No. 22-1066

In the Supreme Court of the United States

CAREDX, INC., ET AL., PETITIONERS

v.

NATERA, INC., ET AL.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

REPLY BRIEF FOR PETITIONERS

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This Court needs to take another Section 101 case and this is an ideal vehicle. Review would enable this Court to (1) confirm that methods in the field of medical diagnostics indeed can be patent eligible, thus solving the biggest practical problem in U.S. patent law; (2) refocus the inquiry on the statutory text and preemption concerns; and (3) clarify the appropriate—and appropriately limited—role of "conventionality" in Section 101. Together, that would provide "much-needed clarification," U.S. *Tropp* Br. 11, and balance this Court's law by illustrating what *is* eligible relative to the string of patents this Court has recently found ineligible.

Respondents contend that this Court's review of a Section 101 case is no longer needed, that *Mayo Collaborative Services* v. *Prometheus Laboratories, Inc.*, 566 U.S. 66 (2012), controls, and that these claims are "conventional." They are wrong on all fronts.

First, this Court's intervention is still needed. The confusion from the Federal Circuit's overreading of *Mayo* continues to discourage innovation, especially in the diagnostics industry. The Federal Circuit has effectively created a wholesale subject-matter exclusion from patentability, driving investment overseas.

Second, *Mayo* is readily distinguishable. The Stanford Patents claim improved methods for measuring the amount of one person's DNA when two people's DNA are intermixed in a sample because of organ donation. Unlike in *Mayo*, the inventiveness lies not in discovering a natural phenomenon (it was previously known), but in identifying specified improvements upon prior methods for distinguishing between a donor's and recipient's DNA fragments. Moreover, unlike in *Mayo*, where the patents effectively claimed *every* method for applying a phenomenon, the Stanford Patents claim *specific* ways of measuring it: For example, the '607 patent uses specific tools (high-throughput sequencing and selective amplification) to identify fragments of particular mutations (single nucleotide polymorphisms (SNPs)) in specified quantities (more than 1,000 SNPs) to differentiate donor DNA.

Third, respondents assert that the Stanford Patents are "conventional" because each underlying laboratory technique previously existed. But it is undisputed that nobody had *combined all those previous techniques to solve this particular problem*. Not only is the combination new, but regardless the Patent Act expressly covers a "new use of a known process." 35 U.S.C. 100(b).

Respondents conspicuously fail to show that it was "conventional" to use this combination of steps to measure this phenomenon. It was not. After a decade of fail-

ure in which scientists sought to measure this phenomenon but had devised only inferior methods for doing so, other researchers concluded that measurement was "difficult and impractical." C.A.J.A. 648. The Stanford Patents nevertheless solved that "difficult" problem by *departing from* the conventional methods for measuring it and devising new, different, and better methods. The resulting improved process fits squarely within the text of Section 101, making this an ideal vehicle for correcting the Federal Circuit's misuse of Section 101 to make an end-run around Section 103's obviousness analysis.

This Court should grant certiorari or, at a minimum, call for the views of the Solicitor General.

A. This Court Needs To Take A Section 101 Case

The Federal Circuit, the Solicitor General, the U.S. PTO, and leaders across industries have urged this Court to take another Section 101 case. See Pet. 15-17. This Court has repeatedly called for the views of the Solicitor General. *Ibid.* And the district court described Section 101 caselaw as "fraught, incoherent, unclear, inconsistent, and confusing, and indeterminate." Pet. App. 36a (cleaned up). That is a clarion call for this Court's intervention.

1. Respondents contend that this Court should deny certiorari because it denied the petitions in *Tropp*, *Interactive Wearables*, and *American Axle*, after the Solicitor General recommended grant. But the fact that this Court has not yet found the right vehicle does not mean the underlying problems with the Federal Circuit's jurisprudence have disappeared. They have not.

This case is also a superior vehicle. Those cases involved luggage, wearable technology, and driveshafts—not medical diagnostics, the field in which "*Mayo* has had particularly significant practical effects." U.S.

Hikma Br. 22. Since *Mayo*, the Federal Circuit has "consistently held diagnostic claims unpatentable as directed to ineligible subject matter." *Illumina, Inc.* v. *Ariosa Diagnostics, Inc.*, 967 F.3d 1319, 1325 (Fed. Cir. 2020). That undermines incentives to innovate and contravenes the basic purpose of the patent laws to "promote the Progress of Science and useful Arts." U.S. Const. Art. I, § 8, Cl. 8.

