Nos. 24-1324, 24-1409

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

NATERA, INC.,

Plaintiff-Appellee,

v.

NEOGENOMICS LABORATORIES, INC.,

Defendant-Appellant.

Appeals from the United States District Court for the Middle District of North Carolina, No. 1:23-cv-00629; Hon. Catherine C. Eagles

NEOGENOMICS LABORATORIES, INC.'S REPLY BRIEF

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MARCH 18, 2024

CERTIFICATE OF INTEREST

Counsel for NeoGenomics Laboratories, Inc. certify under Federal Circuit Rule 47.4 that the following information is accurate and complete to the best of their knowledge:

1. **Represented Entities.** Provide the full names of all entities represented by undersigned counsel in this case.

NeoGenomics Laboratories, Inc.

2. **Real Parties in Interest.** 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.

3. **Parent Corporations and Stockholders.** 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.

NeoGenomics, Inc.

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.

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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)? If yes, concurrently file a separate Notice of Related Case Information that complies with Fed. Cir. R. 47.5(b).

Yes, see separately filed notice.

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).

Not applicable.

Dated: March 18, 2024

/s/ Deanne E. Maynard
Deanne E. Maynard

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INTRODUCTION

Before adjudication on the merits, the district court barred all future uses of an independently inventive cancer-detection test that has been available for years. That is no small thing. Unlike Natera's cited cases, this one is not about riding lawnmowers, snow-plow assemblies, or eye-cleaning devices. Given the stakes here—especially for cancer patients and researchers—the law demanded a compelling showing. Natera's response confirms it never made one.

The invalidity threat alone should have been enough. Natera has no real answer for its own and its experts' past admissions. Those admissions show that all three of the basic DNA-processing steps Natera claimed, with their claimed "specificity," were well known and routinely applied to cell-free DNA. Natera now hangs its hat on the purported breakthrough of multiplex amplification in a "single-reaction volume," but its own patent admits that too was known. Regardless, Natera identifies nothing in its claims that improved on prior-art multiplex amplification.

Natera cannot overcome other similar obstacles. It purports to apply the ordinary claim meaning on infringement but adopts an extraordinary construction collapsing distinct process steps into one. It argues for nexus on harm by pointing to tumor-informed testing (which is undisputedly unclaimed) and without rebutting that RaDaR achieves a highly sensitive tumor-informed assay based on NeoGenomics' proprietary technology (not any alleged infringement). Natera

argues the public will not be harmed because the injunction allows virtually all existing uses, but that ignores that RaDaR will be unavailable for future patients and research projects that would benefit from its unique features.

The injunction cannot stand.

ARGUMENT

THE INJUNCTION CANNOT STAND IN THE FACE OF MULTIPLE ERRORS

A. The District Court Applied The Wrong Legal Standard On Obviousness And Made Unsupported Findings

1. A wealth of evidence, including Natera's and its expert's admissions, creates a substantial question on obviousness

The evidence of obviousness here is far more than needed to establish "[v]ulnerability." *Amazon.com v. Barnesandnoble.com*, 239 F.3d 1343, 1358-59 (Fed. Cir. 2001). The district court never disagreed that NeoGenomics' primary reference Kaper, combined with knowledge in the field, discloses every claim limitation. Appx9-10. It hinged its decision solely on motivation to combine with reasonably expected success. Appx9-10.

But the evidence of motivation to apply Kaper's teachings about DNA-processing steps to cell-free DNA with reasonably expected success was compelling, showing that the same basic DNA-processing steps claimed in the '035 patent had long been applied to cell-free DNA with predictable benefits, including for cancer testing (for more, *see* Neo.Br.21-24; Neo.Stay.Reply.4):

- In *CareDx*, Natera admitted techniques just like Kaper's and those claimed here—including adding "tags," "performing a selective amplification of SNPs," and "sequencing"—were routinely and conventionally applied to "tumor cfDNA in a cancer patient's blood" by at least 2009. Appx12591, Appx12598-12606; Appx12995-12997; Neo.Br.23-24.

- Natera's *CareDx* expert admitted that "by 2009, PCR was also being widely used to measure SNPs in cell-free DNA" and "was routinely used to target and amplify specific, pre-selected genes for further study." Appx13415-13418 ("selectively amplifying at least 1,000 SNPs" was routine), Appx13450 (routine for "cfDNA from any" source).

- In *Illumina*, Natera's expert (its expert here) described how a 2010 Fluidigm patent application discloses that "target-specific primers for 9216 different target nucleic acids can be employed in one mixture" for PCR amplification of "cell-free DNA." Appx13014-13015, Appx13014-13019 ("96 different primer pairs in each aliquot"); Appx13097(¶119) (Fluidigm). Such use of PCR, Natera's expert admitted, "was well-understood and predictable" at least by "2010." Appx12974, Appx13023-13024; Appx12423(87:11-88:6).

- The Fluidigm application describes methods using a "matrix-type microfluidic device" for tagging and amplifying DNA to be sequenced. Appx13098(¶¶130-31). That DNA can come "from any source," including cell-free DNA in "blood." Appx13097(¶122). Fluidigm is the same company behind Kaper, which also discloses a matrix-type microfluidic device. Appx13110; Appx13113.

As seen, this evidence includes what Natera now asserts is the magic ingredient to its claims: amplifying multiple cell-free-DNA targets in a "'single reaction volume,'" i.e., multiplex amplification (Natera.Br.6). Appx13014-13019. And as NeoGenomics explained, but Natera never addresses, the '035 patent itself acknowledges multiplex amplification was known: "the general belief in the art

[wa]s that multiplexing PCR" was already feasible up "to about 100 assays in the same well." Appx163(col.48:25-29), Appx162-163(col.85:14-16,col.87:29-57); Neo.Br.25-26. The patent purports to address only a need for "more than 100," "500," "5,000" or more targets. Appx163(col.87:29-57). Yet Natera claimed amplifying as few as "25" "in a single reaction volume." Appx244(col.249:44-62).

