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 over 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. 10,655,180 (the "'180 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 '180 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 '180 patent, which was duly and legally issued by the United States Patent and Trademark Office ("USPTO") on May 19, 2020.

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 over 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 133 patents issued to date. Natera has

an additional 205 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 ’180 patent. The ’180 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 ’180 patent owned by Natera. CareDx has used Natera’s patented technology without payment or permission.

The ’180 Patent

23. The ’180 patent, issued on May 19, 2020, is titled “Methods for Simultaneous Amplification of Target Loci.” Joshua Babiarz, Tudor Pompiliu Constantin, Lane A. Eubank, George Gemelos, Matthew Micah Hill, Huseyin Eser Kirkizlar, Matthew Rabinowitz, Onur Sakarya, Styrmir Sigurjonsson, and Bernhard Zimmermann are the named inventors. Natera is the original and current owner by assignment of the ’180 patent. A true and correct copy of the ’180 patent is attached hereto as Exhibit B.

24. Claim 1 of the ’180 patent recites:

> 1. A method for measuring an amount of DNA in a biological sample, comprising:

(a) extracting cell-free DNA of mixed origin from a biological sample of a subject, wherein the cell-free DNA comprises DNA from the subject and DNA from a genetically distinct individual, wherein neither the subject nor the genetically distinct individual is a fetus, and wherein the DNA of mixed origin comprises DNA from a transplant;

(b) performing targeted PCR amplification of the cell-free DNA at more than 100 SNP loci in a single reaction volume using more than 100 PCR primer pairs, wherein the amplified SNP loci comprise SNP loci on at least chromosome 1, 2, or 3;

(c) determining the genotypes of the amplified SNP loci and measuring an amount of one or more alleles at the SNP loci, wherein the genotypes of the amplified SNP loci are determined by high-throughput sequencing; and;

(d) measuring an amount of the DNA from the genetically distinct individual present in the biological sample using the amount of one or more alleles at the SNP loci,

wherein the method is performed without prior knowledge of genotypes of the genetically distinct individual.

25. Claim 14 of the ’180 patent recites:

14. A method for measuring an amount of DNA in a biological sample, the method comprising:

(a) performing a targeted PCR amplification for more than 100 SNP loci on one or more chromosomes expected to be disomic in a single reaction

> mixture using more than 100 PCR primer pairs, wherein the reaction mixture comprises cell-free DNA extracted from a biological sample of a subject comprising DNA of mixed origin, wherein the DNA of mixed origin comprises DNA from the subject and DNA from a genetically distinct individual, wherein neither the subject nor the genetically distinct individual is a fetus, wherein the DNA of mixed origin comprises DNA from a transplant, and wherein the amplified SNP loci comprise SNP loci on at least chromosome 1, 2, or 3;
>
> (b) measuring a quantity of each allele at a plurality of amplified SNP loci that comprise an allele present in the genetically distinct individual but not the subject, wherein the quantity of each allele at a plurality of amplified SNP loci are measured by high-throughput sequencing;
>
> (c) measuring an amount of the DNA from the genetically distinct individual in the biological sample using the quantity of each allele at the SNP loci and an expected quantity of each allele at the SNP loci for different DNA fractions,
>
> wherein the method is performed without prior knowledge of genotypes of the genetically distinct individual.

26. The claims of the ’180 patent are not directed to a natural law or natural phenomenon. Rather, they are directed to measuring DNA in a 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 ’180 patent claims are directed to specific, unconventional, non-routine methods for overcoming previously unresolved problems in this area.

CareDx’s Infringing Acts

27. 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.

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

29. As provided in more detail below, each element of at least one claim of the ’180 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.

30. 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.

31. Performance of CareDx’s Accused Products infringe at least one claim of the ’180 patent as set forth in Exhibit A, which is a preliminary and exemplary claim chart detailing CareDx’s infringement of the ’180 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 ’180 patent or any other patents.

32. CareDx has made extensive use of Natera's patented technology, including the technology described and claimed in the '180 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 '180 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 '180 patent.

COUNT I: INFRINGEMENT OF U.S. PATENT NO. 10,655,180

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

34. On information and belief, CareDx has infringed and continues to infringe the '180 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.

35. Attached as Exhibit A is a preliminary and exemplary claim chart detailing CareDx's infringement of the '180 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 '180 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 '180 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 '180 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

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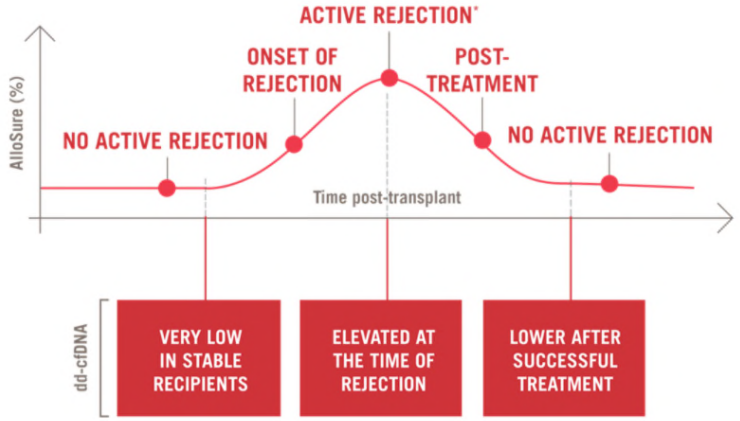
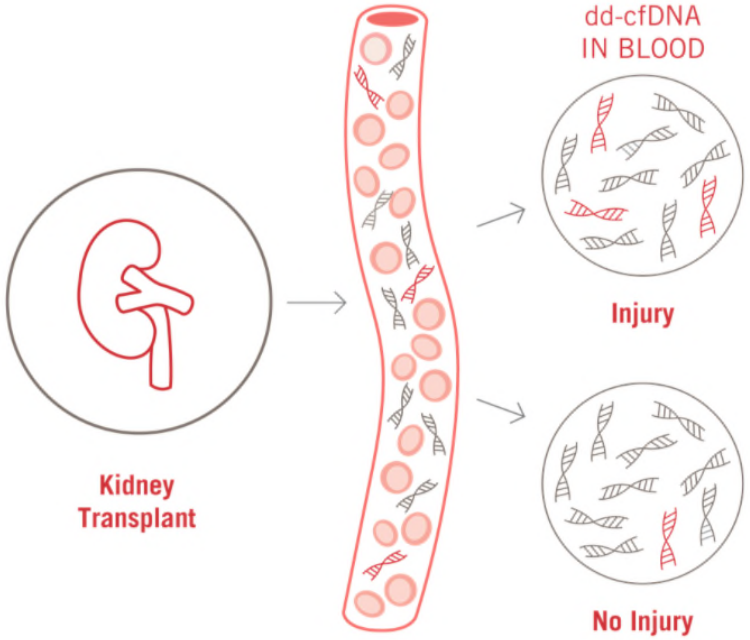
May 13, 2022