2. Respondents note that two Senators have proposed legislation to address these problems. *E.g.*, Eurofins Opp. 2, 18. But those same Senators made a similar proposal four years ago and nothing came to fruition. See Press Release, Sens. Tillis and Coons and Reps. Collins, Johnson, and Stivers Release Draft Bill Text to Reform Section 101 of the Patent Act (May 22, 2019).[1]

Indeed, Natera has been arguing since 2016 that this Court's action is unwarranted because Congress will fix any problems. See Natera Opp., *Sequenom, Inc.* v. *Ariosa Diagnostics, Inc.*, 579 U.S. 928 (2016) (No. 15-1182), 2016 WL 2957119. The Court's actions reject that view. It has repeated called for the views of the Solicitor General, apparently seeking an appropriate vehicle for correcting the Federal Circuit's Section 101 jurisprudence.

The Federal Circuit's jurisprudence is still creating significant real-world problems and this is the ideal vehicle for correcting them. See Pet. 18-20. Notably, those problems do not arise from the statutory text or from this Court's own decisions, as petitioners are not asking to overrule *Mayo*. See pp. 6-8, *infra*. Rather, the problem lies in the Federal Circuit's misinterpretation of this

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[1] https://www.tillis.senate.gov/2019/5/sens-tillis-and-coons-and-reps-collins-johnson-and-stivers-release-draft-bill-text-to-reform-section-101-of-the-patent-act.

Court's precedents to over-expand a narrow "implicit exception." *Ass'n for Molecular Pathology* v. *Myriad Genetics, Inc.*, 569 U.S. 576, 590 (2013).

This Court is the appropriate body to correct that mistake. It regularly grants review to correct misinterpretation of its statutory precedents. *E.g.*, *Groff* v. *DeJoy*, 143 S. Ct. 2279 (2023). And just as this Court has a greater role in correcting misunderstandings of "common-law statute[s]," *Leegin Creative Leather Prod., Inc.* v. *PSKS, Inc.*, 551 U.S. 877, 899 (2007), it has a greater role in ensuring that this judicially-created exception "strikes [the] delicate balance between" incentivizing and impeding "creation, invention, and discovery," *Myriad*, 569 U.S. at 590.

3. Natera asserts that this Court should await a case with a divided panel and numerous amici. Natera Opp. 29-30. But the Federal Circuit's judges and numerous amici have repeatedly urged this Court to step in. See Pet. 15-17. They do not need to repeat that call again and again.

Respondents also have no response to former Chief Judge Michel and Professor Duffy's critique of the Federal Circuit's reasoning or their call for review. Eurofins asserts (Opp. 17 n.5) that amici "misunderstand[]" the patents. There is no misunderstanding. As amici explain (Michel & Duffy Br. 2, 6-10), the Stanford Patents fit comfortably within Section 101 because the statute covers "any new and useful improvement" of a "process," and Congress defined "process" to "include[] a new use of a known process." 35 U.S.C. 101, 100(b).

4. Natera observes (Opp. 27) that this Court has denied patent protection to laws of nature, natural phenomena, and abstract ideas for over 150 years and the United States has remained the "undisputed global

leader in scientific innovation." But it has only been over the last decade that the Federal Circuit's misreading of this Court's recent precedents has imperiled innovation, particularly in diagnostics. See, *e.g.*, Pet. 15-17 (collecting sources).

Moreover, none of Natera's sources address investment in medical diagnostics or biotechnology specifically. Nat'l Acads. Scis., Eng'g, & Med., *Protecting U.S. Technological Advantage* at 55-56 & fig. 3-5 (2022);[2] see Beethika Khan *et al.*, Nat'l Sci. Bd., Sci. & Eng'g Indicators: *The State of U.S. Science & Engineering* at 8-9 & fig. 14 (2020).[3] And recent studies have found that Section 101 jurisprudence has "reduced … investment in technological development generally, [and] particularly in the biotechnology, medical device, and pharmaceutical industries." David O. Taylor, *Patent Eligibility and Investment*, 41 Cardozo L. Rev 2019, 2094 (2020). This Court's intervention is needed.

B. Respondents Misread *Mayo*

Respondents insist that *Mayo* controls. Indeed, Natera cites *Mayo* a remarkable 96 times. But *Mayo* is the counterpoint that proves why this Court should take this case.

