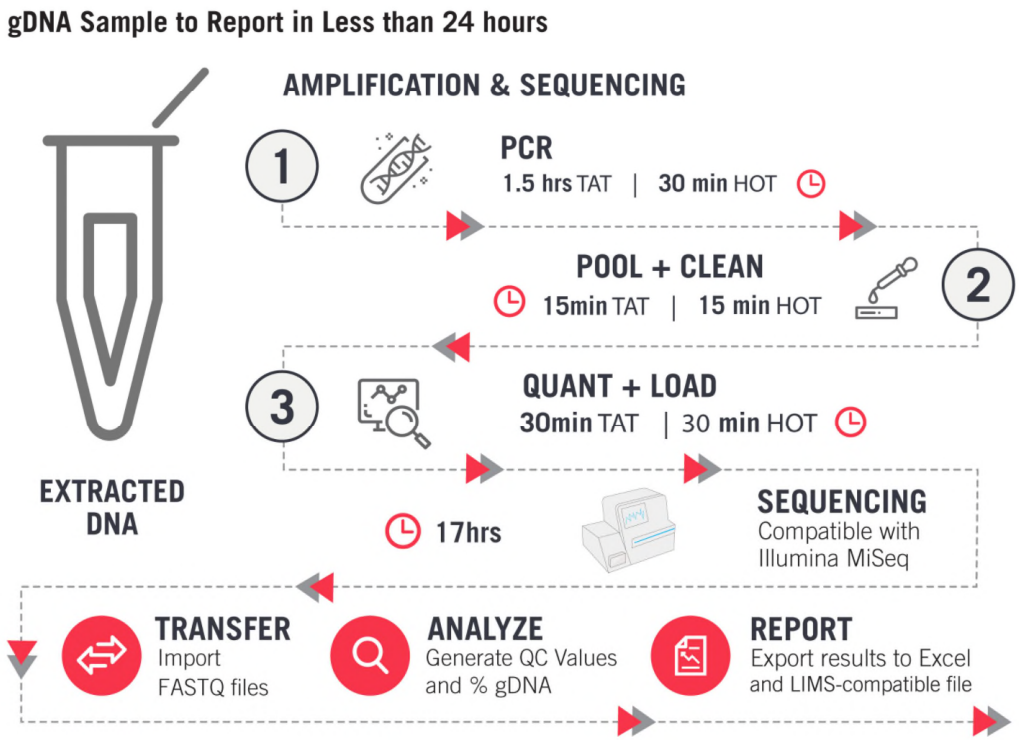
’544 Claim Language	Infringement Support
	 In another example, CareDx’s AlloSeq HCT website (https://caredx.com/products-and-services/transplant-lab-products/post-transplant-surveillance/alloseq-hct/), shown in Exhibit D, at 3, describes preparing a preparation of amplified DNA in AlloSeq that is useful for calculating the percent recipient and donor DNA in post-transplant samples: How does AlloSeq HCT work? The AlloSeq HCT assay enables the amplification and sequencing of 202 single nucleotide polymorphisms (SNPs) across all autosomal chromosomes. The AlloSeq HCT software automatically calculates % recipient and donor DNA in post-transplant samples. The AlloSeq HCT website, Exhibit D, at 3-4, also shows a workflow of the accused AlloSeq product that includes assaying extracted mixed transplant donor and recipient cell-free DNA from a transplant recipient’s blood sample and preparing a preparation of PCR-amplified DNA useful for determining %gDNA in the sample:

’544 Claim Language	Infringement Support
	Rapid workflow with automated analysis 
21[a]. extracting cell-free	The accused CareDx Products meet this limitation.

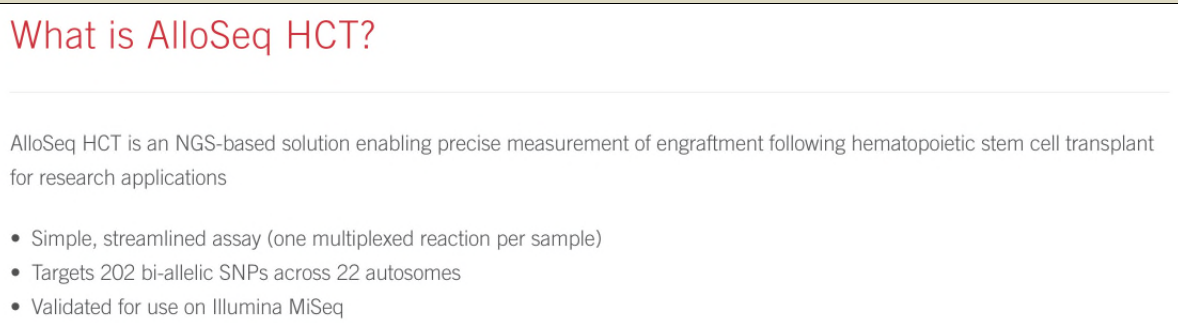
’544 Claim Language	Infringement Support
DNA from the biological sample;	For example, CareDx’s AlloSure website, at Exhibit C, at 5, shows a diagram depicting the cell-free DNA containing a mixture of donor and transplant cell-free DNA in the blood of a kidney transplant subject that is tested in the accused AlloSure product.  CareDx’s AlloSure Kidney Laboratory Services Guide brochure, Exhibit E, at 3, further states that in AlloSure, “[c]ell-free DNA extracted from plasma is used as the template in a next generation sequencing assay.” In another example, the CareDx AlloSeq HCT website, at Exhibit D, at 3-4, shows a workflow of the accused AlloSeq product that includes assaying extracted mixed transplant donor and recipient cell-free DNA from a transplant recipient’s blood sample:

’544 Claim Language	Infringement Support
	Rapid workflow with automated analysis 
21[b]. preparing a preparation of amplified DNA by	The accused CareDx Products meet this limitation.

