Nos. 24-1324, 24-1409

IN THE

United States Court of Appeals

FOR THE FEDERAL CIRCUIT

NATERA, INC.,

Plaintiff-Appellee,

v.

NEOGENOMICS LABORATORIES, INC.,

Defendant-Appellant.

On Appeal from the United States District Court
for the Middle District of North Carolina
No. 1:23-cv-629, Hon. Catherine C. Eagles

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Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00001

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PATENT CLAIMS AT ISSUE

Claim 1 of U.S. Patent No. 11,519,035 recites:

> 1. A method for amplifying and sequencing DNA, comprising:
>
> [a] tagging isolated cell free DNA with one or more universal tail adaptors to generate tagged products, wherein the isolated cell-free DNA is isolated from a blood sample collected from a subject who is not a pregnant women;
>
> [b] amplifying the tagged products one or more times to generate final amplification products, wherein one of the amplification steps comprises targeted amplification of a plurality of single nucleotide polymorphism (SNP) loci in a single reaction volume, wherein one of the amplifying steps introduces a barcode and one or more sequencing tags; and
>
> [c] sequencing the plurality of SNP loci on the cell free DNA by conducting massively parallel sequencing on the final amplification products, wherein the plurality of SNP loci comprises 25-2,000 loci associated with cancer.

Claim 12 of the ’035 Patent recites:

> 12. The method of claim 1, wherein the one or more universal tail adaptors comprise a first universal tail adaptor and a second universal tail adaptor.

Claim 13 of the ’035 Patent recites:

> 13. The method of claim 12, wherein tagging the cell free DNA comprises amplifying the cell free DNA with a first primer comprising the first universal tail adaptor and a second primer comprising the second universal tail adaptor.

Appx244-45 (249:44-62, 251:7-13).

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 24-1324, 24-1409

Short Case Caption Natera, Inc. v. NeoGenomics Laboratories, Inc.

Filing Party/Entity Natera, Inc.

Instructions:

1. Complete each section of the form and select none or N/A if appropriate.
2. Please enter only one item per box; attach additional pages as needed, and check the box to indicate such pages are attached.
3. In answering Sections 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance.
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I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 3/11/2024

Signature: /s/ Jeffrey A. Lamken

Name: Jeffrey A. Lamken

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☑ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☑ None/Not Applicable
Natera, Inc.		

☐ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☐ Additional pages attached

Williams Mullen	Andrew J. Bramhall	Andrew R. Shores
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5. Related Cases. Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

☐ Yes (file separate notice; see below) ☑ No ☐ N/A (amicus/movant)

If yes, concurrently file a separate Notice of Related Case Information that complies with Fed. Cir. R. 47.5(b). **Please do not duplicate information.** This separate Notice must only be filed with the first Certificate of Interest or, subsequently, if information changes during the pendency of the appeal. Fed. Cir. R. 47.5(b).

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

TABLE OF CONTENTS

Page

STATEMENT OF THE CASE....1

I. The '035 Patent's Innovation over the Prior Art and Signatera's Resulting Success....1

A. Obstacles in Prior Art Methods....1

B. Natera Overcomes Those Obstacles....5

C. Signatera Becomes the Market Leader in cfDNA MRD Tests....8

D. RaDaR's Infringement....9

II. Proceedings Below....10

A. Natera's Complaint and Request for Preliminary Injunction....10

B. The District Court's Carefully Crafted Injunction....12

C. The District Court's Denial of the Motions To Stay and Modify the Injunction....16

SUMMARY OF ARGUMENT....18

ARGUMENT....22

I. The District Court Correctly Found No Substantial Question Regarding the '035 Patent's Validity....22

A. The District Court Did Not Apply the Wrong Legal Standard in Assessing Motivation To Combine....23

B. The District Court Did Not Improperly Fail To Tether Its Motivation-To-Combine Analysis to the Claim Scope....26

C. The District Court's Factual Findings Are Not Clearly Erroneous....28

II. The District Court Correctly Found No Substantial Question Regarding Infringement 35

A. Ample Evidence Supports the District Court's Finding of Likely Infringement 35

B. The District Court Did Not Omit Any Required Claim Construction 40

III. The District Court Did Not Abuse Its Discretion in Finding that Natera Would Suffer Irreparable Harm 43

A. Natera's Threatened Loss of Market Share Supports the Finding of Irreparable Harm 43

B. Natera Did Not Unreasonably Delay 46

C. Natera's Evidence of Future Lost Sales Was Sufficient 48

D. NeoGenomics' Infringement Has a Sufficient Causal Nexus 49

E. The District Court Did Not Misapply This Court's Precedents Regarding Two-Party Markets 53

F. Natera's Bond Does Not Foreclose Irreparable Harm 54

IV. The District Court Did Not Abuse Its Discretion in Addressing the Remaining Injunction Factors 55

A. The Public Interest Favors an Injunction 55

B. The Equities Favor an Injunction 58

V. The Court Did Not Abuse Its Discretion with Respect to the Scope of the Injunction 60

A. NeoGenomics Forfeited Any Complaint About the Preliminary Injunction's Scope 61

B. The District Court Did Not Abuse Its Discretion 63

CONCLUSION 65

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00008

TABLE OF AUTHORITIES

Page(s)

CASES

Advanced Commc'ns Design, Inc. v. Premier Retail Networks, Inc.,
46 F. App'x 964 (Fed. Cir. 2002) 46

Allergan, Inc. v. Apotex, Inc.,
754 F.3d 952 (Fed. Cir. 2014) 27, 28

Amazon.com, Inc. v. Barnesandnoble.com, Inc.,
239 F.3d 1343 (Fed. Cir. 2001) 24

Amgen Inc. v. Sandoz Inc.,
923 F.3d 1023 (Fed. Cir. 2019) 19, 37, 38

Apple, Inc. v. Samsung Elecs. Co.,
678 F.3d 1314 (Fed. Cir. 2012) 21, 47, 51

Apple Inc. v. Samsung Elecs. Co.,
695 F.3d 1370 (Fed. Cir. 2012) 15

Apple Inc. v. Samsung Elecs. Co.,
809 F.3d 633 (Fed. Cir. 2015) 51, 52, 55

Ariosa Diagnostics, Inc. v. Sequenom, Inc.,
788 F.3d 1371 (Fed. Cir. 2015) 32, 33, 34

Atlas Powder Co. v. Ireco Chems.,
773 F.2d 1230 (Fed. Cir. 1985) 48

Auris Health, Inc. v. Intuitive Surgical Operations, Inc.,
32 F.4th 1154 (Fed. Cir. 2022) 26

Aventis Pharms. Inc. v. Amino Chems. Ltd.,
715 F.3d 1363 (Fed. Cir. 2013) 35

In re Bilski,
545 F.3d 943 (Fed. Cir. 2008) 34

Bio-Rad Labs., Inc. v. 10X Genomics Inc.,
967 F.3d 1353 (Fed. Cir. 2020) 20, 44, 59

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00009

BlephEx, LLC v. Myco Indus., Inc.,
24 F.4th 1391 (Fed. Cir. 2022) .....*passim*

Bluebonnet Sav. Bank, F.S.B. v. United States,
466 F.3d 1349 (Fed. Cir. 2006) 42

Bos. Sci. SciMed, Inc. v. Iancu,
811 F. App'x 618 (Fed. Cir. 2020) 41

Broadcom Corp. v. Emulex Corp.,
732 F.3d 1325 (Fed. Cir. 2013) 63

Broadcom Corp. v. Qualcomm Inc.,
543 F.3d 683 (Fed. Cir. 2008) 40

Carborundum Co. v. Molten Metal Equip. Innovations, Inc.,
72 F.3d 872 (Fed. Cir. 1995) 62

CareDx, Inc. v. Natera, Inc.,
40 F.4th 1371 (Fed. Cir. 2022) 33, 34

Celsis In Vitro, Inc. v. CellzDirect, Inc.,
664 F.3d 922 (Fed. Cir. 2012) 29, 61

Conoco, Inc. v. Energy & Env't Int'l, L.C.,
460 F.3d 1349 (Fed. Cir. 2006) 40

Cuviello v. City of Vallejo,
944 F.3d 816 (9th Cir. 2019) 46

Douglas Dynamics, LLC v. Buyers Prods. Co.,
717 F.3d 1336 (Fed. Cir. 2013) 44, 45

Favia v. Ind. Univ. of Pa.,
7 F.3d 332 (3d Cir. 1993) 62

Fresenius USA, Inc. v. Baxter Int'l, Inc.,
582 F.3d 1288 (Fed. Cir. 2009) 47, 50

Golden Bridge Tech., Inc. v. Apple Inc.,
758 F.3d 1362 (Fed. Cir. 2014) 42

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00010

Hilgraeve Corp. v. Symantec Corp.,
265 F.3d 1336 (Fed. Cir. 2001) 64

Hybritech Inc. v. Abbott Labs.,
849 F.2d 1146 (Fed. Cir. 1988) 46, 47, 55

i4i Ltd. P'ship v. Microsoft Corp.,
598 F.3d 831 (Fed. Cir. 2010) 59

Int'l Ass'n of Fire Fighters, Local 365 v. City of East Chicago,
56 F.4th 437 (7th Cir. 2022) 46

Intellectual Ventures I LLC v. Symantec Corp.,
838 F.3d 1307 (Fed. Cir. 2016) 34

Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.,
821 F.3d 1359 (Fed. Cir. 2016) 27

In re Invitae Corp.,
No. 24-11362 (Bankr. D.N.J.) 54

Kingsdown Med. Consultants, Ltd. v. Hollister Inc.,
863 F.2d 867 (Fed. Cir. 1988) 47

KSR Int'l Co. v. Teleflex Inc.,
550 U.S. 398 (2007).....25

Littelfuse, Inc. v. Mersen USA EP Corp.,
29 F.4th 1376 (Fed. Cir. 2022) 39

MCM Portfolio LLC v. Hewlett-Packard Co.,
812 F.3d 1284 (Fed. Cir. 2015) 41

Metalcraft of Mayville, Inc. v. Toro Co.,
848 F.3d 1358 (Fed. Cir. 2017) .....*passim*

Miles Labs., Inc. v. Shandon Inc.,
997 F.2d 870 (Fed. Cir. 1993) 28, 30, 34

Mylan Institutional LLC v. Aurobindo Pharma Ltd.,
857 F.3d 858 (Fed. Cir. 2017) 23, 29, 51

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00011

Novartis AG v. Torrent Pharms. Ltd.,
853 F.3d 1316 (Fed. Cir. 2017) 27

O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co.,
449 F. App'x 923 (Fed. Cir. 2011) 61

Pfizer, Inc. v. Teva Pharms., USA, Inc.,
429 F.3d 1364 (Fed. Cir. 2005) 60

Philip Morris, Inc. v. Harshbarger,
159 F.3d 670 (1st Cir. 1998).....61

Phillips v. AWH Corp.,
415 F.3d 1303 (Fed. Cir. 2005) 40

Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.,
315 F.3d 1335 (Fed. Cir. 2003) 31

Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.,
711 F.3d 1348 (Fed. Cir. 2013) 35

PPG Indus., Inc. v. Guardian Indus. Corp.,
75 F.3d 1558 (Fed. Cir. 1996) 22

Presidio Components Inc. v. Am. Tech. Ceramics Corp.,
702 F.3d 1351 (Fed. Cir. 2012) 44, 53

Robert Bosch LLC v. Pylon Mfg. Corp.,
659 F.3d 1142 (Fed. Cir. 2011) 53

Ruiz v. A.B. Chance Co.,
357 F.3d 1270 (Fed. Cir. 2004) 28

Sage Prod., Inc. v. Devon Indus., Inc.,
126 F.3d 1420 (Fed. Cir. 1997) 50

Sanofi-Synthelabo v. Apotex, Inc.,
470 F.3d 1368 (Fed. Cir. 2006) 43, 55

Shuffle Master, Inc. v. VendingData Corp.,
163 F. App'x 864 (Fed. Cir. 2005) 42

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00012

Sofamor Danek Grp., Inc. v. DePuy-Motech, Inc.,
74 F.3d 1216 (Fed. Cir. 1996) 42

Summit 6, LLC v. Samsung Elecs. Co.,
802 F.3d 1283 (Fed. Cir. 2015) 42

TEK Glob., S.R.L. v. Sealant Sys. Int'l, Inc.,
920 F.3d 777 (Fed. Cir. 2019) 51, 52

Tinnus Enters., LLC v. Telebrands Corp.,
846 F.3d 1190 (Fed. Cir. 2017) 35

Titan Tire Corp. v. Case New Holland, Inc.,
566 F.3d 1372 (Fed. Cir. 2009) 23

TiVo Inc. v. EchoStar Corp.,
646 F.3d 869 (Fed. Cir. 2011) 63

Toro Co. v. Deere & Co.,
355 F.3d 1313 (Fed. Cir. 2004) 42

Trebro Mfg., Inc. v. Firefly Equip. LLC,
748 F.3d 1159 (Fed. Cir. 2014) 48

United States v. W.T. Grant Co.,
345 U.S. 629 (1953).....48

STATUTES AND RULES

35 U.S.C. § 101 34

35 U.S.C. § 103 34

Fed. R. Civ. P. 65(c).....55

OTHER AUTHORITIES

9 James Wm. Moore, *Moore's Federal Practice* (3d ed. 2022).....34

Natera, Inc. v. ArcherDX, Inc.,
No. 1:20-cv-00125-GBW, Doc. 685 (D. Del. Jan. 5, 2024).....54

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00013

Press Release, *Medicare Extends Coverage of Natera's Signatera MRD Test to Ovarian Cancer and Neoadjuvant Breast Cancer* (Feb. 26, 2024), https://bit.ly/48u6Eor 9, 56

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00014

STATEMENT OF RELATED CASES

No appeal involving U.S. Patent No. 11,519,035 is, or has previously been, before this Court or any other court. Natera, Inc. is not aware of any other pending case in this or any other tribunal that will directly affect or be directly affected by this Court's decision within the meaning of Federal Circuit Rule 47.5.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00015

STATEMENT OF THE CASE

I. THE '035 PATENT'S INNOVATION OVER THE PRIOR ART AND SIGNATERA'S RESULTING SUCCESS

This case arises out of Natera's groundbreaking invention: an innovative approach to amplifying and sequencing cell-free DNA.