Mayo "rest[ed] upon an examination of the particular claims before" this Court. 566 U.S. at 72. In *Mayo*, the patentholders discovered a natural law: that "concentrations of certain metabolites" indicate that dosage of a drug would "prove ineffective or cause harm." *Id.* at 77. Their claims superficially dressed up that finding in process terms: the steps were (1) "administering" the drug;

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[2] https://nap.nationalacademies.org/catalog/26647/protecting-us-technological-advantage.

[3] https://www.nsf.gov/pubs/2020/nsb20201/nsb20201.pdf.

and (2) "determin[ing]," *i.e.* "measur[ing]," the "level of the relevant metabolites," "wherein" levels above (or below) the discovered thresholds indicated that dosages should be increased (or reduced). *Id.* at 78-79. The claims thus did not identify any particular method for "determin[ing]" metabolite levels. Rather, levels could be measured "through whatever process the doctor or the laboratory wishe[d] to use." *Id.* at 79.

Mayo held that the claims described a law of nature and told doctors to "measure [it] (somehow)." *Id.* at 82. Given the "determin[ing]" step's "high level of generality" and the fact that "scientists routinely measured metabolite[]" levels before the claimed invention, this Court explained, the "determining" step merely appended "well-understood, routine, conventional activity" to a law of nature, rendering the patent ineligible. *Id.* at 79-80, 82. The Court emphasized that the claims reached "all processes that make use of the correlations after measuring metabolites, including later discovered processes that measure metabolite levels in new ways." *Id.* at 87. Such a patent would "disproportionately t[ie] up the use of the underlying natural laws" and "inhibit future innovation premised upon them." *Id.* at 73, 86.

The Stanford Patents are fundamentally different. They *disclaim* discovery of the cell-free DNA correlation, which had been known for a decade. So that is not where the inventiveness resides.

Instead, the inventiveness resides in claiming specific "improved measurement methods" for measuring the donor cell-free DNA in transplant recipients. Pet. 12-13, 22-24; see Pet. C.A. Br. 28-30; Pet. C.A. Reh'g Br. 1-3. They teach that the measurement should be taken using specified tools (NGS or digital PCR) configured to

identify a specific kind of genetic information (polymorphisms) to create profiles unique to the donor or recipient. See Pet. App. 3a-8a. And the '607 patent (which respondents ignore) further requires "selective amplification" and sequencing of "a plurality of genomic regions comprising at least 1,000 [SNPs]." *Id.* at 6a-7a. That additionally requires application of a specific process (selective amplification) to a specific kind of mutation (SNPs) in specific quantities.

The Stanford Patents thus do not merely describe the idea of measuring donor cell-free DNA fragments and telling doctors to measure it "through whatever process the doctor or the laboratory wishes to use." *Mayo*, 566 U.S. at 79. Instead, they identify *specific ways* to measure the phenomenon, which improve upon prior applications of the same phenomenon—because they work for all donors and recipients, and are "sensitive, rapid and inexpensive." C.A.J.A. 118, 142.

The claims in turn would not "disproportionately t[ie] up the use of the underlying natural laws." *Mayo*, 566 U.S. at 73. For example, the claims do not cover the conventional Y-chromosome or HLA allele methods. They leave all other "processes that make use of the [measurement], including later discovered processes that measure [cell-free DNA] in new ways," open for "future innovation." *Id.* at 86-88.

Mayo is therefore inapposite. And a decision by this Court confirming that *Mayo* does not control—thus upholding life-saving method claims—would do much to correct the Federal Circuit's costly mistake.

C. This Case Is An Ideal Vehicle

Respondents' other objections fall flat.

1. Eurofins contends (Opp. 3) that the Stanford Patents cannot be patent eligible because the scientists

"did not discover" the underlying laboratory techniques. Natera similarly asserts (Opp. 22) it "cannot be the case that simply shifting a combination of known techniques from the investigation of one natural phenomenon to the investigation of another" could be patentable.