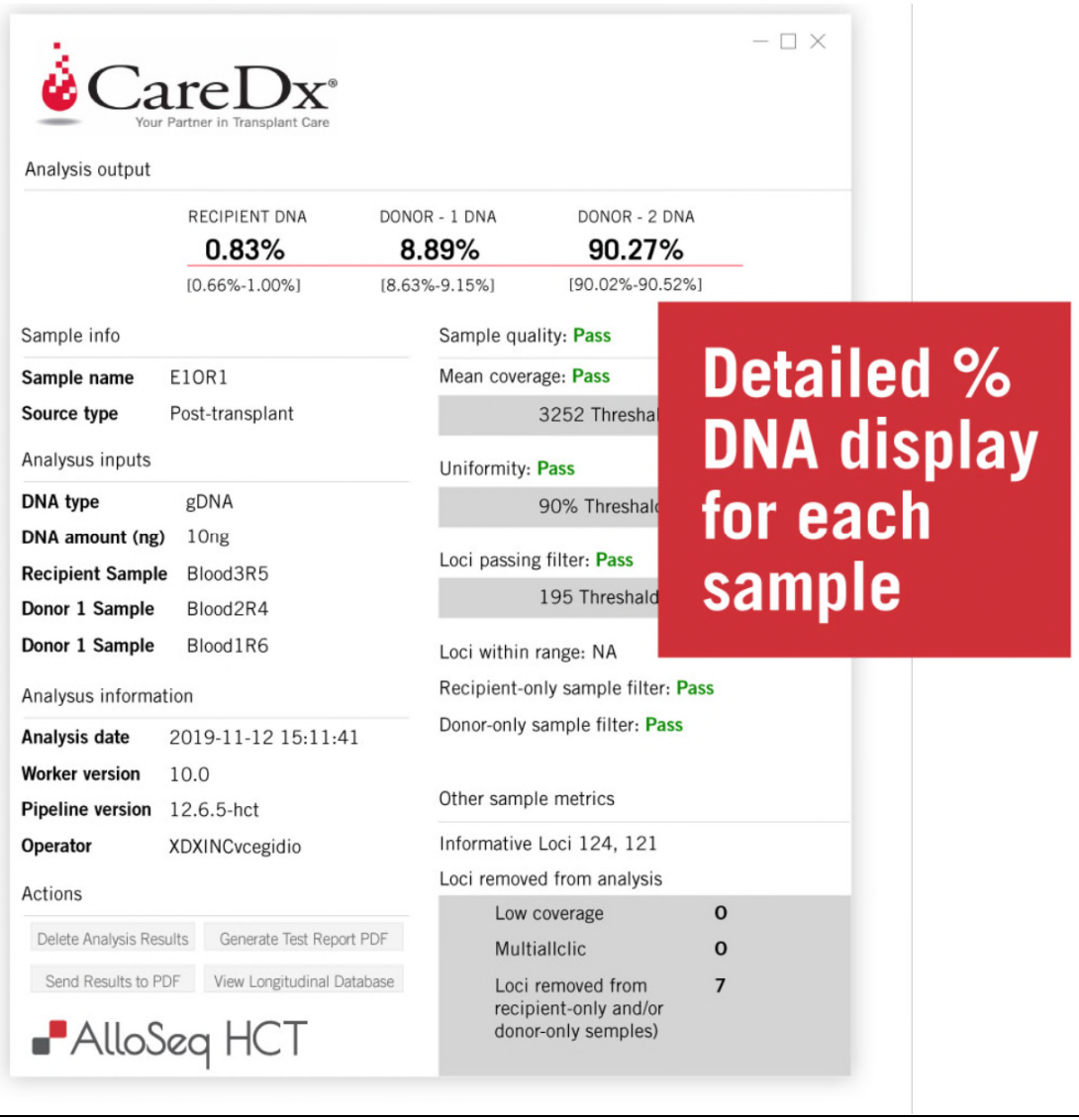
’544 Claim Language	Infringement Support
amplifying a plurality of target loci on the cell-free DNA extracted from the biological sample to generate amplified DNA;	For example, AlloSure involves amplifying a plurality of polymorphic loci on cell-free DNA extracted from the biological sample to generate amplified products. CareDx’s AlloSure Kidney Laboratory Services Guide brochure, Exhibit E, at 2, states that according to the Principle of the [AlloSure] Test: Donor-derived cell-free DNA is measured via targeted amplification and sequencing of a set of carefully selected and validated single nucleotide polymorphisms (SNPs) specifically chosen to discriminate among individuals based on genetic sequence (genotype). The AlloSeq HCT website, Exhibit D, at 3-4, also shows a workflow of the accused AlloSeq product that includes amplifying cell-free DNA extracted from the biological sample to generate amplified products:

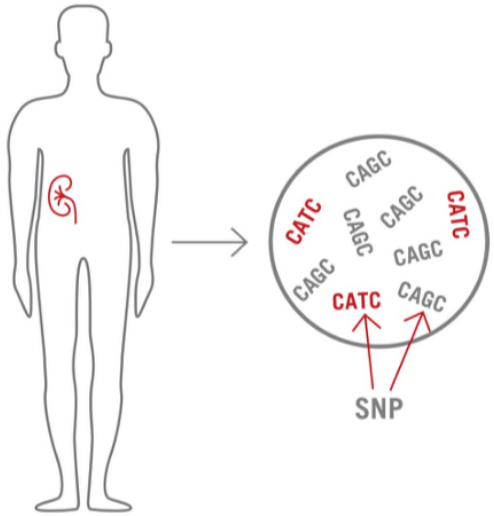
’544 Claim Language	Infringement Support
	Rapid workflow with automated analysis  In another example, CareDx’s AlloSeq website, Exhibit D, at 2, states that AlloSeq performs targeted amplification of a plurality of 202 bi-allelic SNPs:

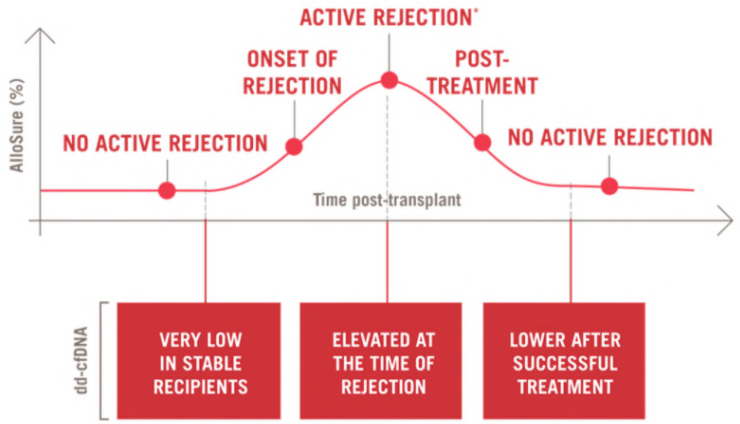
’544 Claim Language	Infringement Support
	What is AlloSeq HCT? AlloSeq HCT is an NGS-based solution enabling precise measurement of engraftment following hematopoietic stem cell transplant for research applications • Simple, streamlined assay (one multiplexed reaction per sample) • Targets 202 bi-allelic SNPs across 22 autosomes • Validated for use on Illumina MiSeq
21[c]. analyzing the preparation of amplified DNA by sequencing the amplified DNA using sequencing-by-synthesis to obtain genetic data of the plurality of target loci, and determining the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of target loci.	The accused CareDx Products meet this limitation. For example, AlloSure uses sequencing of the amplified products by sequencing-by-synthesis to obtain genetic data at the plurality of target loci. CareDx’s AlloSure Test Results Interpretation guide, Exhibit F, at 1, states that AlloSure uses next generation sequencing to measure SNPs to quantify donor-derived DNA: **TEST DESCRIPTION** The AlloSure test is a clinical-grade, targeted, next generation sequencing (NGS) assay that measures single-nucleotide polymorphisms (SNPs) to accurately quantify donor-derived cell-free DNA (dd-cfDNA) in renal transplant recipients without separate genotyping of either the donor or the recipient. The assay quantifies the fraction of dd-cfDNA in both unrelated and related donor-recipient pairs. CareDx’s AlloSeq website, Exhibit D, at 2, further shows that AlloSeq uses sequencing of the amplified products by sequencing-by-synthesis to obtain genetic data at the plurality of target loci using the Illumina MiSeq for measurement of engraftment following hematopoeitic stem cell transplant:

’544 Claim Language	Infringement Support
	 In addition, for example, AlloSure determines the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of target loci. CareDx’s AlloSure Kidney Laboratory Services Guide brochure describes measuring the amount of DNA from the transplant donor present in the biological sample based on allele frequency. *See* Exhibit E, at 2 (“Donor-derived cell-free DNA is measured via targeted amplification and sequencing of a set of carefully selected and validated single nucleotide polymorphisms (SNPs) specifically chosen to discriminate among individuals based on genetic sequence (genotype). The AlloSure bioinformatics software calculates the percent dd-cfDNA in the sample tested and applies the QC criteria.”). Results are then obtained “based on a proprietary algorithm that uses the known population frequencies of the SNPs sequenced and expected distribution of alleles.” *Id*. at 3. The AlloSure Test Results Interpretation guide, Exhibit G at 3, further states that the DNA from the donor is measured using an expected quantity of each allele at the SNP loci for different DNA fractions:

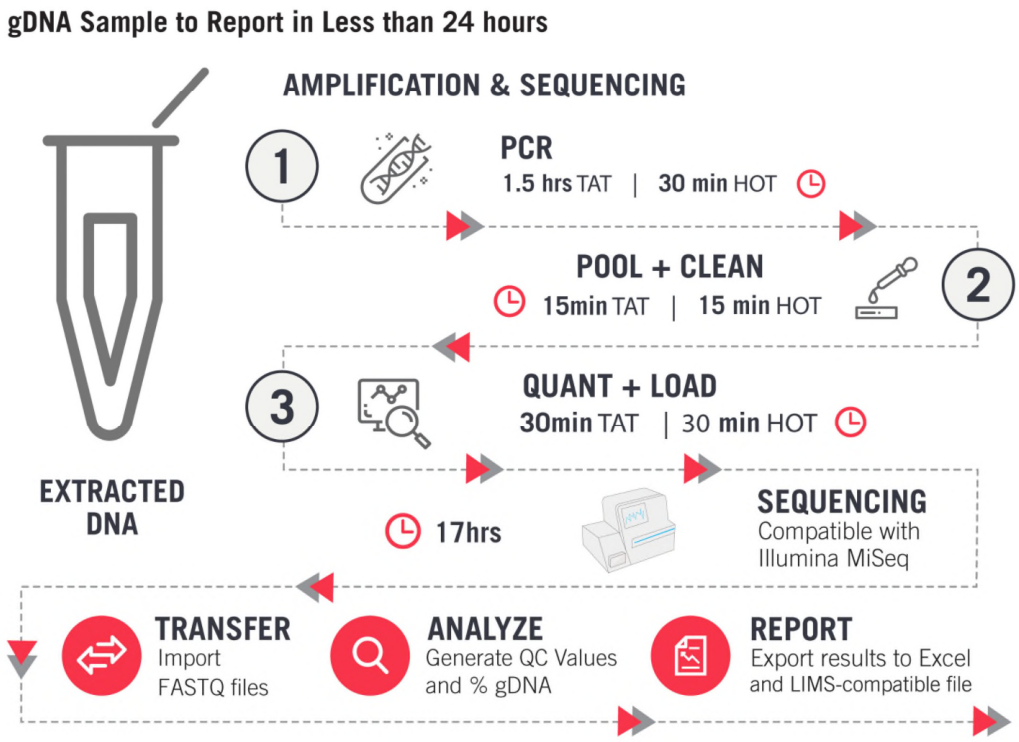
’544 Claim Language	Infringement Support
	INTERPRETATION OF ALLOSURE TEST RESULTS • **>1% dd-cfDNA is associated with active rejection (Ref 2)** dd-cfDNA level greater than 1% indicate a probability of active rejection (antibody-mediated rejection or T cell-mediated rejection). dd-cfDNA levels 1% and below reflect absence of active rejection. For dd-cfDNA greater than 1%, there is a positive predictive value (PPV) of 61% and a negative predictive value (NPV) of 84% for active rejection. The positive and negative predictive values for antibody-mediated rejection at a threshold of 1.0% dd-cfDNA are 44% and 96%, respectively. The reference standard for rejection diagnosis was histological evidence from renal allograft biopsies performed for clinical suspicion. • **0.21% dd-cfDNA is the median observed in a reference population of stable recipients (Ref 3)** dd-cfDNA values greater than 1% were above the 96th percentile of all values in a study of stable kidney transplant recipients i.e. outside the normal range for this population. 75% of stable recipients had an AlloSure result below 0.40% dd-cfDNA. • **>61% increase in dd-cfDNA from a prior sample exceeds the biological and analytical variability observed in the reference population (Ref 3)** An increase of greater than 61% in consecutive dd-cfDNA results in an individual is greater than the change that may be attributable to normal biological and analytical variation. In addition, CareDx’s AlloSeq website, Exhibit D, at 4, shows that AlloSeq determines the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of target loci:

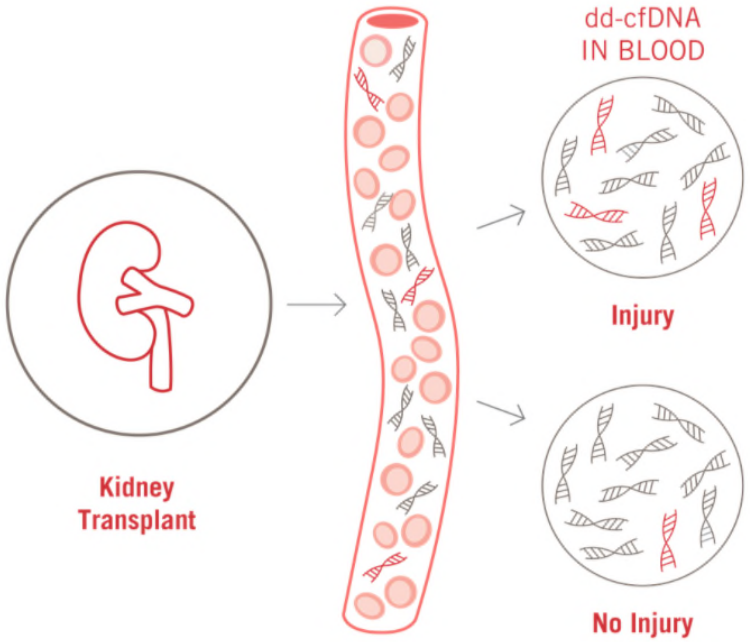
’544 Claim Language	Infringement Support
	

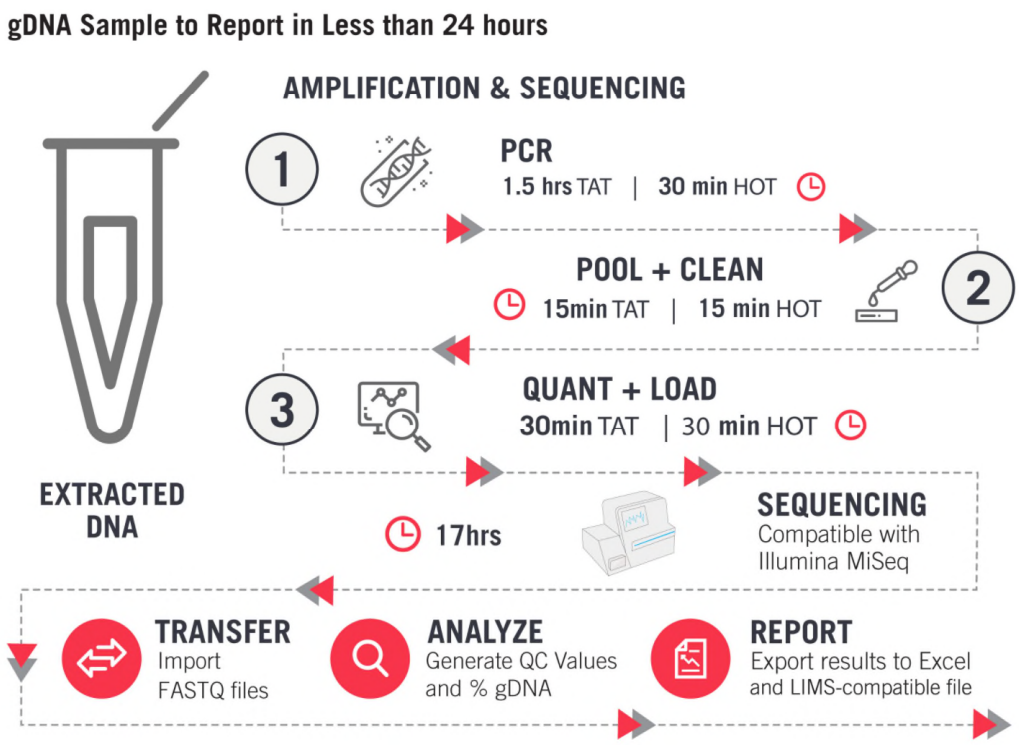
’544 Claim Language	Infringement Support
	A poster describing AlloSeq that is linked on CareDx’s website, Exhibit G, further shows that AlloSeq determines the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of target loci:  Figure 2. Relative quantification of dd-cfDNA (in red), based on SNP sequence.
38[pre]. A method for preparing a preparation of amplified DNA derived from a biological sample of a second individual useful for determining genetic data for DNA from a first individual in the blood sample, the	To the extent the preamble is considered a claim limitation, this limitation is met at least by the accused CareDx Products including CareDx’s AlloSure and AlloSeq tests. The accused CareDx Products include methods for preparing a preparation of amplified DNA derived from a biological sample of a second individual useful for determining genetic data for DNA from a first individual in a biological sample. For example, CareDx’s Wong publication describes preparing a preparation of amplified DNA in