A. Obstacles in Prior Art Methods

DNA is generally contained within cells. Appx7659. Cell-free DNA, or "cfDNA," is DNA that has been released from cells into the bloodstream, typically when a cell dies. Appx7559¶36.

In cancer patients, both healthy cells and cancer cells release cfDNA into the bloodstream. The cfDNA from cancer cells is called circulating tumor DNA, or "ctDNA." Appx7559¶36; Appx18755¶18. Tests capable of measuring ctDNA in the bloodstream can identify cancer relapses early, before tumors are large enough to detect through an MRI or biopsy. Appx241(244:60-245:26); Appx7558-59¶¶34-35.

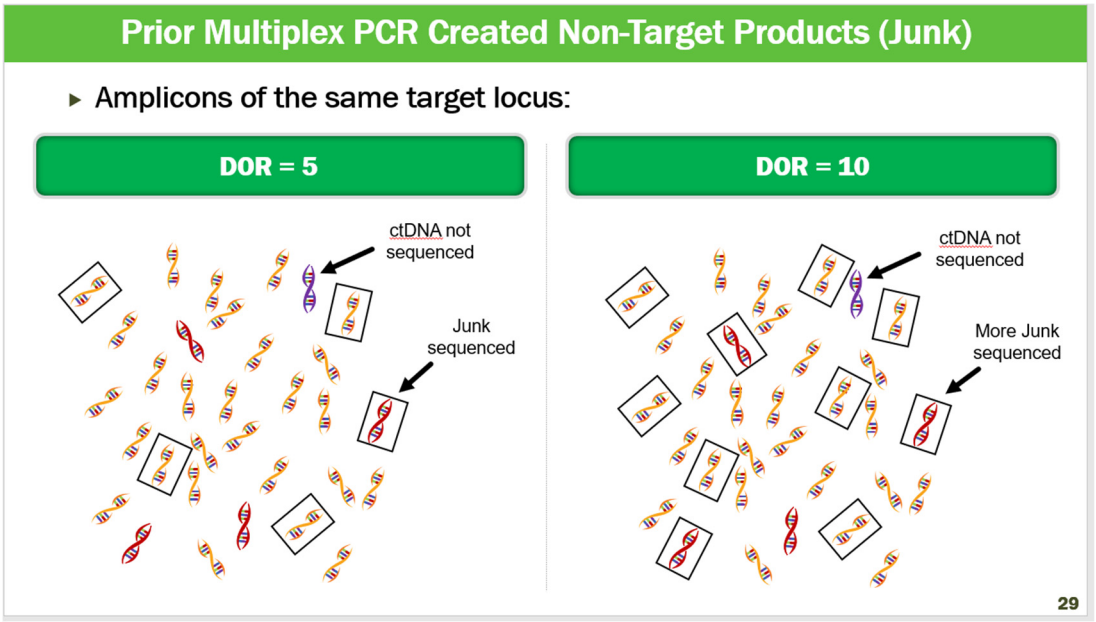
While the theoretical advantages of using cfDNA to monitor health conditions were known in the prior art, Appx121(3:15-52), skilled artisans recognized serious obstacles. For example, although DNA may be processed using a technique called polymerase chain reaction ("PCR") that makes copies of the DNA through "amplification" cycles, skilled artisans perceived major obstacles to amplifying cfDNA in the manner claimed in the '035 Patent—particularly where multiple

sequences would be targeted and amplified together in a single reaction volume (a process known as "targeted multiplex amplification"). Appx138(37:31-42); Appx161-62(84:15-85:20); Appx18829-30¶160.

Among other obstacles, the amount of cfDNA in the bloodstream is very low, and given that ctDNA is a tiny fraction of the total cfDNA in a cancer patient, the amount of ctDNA is far lower still. Appx18756-57¶¶20-21. That low concentration makes it challenging to amplify parts of the DNA (the "target loci") that may indicate cancer. Appx18755-59¶¶18-22; Appx136(34:58-62). Those obstacles are particularly severe when all of the biochemical reagents needed to perform targeted multiplex amplification are mixed together in the same reaction volume: The reagents can interfere with one another and create large amounts of unwanted byproducts, or "junk," that further dilute the already scarce ctDNA. Appx20183-86(30:6-31:14, 33:8-21).

Those byproducts are especially problematic when preparing a sample for high-throughput next-generation DNA sequencing techniques known as "massively parallel sequencing": The byproducts can drown out the signal from the target ctDNA. Appx179(120:10-48); Appx20183-86(30:6-31:14, 33:8-21). Thus, instead of amplifying the relevant targets, the prior art methods reproduced a lot of uninformative "junk" that skewed sequencing and measurements and made them unreliable:

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00017



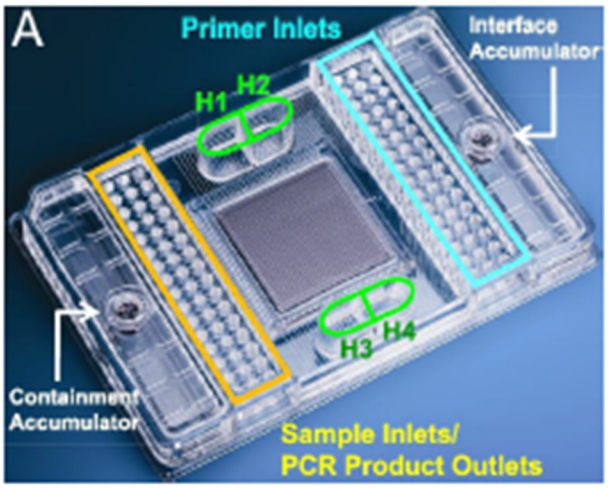
Appx21386; *see also* Appx121(3:4-14) (noting that "improved methods [we]re needed to reduce the formation of non-target amplicons during multiplex PCR").

Another significant obstacle in the prior art was cfDNA's fragmented nature. When cells die, their DNA is broken up into fragments before entering the bloodstream. Appx7559¶36. Those cfDNA fragments are tiny compared to the complete DNA found in cells. Appx18754¶16; Appx7559¶36. That fragmentation makes it more difficult to amplify targets—especially when the targets are very small. Appx163-64(88:55-63, 89:5-29); Appx169(100:51-58); Appx177(115:39-49); Appx18754¶16. That obstacle is particularly acute when a target mutation associated with cancer is a single nucleotide polymorphism or "SNP"—a mutation at a single nucleotide base in the human genome. Appx18754-59¶¶16-22; Appx136-37(34:46-35:2).

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00018

To avoid those problems with targeted multiplex amplification, the prior art focused on "split-and-pool" methods of amplification. Prior art systems like the Fluidigm Access Array, used in NeoGenomics' asserted Kaper reference, would "split" DNA samples into separate reaction wells and then amplify one or a very small number of individual targets in each well. Appx162(85:15-30). Access Array's multiple wells are shown below (marked by yellow and blue rectangles):

Figure 1: The Access Array System



Appx13113(Fig. 1). Skilled artisans understood that "split-and-pool" approach to be necessary to avoid excessive "off-target sequence reads" that would result from amplifying all DNA targets together in a single reaction well. Appx162(85:15-29). According to conventional wisdom, "consolidating multiple reactions into a single volume" would "introduc[e] complications to the reactions, as opposed to facilitating them." Appx18813-14¶135; *see also* Appx18816-19¶¶139, 143.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00019

"Split-and-pool" methods, however, were ineffective for low-concentration DNA sources like ctDNA. Appx162(85:30-33). Because the amount of DNA is already very low, splitting the samples often caused ctDNA molecules in a sample to be missed completely: The ctDNA would be randomly distributed into the individual wells, and there might not be enough ctDNA molecules present to ensure that there is one copy of a given target locus associated with cancer in a well. Appx161-62(84:51-62, 85:21-33). While "split-and-pool" methods worked for high-concentration sources like tumor biopsy tissue, which is composed entirely of cancer DNA, skilled artisans understood them to be "problematic for samples with a limited amount of DNA" like ctDNA. Appx162-63(85:21-33, 87:58-88:8); Appx18827-30¶¶157-160.

B. Natera Overcomes Those Obstacles

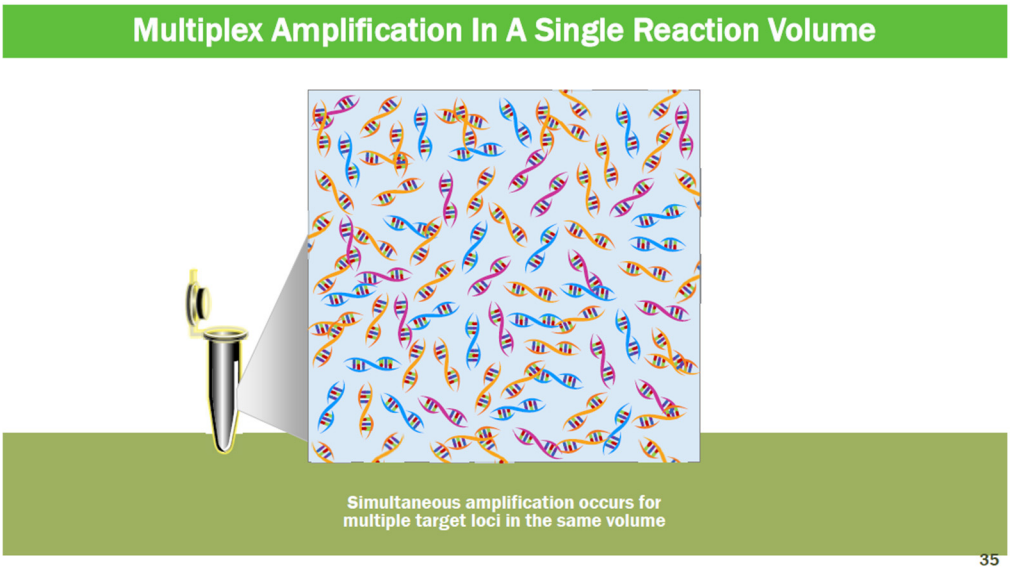
After extensive research and development, Natera overcame the challenges of low-concentration ctDNA by rejecting the prior art's focus on split-and-pool methods. Natera showed that it was possible to prepare cfDNA samples containing ctDNA by amplifying the cfDNA in a ***single reaction volume*** rather than separate pools. For that breakthrough, Natera was awarded the '035 Patent on December 6, 2022, with a priority date of May 18, 2011. Appx23, Appx33.

Claim 1 of the '035 Patent recites three steps: (1) tagging cfDNA, (2) targeted amplification of 25-2,000 target SNPs associated with cancer in a single

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00020

reaction volume, and (3) massively parallel sequencing. Appx244(249:46-62). In the first step, cfDNA is "tagg[ed]" with one or more universal tail adaptors (common sequences of nucleotides). Appx244(249:46-57). That tagging allows DNA segments of interest to be further processed in later steps. Appx178(117:38-48).

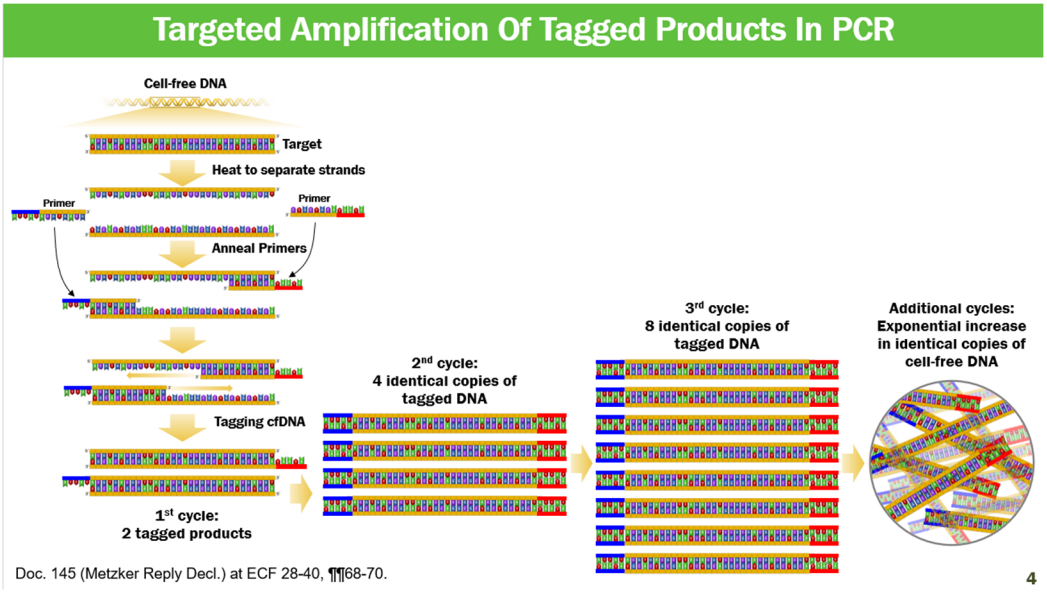
In the second step, those tagged products are "amplif[ied]" one or more times, including through "targeted amplification" of "25-2,000 [SNPs] associated with cancer." Appx244(249:51-62). Departing from prior art split-and-pool methods, this step requires targeted multiplex amplification in a "single reaction volume," Appx244(249:51-55):



Appx21047; *see also* Appx142(46:41-57) (method "simultaneously amplif[ies] a large number of target loci in a single multiplex PCR reaction"). The amplifying step also adds "a barcode and one or more sequencing tags" to the tagged products. Appx244(249:55-57).