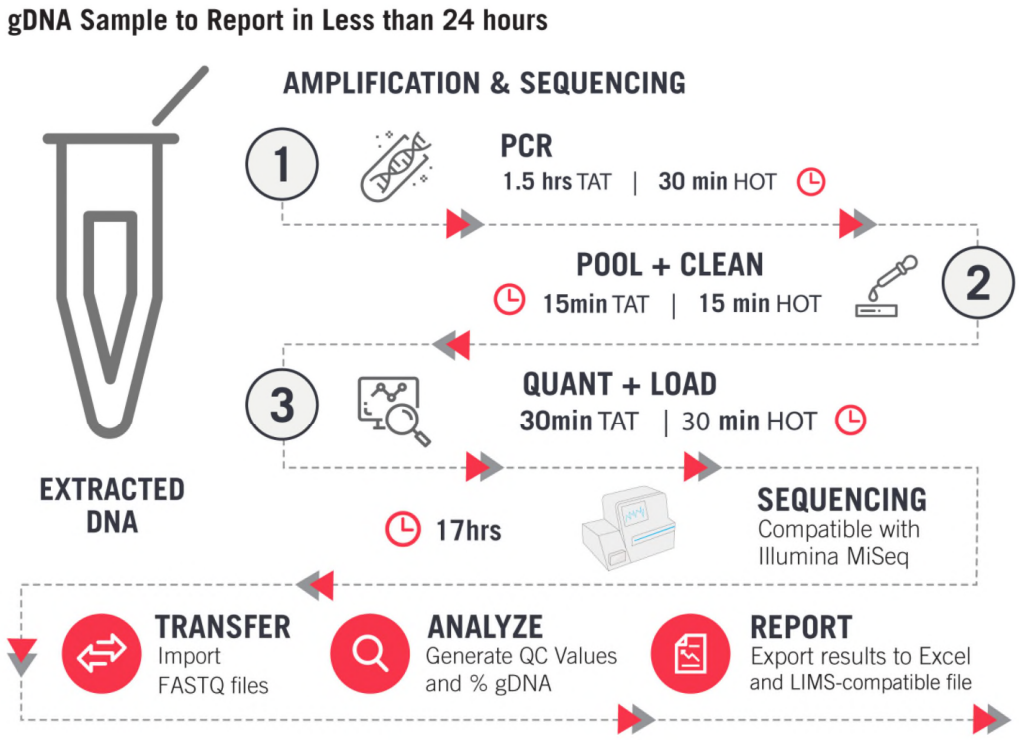
EXHIBIT A

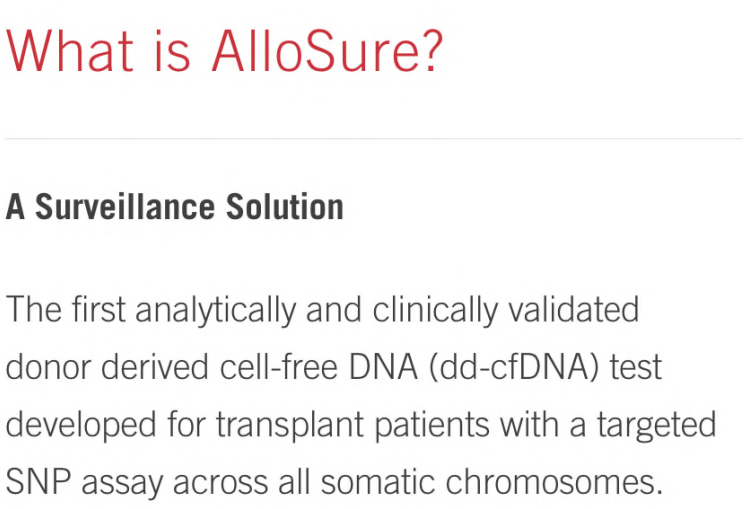
US Patent No. 10,655,180
Infringement Analysis re: CareDx, Inc.