’544 Claim Language	Infringement Support
method comprising:	AlloSure “using PCR conditions optimized for multiplexing.” Wong, Exhibit H, at 2. Wong further explains that for the preparation: > The components of the multiplex master mix were based on the preamplification conditions used for the original AlloSure assay []. The components were optimized for the AlloSure application, including magnesium chloride concentration, enzyme concentration, dNTP concentration, PCR enhancers, DMSO, and primer concentration. The final conditions and chemistry for the library preparation amplification increased hybridization specificity and melting temperature, resulting in improved assay performance. *Id.* CareDx’s AlloSure website (https://caredx.com/products-and-services/transplant-services/kidney/allosure/), shown in Exhibit C, at 5, also describes AlloSure as a “donor derived cell-free DNA (dd-cfDNA) test developed for transplant patients.” The website further shows that the AlloSure test employs a method for determining dd-cfDNA in the blood sample, as results are based on the “% dd-cfDNA” in the sample: 

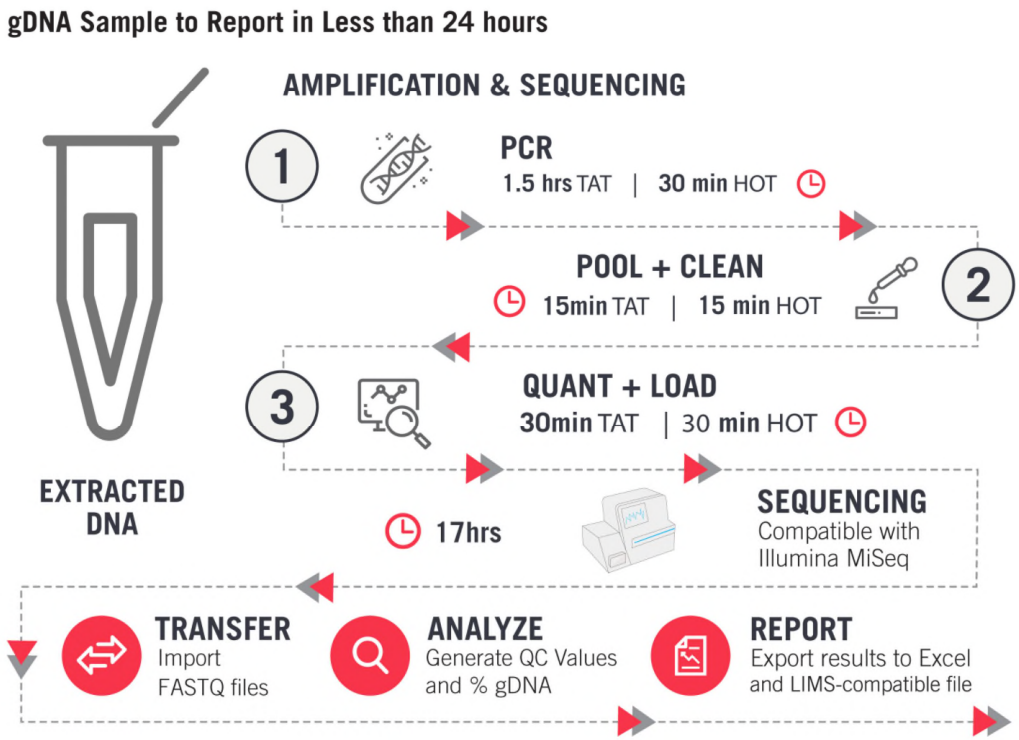
’544 Claim Language	Infringement Support
	In another example, CareDx’s AlloSeq HCT website (https://caredx.com/products-and-services/transplant-lab-products/post-transplant-surveillance/alloseq-hct/), shown in Exhibit D, at 3, describes preparing a preparation of amplified DNA in AlloSeq that is useful for calculating the percent recipient and donor DNA in post-transplant samples: How does AlloSeq HCT work? The AlloSeq HCT assay enables the amplification and sequencing of 202 single nucleotide polymorphisms (SNPs) across all autosomal chromosomes. The AlloSeq HCT software automatically calculates % recipient and donor DNA in post-transplant samples. The AlloSeq HCT website, Exhibit D, at 3-4, also shows a workflow of the accused AlloSeq product that includes assaying extracted mixed transplant donor and recipient cell-free DNA from a transplant recipient’s blood sample and preparing a preparation of PCR-amplified DNA useful for determining %gDNA in the sample:

’544 Claim Language	Infringement Support
	Rapid workflow with automated analysis 
38[a]. extracting cell-free DNA from the biological	The accused CareDx Products meet this limitation.