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00021

Finally, in the third step, the amplified SNP loci are "sequenc[ed]" using "massively parallel sequencing." Appx244(249:58-62). The following slide illustrates one way of tagging cfDNA and amplifying the tagged products according to the '035 Patent:



Appx21361.

Natera's discovery allowed the '035 Patent's method to overcome prior art challenges associated with targeted amplification of cfDNA in a single reaction volume. Appx18752-59¶¶13-22; Appx18825-35¶¶154-169. By counterintuitively performing the amplification in a single reaction volume rather than separate reaction wells, the '035 Patent showed how it was possible to avoid the pitfalls of split-and-pool methods when applied to low-concentration DNA sources like ctDNA, which exists only as a tiny fraction of all cfDNA. Appx18829-30¶160;

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00022

Appx20185-86(32:11-33:21); Appx20192(39:1-15); *see also* Appx143(47:24-28) ("[B]eing able to analyze the target loci in one reaction volume . . . rather than splitting the sample into multiple different reactions reduces variability that can occur between reactions."); Appx143(47:16-19) (similar).

C. Signatera Becomes the Market Leader in cfDNA MRD Tests

Signatera™ is Natera's commercial embodiment of the '035 Patent. Appx2443¶40-41. Launched for research in 2017 and commercial use in 2019, Appx2443¶41, Signatera is a groundbreaking test for minimal residual disease ("MRD")—a sign of cancer relapse—that amplifies cfDNA in a single reaction volume, Appx7613-15¶¶115, 123; Appx7925¶6. Unlike MRD tests that preceded it, Signatera is "tumor-informed" as opposed to "tumor-naïve": Instead of using an off-the-shelf platform that applies to all patients, DNA from a patient's own tumor is used to identify a bespoke signature of specific mutations, which is used to monitor for the cancer's recurrence. Appx2434-35¶24; Appx7925¶5. By using cfDNA, Signatera avoids invasive procedures such as biopsies and can detect cancer relapse at very early stages. Appx7558¶34.

Signatera was the first tumor-informed MRD test on the market. Appx2443¶11541; Appx7925¶¶6-7. When Signatera launched, "many people were skeptical that this personalized, tumor-informed approach for cancer recurrence monitoring could be done at scale across a large population of patients."

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00023

Appx7925¶7. Through a "tremendous amount of effort and investment," Natera "develop[ed] the clinical evidence to convince physicians, researchers, and regulatory authorities that this new approach would work." Appx7926¶8. After Signatera was clinically validated in 2015—in a study that reported "93% (13/14) longitudinal relapse sensitivity and 100% (10/10) specificity in non-small cell lung cancer patients"—Natera became a "serious player in oncology diagnostics." Appx7926¶9.

Natera has remained the market leader. Appx2446¶45. Oncologists prefer Signatera over other tests. Appx16159; Appx2512¶145. With good reason: Clinical studies and over 40 peer-reviewed publications have proven that Signatera identifies cancer "significantly earlier" than imaging or biopsies. Appx2471-72¶79. Signatera has won numerous medical-technology awards and obtained ***three*** FDA Breakthrough Device designations. Appx2443-46¶¶42-44. Medicare covers Signatera for numerous cancers, with coverage continuing to expand. Appx2443-46¶¶42-44; *see* Press Release, *Medicare Extends Coverage of Natera's Signatera™ MRD Test to Ovarian Cancer and Neoadjuvant Breast Cancer* (Feb. 26, 2024), https://bit.ly/48u6Eor.

D. RaDaR's Infringement

In March 2023, NeoGenomics released a competing test, RaDaR, for commercial use. Appx16-17. Like Signatera, RaDaR is a tumor-informed MRD

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00024

test. Appx7560¶37. And like Signatera, RaDaR practices at least claim 1 of the '035 Patent. Appx7590-612¶¶85-114.

Several publications describe how RaDaR works. Appx7598-604¶¶94-102. After a blood sample containing cfDNA is collected, RaDaR performs an initial PCR process. Appx7689. During that process, cfDNA is subjected to at least "15 cycles of amplification." Appx7707; Appx18903-04¶295.

One article that describes certain features of RaDaR's operation explains that RaDaR tags and then amplifies cfDNA during those 15 cycles. Appx7691; Appx18903-04¶295. RaDaR's first PCR cycle tags cfDNA with two universal tail adaptors, CS1 and CS2. Appx18903-04¶295. The tagged DNA molecules are then amplified in the subsequent cycles. Appx18904¶297. Other sources describe the process similarly. *See* Appx7590¶85; Appx7726.

On July 27, 2023, NeoGenomics announced that RaDaR had received its first Medicare coverage, making it "widely accessible to millions." Appx2442¶39; Appx883. NeoGenomics announced its intention to seek Medicare coverage for at least two other cancer indications by the end of 2023. Appx883.

II. PROCEEDINGS BELOW

A. Natera's Complaint and Request for Preliminary Injunction

Natera sued for infringement on July 28, 2023, the day after NeoGenomics announced RaDaR's Medicare coverage. Appx2442¶39; Appx285-310. Natera

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00025

alleged that RaDaR infringed claim 1 of the '035 Patent. Appx908-09. Three days later, Natera sought a preliminary injunction against (1) "making, using, [or] selling" RaDaR in the United States; and (2) "promoting, advertising, marketing, servicing, distributing, or supplying" RaDaR "so as to induce others' infringement." Appx891-93; Appx894-929. The proposed injunction specifically excluded patients already using RaDaR. Appx892.

To support its request, Natera offered expert testimony that RaDaR performed every step of claim 1, including "tagging isolated cell free DNA . . . with one or more universal tail adaptors," "performing targeted amplification" of "25-2,000 loci associated with cancer" in the tagged cfDNA "in a single reaction volume," and "conducting massively parallel sequencing." Appx908.

Natera argued that RaDaR's continued availability threatened irreparable harm—reputational harm, loss of first-mover advantage, and lost sales and biopharmaceutical partnerships. Appx910-19. RaDaR's Medicare coverage threatened to "rapidly and substantially subvert Signatera's tumor-informed MRD market share." Appx910-11. NeoGenomics had already advertised RaDaR to Natera's customers, making "unfounded claims about the superiority of its RaDaR assay." Appx910-11; Appx2510-12¶143.

NeoGenomics disputed infringement, urging that RaDaR did not perform "targeted amplification of ***already*** tagged DNA" as required by claim 1.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00026

Appx10485-86. NeoGenomics also contested the'035 Patent's validity, arguing that a single prior art reference—a 2010 poster by Kaper describing a use of the Fluidigm Access Array—rendered Natera's claims obvious. Appx10489-90.

B. The District Court's Carefully Crafted Injunction

On December 27, 2023—after full briefing, a technology tutorial, Appx20073-152, and an all-day evidentiary hearing, Appx20153-381—the district court granted a preliminary injunction. Appx1. Each of the relevant factors supported injunctive relief. Appx5-21.

1. On infringement, the court found that Natera had made "a strong showing that the RaDaR test . . . uses the method claimed in the '035 patent and infringes." Appx6. The court found that RaDaR "tag[ged]" the target cfDNA strands with an "adaptor sequence" and "then perform[ed] targeted amplification" on the tagged products. Appx6. RaDaR thereby satisfied claim 1 by amplifying "the tagged products one or more times to generate final amplification products, wherein one of the amplification steps comprises targeted amplification." Appx6.

The court rejected NeoGenomics' obviousness arguments. Appx8-10. It noted that Kaper "used DNA samples from tumor tissue, not cfDNA." Appx9. And the court found it "unlikely a person skilled in the art would have been motivated to use cfDNA with Access Array and would have anticipated success in doing so." Appx10. NeoGenomics' experts did not address whether skilled artisans would have

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00027

been motivated to combine and expected success. Appx18782-83¶75; Appx12001-184. The court identified numerous "obstacles to successfully amplifying and sequencing ctDNA with precision" that undermined any motivation to combine: cfDNA "exists in low yield" in the bloodstream; ctDNA "exists in even lower yields"; and cfDNA is "fragmented" such that it may not "contain sites for both primers of a primer pair to bind." Appx9-10 (citing evidence).

Those "challenges associated with cfDNA, and others," made it unlikely skilled artisans would have been motivated to "use cfDNA with Access Array and would have anticipated success in doing so." Appx10. NeoGenomics' contrary arguments, the court found, "show hindsight bias more than they support a substantial question of obviousness." Appx10.

2. The district court also found that Natera would "likely suffer irreparable harm" without an injunction, including lost "customers, profits, business relationships, and clinical opportunities." Appx14-15. The court found that RaDaR was the "only competitor" to Signatera "in the tumor informed MRD marketplace." Appx14. As such, RaDaR was likely to cause Signatera to lose sales and to "lose out on [biopharmaceutical] partnerships that substantially impact Signatera's future success"—losses that were "challenging to quantify." Appx15.

"[I]f RaDaR remains on the market," the court determined, "Natera's position as first mover" would be "unfairly cut short." Appx15. Natera would lose the "brand

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00028

recognition, customer loyalty, and business foundations" to which it was entitled as a "pioneer" in cancer testing. Appx15. The court found it "highly likely" that the tumor-informed market was the relevant market, but Natera showed irreparable harm even in the "larger MRD market." Appx16.

The court rejected NeoGenomics' argument that there was insufficient evidence of lost sales. Appx16. The limited number of historical lost sales was not surprising given that RaDaR "is relatively new to the market." Appx16. In any event, Natera had "shown Moderna used RaDaR in at least one clinical study," and NeoGenomics was "promoting RaDaR to Natera's customers," so ***future*** lost sales were likely. Appx16.

The court rejected NeoGenomics' argument that Natera unreasonably delayed bringing suit: "[S]uing four months after an infringer enters the market is relatively quick." Appx17. Moreover, any delay was justified by Natera's "ongoing patent infringement litigation over related patents." Appx17. That ruling was consistent with the court's earlier comment that, "if [Natera] came in . . . and said that Medicare might approve this, we need a preliminary injunction," the court "would have said come back later." Appx21346(15:12-14).

The court held that a sufficient "causal nexus" existed "between the likely infringement and harm" to Natera. Appx17. The court found it "highly likely" that RaDaR was "built" "using the methods of the '035 patent as a foundation." Appx17.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00029

RaDaR's "likely infringement [of the '035 Patent] allow[ed] NeoGenomics to offer RaDaR as a tumor informed MRD assay." Appx17-18. That was sufficient to show that "the infringing feature drives consumer demand." Appx17 (quoting *Apple Inc. v. Samsung Elecs. Co.*, 695 F.3d 1370, 1375-76 (Fed. Cir. 2012)).

3. Balancing the equities, the court found that Signatera is critical to Natera's success, driving 52.1% of Natera's growth from 2022-2025. Appx18. By contrast, RaDaR is "not a major product in NeoGenomics' portfolio," only one of over 600 different cancer diagnostic tests. Appx19.

The court also determined that the public interest favored an injunction. The court noted that "[i]t is in the public's interest to uphold patent rights." Appx19. It rejected NeoGenomics' assertion of harm to patients, finding that "[a]nyone in need of a tumor informed MRD test will be able to get one" because Signatera "is clinically validated for use with the same cancers as RaDaR." Appx20.

4. Adopting unchallenged language from Natera's proposed injunction (Appx891-93), the court enjoined NeoGenomics from "making, using, selling, or offering [RaDaR] for sale in the United States" or "promoting, advertising, marketing, servicing, distributing, or supplying [RaDaR] so as to induce others' infringement." Appx22-24. The court carefully tailored the injunction. It excluded continued use of RaDaR for "patients already using [RaDaR] before the entry of this injunction," "research and development with other persons or entities on projects or

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00030

studies that began before the entry of this injunction," and "clinical trials in process or already approved." Appx23.

On December 27, 2023, NeoGenomics appealed. Appx20748.

C. The District Court's Denial of the Motions To Stay and Modify the Injunction

NeoGenomics moved for a stay pending appeal and to modify or clarify the injunction's scope. Appx20751; Appx20783.

1. On January 10, 2024, the court required Natera to post a $10 million bond. Appx20916. The court clarified that NeoGenomics could continue to perform RaDaR tests on blood draws taken before Natera posted security, and that the injunction would not apply to three clinical trials for which NeoGenomics already had signed contracts. Appx20916-17.

Natera posted security on January 12, 2024. Appx20937-39. NeoGenomics then filed an amended notice of appeal on January 26, 2024. Appx20942-44.