’180 Claim Language	Infringement Support
1[preamble]. A method for measuring an amount of DNA in a biological sample, 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 and AlloSeq tests. 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 measuring 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:

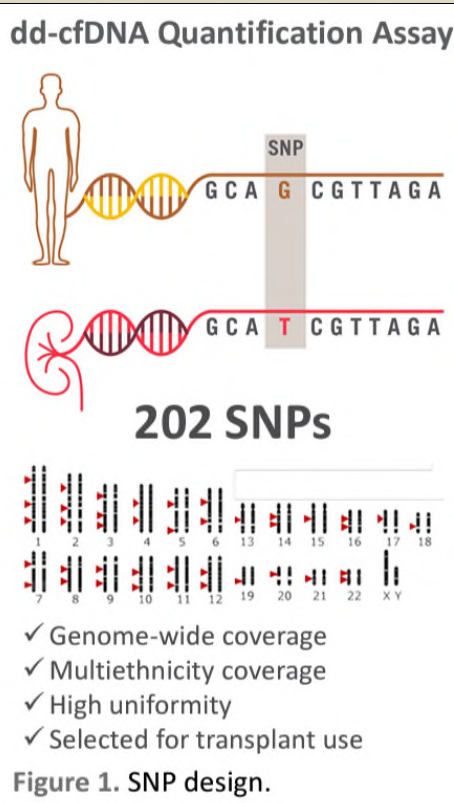
’180 Claim Language	Infringement Support
	How does AlloSeq HCT work? The AlloSeq HCT assay enables the amplification and sequencing of 202 single nucleotide polymorphisms (SNPs) across all autosomal chromosomes. The AlloSeq HCT software automatically calculates % recipient and donor DNA in post-transplant samples.
1[a]. (a) extracting cell-free DNA of mixed origin from a biological sample of a subject, wherein the cell-free DNA comprises DNA from the subject and DNA from a genetically distinct individual, wherein neither the subject nor the genetically distinct individual is a fetus, and wherein the DNA of mixed origin comprises DNA from a transplant;	The accused CareDx Products meet this limitation. 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.

’180 Claim Language	Infringement Support
	 CareDx’s AlloSure Kidney Laboratory Services Guide brochure, Exhibit H, 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:

’180 Claim Language	Infringement Support
	Rapid workflow with automated analysis 
1[b]. (b) performing targeted PCR amplification of the cell-free DNA at more than 100	The accused CareDx Products meet this limitation. For example, AlloSure involves performing targeted PCR amplification of the cell-free DNA at

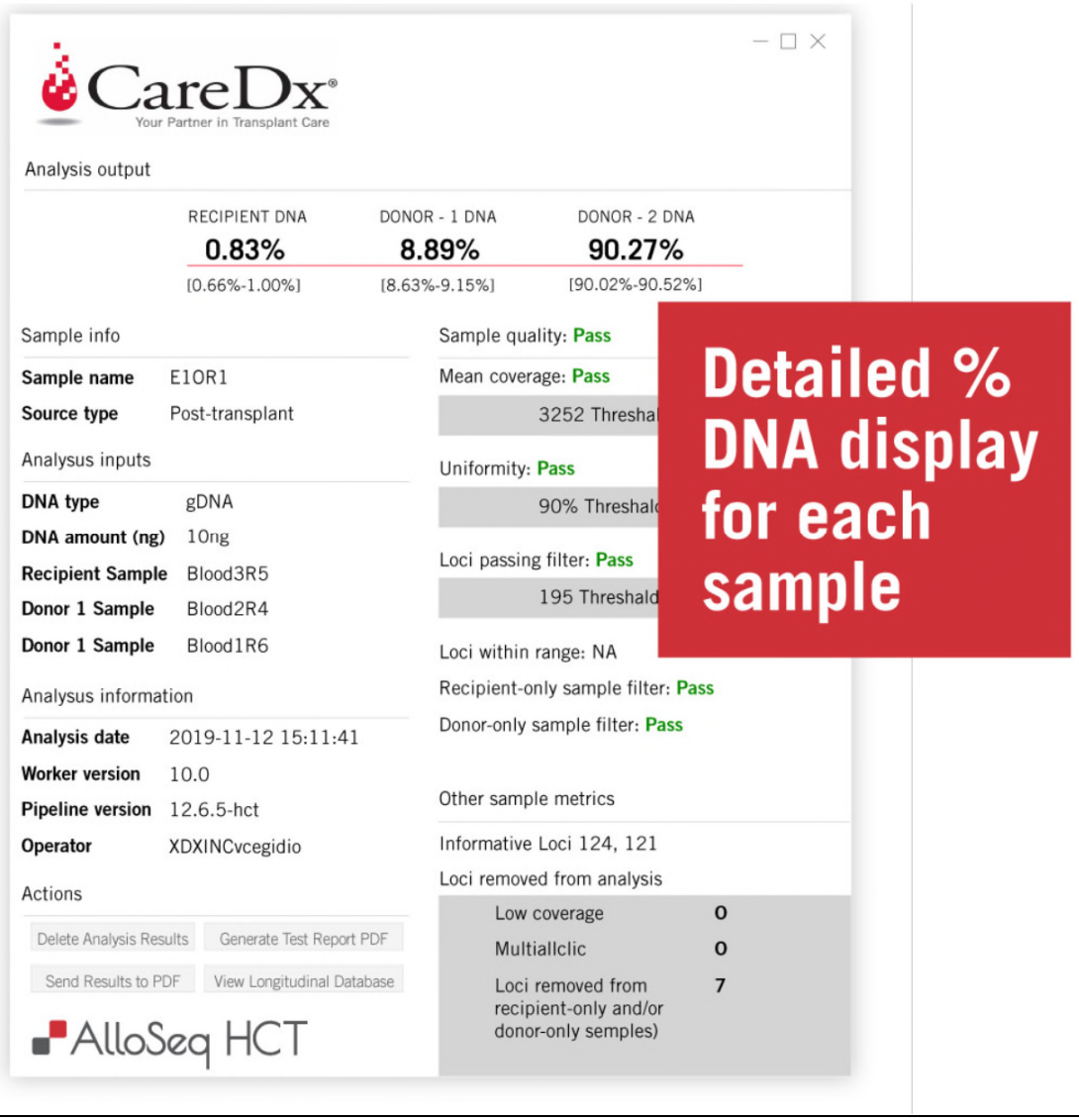
’180 Claim Language	Infringement Support
SNP loci in a single reaction volume using more than 100 PCR primer pairs, wherein the amplified SNP loci comprise SNP loci on at least chromosome 1, 2, or 3;	more than 100 SNP loci in a single reaction volume using more than 100 PCR primer pairs. CareDx’s Wong publication (Wong, *et al.*, *J. Med. Diagn. Methods* (2020) 9:302 (“Wong”)), states that “[t]his AlloSure 3.0 assay evaluates a total of 405 Single Nucleotide Polymorphisms (SNPs) by next-generation sequencing, using PCR conditions optimized for multiplexing.” Wong, Exhibit E, at 2. AlloSure also involves performing targeted PCR amplification wherein the amplified SNP loci comprise SNP loci on at least chromosome 1, 2, or 3. For example, CareDx’s AlloSure website, Exhibit C, at 5, states that AlloSure targets SNPs across “all somatic chromosomes,” indicating they include SNPs on chromosomes 1, 2, and 3, which are somatic chromosomes:  In another example, CareDx’s AlloSeq website, Exhibit D, at 2, states that AlloSeq performs targeted amplification of 202 bi-allelic SNPs across 22 autosomes, which include chromosomes 1,