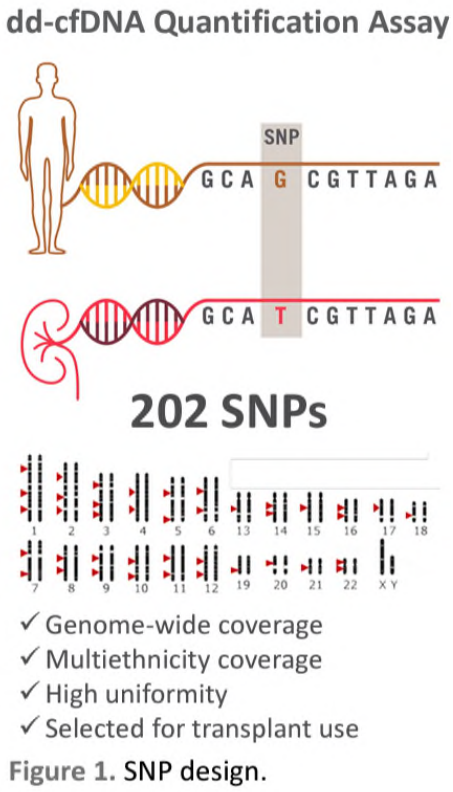
’544 Claim Language	Infringement Support
sample;	For example, CareDx’s AlloSure website, at Exhibit C, at 5, shows a diagram depicting the cell-free DNA containing a mixture of donor and transplant cell-free DNA in the blood of a kidney transplant subject that is tested in the accused AlloSure product.  CareDx’s AlloSure Kidney Laboratory Services Guide brochure, Exhibit E, at 3, further states that in AlloSure, “[c]ell-free DNA extracted from plasma is used as the template in a next generation sequencing assay.”. In another example, the CareDx AlloSeq HCT website, at Exhibit D, at 3-4, shows a workflow of the accused AlloSeq product that includes assaying extracted mixed transplant donor and recipient cell-free DNA from a transplant recipient’s blood sample:

’544 Claim Language	Infringement Support
	Rapid workflow with automated analysis 
38[b]. preparing a preparation of amplified DNA by performing targeted PCR to	The accused CareDx Products meet this limitation. For example, AlloSure involves preparing a preparation of amplified DNA by performing targeted

’544 Claim Language	Infringement Support
amplify a plurality of SNP loci on the cell-free DNA extracted from the blood sample to generate amplified DNA, wherein the SNP loci are on a plurality of chromosomes;	PCR to amplify a plurality of SNP loci on cell-free DNA extracted from the blood sample to generate amplified products. CareDx’s AlloSure Kidney Laboratory Services Guide brochure, Exhibit E, at 2, states that according to the Principle of the [AlloSure] Test: Donor-derived cell-free DNA is measured via targeted amplification and sequencing of a set of carefully selected and validated single nucleotide polymorphisms (SNPs) specifically chosen to discriminate among individuals based on genetic sequence (genotype). The AlloSeq HCT website, Exhibit D, at 3-4, also shows a workflow of the accused AlloSeq product that includes performing targeted PCR to amplify a plurality of SNP loci on cell-free DNA extracted from the blood sample to generate amplified products:

’544 Claim Language	Infringement Support
	Rapid workflow with automated analysis  In another example, CareDx’s AlloSeq website, Exhibit D, at 2, states that AlloSeq performs targeted PCR to amplify a plurality of SNP loci on cell-free DNA extracted from the blood sample to generate amplified products:

’544 Claim Language	Infringement Support
	What is AlloSeq HCT? AlloSeq HCT is an NGS-based solution enabling precise measurement of engraftment following hematopoietic stem cell transplant for research applications • Simple, streamlined assay (one multiplexed reaction per sample) • Targets 202 bi-allelic SNPs across 22 autosomes • Validated for use on Illumina MiSeq In addition, the SNP loci amplified in AlloSure are on a plurality of chromosomes. For example, CareDx’s AlloSure website, Exhibit C, at 5, states that AlloSure targets SNPs across “all somatic chromosomes”: What is AlloSure? **A Surveillance Solution** The first analytically and clinically validated donor derived cell-free DNA (dd-cfDNA) test developed for transplant patients with a targeted SNP assay across all somatic chromosomes. Similarly, the SNP loci amplified in AlloSeq are on a plurality of chromosomes. In addition, a

’544 Claim Language	Infringement Support
	poster describing AlloSeq that is linked on CareDx’s website at https://stage.caredx.com/wp-content/uploads/2020/10/P198-Poster-AQ-cfDNA-1.pdf, Exhibit G, includes a figure showing that AlloSeq targets SNP loci on chromosomes 1 through 22:  Figure 1. SNP design.
38[c]. analyzing the preparation of amplified DNA by sequencing the amplified DNA using sequencing-by-synthesis to obtain genetic	The accused CareDx Products meet this limitation. For example, AlloSure involves analyzing the preparation of amplified DNA by sequencing the amplified products by sequencing-by-synthesis to obtain genetic data at the plurality of target loci.