2. On February 2, 2024, the court issued another order clarifying the injunction. Appx20945-48. That order allowed NeoGenomics to use RaDaR in three more clinical trials that were substantively finalized but awaiting signed contracts. Appx20948.

Less than two weeks later, the district court denied NeoGenomics' motion for a stay pending appeal. Appx21320-26. The court found no substantial question of obviousness or noninfringement to justify a stay. Appx21322-23. And it affirmed

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00031

its prior finding of irreparable harm, noting it had relied on several different factors in making that finding. Appx21323-26.

The court rejected NeoGenomics' argument that the public interest warranted keeping RaDaR on the market because of its supposed "higher sensitivity," explaining that the issue was "disputed" and that "it [was] not at all clear" that RaDaR in fact possesses higher sensitivity. Appx21325-26. The court found no "satisfactory evidence" that RaDaR was "available for cancers for which Natera's product is not." Appx21326.

3. That same day, the district court denied NeoGenomics' motion to modify the injunction by removing its prohibition on "selling" or "offering for sale" RaDaR in the United States. Appx21327-30. That motion, the court ruled, was untimely. Natera had suggested the challenged language in its proposed injunction in July 2023. Appx21329. "NeoGenomics had months to review Natera's proposed preliminary injunction order, . . . yet NeoGenomics did not raise a murmur of opposition . . . ." Appx21329. "NeoGenomics had the opportunity to raise its non-infringement contentions in its preliminary injunction briefing and at the hearing on the preliminary injunction. It does not get to raise those arguments now under the guise of a confusing motion to modify." Appx21331.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00032

SUMMARY OF ARGUMENT

Largely ignoring the demanding standards of review on appeal, NeoGenomics reargues a long list of factual disputes and discretionary determinations it lost in the district court. The district court's findings were well supported by the record, and NeoGenomics fails to show any abuse of discretion.

I. The district court neither applied the wrong legal standards nor committed clear error in finding no substantial question over the '035 Patent's validity. Even at the preliminary injunction stage, a party cannot challenge a patent merely by arguing that all of its elements independently existed in the prior art. There must be a motivation to combine. *See Metalcraft of Mayville, Inc. v. Toro Co.*, 848 F.3d 1358, 1367 (Fed. Cir. 2017). The district court carefully analyzed the record and properly determined that skilled artisans would not have been motivated to apply Kaper to the far more challenging context of cell-free DNA. Appx9-10.

The district court did not apply an incorrect legal standard merely by observing that the "challenges associated with cfDNA . . . presented obstacles to successfully amplifying and sequencing ctDNA ***with precision*** during the relevant time period." Appx10 (emphasis added). Lack of precision is relevant to whether there was a motivation to combine, whether or not it is a claim element. Skilled artisans regularly consider things like cost, safety, and precision in deciding whether to combine prior art elements.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00033

Nor did the district court commit clear error in finding no motivation to combine. NeoGenomics points to other references that disclosed methods of testing cfDNA. But the '035 Patent does not claim just ***any*** method; it claims a specific, innovative method that involves targeted amplification of 25-2,000 SNPs in a single reaction volume, massively parallel sequencing, and other elements. None of NeoGenomics' references discloses all those features.

II. Nor did the district court commit clear error in finding no substantial question of infringement. NeoGenomics does not dispute that RaDaR tags cfDNA, amplifies the tagged DNA comprising 25 to 2,000 SNPs associated with cancer in a single reaction volume, and then sequences the products by massively parallel sequencing. NeoGenomics argues only that it does not infringe because the first two steps of tagging and targeted amplification occur in separate cycles of a single PCR process, rather than in separate PCRs with separate primers. Nothing in the '035 Patent requires that the steps occur in separate PCRs with separate primers. NeoGenomics is simply engrafting additional limitations onto the claim.

Amgen Inc. v. Sandoz Inc., 923 F.3d 1023 (Fed. Cir. 2019), does not support NeoGenomics' argument. In that case, the patent recited separate "washing" and "eluting" steps, and the accused product had no separate washing and eluting steps at all. *Id.* at 1028. Here, by contrast, the parties agree that claim 1 requires separate tagging and amplifying steps; the only dispute is whether those steps must occur in

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00034

separate PCR processes with separate primers, or instead may occur in separate amplification cycles within a single PCR. *Amgen* does not speak to that issue.

Finally, NeoGenomics urges that the district court should have conducted a formal claim construction before rejecting its non-infringement argument. NeoGenomics forfeited that argument by not requesting the claim construction below. Regardless, the court was not required to construe the claim before applying it according to its plain terms.

III. The district court's finding of irreparable harm was also well within its discretion. RaDaR's widespread availability would have cost Natera the market share, clinical partnerships, and exclusivity to which it was entitled as the first mover in tumor-informed MRD testing. Those are all classic examples of irreparable harm. *See Bio-Rad Labs., Inc. v. 10X Genomics Inc.*, 967 F.3d 1353, 1378-80 (Fed. Cir. 2020). NeoGenomics' stale market reports and cherry-picked comments from Natera's CEO—most of which pre-date NeoGenomics' Medicare announcement—do not demonstrate an abuse of discretion.

Nor did Natera delay in seeking a preliminary injunction. Natera sought an injunction just ***four days*** after NeoGenomics announced RaDaR's Medicare coverage. That coverage made RaDaR widely accessible to millions of customers, threatening grave harm. Even measuring from the date the '035 Patent issued in

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00035

December 2022, Natera filed suit seven months later, a period far shorter than what many courts have approved.

The evidence of lost sales supported the district court's finding. Natera demonstrated that RaDaR had cost it at least two clinical trials. And future losses were imminent given the recent Medicare coverage announcement.

NeoGenomics' causal nexus argument lacks merit. NeoGenomics failed to raise its current argument in the district court. Regardless, the evidence amply showed that the '035 Patent's technology was a key driver of RaDaR's demand. That showing was more than sufficient to show a causal nexus. *See Apple, Inc. v. Samsung Elecs. Co.*, 678 F.3d 1314, 1324 (Fed. Cir. 2012).

Finally, the district court did not erroneously treat the two-party status of the market as dispositive. The court merely weighed that fact along with other factors. And the court's finding that the tumor-informed market was two-party was well supported by the evidence—NeoGenomics' own expert admitted as much.

IV. The district court properly considered the public interest. The court recognized the strong public interest in protecting intellectual property rights. And the court properly found that there were no countervailing interests in this case. The court found that anyone who needed an MRD test could get one from Natera. And the court carefully tailored the injunction by excluding ongoing uses by patients and in clinical studies.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00036

The balance of equities also favored an injunction. The district court found that Signatera was Natera's "most valuable offering," whereas RaDaR was "not a major product in NeoGenomics' portfolio." Appx18-19. The threatened harm to Natera far outweighed any harm to NeoGenomics.

V. Finally, the district court did not err by enjoining NeoGenomics from "making," "selling," or "offering for sale" RaDaR in the United States. Appx22-24. Natera proposed that language at the outset of the litigation. NeoGenomics never raised any concerns about it until ***after*** the court ruled. In any case, the district court properly enjoined NeoGenomics from making or selling RaDaR to protect against future infringement. *See BlephEx, LLC v. Myco Indus., Inc.*, 24 F.4th 1391, 1405 (Fed. Cir. 2022).

ARGUMENT

I. THE DISTRICT COURT CORRECTLY FOUND NO SUBSTANTIAL QUESTION REGARDING THE '035 PATENT'S VALIDITY

To avoid a preliminary injunction, a defendant must show a "substantial question" of invalidity. *Metalcraft of Mayville, Inc. v. Toro Co.*, 848 F.3d 1358, 1366-67 (Fed. Cir. 2017). The evidence must be "sufficiently persuasive that it is likely to overcome the presumption of patent validity." *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996). While the defendant need not ***prove*** invalidity by clear and convincing evidence at this stage, "[t]he fact that, at trial on the merits, the proof of invalidity will require clear and convincing

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00037

evidence" is relevant to whether a substantial question exists. *Titan Tire Corp. v. Case New Holland, Inc*., 566 F.3d 1372, 1380 (Fed. Cir. 2009).

The district court properly applied those standards. NeoGenomics does not dispute that ***no*** prior art reference disclosed all elements of the '035 Patent claims, leaving a "gap" between the prior art and Natera's invention. Br.22. The district court carefully analyzed that gap and concluded that skilled artisans would not have been motivated to combine existing DNA analysis techniques with cfDNA because of the unique challenges that cfDNA poses. Appx9-10.

A. The District Court Did Not Apply the Wrong Legal Standard in Assessing Motivation To Combine

NeoGenomics argues that the district court should have denied an injunction because the '035 Patent claims only "the predictable use of prior-art elements according to their established functions." Br.21-24. But the district court applied the correct legal standards in rejecting that argument.

Even on a preliminary injunction motion, "it is not enough . . . to merely demonstrate that elements of the claimed invention were independently known in the prior art." *Metalcraft*, 848 F.3d at 1367. There must be a "motivation to combine." *Id.* This Court regularly finds no "substantial question of validity" where "there would not have been a motivation to combine." *Id.*; *see BlephEx, LLC v. Myco Indus., Inc.*, 24 F.4th 1391, 1403-04 (Fed. Cir. 2022) (affirming injunction based on lack of motivation to combine); *Mylan Institutional LLC v. Aurobindo*

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00038

Pharma Ltd., 857 F.3d 858, 870-71 (Fed. Cir. 2017) (similar); *contrast Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1358-63 (Fed. Cir. 2001) (reversing injunction because particular facts showed "a substantial question of invalidity," not because motivation to combine was per se irrelevant).

The district court correctly applied those principles. As the court observed, and as NeoGenomics admits (Br.22), Kaper does not disclose applying the '035 Patent's claimed features to cfDNA—it involves the far less challenging context of biopsied tumor tissue. Appx9. Kaper does not even ***mention*** cfDNA. Appx13113. The court thus examined whether there was a motivation to apply Kaper to that new and very different context. Appx9-10. Citing extensive evidence and crediting Natera's expert testimony, the court held that there was not. Appx9-10. That is exactly the inquiry that cases like *Metalcraft* require. 848 F.3d at 1367.

NeoGenomics' argument that the court "applied the wrong legal standard" is hard to discern. Br.21. NeoGenomics urges that "[m]ere '[v]ulnerability' to an invalidity challenge suffices to defeat a preliminary injunction." *Id.* But "mere vulnerability" is not a substitute for motivation to combine. It is merely another way of expressing the idea that a defendant opposing a preliminary injunction need only show a "substantial question" of invalidity. *See, e.g.*, *Amazon.com*, 239 F.3d at 1359 (referring to both standards interchangeably). That is the standard the district court applied. Appx8; Appx10.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00039

NeoGenomics urges that the '035 Patent is invalid because it "claims nothing more than 'prior art elements according to their established functions.'" Br.24 (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007)). But *KSR* does not dispense with motivation to combine either. While *KSR* states that an invention must be "more than the ***predictable*** use of prior art elements according to their established functions," "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." 550 U.S. at 417-18 (emphasis added). A critical consideration is whether there was some "reason . . . to combine the elements in the way the claimed new invention does." *Id.* at 418. Motivation to combine thus bears directly on whether the combination of prior art elements was, in fact, "predictable." That is the analysis the district court undertook. Appx8-10.

Finally, NeoGenomics argues that the court erred because "***NeoGenomics' evidence*** . . . showed skilled artisans would and could have bridged any gap." Br.22 (emphasis added). That is just a factual argument about what evidence the trial court chose to credit. Later in its brief, NeoGenomics does make a clear error argument. Br.27-28. NeoGenomics cannot avoid that demanding standard of review simply by moving most of its factual analysis to an earlier section of its brief and treating it as if it were some sort of legal error instead. Br.22-24.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00040

B. The District Court Did Not Improperly Fail To Tether Its Motivation-To-Combine Analysis to the Claim Scope

The closest NeoGenomics comes to a challenge to the district court's legal standard rests on two words the court used when finding no motivation to combine: "These challenges associated with cfDNA, and others, presented obstacles to successfully amplifying and sequencing ctDNA ***with precision*** during the relevant time period." Appx10 (emphasis added). NeoGenomics asserts that, because the '035 Patent does not expressly claim a particular level of "precision," that consideration is irrelevant to whether skilled artisans would have "a reasonable expectation of success of developing the ***claimed invention***." Br.25-27.

That argument misreads the district court's reasoning. The court mentioned lack of precision, not because it is a claim limitation, but because it is a reason why it was "unlikely a person skilled in the art would have been motivated to use cfDNA with [Kaper's] Access Array." Appx10. Facts can be relevant to motivation to combine even if they are not elements of the invention. In *Auris Health, Inc. v. Intuitive Surgical Operations, Inc.*, 32 F.4th 1154 (Fed. Cir. 2022), for example, this Court held that "evidence that . . . a combination would come at the expense of precision required for surgery" was relevant to a motivation to combine, even though the patent claims did not require "precision." *Id.* at 1159.

Similarly, factors like cost or safety may weigh against a motivation to combine, even if they are not claim limitations. In *BlephEx*, this Court affirmed a

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00041

finding of no motivation to combine because the defendant "failed to explain how a skilled artisan would have addressed the safety concerns of its proposed modification," even though the patent claims did not recite a safety limitation. 24 F.4th at 1404. And in *Novartis AG v. Torrent Pharmaceuticals Ltd.*, 853 F.3d 1316 (Fed. Cir. 2017), this Court affirmed a Board decision that considered "expense" in evaluating motivation to combine, even though expense was not a claim limitation. *Id.* at 1327. This case is no different: The fact that Kaper's Access Array was understood to be too imprecise to work with cfDNA would weigh against any motivation to combine, even if the ***patent claims*** do not expressly require precision.