The record also disproves Natera's assertion that single-volume multiplex amplification and "split-and-pool" amplification are mutually exclusive options and that Kaper "*taught away*" from a single-volume approach. Natera.Br.4-5,30-31. Both the '035 patent and Kaper describe both approaches, and using them together. The patent describes selecting primers and "divid[ing] them into different pools"; "[e]ach pool can be used to simultaneously amplify a large number of target loci (or a subset of target loci) in a single reaction volume." Appx126(col.13:6-15). That is just like Kaper's approach: dividing primer pairs into pools for targeted multiplex amplification of "10 pairs each" per reaction volume. Appx12092. Natera itself previously admitted (though now omits) that Kaper teaches "amplifying only up to 10 loci in each reaction volume." Natera.Stay.Opp.14.

In addition to these facts (most of which Natera concedes), Natera is noticeably silent about the clear objective evidence of obviousness: mere months after the alleged priority date and before Natera's application became public, Dr. Timothy Forshew submitted his own publication describing successfully using

Kaper's Access Array with cell-free DNA without modification. Appx7693, Appx7702, Appx7706-7710; Neo.Br.16, Neo.Stay.Reply.4. Dr. Forshew cofounded Inivata (now a NeoGenomics subsidiary) and is a current NeoGenomics scientist. Appx20332. That publication, Forshew 2012, was the district court's basis for infringement likelihood-of-success. Appx6. Such "independent" development "within a comparatively short space of time" is "persuasive evidence" of obviousness and speaks to what skilled artisans were in fact motivated to do, and succeeded in doing, at that time. *Concrete Appliances v. Gomery*, 269 U.S. 177, 184-85 (1925).

2. Natera cannot excuse away legal errors

The district court pushed past all this evidence and held the claims not vulnerable on obviousness by misapplying legal standards. Neo.Br.24-27. Natera responds by knocking down straw-man arguments NeoGenomics never made, such as whether "vulnerability" and "substantial question" of invalidity are "interchangeabl[e]" standards (they are) or whether motivation and reasonable expectation are "irrelevant" at the preliminary-injunction stage (they may be relevant). Natera.Br.23-24.

NeoGenomics' point is that the district court legally erred in two ways. First, it demanded more than a substantial question of invalidity. On this record, that is legal error, not factual. *Contra* Natera.Br.25. Even taking all the facts as the district

court found them, Natera still failed to prove NeoGenomics' obviousness defense lacks substantial merit. *Amazon.com*, 239 F.3d at 1358-60; *Nat'l Steel Car v. Canadian Pac. Ry.*, 357 F.3d 1319, 1334-35 (Fed. Cir. 2004) (patentee's burden).

Second, the district court legally erred by treating as dispositive supposed "obstacles to successfully amplifying and sequencing ctDNA *with precision*." Appx9-10 (emphasis added). The claims undisputedly require no level of precision (Natera.Br.26-28)—making the district court's "failure to consider" their "appropriate scope" "legal error." *Allergan v. Apotex*, 754 F.3d 952, 966 (Fed. Cir. 2014). Natera scoffs at this error as merely "two words," saying the district court "simply mentioned an additional factor." Natera.Br.26-28. Yet those "two words" were the linchpin of the district court's obviousness reasoning and there was no other basis for its conclusion:

> NeoGenomics contends that it would have been obvious to modify Access Array for cfDNA because cfDNA was known at this time to be useful for cancer detection. But there were many well-known barriers to using cfDNA. These challenges associated with cfDNA, and others, presented obstacles to successfully amplifying and sequencing ctDNA *with precision* during the relevant time period, making 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. NeoGenomics' assertions about Access Array appear to show hindsight bias more than they support a substantial question of obviousness.

Appx9-10 (emphasis added; citations omitted). The district court never found, contrary to Natera's suggestion, that "Access Array was understood to be too imprecise to work with cfDNA." Natera.Br.26-27.

Quite the opposite, the district court's rationale suggests Access Array *would* work with cell-free DNA, just without (in the court's view) an unspecified level of precision. Appx9-10. Even Natera alleges only that processing cell-free DNA could be "more difficult" or "unreliable"—yet never identifies anything in its claims overcoming those supposed challenges. Natera.Br.1-6. At the least, the district court made no finding that a skilled artisan would not have expected Kaper's teachings to work with cell-free DNA; instead, it demanded more than the claims require. Appx10; *Allergan*, 754 F.3d at 966.

Natera ultimately concedes that departing from the claims' scope is legal error for "reasonable expectation of success" but argues motivation is different. Natera.Br.27-28 (citing, e.g., *Auris Health v. Intuitive Surgical*, 32 F.4th 1154 (Fed. Cir. 2022); *Intelligent Bio-Sys. v. Illumina Cambridge*, 821 F.3d 1359 (Fed. Cir. 2016)). That concession is fatal for two reasons. First, on its face, the district court's "with precision" rationale addresses only reasonable expectation of success: whether artisans would have expected to "successfully amplify[] and sequenc[e] ctDNA with precision." Appx10. Natera's arguments confirm expected success is the disputed issue here. After all, the "advantages of using cfDNA" (including from

tumors) with the known tagging, amplifying, and sequencing steps claimed here are undisputed, which is why Natera itself focuses on purported "obstacles" to success. Natera.Br.1-5,25. The district court's rationale was thus legal error even under Natera's understanding of the law. Natera.Br.27-28.

Second, even if the "with precision" rationale addresses motivation, the same legal rule governs: the "inquiry is 'whether a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve *the claimed invention*.'" *Axonics v. Medtronic*, 73 F.4th 950, 957 (Fed. Cir. 2023) (Court's emphasis). *Axonics* rejected a no-motivation finding based on "a legally incorrect framing" that departed from the "claims' actual limitations." *Id.* at 957-58.

Although NeoGenomics cited *Axonics* for this point, Natera has no response. Neo.Br.26-27; Natera.Br.26-28. None of Natera's cited decisions even hinted at a rule requiring challengers to show a motivation to achieve something more than the claimed invention, which would contradict plain statutory text focusing on "differences between the claimed invention and the prior art." 35 U.S.C. § 103. *Auris* rejected an argument like Natera's, holding that "generic industry skepticism cannot, standing alone, preclude a finding of motivation"; it "held" nothing about "precision" (*contra* Natera.Br.26), merely mentioning an argument not before the Court. 32 F.4th at 1159. And *Illumina* expressly applied the same rule as *Axonics*; it mentioned improving "*efficiency, reliability, and robustness*" not to distinguish

the claims and prior art but because they were the challenger's "*sole* argument" on motivation. 821 F.3d at 1367-68 (Court's emphasis).