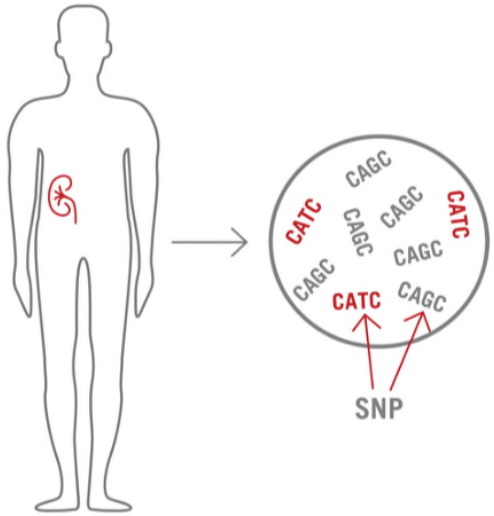
’180 Claim Language	Infringement Support
	2, and 3, in a single reaction volume, *i.e.*, as one multiplexed reaction per sample. What is AlloSeq HCT? AlloSeq HCT is an NGS-based solution enabling precise measurement of engraftment following hematopoietic stem cell transplant for research applications • Simple, streamlined assay (one multiplexed reaction per sample) • Targets 202 bi-allelic SNPs across 22 autosomes • Validated for use on Illumina MiSeq In addition, a 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 F, includes a figure showing that AlloSeq targets SNP loci on chromosomes 1, 2, and 3:

’180 Claim Language	Infringement Support
	 Figure 1. SNP design.
1[c]. (c) determining the genotypes of the amplified SNP loci and measuring an amount of one or more alleles at the SNP loci, wherein the genotypes of the amplified SNP loci are determined by high-throughput sequencing;	The accused CareDx Products meet this limitation. For example, AlloSure involves determining the genotypes of the amplified SNP loci and measuring an amount of one or more alleles at the SNP loci. CareDx’s AlloSure Test Results Interpretation Guide, available on its website at https://www.caredx.com/wp-content/uploads/2020/10/LT-10057-AlloSure-Test-Results-Interpretation-Guide.pdf, Exhibit G, at 1, states that AlloSure measures SNPs to quantify donor-derived cell-free

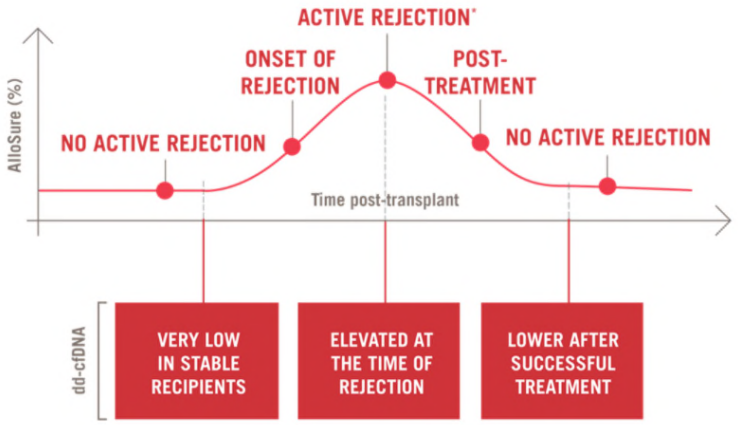
’180 Claim Language	Infringement Support
and	DNA in renal transplant recipients. **TEST DESCRIPTION** The AlloSure test is a clinical-grade, targeted, next generation sequencing (NGS) assay that measures single-nucleotide polymorphisms (SNPs) to accurately quantify donor-derived cell-free DNA (dd-cfDNA) 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. In another example, CareDx’s AlloSeq HCT website, Exhibit D, at 2-3, states that the accused AlloSeq product determines the genotypes of the amplified SNP loci, as it is “[a]ble to determine up to 3 genomes in a single sample”: What are the benefits of AlloSeq HCT? • Streamlined workflow with minimal hands-on time (2 hrs) • Sample to result in less than 24 hours • Highly sensitive (0.3% limit of detection) • Accurate, precise, and reproducible results • User-friendly AlloSeq HCT software features automatic determination of informative loci, chimerism calculation, and results tracking • Able to determine up to 3 genomes in a single sample; useful for double cord blood transplants In addition, for example, AlloSure and AlloSeq involve determining the SNP genotypes by high-throughput sequencing. 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 E, at 2. CareDx’s AlloSeq website, Exhibit D, at 2, further shows that determining genotypes and