Allergan, Inc. v. Apotex Inc., 754 F.3d 952 (Fed. Cir. 2014), is not to the contrary. In that case, the Court held that the district court erred by "fail[ing] to consider the appropriate scope of the . . . claimed invention in evaluating the ***reasonable expectation of success***." *Id.* at 965-66 (emphasis added). A skilled artisan's reasonable expectation of success of practicing a claimed invention necessarily depends on the invention's scope. *Id.* By contrast, many factors (cost, safety, precision, etc.) may be relevant to motivation to combine, whether they are claim limitations or not. *See Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367-68 (Fed. Cir. 2016) (explaining that "reasonable expectation of success and motivation to combine" are "two different legal concepts"). Why try a

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00042

combination that would be exorbitantly costly, hazardous to use, or too imprecise to be commercially useful? The district court properly considered such factors here.

In *Allergan*, moreover, the prior art contained a "plethora" of references that taught towards particular structures within the patent's broad claim scope. 754 F.3d at 966. The district court erred in that case because it focused on only one specific structure when analyzing motivation to combine. *Id.* This Court reversed because there was plenty of motivation to combine to create ***other*** claimed structures, and that was sufficient to invalidate the claim. *Id.* Here, the district court did not ignore any claim element; it simply mentioned an additional factor (precision) that was also relevant to motivation to combine.

C. The District Court's Factual Findings Are Not Clearly Erroneous

NeoGenomics' attacks on the district court's factual findings of no motivation to combine and no reasonable expectation of success likewise fall short. Br.22-24, 27-29. Those factual findings are reviewed only for clear error. *Metalcraft*, 848 F.3d at 1366. That standard permits reversal "only when this court is left with a 'definite and firm conviction' that the district court was in error." *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004). "Where the factfinder's account of the evidence is plausible in light of the entire record or where it chooses one of two permissible views of the evidence, it has committed no clear error." *Miles Labs., Inc. v. Shandon Inc.*, 997 F.2d 870, 874 (Fed. Cir. 1993). This Court reviews such

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00043

findings "with deference, especially at the preliminary injunction stage." *Mylan*, 857 F.3d at 870. The district court's findings easily satisfy that standard.

1. Ample evidence supports the district court's findings that there were "many well-known barriers to using cfDNA," "making it unlikely a person skilled in the art would have been motivated to use cfDNA with [Kaper] and would have anticipated success in doing so." Appx9-10. For example, the court credited testimony from Natera's expert, Dr. Metzker. Appx18752-59¶¶13-22; Appx18825-35¶¶154-169. Dr. Metzker explained that cfDNA exists in low concentrations in the bloodstream and that ctDNA exists in even lower concentrations, mixed together with other cfDNA. Appx18753¶15. Those circumstances make ctDNA much harder to prepare and analyze than biopsy samples from tumors, in which all the DNA is tumor-derived. Appx18753¶15. Unlike cellular DNA, moreover, cfDNA is "fragmented" into tiny pieces. Appx18755-56¶19. That makes it "difficult to manipulate through existing techniques." Appx18755-56¶19; Appx18754-59¶¶16-22. A district court has "wide discretion to weigh expert credibility," and this Court "defer[s] heavily" to those credibility determinations. *Celsis In Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 929 (Fed. Cir. 2012).[1]

[1] That Kaper refers to testing small amounts such as "50ng [of] human genomic DNA" does not show it was obvious to use Kaper with cfDNA. Appx13113. cfDNA is much harder to work with than tumor biopsy DNA because it exists in low ***concentrations*** strewn throughout the bloodstream. Appx18753¶15.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00044

The district court also relied on articles by Volik and Forshew. Volik explained that "the low amount, high degradation, and high admixture of normal DNA in cfDNA pose major challenges for the development of sensitive and robust detection pipelines." Appx19069. Forshew highlighted "the challenges involved in analysis of circulating tumor DNA." Appx7691. NeoGenomics' own expert agreed. Appx18753-54¶15 ("[Forshew is] referring to past challenges that involve the analysis of circulating tumor DNA. ***I agree with that***."). That evidence provided more than "plausible" support for the court's findings. *Miles Labs.*, 997 F.2d at 874.

2. NeoGenomics urges that "skilled artisans would and could have bridged any gap" because "it was already well known to use cell-free DNA for cancer monitoring and detection." Br.22. But the '035 Patent does not recite monitoring and detection. It claims preparing a sample using a specific method of tagging and targeted amplification to amplify 25-2,000 SNPs in a "single reaction volume," massively parallel sequencing, and other elements. Appx244(249:44-62).

That approach was a breakthrough. Prior art methods taught toward amplification by "split[ting]" a sample into separate reaction wells and then analyzing one individual target in each well, to avoid an excessive number of "off-target sequence reads." Appx162(85:15-29). Those "split-and-pool methods," however, were ineffective for low-concentration sources like ctDNA, because there would often not be enough ctDNA molecules in each well and fragments containing

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00045

a specific target locus of interest could be missed altogether. Appx162(85:30-33); *see also* Appx18829-30¶160; Appx20185-86(32:11-33:21); Appx20192(39:1-15). The '035 Patent navigated those problems by showing how to use a ***single*** reaction volume, rather than separate reaction wells, to analyze cfDNA. Appx126(13:6-15); Appx18829-30¶160.

The evidence thus showed numerous gaps in the prior art. *See, e.g.*, Appx18833¶165 (Kaper does not teach "single reaction volume"); Appx18834-35¶168 (Kaper does not teach "sequencing 25-2,000 SNP loci"); Appx19196-97 (citing same); Appx20185-86(32:11-33:21); Appx20192(39:1-15). In fact, Kaper ***taught away*** from the claimed invention by using a split-and-pool method rather than a single reaction volume. Appx13113. That the district court did not specifically mention every portion of Dr. Metzker's testimony on those issues does not mean the court overlooked them. *See Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1342-43 (Fed. Cir. 2003) ("The fact that the district court did not in its opinion recite every piece of evidence does not mean that the evidence was not considered."); Appx2 n.1.

NeoGenomics invokes only three references from before the '035 Patent's 2011 priority date that purportedly show that using cfDNA for "cancer monitoring and detection" was well-known: patent applications filed by Cantor (2005), Ehrich (2008), and Lo (2009). Br.22-23. None of those references resembles the '035

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00046

Patent. Cantor claimed a "method of determining a single gene disorder in a fetus" by amplifying, replicating, and detecting a "single" SNP. Appx13186. Ehrich claimed a "method for detecting the presence or absence of a plurality of target alleles." Appx13239. Lo claimed a "method for determining whether a nucleic acid sequence imbalance exists within a biological sample." Appx13327. None of those methods disclosed targeted amplification of 25-2,000 SNPs in a single reaction volume as claimed.

Moreover, the three references teach away from the claimed invention by emphasizing the difficulties of working with cfDNA. Lo, for example, explains that cfDNA "represented a considerable challenge" and that there were "controversies regarding the effectiveness" of testing cfDNA. Appx13257-58¶¶6-8; *see also* Appx13146 (Cantor); Appx13199 (Ehrich). Those are the same challenges Natera's expert relied on. Appx18752-59¶¶13-22; Appx18825-35¶¶154-169.

3. NeoGenomics fares even worse when it invokes various ***post***-priority-date statements from this Court's cases and Natera's submissions in other cases. Br.23-24, 27-28. None of those references describes the unique features of the claimed invention.

In *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015), for example, the patent claimed a method for "amplifying" and "detecting" cell-free fetal DNA that purported to extend to essentially ***all*** such testing by any method

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00047

whatsoever. *Id.* at 1373-74. The patent disclosed nothing about tagging and targeted amplification of 25-2,000 SNPs in a single reaction volume combined with massively parallel sequencing. The Court's statement that using PCR to amplify and detect cfDNA ***in general*** was "well-understood, routine, and conventional" says nothing about the specific, superior method claimed here. *Id.* at 1377.

Similarly, in *CareDx, Inc. v. Natera, Inc.*, 40 F.4th 1371 (Fed. Cir. 2022), the patent claims covered methods for detecting organ transplant status by "multiplex sequencing." *Id.* at 1373-75. As in *Ariosa*, the patent claims did not involve targeted amplification of 25-2,000 SNPs in a single reaction volume. The Court concluded that "collecting a sample, genotyping, sequencing, and quantifying" cfDNA was "straightforward, logical, and conventional." *Id.* at 1380. But it said nothing that casts doubt on the ***particular*** method claimed here.

Natera's summary judgment brief in *CareDx* (Appx12583) and expert declaration in *Natera Inc. v. Illumina, Inc.*, No. IPR2018-01317 (PTAB) (Appx12959) are irrelevant for similar reasons: They concerned only the particular patents at issue in those cases, not the distinct method of the '035 Patent that involves targeted amplification of 25-2,000 SNPs in a single reaction volume combined with massively parallel sequencing. NeoGenomics must do more than show that the prior art disclosed ***some*** method of analyzing cfDNA to raise a substantial question of validity about the ***specific*** method claimed in the '035 Patent.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00048

Ariosa and *CareDx* are also irrelevant for another reason: They concerned subject-matter eligibility under § 101, not obviousness under § 103. *See Ariosa*, 788 F.3d at 1377-78; *CareDx*, 40 F.4th at 1380. "[W]hether a claimed process is novel or non-obvious is irrelevant to the § 101 analysis." *In re Bilski*, 545 F.3d 943, 958 (Fed. Cir. 2008); *see also Intellectual Ventures I LLC v. Symantec Corp.*, 838 F.3d 1307, 1315 (Fed. Cir. 2016). Those cases did not consider the legal standards that govern motivation to combine or reasonable expectation of success under § 103.

NeoGenomics' post-priority-date references would not justify reversal even if they spoke to the relevant issue. "[T]he 'clearly erroneous' standard does not entitle this court to reverse the district court's finding simply because it would have decided the case differently." *Miles Labs.*, 997 F.2d at 874. The finding need only be a "plausible" choice among "permissible views of the evidence." *Id.* A finding thus is not "clearly erroneous" merely because it purportedly conflicts with a finding that a different court made in a different case involving a different record. *See* 9 James Wm. Moore, *Moore's Federal Practice* § 52.31[1] (3d ed. 2022) (findings not clearly erroneous merely because they "diverge from those made by another court"). The district court did not commit clear error by relying on the evidence it found most credible and probative, even if this Court or another court might have weighed different evidence in a different case differently.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00049

II. THE DISTRICT COURT CORRECTLY FOUND NO SUBSTANTIAL QUESTION REGARDING INFRINGEMENT

To obtain a preliminary injunction, a patentee need only show that "it will ***likely*** prove infringement of the asserted claims." *Metalcraft*, 848 F.3d at 1363-64 (emphasis added). "Infringement is a question of fact, which [this Court] review[s] on appeal for clear error." *Tinnus Enters., LLC v. Telebrands Corp.*, 846 F.3d 1190, 1203 (Fed. Cir. 2017). Overwhelming evidence showed that RaDaR infringes the '035 Patent—which is doubtless why NeoGenomics did not even make a non-infringement argument when moving for a stay pending appeal.

A. Ample Evidence Supports the District Court's Finding of Likely Infringement

The district court properly found that RaDaR likely infringes under the plain terms of the '035 Patent. "There is a ***heavy presumption*** that claim terms are to be given their ordinary and customary meaning." *Aventis Pharms. Inc. v. Amino Chems. Ltd.*, 715 F.3d 1363, 1373 (Fed. Cir. 2013) (emphasis added). "If the claim term has a plain and ordinary meaning, [the court's] inquiry ends." *Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 711 F.3d 1348, 1361 (Fed. Cir. 2013). Those principles are dispositive here.

Claim 1 of the '035 Patent recites three steps: (1) tagging cfDNA, (2) targeted amplification of 25-2,000 target SNPs associated with cancer in a single

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00050

reaction volume, and (3) massively parallel sequencing. Appx244(249:46-62). The parties dispute only whether RaDaR practices the first two steps. Br.29-31.

The district court correctly found that it does. ***First***, the court found that "RaDaR . . . tags the products with [an] adaptor sequence"—the first step. Appx6. ***Second***, the court found that RaDaR "performs targeted amplification"—the second step. *Id.* RaDaR thus "amplifies 'the tagged products one or more times to generate final amplification products, wherein one of the amplification steps comprises targeted amplification' "—precisely what the '035 Patent requires. Appx6-7.

Ample evidence supports those findings. Natera's expert Dr. Metzker explained that RaDaR includes an initial multi-cycle PCR process with ***15 separate amplification cycles***. Appx18903-04¶295; *see also* Appx7707 ("15 cycles of amplification"). During the "first cycle," he explained, RaDaR "tags cell-free DNA with universal tail adaptors." Appx18903-05¶¶295-297; *see also* Appx7594-95¶¶88-89. NeoGenomics' expert agreed that "[d]uring the first cycle a first tail adaptor is introduced." Appx12044¶101. The first cycle thus satisfies claim 1's first step of "tagging" cfDNA.