Here, the rationale for applying Kaper to cell-free DNA was not based on improving precision, cost, or any of the other factors Natera mentions. Rather, NeoGenomics identified an age-old motivation: "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR Int'l v. Teleflex*, 550 U.S. 398, 417 (2007). As NeoGenomics' expert detailed when addressing motivation—and he did address motivation (*contra* Natera.Br.12-13)—"a skilled artisan would have been well-aware" of the benefits of tagging, amplifying, and sequencing cell-free DNA, "particularly in the cancer detection context," the very same context as Kaper. Appx12095-12097 (would "yield[] predictable results"). The district court legally erred in requiring more.

3. Natera cannot paper over clear factual errors

Natera also cannot overcome clear factual errors. It hides behind the clear-error standard as if this appeal follows a merits trial, arguing the record at least "plausibl[y]" supports "findings of no motivation to combine and no reasonable expectation of success." Natera.Br.28-34 (citing *Miles Lab'ys v. Shandon*, 997 F.2d 870, 874 (Fed. Cir. 1993) (final-judgment appeal)). But that framing betrays the

same error infecting the district court's decision, suggesting it was deciding the ultimate question of obviousness and underlying factual issues. *Supra* pp. 5-6. Regardless, like obviousness, whether Natera showed the absence of a substantial question of obviousness is ultimately a legal question. *See Amazon.com*, 239 F.3d at 1358-59; *KSR*, 550 U.S. at 427.

The record shows Natera failed to make the required showing. Among other evidence, it cannot escape its own admissions and judicial success in proving that the very things the district court thought "presented obstacles" (Appx10)—tagging, amplifying, and sequencing cell-free DNA, including in a single volume——were routine, conventional technology before 2011. Natera.Br.29-30; *supra* pp. 2-4. Natera trots out statements from its expert and others about "well-known barriers" but never reconciles them with the same expert's and Natera's past statements acknowledging skilled artisans had been successfully applying the claimed techniques to cell-free DNA long before 2011, barriers or not. Natera.Br.29-30 (citing Appx18752-18759(¶¶13-22); Appx18825-18835(¶¶154-69); Appx19069 (Volik); Appx7691 (Forshew)). Nor does Natera ever explain how the claimed invention purportedly overcame any such barriers. Natera.Br.1-8,28-30. And contrary to Natera's assertion, the district court made no "credibility determinations" on this cold record involving no evidentiary hearing. Natera.Br.12,29; Appx1-21.

The court stated it held "oral argument," without new evidence. Appx10 n.5; Appx19927-19938.

Natera mostly ignores its and its experts' prior statements and tries to dismiss this Court's holdings in *CareDx* and *Ariosa* as "concern[ing] subject-matter eligibility" of different claims. Natera.Br.32-34. But NeoGenomics relied on those decisions for what they show about the state of the prior art, and particularly what Natera, a prevailing party in both, admitted about the art specific to the exact issues here. *Supra* pp. 2-4; Neo.Br.27-28.

Natera's admissions are especially devastating because the relevant subject-matter-ineligibility standard is tougher than obviousness—the routine-and-conventional standard "goes beyond what was simply known in the prior art." *Berkheimer v. HP*, 881 F.3d 1360, 1369 (Fed. Cir. 2018). NeoGenomics made this point (Neo.Stay.Reply.5-6), but Natera ignores it. In any event, *Illumina* was about obviousness, which is where Natera and its expert admitted that simultaneous amplification of dozens, and even thousands, of targets in a single reaction volume was known for cell-free DNA. Appx13014-13019. Unable to explain away this evidence, Natera labels it "*post*-priority-date statements." Natera.Br.32-34 (Natera's emphasis). But that wordplay is unavailing—Natera never contests the statements describe the *pre*-priority state of the art.

Natera shifts to "findings" the district court never made, arguing "numerous gaps in the prior art" and teaching away. Natera.Br.30-32 (citing Appx13156; Appx13202, Appx13317). But the district court found neither (and the "mere existence" of gaps cannot defeat obviousness anyway). Appx9-10; *Dann v. Johnston*, 425 U.S. 219, 229-30 (1976). The prior art actually teaches towards the invention, showing skilled artisans long pursued cell-free DNA despite recognizing potential challenges. *See PAR Pharm. v. TWI Pharms.*, 773 F.3d 1186, 1198-99 (Fed. Cir. 2014) (reference "merely 'caution[ing]'" about risks not teaching away).

Natera's repeated insistence on a motivation directed at this "*particular*," "*specific* method" also fails. Natera.Br.30-34 (Natera's emphasis). The only thing the district court found missing in Kaper was applying the known claim steps to cell-free DNA. Appx9-10. But the already routine nature of those steps and cell-free DNA's undisputedly well-known benefits provided ample motivation with reasonably expected success—which is exactly the combination Inivata-founder Dr. Forshew disclosed within a year after Kaper and roughly contemporaneously with the alleged priority date. Appx7693, Appx7702, Appx7706-7710. Regardless, teachings directed specifically at the claimed combination are unnecessary; "any need or problem known in the field" at the time "and addressed by the patent" suffices. *KSR*, 550 U.S. at 420.

These errors on obviousness alone require reversal.

B. The District Court Failed To Resolve A Key Claim-Construction Dispute, And NeoGenomics Does Not Infringe Under The Correct Construction

1. Natera has no answer for the plain claim text, consistent description, and its own concessions

The district court concluded there was a likelihood of infringement only by applying an implicit, erroneous claim construction. Neo.Br.29-40. Natera embraces that implicit construction, openly acknowledging its infringement theory is based on reading the distinct tagging and amplification steps to cover performing a single PCR. Natera.Br.35-37. Its expert admitted the same, asserting that the claims purportedly cover "tagging and amplifying the tagged products occur[ring] in the same PCR." Appx20164.