’180 Claim Language	Infringement Support
	measurement of SNP alleles is performed by high throughput sequencing using the Illumina MiSeq: 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
1[d]. (d) measuring an amount of the DNA from the genetically distinct individual present in the biological sample using the amount of one or more alleles at the SNP loci,	The accused CareDx Products meet this limitation. For example, AlloSure and AlloSeq measure an amount of the DNA from the genetically distinct individual present in the biological sample using the amount of one or more alleles at the SNP loci. For example, 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 H, 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. In addition, CareDx’s AlloSeq website, Exhibit D, at 4, shows that AlloSeq measures amounts of donor and recipient DNA in the sample using alleles at the SNP loci:

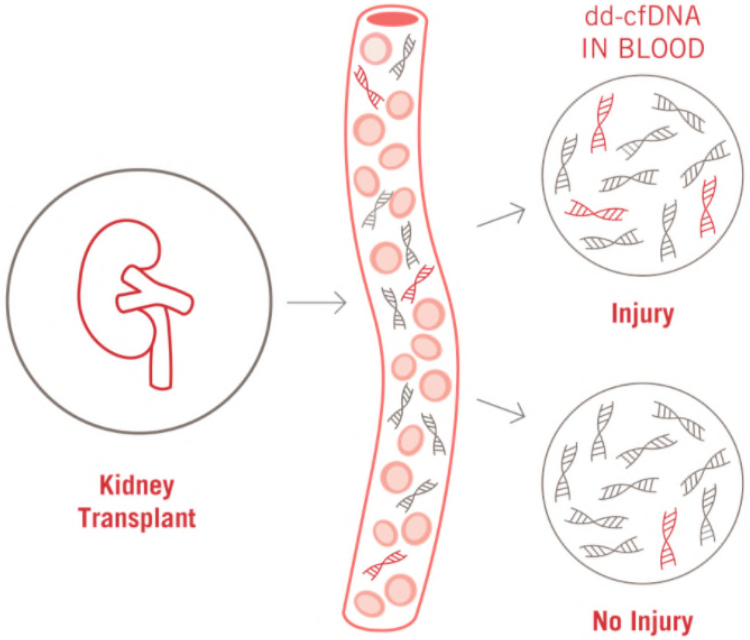
’180 Claim Language	Infringement Support
	

’180 Claim Language	Infringement Support
	A poster describing AlloSeq that is linked on CareDx’s website, Exhibit F, further shows that AlloSeq measures an amount of the DNA from the genetically distinct individual present in the biological sample using the amount of one or more alleles at the SNP loci:  Figure 2. Relative quantification of dd-cfDNA (in red), based on SNP sequence.
1[wherein]. wherein the method is performed without prior knowledge of genotypes of the genetically distinct individual.	The accused CareDx Products meet this limitation. For example, AlloSure and AlloSeq are performed without prior knowledge of genotypes of the genetically distinct individual. CareDx’s AlloSure Test Results Interpretation Guide, Exhibit G, at 1, states that AlloSure does not require separate genotyping of either the donor or the recipient:

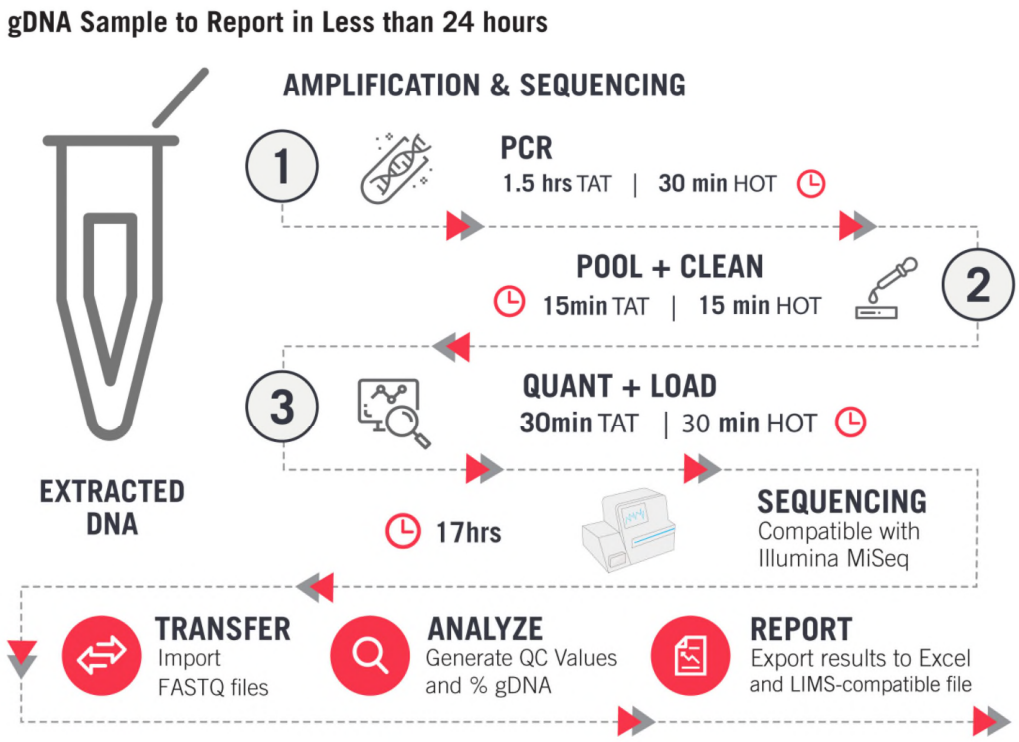
'180 Claim Language	Infringement Support
	TEST DESCRIPTION The AlloSure test is a clinical-grade, targeted, next generation sequencing (NGS) assay that measures single-nucleotide polymorphisms (SNPs) to accurately quantify donor-derived cell-free DNA (dd-cfDNA) in renal transplant recipients without 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. In another example, AlloSeq performs the claimed method without prior knowledge of genotypes of the donor or recipient. A CareDx poster linked on CareDx's website, Exhibit F, states that the AlloSeq "assay combines a clinical laboratory compatible protocol with streamlined workflow and a fully automated analysis software to accurately quantify dd-cfDNA without requiring separate genotyping of either donor or recipient."
14[preamble]. A method for measuring an amount of DNA in a biological sample, 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 and AlloSeq tests. 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 measuring dd-cfDNA in the blood sample, as results are based on the "% dd-cfDNA" in the sample:

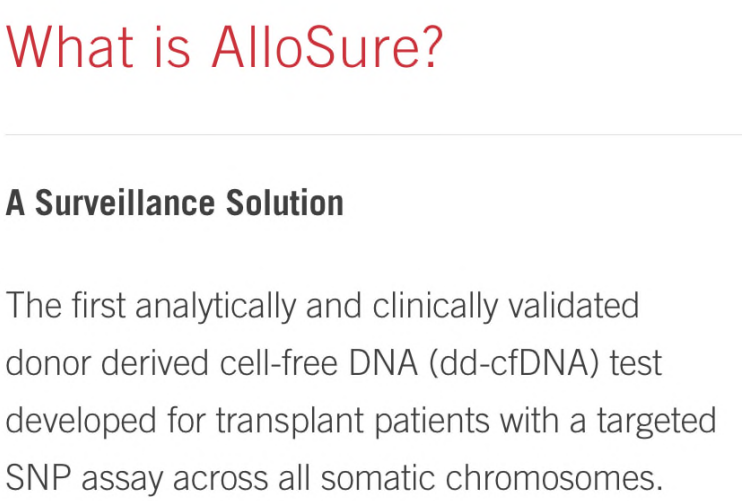
’180 Claim Language	Infringement Support
	 In another example, CareDx’s AlloSeq HCT website (https://caredx.com/products-and-services/transplant-lab-products/post-transplant-surveillance/alloseq-hct/), shown in Exhibit D, at 3, describes AlloSeq as a method for measuring the percent recipient and donor 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.
14[a]. (a) performing a targeted PCR amplification for more than 100 SNP loci on one or more chromosomes	The accused CareDx Products meet this limitation. For example, AlloSure and AlloSeq involve performing targeted PCR amplification of the cell-free DNA at more than 100 SNP loci in a single reaction volume using more than 100 PCR primer

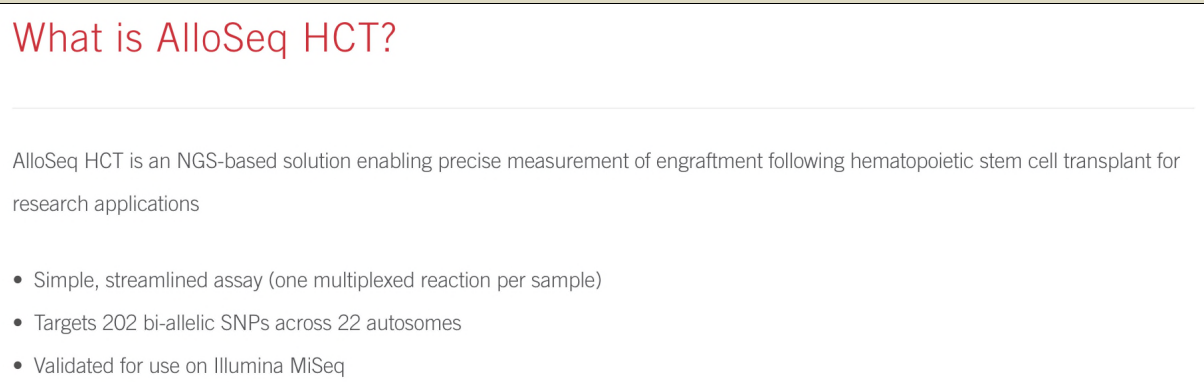
’180 Claim Language	Infringement Support
expected to be disomic in a single reaction mixture using more than 100 PCR primer pairs, wherein the reaction mixture comprises cell-free DNA extracted from a biological sample of a subject comprising DNA of mixed origin, wherein the DNA of mixed origin comprises DNA from the subject and DNA from a genetically distinct individual, wherein neither the subject nor the genetically distinct individual is a fetus, wherein the DNA of mixed origin comprises DNA from a transplant, and wherein the amplified SNP loci comprise SNP loci on at least chromosome 1, 2, or 3;	pairs. CareDx’s Wong publication (Wong, *et al.*, *J. Med. Diagn. Methods* (2020) 9:302 (“Wong”)), states that “[t]his AlloSure 3.0 assay evaluates a total of 405 Single Nucleotide Polymorphisms (SNPs) by next-generation sequencing, using PCR conditions optimized for multiplexing.” Wong, Exhibit E, at 2. In another example, CareDx’s AlloSeq website, Exhibit D, at 2, states that AlloSeq performs targeted amplification of 202 bi-allelic SNPs: 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 CareDx’s AlloSure website, at Exhibit C, at 5, further 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.