Natera's expert then explained that "[t]he subsequent cycles of PCR amplify the target region of interest, thereby performing targeted amplification of already tagged DNA." Appx18904-05¶297 (emphasis omitted); *see also* Appx7603-

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00051

04¶101; Appx12058-59¶131. Cycles 2 through 15 of the PCR thus satisfy claim 1's second step of "amplifying" the tagged cfDNA through targeted amplification.

NeoGenomics disputes none of that. Instead, it tries to avoid infringement by adding requirements found nowhere in the claim. According to NeoGenomics, RaDaR does not infringe because its "first" and "second" steps are both sub-steps within a single larger "step"—what NeoGenomics refers to as a "single PCR." Br.31. According to NeoGenomics, the '035 Patent requires that the first and second steps each involve "a ***distinct*** PCR with ***distinct*** primers from any used to perform the [prior] step." *Id.* (emphasis added). Nothing in claim 1 supports those additional limitations.

Claim 1 requires that DNA be "tagg[ed]" in one step and then "amplif[ied]" in one or more subsequent steps. Appx244(249:46-57). It does not require that each step involve its own separate PCR process with different primers, rather than being separate cycles of a PCR process. Appx244(249:44-62). NeoGenomics invents those additional limitations out of whole cloth.

Amgen Inc. v. Sandoz Inc., 923 F.3d 1023 (Fed. Cir. 2019), does not help NeoGenomics. The patent in *Amgen* recited a "method of purifying a protein" that involved separate steps of "washing the separation matrix" and "eluting the protein from the separation matrix." *Id.* at 1026. The accused process did not involve separate "washing" and "eluting" steps at all—instead, the plaintiff argued it was

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00052

sufficient that "washing precedes elution at any given point in the separation matrix; that is, washing may occur toward the bottom of the matrix at the same time that elution occurs toward the top." *Id.* at 1028. This Court disagreed, explaining that "the claim language logically requires that the process steps . . . be performed in sequence." *Id.*

That reasoning is inapposite here. Natera agrees that the '035 Patent requires multiple steps—a "tagging" step followed by one or more "amplification" steps. Appx244 (249:46-57). The accused process in *Amgen* had no meaningful "steps" ***at all***: The patentee was arguing infringement because, at any given point in time, somewhere in the accused process, "washing" was happening before "eluting." RaDaR, by contrast, tags DNA in a ***first*** cycle and then amplifies the tagged DNA in ***subsequent*** cycles of a larger PCR process with at least ***15 separate cycles***. Appx18903-05¶¶295-297; Appx7594-95¶¶88-89. *Amgen* may require "steps" of some sort, but it does not require that the steps be defined at some arbitrarily broad level of generality, like an entire multi-cycle PCR process rather than individual cycles within a single PCR.

In *Amgen*, moreover, "washing and eluting [we]re consistently described in the specification as separate steps performed by ***different solutions***." 923 F.3d at 1028 (emphasis added). There is no analogous claim language here. NeoGenomics argues that claim 1 implies that "tagging" must precede "amplifying" and

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00053

"amplifying" must precede "sequencing." Br.35-36. Natera agrees. But none of that claim language suggests the steps must occur in completely separate PCR processes with separate primers, rather than in separate amplification cycles of a PCR process. The claim says nothing about PCR at all. Appx244(249:46-62).

NeoGenomics' reliance on dependent claim 13 is similarly misplaced. Br.37. Claim 13 recites "tagging the cell free DNA" by "amplifying the cell free DNA with a first primer comprising the first universal tail adaptor and a second primer comprising the second universal tail adaptor." Appx245(251:10-13). That dependent claim merely illustrates that the tagging in claim 1's tagging step may be performed by its own amplification process, separate and apart from the amplification that occurs in the amplification step. That language does not imply anything about whether the steps in claim 1 may be performed in separate cycles of a larger PCR process. *See Littelfuse, Inc. v. Mersen USA EP Corp.*, 29 F.4th 1376, 1380 (Fed. Cir. 2022) ("By definition, an independent claim is broader than a claim that depends from it . . . .").

NeoGenomics' reliance on embodiments in the specification involving separate PCRs is even further afield. Br.38. This Court has "expressly rejected the contention that . . . the claims of the patent must be construed as being limited to

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00054

[an] embodiment." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005) (en banc). The district court committed no clear error in following that rule.[2]

B. The District Court Did Not Omit Any Required Claim Construction

Unable to overcome the unambiguous claim language, NeoGenomics asserts that the district court committed a procedural error by not engaging in explicit claim construction before holding that RaDaR likely infringes. Br.32-33. That argument is both forfeited and meritless.

1. "[A] party may not introduce new claim construction arguments on appeal or alter the scope of the claim construction positions it took below." *Conoco, Inc. v. Energy & Env't Int'l, L.C.*, 460 F.3d 1349, 1358-59 (Fed. Cir. 2006); *see also Broadcom Corp. v. Qualcomm Inc.*, 543 F.3d 683, 694 (Fed. Cir. 2008). NeoGenomics attempts to do precisely that. NeoGenomics' opposition to Natera's preliminary injunction motion never asked the district court to construe whether claim 1's tagging and amplifying steps must occur in ***separate PCRs with separate primers***, rather than ***different cycles of a single PCR***. Appx10475-508. In fact, NeoGenomics did not mention claim construction in its opposition brief ***at all***. *Id.* Nor did NeoGenomics' expert address that issue. Appx12001-184. Although his

[2] NeoGenomics also mischaracterizes the testimony of Natera's expert. Br.39. Natera's expert made clear that he was "relying on those [PCR] cycles that amplify the tagged products" for claim 1's amplification step. Appx12424(92:12-13). He never said the PCR cycles satisfy only the tagging step.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00055

declaration included a section called "claim construction," it concerned a different question over the meaning of the term "amplifying." Appx12025-26¶¶64-65 ("I construe the term 'amplifying' . . . to mean 'increasing the number [of] copies of a molecule, such as a molecule of DNA.'"). NeoGenomics' arguments on appeal have nothing to do with ***that*** proposed construction.

Nor did NeoGenomics raise this issue during the technology tutorial or preliminary injunction hearing. Appx19868-946; Appx20154-381. NeoGenomics mentioned only the separate dispute over construction of the term "amplifying"—a dispute irrelevant to the issues on appeal. Appx20289-90(136:4-137:23) (arguing that "the key claim construction issue" was "what that amplifying term means"). NeoGenomics never asked the district court for claim construction on the issue it presses now.[3]

The first time NeoGenomics raised this claim construction argument was in its motion for a stay pending appeal, ***after*** the district court had already granted the preliminary injunction. Appx20769-72. That was far too late. As the court observed, NeoGenomics' stay motion was "nothing more than an argument for reconsideration." Appx21323. "An argument made for the first time in a motion

[3] Even if NeoGenomics had mentioned the issue at the hearing, a party forfeits a claim construction argument by mentioning it for the first time at a hearing. *See MCM Portfolio LLC v. Hewlett-Packard Co.*, 812 F.3d 1284, 1294 n.3 (Fed. Cir. 2015); *Bos. Sci. SciMed, Inc. v. Iancu*, 811 F. App'x 618, 629 (Fed. Cir. 2020).

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00056

for reconsideration comes too late and is ordinarily deemed waived." *Golden Bridge Tech., Inc. v. Apple Inc.*, 758 F.3d 1362, 1369 (Fed. Cir. 2014); *see also Bluebonnet Sav. Bank, F.S.B. v. United States*, 466 F.3d 1349, 1361 (Fed. Cir. 2006).

2. In any event, the district court was not required to do more before rejecting NeoGenomics' non-infringement arguments. "[A] trial court has no obligation to interpret [claims] conclusively and finally during a preliminary injunction proceeding." *Sofamor Danek Grp., Inc. v. DePuy-Motech, Inc.*, 74 F.3d 1216, 1221 (Fed. Cir. 1996). Rather, the court "may exercise its discretion to interpret the claims at a time when the parties have presented a full picture of the claimed invention and prior art." *Id.*

NeoGenomics invokes this Court's unpublished decision in *Shuffle Master, Inc. v. VendingData Corp.*, 163 F. App'x 864 (Fed. Cir. 2005), to argue that "some form of claim construction" is required even on a preliminary injunction motion. Br.32. But *Shuffle Master* recognized that claim construction need not be "explicit" if an issue "is a simple one that needs no analysis, or in which there is no reasonable ground for dispute as to claim meaning." 163 F. App'x at 868 (citing *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1322 (Fed. Cir. 2004)); *see also Summit 6, LLC v. Samsung Elecs. Co.*, 802 F.3d 1283, 1291 (Fed. Cir. 2015) ("Because the plain and ordinary meaning of the disputed claim language is clear, the district court did not err by declining to construe the claim term.").

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00057

That describes this situation. This is not a case where the parties disputed the meaning of some genuinely ambiguous claim term. Rather, Natera argued below that RaDaR infringes under the plain meaning of the claim terms, and NeoGenomics now argues that this Court should reach a different result by importing additional unwritten limitations into the claims that it never mentioned below. The district court did not simply "assum[e] Natera's construction without explanation." Br. 32. It applied the claim according to its plain meaning. The court was not required to conduct a *Markman* hearing before doing so.

III. THE DISTRICT COURT DID NOT ABUSE ITS DISCRETION IN FINDING THAT NATERA WOULD SUFFER IRREPARABLE HARM

NeoGenomics contests a litany of factual findings on irreparable harm. Br.40-44, 46-49. But its arguments fall far short of the demanding standards that apply: clear error for factual findings, *see BlephEx*, 24 F.4th at 1405, and abuse of discretion for granting relief, *see Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1374 (Fed. Cir. 2006).

A. Natera's Threatened Loss of Market Share Supports the Finding of Irreparable Harm

The district court found that, absent injunctive relief, Natera could "lose out on partnerships that substantially impact Signatera's future success," Natera's "position as first mover will be unfairly cut short," and "lost sales from RaDaR are likely to occur." Appx14-17. Those are classic examples of irreparable harm. *See*

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00058

Bio-Rad Labs., Inc. v. 10X Genomics Inc., 967 F.3d 1353, 1378-80 (Fed. Cir. 2020) (loss of "first mover advantage" constitutes irreparable harm); *Douglas Dynamics, LLC v. Buyers Prods. Co.*, 717 F.3d 1336, 1344 (Fed. Cir. 2013) ("Irreparable injury encompasses . . . lost sales and erosion in reputation and brand distinction.").

NeoGenomics argues that Natera's dominant market position cuts against a finding of irreparable harm. Br.40-41. That is wrong. "[M]arket exclusivity" is an asset to which patentees are entitled. *See Douglas Dynamics*, 717 F.3d at 1345. Courts routinely find irreparable harm where a competitor's infringement threatens that exclusivity. *See id.* (harm of "being forced to compete against products that incorporate and infringe" is "often irreparable"). Courts are especially likely to find irreparable harm where the patentee has refused to license its invention. *See Presidio Components Inc. v. Am. Tech. Ceramics Corp.*, 702 F.3d 1351, 1363-64 (Fed. Cir. 2012) ("unwillingness to license" favors finding of irreparable harm). Natera has never licensed the '035 Patent. Appx7930¶16. The district court correctly found that RaDaR's continued sale would threaten Natera's hard-earned exclusivity and Natera would likely suffer irreparable harm as a result. Appx15.

NeoGenomics concedes that Natera will lose market share absent injunctive relief. Br.41. But it tries to downplay the extent of the loss, urging that Natera will lose "just 7%" and NeoGenomics will gain "only 2%." Br.41. That assertion is no basis for reversal. This Court has held that even smaller losses in market share are

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00059

sufficient to show irreparable harm. *See Douglas Dynamics*, 717 F.3d at 1345 (finding irreparable harm even though patentee's market share increased).

NeoGenomics, moreover, understates the threatened harm. NeoGenomics relies on a report issued ***before*** RaDaR's Medicare approval on July 27, 2023. Appx7308; Appx2442¶39. That approval threatened an explosive impact on RaDaR's growth because it greatly affected oncologists' willingness to order the product. Appx2937; Appx7930¶17. Medicare coverage would make RaDaR "widely accessible to millions." Appx2442¶39; Appx887. Moreover, the report NeoGenomics cites does not differentiate between tumor-informed and tumor-naïve tests. Appx7308; Appx7318; Appx7323. Stale data regarding a separate market does not render the district court's findings clearly erroneous.

NeoGenomics' cherry-picked statements from Natera's CEO say nothing about the harm Natera would suffer ***if*** RaDaR were allowed to exploit the market despite Natera's patents. Br.41. All but one were made ***before*** RaDaR's Medicare approval. Appx11536; Appx11545. The lone statement that post-dated RaDaR's Medicare approval (by a few weeks) merely recounted what Natera was seeing "in the field today." Appx11549. That RaDaR had not immediately dominated the market in the few weeks following its Medicare approval does not undermine the district court's finding that Natera faced a threat of irreparable harm.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00060

B. Natera Did Not Unreasonably Delay

NeoGenomics misguidedly accuses Natera of delay in seeking an injunction. Br.41-42. But Natera sought an injunction on July 31, 2023, just ***four days*** after NeoGenomics announced Medicare coverage that made RaDaR "widely accessible to millions." Appx2442¶39; Appx887. NeoGenomics omits that critical date from its timeline. Br.42. That spike in RaDaR's availability threatened serious additional harm. Appx2442¶39; Appx2504-05¶¶132-33. Indeed, the district court commented that, "if [Natera] came in . . . and said that Medicare might approve this, we need a preliminary injunction," the court "would have said come back later." Appx21346(15:12-14).