But the claim text expressly addresses using a single PCR with a single set of primers to perform tagging, and it identifies that conduct as falling only within claim 1's tagging step, and not in the distinct process step of "amplifying the tagged products." Claim 13 recites "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." Appx245(col.251:10-13) (emphasis added). Natera concedes that text recites tagging using a PCR (i.e., "amplification") that is "its own amplification process, separate and apart from the amplification that occurs in the amplification step." Natera.Br.39. Natera nevertheless argues claim 13 "does not imply anything" on the

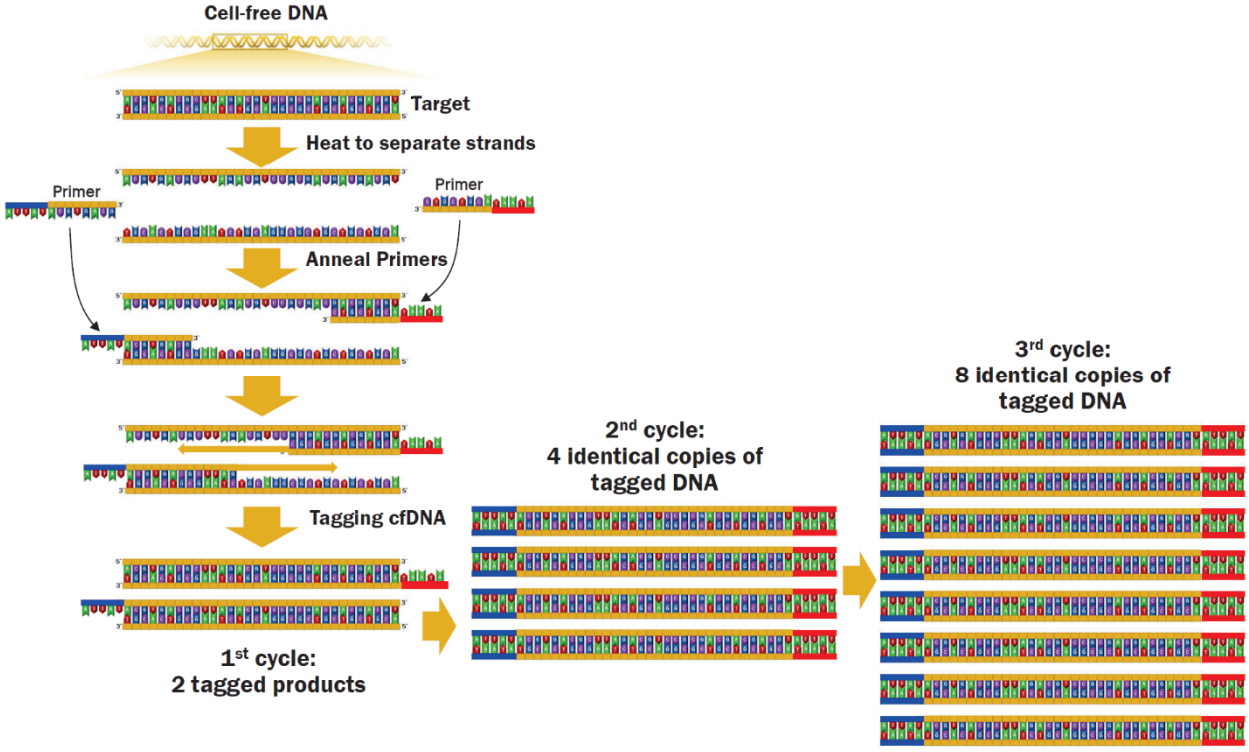
dispute here because "'an independent claim is broader than'" a dependent one. Natera.Br.39 (quoting *Littelfuse v. Mersen*, 29 F.4th 1376, 1380 (Fed. Cir. 2022)).

In invoking that truism, Natera misses the point and, ultimately, gives up the game. All parties agree there are two ways to perform the tagging step: "by either ligation -- which is a technical term that means just gluing two pieces of DNA together -- or by PCR." Appx20170 (Natera's expert); Appx18759(¶24). Although claim 1 is not limited to either, the patent includes dependent claims reciting each: claim 2 recites tagging that "comprises ligating" universal tail adaptors; and claim 13 recites tagging that "comprises" a PCR, i.e., "amplifying the cell free DNA" with primers having universal tail adaptors. Appx244-245(col.249:63-65,col.251:10-13). And critically, all now agree that both "tagging" approaches are "separate and apart from the amplification that occurs in the amplification step." Natera.Br.39; Appx20170 (ligation is "just gluing," i.e., not amplifying at all). Thus, these dependent claims provide further proof of the tagging step's plain meaning: they show that, in these claims, "tagging" using universal tail adaptors is "separate and apart" from the subsequent targeted amplification. *Phillips v. AWH*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (en banc) (term's "usage" in dependent claims "can often illuminate" meaning).

Natera's contrary construction is divorced from the undisputed science of PCR, which Natera ignores. Natera argues nothing in the claim text precludes

performing the tagging step in a "*first* cycle" of a PCR and targeted amplification "in *subsequent* cycles of a larger PCR process." Natera.Br.38 (Natera's emphasis). But in a PCR using primers with tags, all cycles are both amplifying (as that is what PCR does) and tagging. As NeoGenomics explained and Natera never contests, a single PCR is performed by: (1) combining a DNA sample and all reagents—including polymerase and a set of one or more primer pairs; and (2) repeatedly heating and cooling the mixture. Neo.Br.5-7. What Natera artificially carves out as separate parts "of a larger PCR process" is nothing more than continuing to heat and cool the same mixture. Neo.Br.5-7.

Natera includes a slide that, although inaccurate, confirms this and shows Natera treats distinct claim process steps as covering the same, continuous conduct:



Appx21361 (cropped).[1] Natera argues the slide shows that when the mixture is first heated and cooled, tagging occurs because primers with tags (the blue and red portions) anneal to the separated strands, which are then replicated by polymerase. Natera.Br.7. But as more heating and cooling occurs, Natera says targeted amplification happens. Natera.Br.7. Why? Because of the same annealing of the same primers with tags and then replication. Natera.Br.7.