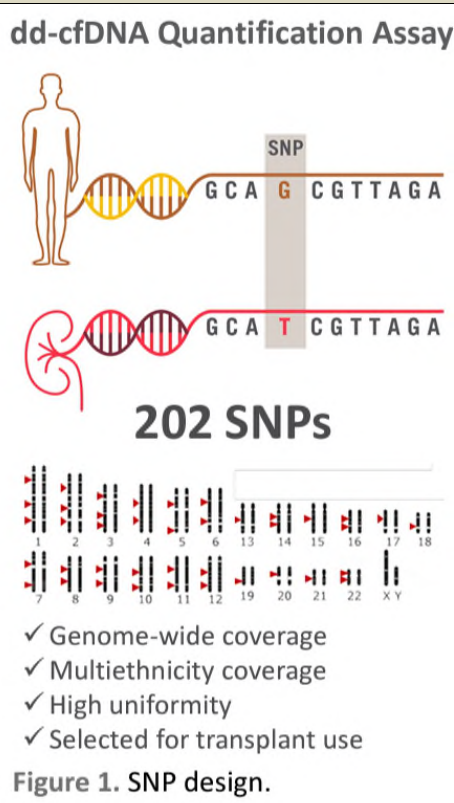
’180 Claim Language	Infringement Support
	 The CareDx AlloSeq HCT website, Exhibit D, at 2-3, likewise states that AlloSeq assays cell-free DNA of mixed origin, wherein it is “[a]ble to determine up to 3 genomes in a single sample” and cell-free DNA from a subject and a genetically distinct individual as it is “useful for double cord blood transplants”:

’180 Claim Language	Infringement Support
	What are the benefits of AlloSeq HCT? • Streamlined workflow with minimal hands-on time (2 hrs) • Sample to result in less than 24 hours • Highly sensitive (0.3% limit of detection) • Accurate, precise, and reproducible results • User-friendly AlloSeq HCT software features automatic determination of informative loci, chimerism calculation, and results tracking • Able to determine up to 3 genomes in a single sample; useful for double cord blood transplants 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 performing PCR in a single reaction mixture:

’180 Claim Language	Infringement Support
	Rapid workflow with automated analysis  In addition, for example, the AlloSure and AlloSeq products target SNP loci on at least chromosomes 1, 2, and 3.

’180 Claim Language	Infringement Support
	CareDx’s AlloSure website, Exhibit C, at 5, states that AlloSure targets SNPs across “all somatic chromosomes,” indicating they include SNPs on chromosomes 1, 2, and 3, which are somatic chromosomes:  In another example, CareDx’s AlloSeq website, Exhibit D, at 2, states that AlloSeq performs targeted amplification of 202 bi-allelic SNPs across 22 autosomes, which include chromosomes 1, 2, and 3, in a single reaction volume, *i.e.*, as one multiplexed reaction per sample.

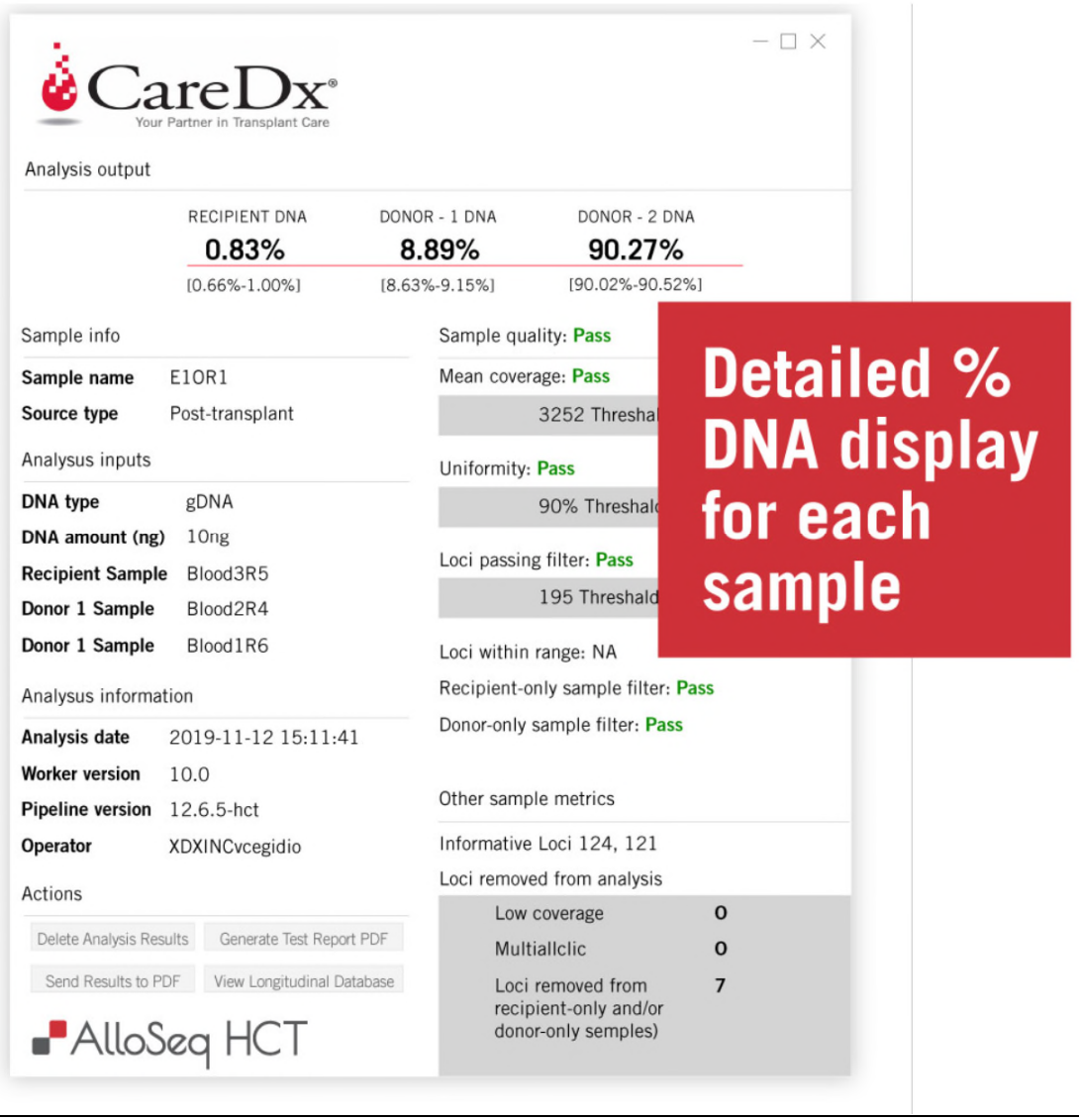
’180 Claim Language	Infringement Support
	 In addition, a poster describing AlloSeq that is linked on CareDx’s website at https://stage.caredx.com/wp-content/uploads/2020/10/P198-Poster-AQ-cfDNA-1.pdf, Exhibit F, includes a figure showing that AlloSeq targets SNP loci on chromosomes 1, 2, and 3:

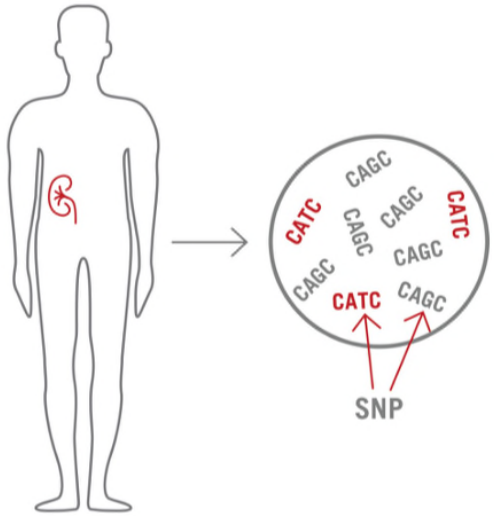
’180 Claim Language	Infringement Support
	 Figure 1. SNP design. At least 100 of the SNPs assayed are expected to be disomic because, otherwise, the genomes of the transplant donor and/or recipient would not be compatible with life.
14[b]. (b) measuring a quantity of each allele at a plurality of amplified SNP loci that comprise an allele present in the genetically distinct individual but not the	The accused CareDx Products meet this limitation. For example, AlloSure and AlloSeq involve measuring a quantity of each allele at a plurality of amplified SNP loci that comprise alleles present in donor-derived, but not recipient-derived, cell-free DNA.

’180 Claim Language	Infringement Support
subject, wherein the quantity of each allele at a plurality of amplified SNP loci are measured by high-throughput sequencing;	CareDx’s AlloSure Test Results Interpretation Guide, Exhibit G, at 1, states that AlloSure measures SNPs to quantify donor-derived cell-free DNA in renal transplant recipients: **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. In another example, CareDx’s AlloSeq HCT website, Exhibit D, at 2-3, states that AlloSeq is “[a]ble to determine up to 3 genomes in a single sample”: What are the benefits of AlloSeq HCT? • Streamlined workflow with minimal hands-on time (2 hrs) • Sample to result in less than 24 hours • Highly sensitive (0.3% limit of detection) • Accurate, precise, and reproducible results • User-friendly AlloSeq HCT software features automatic determination of informative loci, chimerism calculation, and results tracking • Able to determine up to 3 genomes in a single sample; useful for double cord blood transplants In addition, AlloSure and AlloSeq involve determining the SNP genotypes by high-throughput sequencing. CareDx’s Wong publication states that for AlloSure, “[t]he assay is run on the Illumina NextSeq 550 using either mid- or high-output flow cells.” Wong, Exhibit E, at 2. CareDx’s AlloSeq website, Exhibit D, at 2, further shows that determining genotypes and

’180 Claim Language	Infringement Support
	measurement of SNP alleles is performed by high throughput sequencing using the Illumina MiSeq: 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
14[c]. (c) measuring an amount of the DNA from the genetically distinct individual in the biological sample using the quantity of each allele at the SNP loci and an expected quantity of each allele at the SNP loci for different DNA fractions,	The accused CareDx Products meet this limitation. For example, AlloSure and AlloSeq measure an amount of the DNA from the genetically distinct individual present in the biological sample using the quantity of each allele at the SNP loci and an expected quantity of each allele at the SNP loci for different DNA fractions. 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 H, 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:

'180 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 measures amounts of donor and recipient DNA in the sample using alleles at the SNP loci:

’180 Claim Language	Infringement Support
	

’180 Claim Language	Infringement Support
	A poster describing AlloSeq that is linked on CareDx’s website, Exhibit F, further shows that AlloSeq measures an amount of the DNA from the genetically distinct individual present in the biological sample using the amount of one or more alleles at the SNP loci:  Figure 2. Relative quantification of dd-cfDNA (in red), based on SNP sequence.
14[wherein]. wherein the method is performed without prior knowledge of genotypes of the genetically distinct individual.	The accused CareDx Products meet this limitation. For example, AlloSure and AlloSeq are performed without prior knowledge of genotypes of the genetically distinct individual. CareDx’s AlloSure Test Results Interpretation Guide, Exhibit G, at 1, states that AlloSure does not require separate genotyping of either the donor or the recipient:

’180 Claim Language	Infringement Support
	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. A CareDx poster linked on CareDx’s website, Exhibit F, also states that the AlloSeq “assay combines a clinical laboratory compatible protocol with streamlined workflow and a fully automated analysis software to accurately quantify dd-cfDNA without requiring separate genotyping of either donor or recipient.”