Even measured from the '035 Patent's issuance in December 2022, Natera sought a preliminary injunction within seven months. Appx33. Courts regularly hold that far longer delays do not preclude a finding of irreparable harm. *See, e.g.*, *Advanced Commc'ns Design, Inc. v. Premier Retail Networks, Inc.*, 46 F. App'x 964, 983-84 (Fed. Cir. 2002) (12-month delay); *Int'l Ass'n of Fire Fighters, Local 365 v. City of East Chicago*, 56 F.4th 437, 451 (7th Cir. 2022) (18-month delay); *Cuviello v. City of Vallejo*, 944 F.3d 816, 833-34 (9th Cir. 2019) (17-month delay).

In any event, while "delay" can be a relevant factor, a "showing of delay does not preclude, as a matter of law, a determination of irreparable harm." *Hybritech Inc. v. Abbott Labs.*, 849 F.2d 1146, 1457 (Fed. Cir. 1988). It is "but one

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00061

circumstance" to consider. *Id.* Here, the district court found Natera had "good reason" for not suing NeoGenomics sooner: It was embroiled in other infringement litigation. Appx17. Such circumstances can justify even "prolonged delay[s]." *Hybritech*, 849 F.2d at 1457.

NeoGenomics' suggestion that Natera delayed in ***applying*** for the '035 Patent is irrelevant. Br.42. This Court's precedents confirm that "delay" is measured from the date of the patent's ***issuance***—here, December 2022. *See, e.g.*, *Apple, Inc. v. Samsung Elecs. Co., Ltd.*, 678 F.3d 1314, 1325-26 (Fed. Cir. 2012) (measuring delay from date of patent's issuance). That makes sense: Natera could not have enforced its patent rights until the patent issued. NeoGenomics did not dispute below that delay should be measured from the date of issuance. Appx20315-17(162:21-164:7). It cannot contest the issue for the first time on appeal. *See Fresenius USA, Inc. v. Baxter Int'l, Inc.*, 582 F.3d 1288, 1296 (Fed. Cir. 2009).[4]

NeoGenomics asserts that, because of Natera's purported delay, the injunction now "change[s] . . . the status quo" by "remov[ing] . . . a product from the market." Br.42-43. NeoGenomics ignores that the district court carefully ***preserved*** the status quo by exempting from the injunction virtually all ongoing use of RaDaR, including

[4] NeoGenomics protests that Natera applied for the '035 Patent only after RaDaR launched for research use. Br.42. But "there is nothing improper, illegal or inequitable in filing a patent application for the purpose of obtaining a right to exclude a known competitor's product from the market." *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 874 (Fed. Cir. 1988).

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00062

all ongoing clinical studies, six studies about to begin, and tests of blood draws already taken. Appx23; Appx20911-17. The injunction merely prohibits ***NeoGenomics*** from disturbing the status quo by engaging in new, ***future*** infringing uses of Natera's patented technology, including substantial commercial uses made possible by its new Medicare coverage. The injunction ***preserves*** rather than disturbs the status quo. *See Atlas Powder Co. v. Ireco Chems.*, 773 F.2d 1230, 1232 (Fed. Cir. 1985) (preliminary injunction "preserves the status quo if it prevents future trespasses but does not undertake to assess the pecuniary or other consequences of past trespasses").

C. Natera's Evidence of Future Lost Sales Was Sufficient

NeoGenomics complains that "Natera could not show a single contract lost to NeoGenomics." Br.43. That statement is both irrelevant and wrong.

A patentee is not required to ***suffer*** lost sales before seeking a preliminary injunction to ***prevent*** lost sales. "The purpose of an injunction is to prevent ***future violations*** and, of course, it can be utilized even without a showing of past wrongs." *United States v. W.T. Grant Co.*, 345 U.S. 629, 633 (1953) (citation omitted) (emphasis added). This Court has approved injunctive relief, even without substantial lost sales, where the patentee demonstrated a risk of future harm. *See, e.g.*, *Trebro Mfg., Inc. v. Firefly Equip., LLC*, 748 F.3d 1159, 1170 (Fed. Cir. 2014).

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00063

The evidence showed precisely that threat here. RaDaR and Signatera are "direct competitors." Appx14. Natera's expert testified that RaDaR threatened to deprive Natera of market share, independent market analysts agreed, and the district court credited that evidence. Appx2500-05¶¶128-33; Appx7311. NeoGenomics' Medicare approval amplified that threat exponentially.

NeoGenomics' argument is also factually incorrect. Natera ***has*** lost business to RaDaR, as the district court found. Appx16. A Merck/Moderna study "used [RaDaR] instead of Signatera." Appx7933-34¶¶25-26. And AstraZeneca formerly used Signatera for clinical trials but switched to RaDaR. Appx10784(124:18-125:8). As the district court found, those partnerships are important: They provide clinical data validating a product's effectiveness, enabling "entry into the larger clinical marketplace." Appx15. Even if prior lost sales were required, the district court found past lost sales here.

D. NeoGenomics' Infringement Has a Sufficient Causal Nexus

The district court found ample evidence that Natera would suffer serious harm, especially in the distinct "tumor-informed testing" market. Appx14-17. NeoGenomics attacks the causal nexus between RaDaR's infringement and that harm, urging that the '035 Patent does not claim "tumor-informed testing." Br.44-45. But NeoGenomics forfeited that argument by not raising it below. And the district court's findings are sufficient regardless.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00064

1. In the district court, NeoGenomics devoted just ***three sentences*** to its causal nexus argument. Appx10503. And the argument it made differs from the one it presses now. Below, NeoGenomics argued only that "[t]here is insufficient nexus because RaDaR's sales are driven by the sensitivity that comes from RaDaR's 48 tumor-specific variants, and advanced bioinformatics, not Natera's patents." Appx10503. That is the argument the district court addressed. Appx17.

On appeal, NeoGenomics makes a different argument: that the district court erred because it focused on the harm to Natera in the "tumor informed MRD market" even though "tumor-informed testing is not a patented feature of the '035 patent." Br.44-45. That is different from NeoGenomics's argument below, which did not even mention the '035 Patent. Appx10503-04.

A party forfeits an argument for appeal where it "fails to raise [the] argument before the trial court, or presents only a skeletal or undeveloped argument." *Fresenius*, 582 F.3d at 1296. Moreover, an objection on a different ground below "does not preserve all possible challenges to [the] finding." *Id.* at 1296; *see also Sage Prods., Inc. v. Devon Indus., Inc.*, 126 F.3d 1420, 1426 (Fed. Cir. 1997). By failing to make its current causal nexus argument below, or indeed any meaningful causal nexus argument at all, NeoGenomics forfeited the argument.

2. In any case, the district court's findings are sufficient. This Court requires only "a showing of ***some*** causal nexus between [the] infringement and the

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00065

alleged harm." *Apple*, 678 F.3d at 1324 (emphasis added). The patented feature need not "be the ***only*** basis of consumer demand." *TEK Glob., S.R.L. v. Sealant Sys. Int'l, Inc.*, 920 F.3d 777, 792 (Fed. Cir. 2019) (emphasis added).

Properly applying those standards, the district court found a "causal nexus between the likely infringement and harm" because the "infringement allows NeoGenomics to offer RaDaR as a tumor informed MRD assay." Appx17-18. The court thus specifically found that the patented features ***enabled*** RaDaR to compete with Signatera in the tumor-informed testing market. Appx17. Far from "confirm[ing] that any likely harm . . . would be caused by unclaimed features," Br.45, the court merely found harm in a specific market. RaDaR and Signatera are both tumor-informed products. But the relevant point is that NeoGenomics ***could not have offered*** RaDaR's MRD assay at all without infringing—whether its infringing product was tumor-informed or tumor-naïve—because the '035 Patent still would have covered RaDaR's workflow. Appx10836-37(98:18-104:25); *see Mylan*, 857 F.3d at 872-73 (affirming causal nexus where infringing product "would not be on the market if [infringer] had not obtained [FDA] approval for a product that will likely be found to be covered by the patents").

This Court has found a sufficient causal nexus in similar cases. In *Apple Inc. v. Samsung Electronics Co.*, 809 F.3d 633 (Fed. Cir. 2015), for example, a jury found that Samsung had infringed Apple's patents covering critical iPhone features. 809

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00066

F.3d at 637-38. The district court found no causal nexus because "Apple did not show that the infringing features 'drive consumer demand for Samsung's infringing products.'" *Id.* at 639, 641. This Court disagreed. *Id.* at 647. To prove a causal nexus, it held, a patentee need not rule out other "available features" as driving consumer demand. *Id.* at 641. All Apple had to show was that "the patented features impact consumers' decisions to purchase the accused devices." *Id.* at 642. This Court has repeatedly reaffirmed that principle. *See, e.g.*, *TEK Glob.*, 920 F.3d at 792 ("It was enough for TEK to show that a significant reason consumers bought its device was the presence of the patented features.").

The record here showed a similar causal relationship between infringement and harm. As Natera's expert testified, the patented method is central to RaDaR's workflow—RaDaR cannot be used without infringing. Appx7590-612¶¶85-114; Appx2458-59¶66; Appx17. NeoGenomics advertised to potential customers, including Natera's customers, that RaDaR was an alternative to Signatera. Appx2510-12¶143. That marketing and actual use as an alternative test were wholly dependent on RaDaR's infringement. NeoGenomics' claims about RaDaR's allegedly higher sensitivity are beside the point—RaDaR would not function ***at all*** without infringing the '035 Patent's claims. The court was well within its discretion to find that NeoGenomics' infringement enabled RaDaR to compete with Signatera and was significant in driving demand.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00067

E. The District Court Did Not Misapply This Court's Precedents Regarding Two-Party Markets

Nor did the district court "misread this Court's precedent[s]" by improperly "presuming irreparable harm for alleged two-competitor markets." Br.45. Far from imposing a "universal rule" that infringement in two-player markets automatically creates irreparable harm, Br.45-46, the court stated only that "'the existence of a two-player market' ***supports*** the granting of an injunction." Appx16 (quoting *Robert Bosch LLC v. Pylon Mfg. Corp.*, 659 F.3d 1142, 1151 (Fed. Cir. 2011)) (emphasis added). The court considered other factors too. Appx16-17.

When denying a stay pending appeal, the district court confirmed that it never applied the categorical rule NeoGenomics attributes to it. Appx21324. The court explained it had considered numerous factors, including "the potential for lost customers, profits, business relationships, and clinical opportunities, as well as lost biopharmaceutical partnerships." Appx21324 (citing Appx15-17). NeoGenomics acknowledges that "[d]irect competition in the same market is certainly ***one factor suggesting strongly*** the potential for irreparable harm." Br.46 (quoting *Presidio*, 702 F.3d at 1363) (emphasis altered). That is how the district court treated the factor—as one among many. Appx16-17.

NeoGenomics disputes the district court's finding that the tumor-informed market is in fact "two-player." Br.47. But it nowhere shows that factual determination was clearly erroneous. NeoGenomics' ***own expert*** testified that the

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00068

market was two-player: Apart from "minor players," he explained, Natera holds "above 90%" market share and NeoGenomics the "residual." Appx19518(60:1-19). NeoGenomics' sources do not show otherwise. The investment bank report it cites conflates tumor-informed test providers with tumor-naïve test providers like Guardant. Appx7332; Appx4. And NeoGenomics' reliance on Invitae defies reality. Invitae was enjoined from selling its tumor-informed product and has attested that it has complied with that injunction. Appx4 n.3; *Natera, Inc. v. ArcherDX, Inc.*, Case No. 1:20-cv-00125-GBW, Doc. 685 (D. Del. Jan. 5, 2024). While Invitae claims to have developed a design-around product, it recently filed for bankruptcy. *See In re Invitae Corp.*, No. 24-11362 (Bankr. D.N.J. Feb. 13, 2024).

The district court was not required to accept NeoGenomics' assertion that "Natera and NeoGenomics compete for different customers." Br.47. The evidence showed that NeoGenomics was "promoting RaDaR to Natera's customers." Appx16. Multiple customers switched from Signatera to RaDaR. Appx7933-34¶¶25-26; Appx10784(124:18-125:8).

F. Natera's Bond Does Not Foreclose Irreparable Harm

Finally, NeoGenomics asserts—without authority—that "Natera's requested bond amount contradicts any alleged irreparable harm." Br.48. That bond, however, is designed to "protect NeoGenomics during the preliminary injunction," not to measure the harm ***to Natera*** from NeoGenomics' infringement. Br.48-49. The bond

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00069

amount sheds no light on Natera's harm and whether it can be redressed by damages. Moreover, Rule 65(c) ***requires*** a party to post security to obtain a preliminary injunction. Fed. R. Civ. P. 65(c). Compliance with that requirement is not a concession that damages are adequate.

IV. THE DISTRICT COURT DID NOT ABUSE ITS DISCRETION IN ADDRESSING THE REMAINING INJUNCTION FACTORS

The district court also reasonably found that the public interest and balance of equities favor an injunction.

A. The Public Interest Favors an Injunction

This Court has "long acknowledged the importance of the patent system in encouraging innovation." *Sanofi-Synthelabo*, 470 F.3d at 1383. NeoGenomics admits that "there exists a public interest in protecting rights secured by valid patents." Br.49 (quoting *Hybritech*, 849 F.2d at 1458). NeoGenomics asserts, however, that the district court "lost sight" of patient interests. Br.49. But the district court kept those countervailing interests squarely in view. The court carefully tailored its injunction to protect the very interests NeoGenomics identifies. Appx19-21; Appx22-23; Appx20915-17. And it found that any residual impact did not outweigh protecting patent rights in these circumstances. Appx19-21.