Hence, as Natera's expert admitted, "[e]very time a primer" with a tag anneals, "it is tagging the product with a new tag." Appx12040-12041(¶¶98-99;emphasis omitted). Natera accuses NeoGenomics of "mischaracteriz[ing]" because the expert "never said the PCR cycles satisfy *only* the tagging step." Natera.Br.40 n.2 (emphasis added). But NeoGenomics merely said the testimony shows the entire PCR is tagging and produces tagged products. Neo.Br.39. Natera's carefully placed "only" concedes this is true and shows Natera is collapsing the tagging and amplifying steps—despite elsewhere acknowledging that they are "separate." Natera.Br.19-20.

Natera's argument is thus just like the losing argument in *Amgen v. Sandoz*, 923 F.3d 1023 (Fed. Cir. 2019). Like here, the *Amgen* claim recited two distinct steps: "washing the separation matrix" and "eluting the protein from the separation

[1] After the second cycle, no DNA would include red *and* blue tags on both individual strands. Appx21001.

matrix." *Id.* at 1026. The patentee argued the same conduct—continuously pouring a single solution into the matrix—could satisfy the plain terms of both steps so long as the functions of washing and eluting happened in the recited order. *Id.* at 1028-29. This Court rejected that argument as based on an incorrect claim construction: the recited steps were not mere "functions" but "actual process steps" that required distinct acts—in *Amgen*, "adding discrete solutions." *Id.* A one-step, one-solution process was outside the claim's plain meaning, just as a one-step, one-PCR process is outside the plain meaning here. *See id.* This conclusion does not create "additional limitations out of whole cloth." Natera.Br.37. It merely explains what a plain-meaning construction requiring distinct tagging and targeted-amplification steps means in the context here.

Natera has no good response. It says *Amgen*'s "washing and eluting were consistently described in the specification as separate steps performed by *different solutions*" but "[t]here is no analogous claim language here." Natera.Br.38-39 (Natera's emphasis). In switching from what the specification described in *Amgen* to what the claims recite here, Natera elides that the *Amgen* claims did not recite "different solutions." 923 F.3d at 1026-28. Rather, the different-solutions construction followed from the claim text's "logic" and "grammar" combined with the *specification's* consistent description using different solutions. *Id.*

That just highlights that the intrinsic evidence here is even more compelling: the claims and specification consistently describe tagging and targeted amplification as separate steps that, when performed with PCR, use distinct PCRs with distinct primers. Appx255-245(col.249:44-65,col.251:10-13); Neo.Br.37-39 (specification examples). Natera concedes claim 13 describes tagging "performed by its own amplification process, separate and apart from the amplification that occurs in the" targeted-amplification step. Natera.Br.39; Appx245(col.251:10-13). Natera also concedes that the specification examples show "separate PCRs" for the separate steps. Natera.Br.37-38. And Natera never disputes NeoGenomics' explanation that the specification disparages a single-step, single-PCR approach. Neo.Br.37-38; Natera.Br.39-40. No intrinsic evidence discloses what Natera now says its claims cover. Just as in *Amgen*, this intrinsic evidence is dispositive and cannot be swept away as merely "embodiments" (Natera.Br.39-40). 923 F.3d at 1026.

In the face of this unrebutted intrinsic and extrinsic evidence, Natera makes no affirmative argument for its interpretation, simply asserting it is applying "plain and ordinary" meaning. Natera.Br.35-40. But the plain-and-ordinary meaning supports NeoGenomics, including because "as a matter of logic [and] grammar" the claim text, especially given claim 13, can only be read as requiring that targeted amplification occur separately, and after completion of, tagging. *Amgen*, 923 F.3d at 1028; *Mformation Techs. v. Rsch. in Motion*, 764 F.3d 1392, 1391 (Fed. Cir.

2014). After all, the targeted-amplification step requires as its input the output from the tagging step: "amplifying the *tagged products*." Appx244(col.249:44-62) (emphasis added).

This claim-construction issue is dispositive. Natera never contests there is no likelihood of infringement under NeoGenomics' proposed construction. Neo.Br.39-40; Natera.Br.35-43. The preliminary injunction should be set aside for this reason alone.

2. This claim-construction dispute was squarely presented, so at least a remand is required

It is uncontested that the district court never addressed this claim-construction dispute. Neo.Br.32-33; Natera.Br.40-43. Yet "a correct claim construction is almost always a prerequisite for imposition of a preliminary injunction." *Chamberlain v. Lear*, 516 F.3d 1331, 1339-40 (Fed. Cir. 2008). Natera says (Natera.Br.42) courts need not "conclusively and finally" interpret claims during a preliminary-injunction proceeding. *Sofamor Danek v. DePuy-Motech*, 74 F.3d 1216, 1220-21 (Fed. Cir. 1996). That just means preliminary-injunction rulings are generally "*not binding* at trial." *Id.* (Court's emphasis). But *Sofamor* confirmed likelihood of success often "depends on the meaning of disputed claim terms," which this Court then addressed. *Id*. Given the undisputedly dispositive nature of the claim-construction issue here, the district court's failure to do the same warrants at least vacatur. *Shuffle Master v. VendingData*, 163 F. App'x 864, 867-69 (Fed. Cir. 2005).

Neither Natera response supports a different conclusion. *First*, Natera reargues the merits, asserting claim construction is unnecessary for "simple" issues with "no reasonable ground for dispute." Natera.Br.42 (quoting *Shuffle Master*, 163 F. App'x at 868). But *Shuffle Master*'s card-shuffling technology was simple; regardless, any lack of reasonable dispute favors NeoGenomics. *Supra* Part B.1.

Second, Natera asserts NeoGenomics forfeited this issue because "[t]he first time NeoGenomics raised this claim[-]construction argument was in its motion for a stay pending appeal" to the district court. Natera.Br.40-42. But during that briefing, Natera said NeoGenomics was "repeat[ing] its past flawed arguments" and "NeoGenomics' re-arguments fail because" purportedly based on "treating the pre-amplification [PCR] step as a single, indivisible process." Appx20897-20899. The district court viewed it similarly, denying a stay because NeoGenomics' claim "interpretation" sought "reconsideration," "reasserting the same arguments the Court has already considered." Appx21323.