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data of the plurality of SNP loci, wherein the sequencing-by-synthesis comprises clonal amplification of the amplified DNA and measurement of sequences of the clonally amplified DNA, and determining the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of SNP loci.	CareDx’s AlloSure Test Results Interpretation guide, Exhibit F, at 1, states that AlloSure uses next generation sequencing to measure SNPs to quantify donor-derived DNA: **TEST DESCRIPTION** The AlloSure test is a clinical-grade, targeted, next generation sequencing (NGS) assay that measures single-nucleotide polymorphisms (SNPs) to accurately quantify donor-derived cell-free DNA (dd-cfDNA) in renal transplant recipients without separate genotyping of either the donor or the recipient. The assay quantifies the fraction of dd-cfDNA in both unrelated and related donor-recipient pairs. CareDx’s AlloSeq website, Exhibit D, at 2, further shows that AlloSeq involves sequencing the amplified products by sequencing-by-synthesis to obtain genetic data at the plurality of target loci using the Illumina MiSeq for measurement of engraftment following hematopoeitic stem cell transplant: What is AlloSeq HCT? AlloSeq HCT is an NGS-based solution enabling precise measurement of engraftment following hematopoietic stem cell transplant for research applications • Simple, streamlined assay (one multiplexed reaction per sample) • Targets 202 bi-allelic SNPs across 22 autosomes • Validated for use on Illumina MiSeq The sequencing-by-synthesis performed in AlloSure further comprises clonal amplification of the amplified products. For example, CareDx’s Wong publication states that “[t]he assay is run on the Illumina NextSeq 550 using either mid- or high-output flow cells.” Wong, Exhibit H, at 2. Illumina’s website states that “[t]he NextSeq 550 System harnesses proven Illumina sequencing by synthesis (SBS) technology to deliver highly accurate data and robust performance for multiple applications.” Exhibit I, https://www.illumina.com/systems/sequencing-

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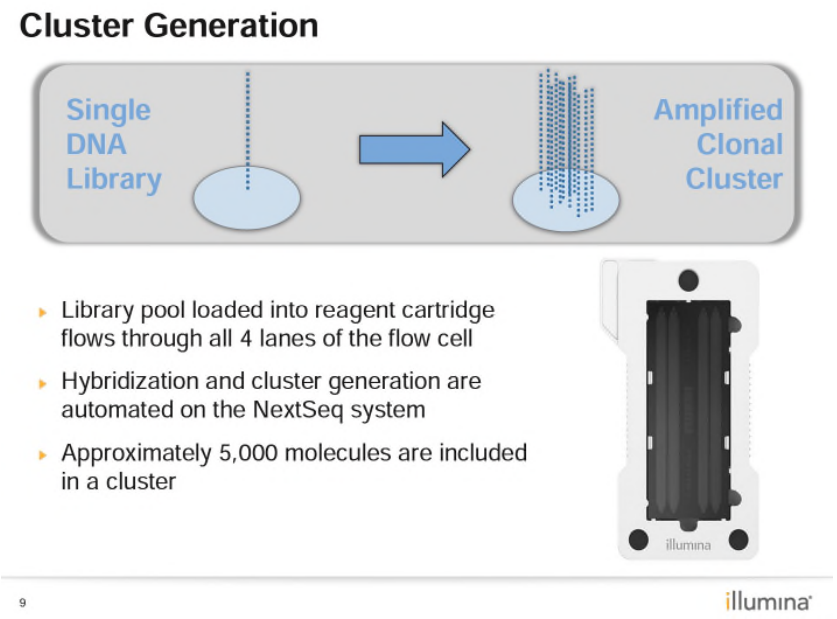
	platforms/nextseq/specifications.html#:~:text=Sequencing%20by%20Synthesis,-%26amp%3Bamp&text=The%20NextSeq%20550%20System%20leverages,that%20sets%20Illumina%20systems%20apart. Illumina discloses in the MiSeq Application Note: DNA Analysis for MiSeq that its MiSeq System comprises clonal amplification of the amplified products. *See* Application Note: DNA Analysis, Exhibit J, at 1 (“The MiSeq system features enhanced fluidics architecture, enabling a five-fold decrease in chemistry cycle time to provide results in hours, rather than the weeks required by CE. Preparing a sequencing library takes just 90 minutes, with clonal amplification and sequencing completed within as little as 4.5 hours.”). Illumina also discloses in a teaching presentation that the NextSeq products use clonal amplification and sequence clonally amplified DNA: 

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	See Illumina publication “Introduction to the NextSeq System,” Exhibit K, at slide 9. In addition, for example, AlloSure determines the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of SNP loci. CareDx’s AlloSure Kidney Laboratory Services Guide brochure describes measuring the amount of DNA from the transplant donor present in the biological sample based on allele frequency. *See* Exhibit E, at 2 (“Donor-derived cell-free DNA is measured via targeted amplification and sequencing of a set of carefully selected and validated single nucleotide polymorphisms (SNPs) specifically chosen to discriminate among individuals based on genetic sequence (genotype). The AlloSure bioinformatics software calculates the percent dd-cfDNA in the sample tested and applies the QC criteria.”). Results are then obtained “based on a proprietary algorithm that uses the known population frequencies of the SNPs sequenced and expected distribution of alleles.” *Id*. at 3. The AlloSure Test Results Interpretation guide, Exhibit G at 3, further states that the DNA from the donor is measured using an expected quantity of each allele at the SNP loci for different DNA fractions:

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	INTERPRETATION OF ALLOSURE TEST RESULTS • **>1% dd-cfDNA is associated with active rejection (Ref 2)** dd-cfDNA level greater than 1% indicate a probability of active rejection (antibody-mediated rejection or T cell-mediated rejection). dd-cfDNA levels 1% and below reflect absence of active rejection. For dd-cfDNA greater than 1%, there is a positive predictive value (PPV) of 61% and a negative predictive value (NPV) of 84% for active rejection. The positive and negative predictive values for antibody-mediated rejection at a threshold of 1.0% dd-cfDNA are 44% and 96%, respectively. The reference standard for rejection diagnosis was histological evidence from renal allograft biopsies performed for clinical suspicion. • **0.21% dd-cfDNA is the median observed in a reference population of stable recipients (Ref 3)** dd-cfDNA values greater than 1% were above the 96th percentile of all values in a study of stable kidney transplant recipients i.e. outside the normal range for this population. 75% of stable recipients had an AlloSure result below 0.40% dd-cfDNA. • **>61% increase in dd-cfDNA from a prior sample exceeds the biological and analytical variability observed in the reference population (Ref 3)** An increase of greater than 61% in consecutive dd-cfDNA results in an individual is greater than the change that may be attributable to normal biological and analytical variation. In addition, CareDx’s AlloSeq website, Exhibit D, at 4, shows that AlloSeq determines the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of SNP loci:

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	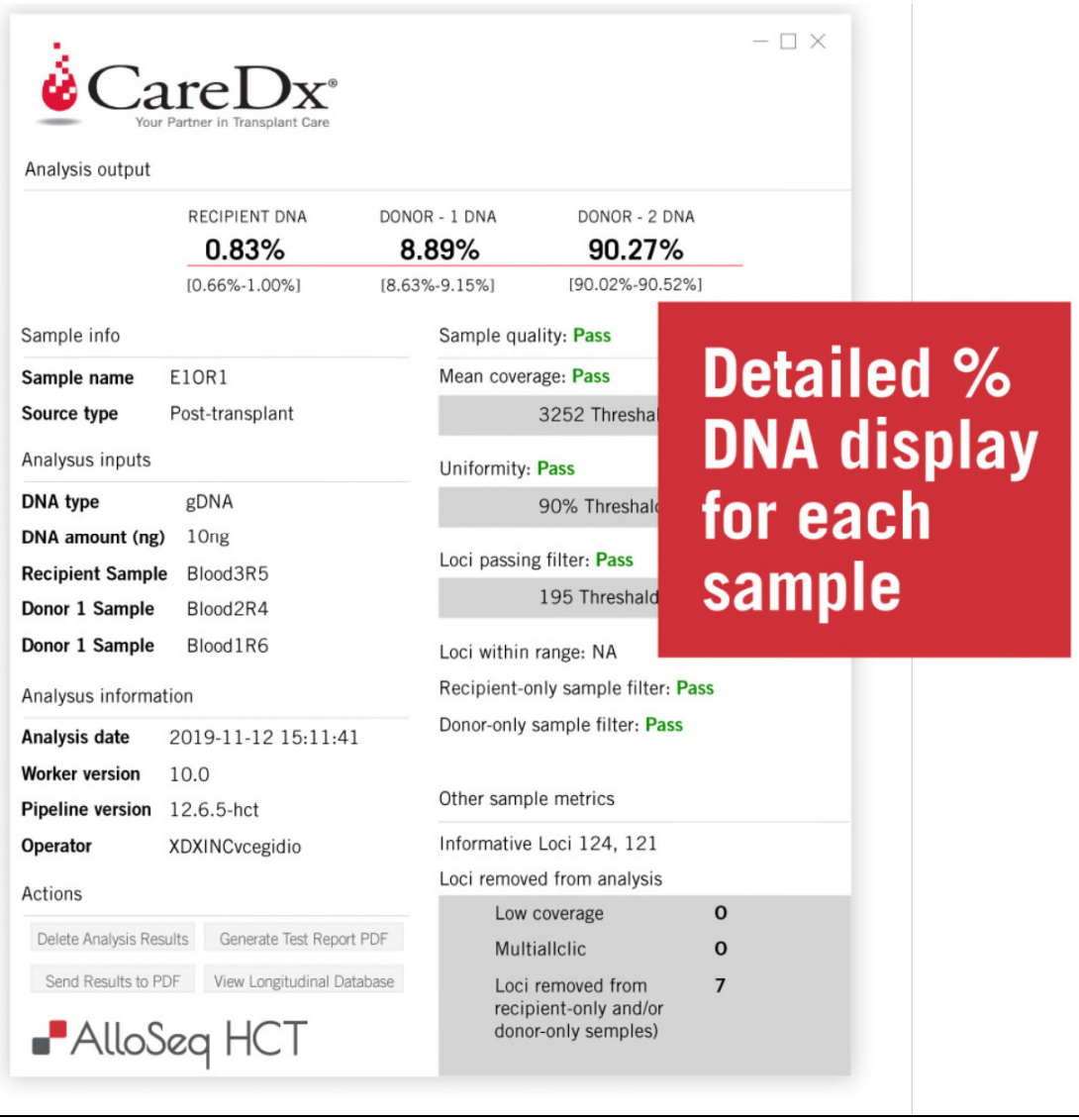

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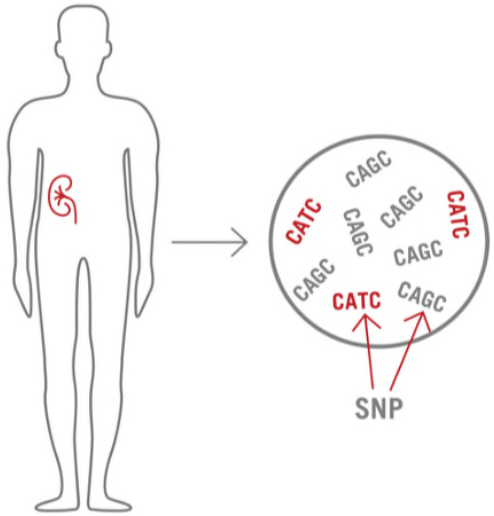
	A poster describing AlloSeq that is linked on CareDx’s website, Exhibit G, further shows that AlloSeq determines the most likely genetic data for DNA from the first individual based on allele frequencies in the genetic data at the plurality of SNP loci:  **Figure 2.** Relative quantification of dd-cfDNA (in red), based on SNP sequence.