NeoGenomics' attacks on the district court's factual findings ignore the demanding clear error standard that applies. *See Apple*, 809 F.3d at 639. For example, NeoGenomics disputes the court's finding that "patients 'in need of a

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00070

tumor informed MRD test will be able to get one from Natera.'" Br.51. But the court cited evidence more than sufficient to support that finding. Appx20. It saw no "satisfactory evidence that [RaDaR] is available for cancers for which Natera's product is not." Appx21326. Moreover, evidence showed that Signatera is the most clinically validated test on the market, with over 40 peer-reviewed publications confirming that it identifies MRD significantly earlier than standard diagnostic tools. Appx2471-72¶79; Appx2502-04¶131. And Signatera is the MRD test preferred by a majority of oncologists. Appx16159.

While NeoGenomics asserts that it is "being ***considered*** for Medicare coverage for cancers . . . for which Natera has not even applied," those pending ***applications*** are not approvals. Br.51 (emphasis added). NeoGenomics is well aware of the distinction, given that Medicare has previously rejected RaDaR for coverage. *See, e.g.*, Appx930; Appx2910.[5]

NeoGenomics argues that "the record one-sidedly shows no current cancer test can substitute for RaDaR" because of RaDaR's "high sensitivity." Br.49-51. The district court found the opposite: "[I]t is not at all clear" that "RaDaR has a higher sensitivity than Natera's product." Appx21325-26. NeoGenomics' only

[5] Meanwhile, Signatera continues to receive Medicare approvals, making it available to even more patients. *See* Press Release, *Medicare Extends Coverage of Natera's Signatera™ MRD Test to Ovarian Cancer and Neoadjuvant Breast Cancer* (Feb. 26, 2024), https://bit.ly/48u6Eor.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00071

support for its assertion of "high sensitivity" are affidavits from a single NeoGenomics executive. Br.49-51 (citing Appx11279-89¶¶29-47; Appx20805-07¶¶3-5). The affidavits repeatedly ***assert*** that RaDaR is more sensitive without any proof. *See, e.g.*, Appx11280-83¶¶31-33. Most of the cited portions concern problems with switching from RaDaR to Signatera partway through an ongoing clinical study (Appx11281-83¶¶31-34)—concerns rendered irrelevant by the district court's exclusion of ongoing studies from the injunction. Appx23; Appx20911-17.[6]

As Natera's expert explained, there are ***no*** "head-to-head studies comparing the sensitivity and specificity of RaDaR™ against another MRD test" like Signatera. Appx7565¶47; *see* Appx7294 (analyst report confirming that, "[t]o date, no study has compared any commercial tests head to head"). Nor is there any other "evidence that [RaDaR's] claimed analytical sensitivity is validated or supported by clinical data." Appx7565¶47; s*ee also* Appx2512¶¶144-145. NeoGenomics' assertions rest on "a small analytical study using contrived cell line mixtures," not "real clinical samples," and they are "not supported by subsequent evidence" from blinded

[6] NeoGenomics' other sources provide no better support. The TD Cowen report is an ***investment bank's*** analysis that asserts—with no scientific or other support—that RaDaR has a "sensitivity profile that ***can*** offer advantages over existing players." Appx7311 (emphasis added). A lone oncologist's two-page letter touts RaDaR's sensitivity but identifies no support. Appx11860-61. And the "key opinion leader" presentation concludes that RaDaR's sensitivity is "imperfect." Appx11683; Appx11685; Appx11692.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00072

analytical studies or other clinical studies. Appx7932¶22. And although there are no head-to-head studies, other evidence shows that Signatera is just as sensitive as RaDaR. Appx7932¶22. Besides, sensitivity is just one factor oncologists consider in deciding what test to use. *See* Appx7349 (listing seven other factors); Appx7932-33¶23. The district court was not required to credit NeoGenomics' contrary assertions.

The district court also carefully tailored the injunction to mitigate any remaining risk of harm. The injunction excludes "clinical trials and research projects already in process as well as treatment for patients already using RaDaR." Appx21325; Appx22-25. The court also allowed six additional clinical trials that had been "substantively finalized" but were not yet underway. Appx30-31; Appx20946. It was sensitive to the public interest and accommodated the very concerns that NeoGenomics raised. The court permissibly found that the public interest in protecting intellectual property rights was paramount.

B. The Equities Favor an Injunction

NeoGenomics urges that the district court "discount[ed] the significant harm the injunction is inflicting on NeoGenomics." Br.52. But the court carefully considered the hardships to each party and concluded that "[t]he harm to Natera if a preliminary injunction is not granted outweighs the harm to NeoGenomics in granting the injunction." Appx18-19. That was not an abuse of discretion.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00073

This Court regularly considers the "parties' sizes, products, and revenue sources" when balancing hardships. *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 862 (Fed. Cir. 2010), *aff'd*, 564 U.S. 91 (2011). That is what the district court did. The court recognized that Signatera, Natera's "most valuable offering," is expected to drive 52.1% of Natera's revenue growth, making it a "major contributor to Natera's future success." Appx18-19. RaDaR, by contrast, is "not a major product in NeoGenomics' portfolio," representing just one of 600 cancer-detection products. Appx19. NeoGenomics, moreover, is not projected to make material revenue from MRD testing until 2025. Appx20854-55. NeoGenomics does not explain why its interests outweigh Natera's interest in protecting its most valuable product.

NeoGenomics complains that the district court should have considered its "substantial investment to acquire RaDaR." Br.52. Not so: "[E]xpenses incurred in creating the infringing product[ ]" are irrelevant. *Bio-Rad Labs.*, 967 F.3d at 1378. And Natera also invested heavily. Appx7927¶11. NeoGenomics invokes its "years of research." Br.52. That is just another way of touting NeoGenomics' investment in an infringing product. Natera, the first mover, invested extraordinary time and resources in developing the patented method and overcoming skepticism of the technology—efforts on which NeoGenomics now seeks to free-ride. Appx7925-

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00074

7930¶¶5-18; Appx22-25; Appx21325. No infringer has a legitimate interest in commercializing someone else's invention.

NeoGenomics urges that its "tiny market foothold" may be unrecoverable. Br.52. But the injunction already preserves that foothold. Regardless, an "alleged infringer's loss of market share and customer relationships, without more, does not . . . overcome the loss of exclusivity experienced by a patent owner due to infringing conduct." *Pfizer, Inc. v. Teva Pharms., USA, Inc.*, 429 F.3d 1364, 1382 (Fed. Cir. 2005). And if NeoGenomics' assertions of RaDaR's superiority were true—they are not—then RaDaR should have no difficulty penetrating the market if NeoGenomics ultimately prevails. Regardless, the $10 million bond Natera posted—a year's worth of NeoGenomics' revenue from its MRD-testing business—greatly mitigates any potential harm. Appx22-23; Appx20916; Appx21323-26.

V. THE COURT DID NOT ABUSE ITS DISCRETION WITH RESPECT TO THE SCOPE OF THE INJUNCTION

NeoGenomics challenges the injunction's scope, urging that the district court should not have prohibited it from "making" or "selling" RaDaR in the United States except when that product is "used" in the United States. Br.53-56. That argument is forfeited and meritless.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00075

A. NeoGenomics Forfeited Any Complaint About the Preliminary Injunction's Scope

NeoGenomics forfeited its challenge to the injunction's scope by not timely raising the objection in the district court. This Court will "decline[ ] to review [an] argument that the scope of the preliminary injunction is overbroad" where a party "did not raise th[e] objection before the district court." *Celsis In Vitro*, 664 F.3d at 932; *see also O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co.*, 449 F. App'x 923, 934 (Fed. Cir. 2011) (party "waive[s] its right to appeal" injunction's scope if it "failed to raise before the district court any of [its] overbreadth and extraterritorial[ity] arguments"); *Philip Morris, Inc. v. Harshbarger*, 159 F.3d 670, 680 (1st Cir. 1998) ("As a general rule, a disappointed litigant cannot surface an objection to a preliminary injunction for the first time in an appellate venue."). NeoGenomics did not timely preserve its objection here.

Three days after filing this case in July 2023, Natera sought an injunction, proposing the same language NeoGenomics is now complaining about. *See* Appx891-92 (seeking an injunction against "making, using, selling, offering for sale in the United States" RaDaR or any similar product). NeoGenomics never once complained about that language over many months of litigation. In December 2023, the district court entered an injunction with that exact same language. Appx22-23.

After the court entered that injunction, NeoGenomics moved to modify the injunction to remove the language. Appx20783-85; Appx20794-96. But as the

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00076

district court observed when denying that motion, "NeoGenomics had months to review Natera's proposed preliminary injunction order, . . . yet NeoGenomics did not raise a murmur of opposition to or concern about the language it now challenges." Appx21329. NeoGenomics' failure to timely assert its objection in the district court forecloses review here.

NeoGenomics asserts that it was not required to make its objection sooner because, while Natera's "cover motion . . . mouthed a broad request," the legal memorandum did not elaborate on it. Br.53. That argument misses the point. If the proposed injunction sought unwarranted relief the legal memorandum did not support, that should have been ***all the more reason*** to object. NeoGenomics said nothing to alert the district court to any concern. The language NeoGenomics now challenges was not tucked away somewhere inconspicuous; it was on the face of the three-page proposed injunction that Natera submitted (as well as the two-page cover motion). Appx891-93; Appx887-88. NeoGenomics has no excuse for not timely objecting.

NeoGenomics cannot avoid the consequences of its neglect by moving to modify the injunction after the fact. *See Carborundum Co. v. Molten Metal Equip. Innovations, Inc.*, 72 F.3d 872, 882 (Fed. Cir. 1995) (affirming denial of infringer's motion to modify injunction because infringer "fail[ed] to object to the scope of the permanent injunction [during] the trial"); *Favia v. Ind. Univ. of Pa.*, 7 F.3d 332, 338

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00077

(3d Cir. 1993) ("A motion to modify a preliminary injunction is meant only to relieve inequities that arise after the original order."). In any event, the district court's well-reasoned denial of NeoGenomics' motion to modify is not before this Court, having been issued after this appeal was underway. Appx21329. The only decision before the Court is the original preliminary injunction order, issued when NeoGenomics had not said a word about its current complaints.

B. The District Court Did Not Abuse Its Discretion

The district court did not abuse its discretion regardless. "[D]istrict courts are in the best position to fashion an injunction tailored to prevent or remedy infringement." *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1339 (Fed. Cir. 2013). Although this Court has "discouraged judicial restraint of noninfringing activities," it has "never barred it outright and instead ha[s] repeatedly stated that district courts are in the best position to fashion an injunction tailored to prevent or remedy infringement." *TiVo Inc. v. EchoStar Corp.*, 646 F.3d 869, 890 n.9 (Fed. Cir. 2011) (en banc). Consistent with those principles, this Court has upheld injunctions against "making" or "selling" articles to prevent infringing "use" of a patented method.

In *BlephEx, LLC v. Myco Industries, Inc.*, 24 F.4th 1391 (Fed. Cir. 2022), for example, the patent claimed a method for treating an eye disorder. *Id.* at 1394-95. After a competitor marketed a product for treating the disorder, the patentee sued.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00078

Id. at 1395. The district court enjoined the infringer from "selling, distributing, or offering to sell or distribute" the product. *Id.* The accused infringer challenged the injunction, arguing that it went beyond infringing ***use*** by prohibiting "all domestic ***sales***." *Id.* at 1405 (emphasis added). This Court rejected that argument, finding no abuse of discretion in "bar[ring] all domestic sales" because the injunction was "necessary to avoid future infringement." *Id.* at 1406; *see also Hilgraeve Corp. v. Symantec Corp*., 265 F.3d 1336, 1343 (Fed. Cir. 2001) ("sale of a device may induce infringement").

This case is no different. The record shows that RaDaR ***cannot function*** without practicing the patented method. Appx7590-612¶¶85-114; Appx6-7. NeoGenomics alludes to hypothetical non-infringing uses, such as performing the allegedly infringing steps overseas. Br.53. But, as the district court found when denying the motion to modify the injunction, there is no evidence that anyone ***actually uses*** RaDaR in that, or any other, non-infringing manner. Appx21328-29. NeoGenomics made "no showing that when it uses RaDaR any of the steps in the '035 patent method are performed abroad." Appx21329. And "NeoGenomics never presented an argument during the preliminary injunction proceedings that it was not infringing the '035 method because it performed steps overseas, an argument it made repeatedly as to the '454 patent." Appx21329.

Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00079

The district court was not required to tailor its preliminary injunction to accommodate these hypothetical non-infringing uses. The court did not abuse its discretion in entering the injunction Natera proposed.

CONCLUSION

This Court should affirm the district court's preliminary injunction.

March 11, 2024

Respectfully submitted,

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Natera, Inc. Exhibit 2064
NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00080

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NeoGenomics Lab'ys, Inc. v. Natera, Inc.
IPR2025-00455
Page 00081

FORM 19. Certificate of Compliance with Type-Volume Limitations **Form 19**
July 2020

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATIONS

Case Number: 24-1324, 24-1409

Short Case Caption: Natera, Inc. v. NeoGenomics Laboratories, Inc.

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