That nobody thought this issue new is unsurprising. NeoGenomics raised it in its preliminary-injunction opposition, expert report, and oral argument. NeoGenomics disputed that a single "PCR step somehow satisfies both the tagging step and the post-tagging targeted amplification step" and showed, for a variety of reasons, why "the claim language proves conclusively" that "theory is wrong." Appx10485-10486, Appx12038-12040(¶¶95-97), Appx12043 ("contradicts and

cannot be squared with the language of other claims"). It argued the steps must be distinct by pointing, among other things, to claim 13 and Natera's expert admissions, the same evidence NeoGenomics cites now. Appx12041-12043. It told the district court the "question now"—"the key claim construction issue"—was whether "tagging" is the "first cycle of the PCR, or is it all the cycles." Appx20289-20290. Natera responded by disputing that the "claim language" shows targeted amplification "had to be a separate step from tagging." Appx20354-20355. This history reveals Natera's forfeiture argument as an unfounded attempt to avoid review of an issue it cannot win.

C. The District Court Legally Erred In Determining Irreparable Harm Divorced From Claim Scope And Made Unsupported Findings

1. Natera's attempt to shift the burden to NeoGenomics exposes Natera's failures on irreparable harm

Natera came nowhere close to carrying *its* heavy burden of a "clear showing" that "irreparable injury is *likely* in the absence of an injunction." *Winter v. Nat. Res. Defense Council*, 555 U.S. 7, 22 (2008) (Court's emphasis); NeoBr.40-49. Natera's response proves NeoGenomics' point. It includes a single paragraph citing district court findings, without identifying any supporting evidence, and then spends the rest of its section attacking NeoGenomics' evidence and arguments. Natera.Br.43-55.

Natera relies on pre-*eBay* decisions (Natera.Br.43-55), such as ones addressing whether a patentee's delay "rebutted the presumption of irreparable

harm." *Advanced Commc'ns v. Premier Retail Networks*, 46 F. App'x 964, 983-84 (Fed. Cir. 2002). It argues an injunction is warranted because "patentees are entitled" to market exclusivity and points to alleged economic harms without explaining why legal remedies are insufficient. Natera.Br.44,48-49. And in trying to overcome the district court's errors, Natera attacks the TD Cowen market report Natera itself submitted, and on which the district court repeatedly relied, as "[s]tale," purportedly failing to "differentiate" or "conflat[ing]" markets, and for allegedly "issu[ing] *before*" what Natera now asserts is the relevant period. Natera.Br.20,45,54 (citing Appx7307-7391, an exhibit to Natera's expert declaration; Natera's emphasis); *see* Appx3-4, Appx14-16 (district court repeatedly relying on same as Doc. 92-1).

But the days when patentees could simply point to exclusive patent rights to justify an injunction are long gone. *eBay v. MercExchange*, 547 U.S. 388, 393-94 (2006). Like all preliminary-injunction movants, patentees must justify pre-trial relief by making a clear showing of likely "immediate" and "substantial" harm that legal remedies cannot compensate. *O'Shea v. Littleton*, 414 U.S. 488, 502 (1974). Natera's attempt to sidestep that burden, or shift it to NeoGenomics, is reason alone that the injunction cannot stand.

That is especially true on these facts, where there should be no question that the injunction disturbs the status quo. *Stemple v. Bd. of Educ.*, 623 F.2d 893, 898

(4th Cir. 1980). Natera's contrary argument is form over substance—and wrong on form to boot. Natera.Br.47-48. This is not a situation where a district court prevented an impending launch (or delayed a very recent one) of a copycat product to preserve affairs until after trial. Instead, years after RaDaR's launch, the injunction has removed this independently inventive, competing product from the market before any evidence went to a jury. As a result, NeoGenomics has had to take drastic actions to stop activities it has been doing without complaint for years, including ending clinical services for RaDaR, removing information about RaDaR from its website, limiting scientific discourse of RaDaR, ordering its sales team to cease promoting RaDaR, and notifying customers not to request tests. Appx21520-21536.

Natera never disputes that granting such relief is historically disfavored, warrants close scrutiny, and requires an especially strong showing of harm. Neo.Br.42-43. Instead, it tries to avoid that burden by tying the status quo to "Medicare coverage"—without legal or factual basis. Natera.Br.47-48. Natera's requested injunction was not limited to Medicare-covered services, and both Natera and the district court's reasoning focused on non-Medicare-covered activity like research partnerships (*infra* pp. 28). Natera's suggestion that the status quo is undisturbed because the injunction prevents only "*future* infringing uses" seeks an impermissible patent-specific rule (Natera.Br.47-48; Natera's emphasis)—*all*

injunctions concern future activity and must be justified by the same heavy burden. *eBay*, 547 U.S. at 393-94.

2. The district court never found, nor does Natera show, any nexus to claimed features

a. Lack of legally required nexus is clear

The district court's tethering of its irreparable-harm determination to an unclaimed feature independently warrants relief. Neo.Br.44-45. Natera never disputes tumor-informed testing is not a claimed feature. Natera.Br.49-52. Nor does it contest that the distinction between tumor-informed and tumor-naïve testing drove the district court's decision. Natera.Br.49-52. The district court thus did what this Court prohibits: allowed Natera "to leverage its patent for competitive gain beyond that which the inventive contribution and value of the patent warrant." *Apple v. Samsung*, 695 F.3d 1370, 1374-75 (Fed. Cir. 2012). That is legal error. *Id.*

Natera's main response argues for a finding the district court never made and the record does not support. It asserts nexus because "NeoGenomics *could not have offered* RaDaR's MRD assay at all without infringing—whether its infringing product was tumor-informed or tumor-naïve." Natera.Br.51 (Natera's emphasis). But far from making that finding, the district court stated without support—and in a finding Natera never tries to defend—that "[i]t appears highly likely that NeoGenomics' predecessor built RaDaR using the methods of the '035 patent as a foundation." Appx17. Not so: it is undisputed Inivata independently invented

RaDaR before publication of the alleged priority application, and Natera filed for the '035 patent only after RaDaR was public. *Supra* pp. 4-5; Natera.Br.47n.4.

The rest of the district court's reasoning was express in finding a nexus to only tumor-informed testing, an unclaimed feature. It reasoned: doctors allegedly "prefer tumor informed tests" and "RaDaR's ability to perform tumor informed testing is what drives consumer demand for it." Appx17-18. The district court never found NeoGenomics "could not have offered" RaDaR "without infringing" (Natera.Br.51) because there is no evidence it is true. The only evidence Natera cites is deposition testimony about something else (how RaDaR allegedly practices tagging). Appx10836-10837.

In reality, as NeoGenomics showed and Natera never rebuts, RaDaR's highly sensitive, tumor-informed nature comes from what happens before and after the basic DNA-processing steps accused of infringement. Neo.Br.43-44; Neo.Stay.Reply.8-9. Before processing any cell-free DNA, a patient's tumor sample is collected and sequenced. Appx11270(¶10). NeoGenomics uses proprietary bioinformatics to design a patient-specific primer panel from that sample to identify up to 48 tumor-specific variations (Signatera identifies merely 16). Appx11270-11288(¶¶10,39,44). Only then is cell-free DNA amplified or sequenced. Appx11270-11288(¶¶10,39,44). After sequencing, NeoGenomics applies its own

post-sequencing analytics, which are also key to RaDaR's sensitivity. Appx11270-11288(¶¶10,39,44).

Natera alleges the infringing steps are "central to RaDaR's workflow" but that is factually and legally wrong. Natera.Br.52. Natera cites only declarations saying nothing of the sort, like its expert's general infringement opinion. Natera.Br.52 (citing Appx7590-7612; Appx2458-2459). Nor is "central to the workflow" the test. *Apple* rejected that nexus is met for any "core" feature "simply because removing" it might leave a product "less valued or inoperable." 695 F.3d at 1376.

Natera cites a different *Apple v. Samsung* decision that drives home the point: Natera was required to show, and the district court to find, that "patented features impact consumers' decisions to purchase the accused" testing. Natera.Br.51-52 (quoting 809 F.3d 633, 642 (Fed. Cir. 2015)). Natera cannot identify any such finding and makes no attempt to argue its purported innovation—using a "single reaction volume"—drives sales of RaDaR or Signatera. Natera.Br.43-55. And although Natera baldly states "NeoGenomics advertised" patented features (Natera.Br.52), it merely cites statements that RaDaR "is 10x more sensitive than" other tests, a sensitivity unrelated to alleged infringement. Appx2510-2512(¶143).

b. Natera wrongly asserts forfeiture and shifts the burden

Natera asserts forfeiture, but its own quotation shows NeoGenomics has consistently pressed the same issue: "'[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.'" Natera.Br.50 (quoting NeoGenomics, Appx10503). That is the identical issue NeoGenomics presses now. *Supra* Part 24-26. Natera complains NeoGenomics did not state that "tumor-informed testing is not a patented feature" (Natera.Br.50), but that is what NeoGenomics said: RaDaR's sales are driven by its "tumor-specific" sensitivity, which is unclaimed. Appx10503.

Natera has no basis for arguing NeoGenomics was required to "mention the '035 Patent" specifically. Natera.Br.50. That is especially so because Natera bore the burden. *Apple*, 695 F.3d at 1374-75. Natera's nexus arguments never distinguished between the '454 patent, which claims a form of tumor-informed testing, and the '035 patent, which does not claim tumor-informed testing at all. Appx532(col.171:25-43); Appx244(col.249:44-62). It thus was Natera's litigation choices, not anything by NeoGenomics, that led to the district court improperly tying irreparable harm to an unclaimed feature.

3. Natera cannot explain away its delay and lack of evidence of concrete harm

Delay: Also defeating irreparable harm is Natera's significant delay, for which it has no excuse. Natera does not dispute it: (1) claimed the purported invention only after RaDaR was on the market, (2) sued NeoGenomics' subsidiary Inivata in Delaware based on RaDaR without asserting the already-issued '035

patent or seeking a preliminary injunction, and instead (3) voluntarily delayed seeking relief seven-plus months, three-plus years after RaDaR became available. Natera asks the Court to excuse that delay because RaDaR initially lacked Medicare approval. Natera.Br.46-48. But like the district court, Natera repeatedly relies on alleged harms in the non-Medicare market for biopharmaceutical partnerships and clinical studies, a market RaDaR entered in 2020. Natera.Br.43-55.

Natera also calls its application-filing delay "irrelevant" but cannot back that up. Its only cited support is an example where this Court affirmed reliance on delay while observing a party cannot be faulted for "not filing suit" before patent issuance. *Apple v. Samsung*, 678 F.3d 1314, 1325 (Fed. Cir. 2012). But that observation says nothing about application-filing delay, nor was there any suggestion the *Apple* patentee had filed its application *after* the accused infringer was on the market. *Id.* NeoGenomics did not agree that only suit-filing delay matters (Natera.Br.47); the discussion Natera cites shows NeoGenomics also explained RaDaR "was introduced in 2020 before the claims" here "were even drafted." Appx20315-20317(162:21-164:7).

No lost sales/contracts: Natera's remaining arguments recycle flawed reasoning NeoGenomics rebutted twice. Neo.Br.40-49; Neo.Stay.Reply.7-11. RaDaR has been available for years, so Natera cannot chalk up lack of lost sales and contracts to recent market entry. Natera.Br.48-49. Natera wrongly states the district

court found Natera "lost business" from Moderna (Natera.Br.49), but the court merely noted "Moderna used RaDaR," without concluding whether that took an opportunity from Natera. Appx16. Natera never rebuts evidence showing Signatera's reduced sensitivity meant it "would not have been eligible" for the Moderna trial (or the AstraZeneca trial Natera mentions). Appx11279-11282(¶¶28-32).

No cherry-picking: Nor were Natera's CEO's statements "cherry-pick[ed]." Natera.Br.45. They speak for themselves and were made after RaDaR's market entry, including many made after RaDaR's Medicare approval: "We very, very rarely see any competitors in the field" because "we're at these very early stages in very big underpenetrated markets." Appx11549, Appx11536. The "only" competitor is "Guardant Health." Appx11545. Elsewhere, Natera seeks a Lanham-Act injunction to prevent Guardant from "erod[ing] [Natera's] market share," another previously explained bad-for-Natera fact that Natera ignores. *Guardant Health v. Natera*, No. 3:21-cv-004062, ECF90 (N.D. Cal.); Neo.Stay.Reply.10-11.

No two-player market: Natera cannot resuscitate the district court's misinterpretation of precedent in giving undue weight to whether the market is two-player. Natera points to the district court's subsequent statements in denying a stay but never actually contradicts NeoGenomics' point (Neo.Br.45-46) that the facts here are nothing like those in the two-player-market decisions the district court cited.

Natera.Br.53-54; Appx14-16 (citing *Douglas Dynamics v. Buyer Prods.*, 717 F.3d 1336 (Fed. Cir. 2013); *Presidio Components v. Am. Tech. Ceramics*, 702 F.3d 1351 (Fed. Cir. 2012); *Robert Bosch v. Pylon*, 659 F.3d 1142 (Fed. Cir. 2011)). Yet it is the application of those decisions well beyond their facts that shows the district court over-generalized the relevance of whether the market is two-player.

Regardless, the tumor-informed market is not two-player but includes "the majority of the publicly-traded players" plus non-public ones. Appx7310, Appx7327-7334; Appx16161. That includes Invitae; reliance on that company hardly "defies reality," given its test can be ordered online today. *Contra* Natera.Br.54.[2] When Natera says "NeoGenomics' *own expert* testified that the market was two-player," Natera disproves itself by quoting him actually saying the market includes Natera with "above 90%," NeoGenomics, and other "minor players"—everyone is a minor player when Natera holds such a dominant position. Natera.Br.53-54 (quoting Appx19518; Natera's emphasis).

The legal and clear factual errors on irreparable harm independently warrant relief.

[2] https://www.invitae.com/us/providers/test-catalog/personalized-cancer-monitoring?tab=tests.

D. The District Court Committed A Clear Error Of Judgment In Overlooking Compelling Public Interests And In Balancing The Harms

In addition to the real harms to NeoGenomics, particularly as it increased investment during Natera's delay (Neo.Br.52-53), the preliminary injunction should have been denied because of its substantial harm to the public. The "focus" of the "public interest analysis should be whether there exists some critical public interest that would be injured." *Hybritech v. Abbott*, 849 F.2d 1446, 1458 (Fed. Cir. 1988). The critical public interest being injured is access to RaDaR, as its sensitivity and features make it the only option for some patients and studies. Neo.Br.49-53.

Natera fails to rebut that fact. It concedes sensitivity is "one factor oncologists consider" but complains of a lack of "head-to-head studies" and about NeoGenomics' reliance on an executive. Natera.Br.55-58. But there is head-to-head evidence, and not just from NeoGenomics executives. A prominent oncologist, who has published in the New England Journal of Medicine (among others), found that "RaDaR is more sensitive than Signatera to detect ctDNA levels because of its established analytical sensitivity, especially in low shedding cancers such as melanoma and certain breast cancers." Appx11264-11265. Natera says he identifies "no support" (Natera.Br.57 n.6) but is wrong: the oncologist explained his conclusions were based on "routinely" using "both Natera's Signatera assay and NeoGenomics' RaDaR assay" with his own cancer patients. Appx11264-11265. A

key opinion-leader reached a similar conclusion, reporting positive results with RaDaR while advising against Signatera. Appx11264-11265; Appx11685-11692. That the report concluded "RaDaR's sensitivity is 'imperfect'" (Natera.Br.57 n.6) is hardly a ding since no MRD test is perfect.

Natera is also flat wrong that NeoGenomics' executive "*assert[s]* that RaDaR is more sensitive without any proof." Natera.Br57 (citing Appx11280-11283; Natera's emphasis). He explained in detail why RaDaR was more sensitive than Signatera, providing data and attaching twelve supporting exhibits, including peer-reviewed articles. Appx11287-11289 (¶¶44-47) (citing, e.g., Appx11695-11705; Appx7727-7744). Natera cites its own executive taking pot-shots at the studies and evidence but fails to identify any head-to-head data of its own supporting a different conclusion. Natera.Br.57-58; Appx7932(¶22) (admitting no head-to-head supporting Natera).

The evidence of RaDaR's superior sensitivity continues to pour in. Recent peer-reviewed research confirms RaDaR's higher sensitivity has "clinical impact," reporting RaDaR detected circulating-tumor DNA at as low as .0011% variant allele frequency. Coakley, *Clinical Cancer Research* (2024), http://tinyurl.com/coakleystudy (cited, Appx20932). Signatera's theoretical limit (.01%) is less sensitive. Appx11287(¶44).

In the end, the critical point the district court failed to grasp is the importance of choice for patients, doctors, and researchers. Unlike an ANDA case, these are not drop-in replacement products, and different patients with different cancers may benefit from different approaches. Even the survey Natera invokes (of just 14 oncologists) confirmed patient and clinician choice matters—and over 35% did not agree that Signatera is "preferred." Appx16159. Thus, although Natera repeats the district court's statement that patients "will be able to get" Signatera, it never rebuts Signatera's inadequacy for certain uses or that choice benefits patients. Natera.Br.55-56 (citing declarations merely making other points).

Natera also undermines its own asserted irreparable harm. According to Natera, the public is fully protected because the injunction allows "virtually all ongoing use of RaDaR" and "hypothetical impacts on potential future studies" are "speculat[ion]." Natera.Br.47-48; Natera.Stay.Opp.2,23. Yet Natera simultaneously argues it needs the injunction to prevent losing future studies to NeoGenomics. Natera.Br.49,53. Actually, the unrebutted evidence shows Signatera cannot substitute for RaDaR—so while the threat to future studies is real, only the public and NeoGenomics face harm. *Supra* pp. 25-26,28-29.

* * * * *

For these reasons, the preliminary injunction should be set aside. If it nevertheless were to stand, this Court need not address its scope. Since

NeoGenomics' opening brief, the district court has addressed that issue (Natera.Br.63), clarifying the injunction is "limited to the United States" and indicating a willingness to consider its ongoing scope upon further record development. Appx21329-212330.

CONCLUSION

The preliminary injunction should be reversed or vacated, and NeoGenomics' stay motion granted until then.

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Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

The foregoing filing complies with the relevant type-volume limitation of the Federal Rules of Appellate Procedure and Federal Circuit Rules because the filing has been prepared using a proportionally-spaced typeface and includes 6,992 words, excluding the parts of the brief exempted by the Rules.

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