But it is undisputed that the Stanford scientists *did* discover that these particular techniques could be combined and applied to measure this particular phenomenon—and that it works better than the prior art measurement methods. That falls squarely within Section 101. Section 101 covers "improve[d]" processes. 35 U.S.C. 101. This Court has long held that a "new combination of steps" that achieves "a result heretofore unknown in the art" through the "*application* of" a natural phenomenon, is patentable "even [if] all the constituents of the combination were well known and in common use before the combination was made." *Diamond* v. *Diehr*, 450 U.S. 175, 187-88, 193 n.15 (1981); see *Mayo*, 566 U.S. at 80 (requiring review of claims "as a whole"); *Tilghman* v. *Proctor*, 102 U.S. 707, 718, 729 (1880).

And even if the combination of techniques had previously been used in another context, *the statutory text would still foreclose respondents' argument*: The Patent Act expressly covers a "new use of a known process, machine, manufacture, composition of matter, or material." 35 U.S.C. 100(b); see Michel & Duffy Br. 2, 7-8.

Respondents harp on "conventionality," but conspicuously fail to explain how applying this combination of steps to improve the measurement of this phenomenon was "conventional." Respondents do not dispute (1) that a decade of motivated scientists pursued inferior measurement approaches; (2) that the Stanford Patents broke from those prior methods for measuring this phenomenon; and (3) that the Stanford Patents work better.

If they were "conventional," somebody else would have tried them instead of the inferior Y-chromosome and HLA allele methods.

Eurofins echoes (Opp. 34) the Federal Circuit's unsupported assertion that applying this combination of techniques to this context was somehow "logical" and "straightforward." That analysis is factually wrong, but more importantly has no role in Section 101. That is not an effort to ferret out whether these patents claim a natural phenomenon. It is an inappropriate and conclusory obviousness analysis that circumvents the guardrails in this Court's Section 103 jurisprudence "against slipping into use of hindsight." *Graham* v. *John Deere Co.*, 383 U.S. 1, 36 (1966).

This is a particularly good vehicle for illustrating the mistake because the district court could not have granted summary judgment on obviousness. For example, after a decade of failures, an article shortly before the invention concluded that measurement of the phenomenon was "difficult and impractical." C.A.J.A. 648. The Patents solved that "difficult" problem by departing from the conventional Y-chromosome and HLA allele methods. Afterwards, a leading peer-reviewed journal published the research and that article was cited hundreds of times. D. Ct. Doc. 104-4 ¶ 127 (July 9, 2020). None of that would have happened if the patents "merely reflect[ed] science that had become routine and conventional." *Ibid.* Respondents ignore that evidence, which makes this an unusually strong vehicle.

2. The Federal Circuit further erred by including "conventionality" in step one. Respondents blame petitioners, asserting that petitioners' "improvement[]" argument made that "unavoidable." Eurofins Opp. 33; see Natera Opp. 20-21. But the mistake is easy to avoid—

and the magistrate judge avoided it. As he recognized, the Stanford Patents are directed only to improving upon prior measurement methods, not to the underlying correlation itself. Pet. App. 77a-80a. "How could it be," the magistrate judge asked, that the "focus" of these claims "is to a naturally-occurring correlation, when the patent repeatedly states that this very correlation was already well-known in the art?" *Id.* at 76a-77a. Respondents have no answer.

3. Respondents deny that this case involves "improvements." Natera Opp. 14, 21; Eurofins Opp. 11-12, 21-22. But respondents do not dispute that the patented methods are new, different, and better than the prior methods for measuring this same phenomenon. That makes them "improvement[s]" upon those prior "process[es]." 35 U.S.C. 101.

Respondents assert that there is no reason to think that "improve[d]" methods are more easily shown to satisfy Section 101. See Eurofins Opp. 29. Yes there is. Improvements are necessarily human-made, not natural. And when a patent claims an improved method for measuring a phenomenon, it cannot claim all use of the phenomenon because the previous methods for measuring it necessarily must remain on the table. Pet. 22-23; Michel & Duffy Br. 11-13. "Improvement[s]" thus obviate the preemption concerns that "drive[]" this Court's Section 101 jurisprudence. *Alice Corp. Pty.* v. *CLS Bank Int'l*, 573 U.S. 208, 216 (2014).

4. Respondents have little to say about preemption. Remarkably, Natera does not even mention preemption.

Eurofins does not dispute that the prior art methods are unclaimed, as are any methods using different approaches. Eurofins still asserts (Opp. 7, 31) that the '652

patent "would have a dramatic preemptive effect" because of its "high[] level of generality."

But Eurofins elides critical claim limitations. Contrary to Eurofins' description, the '652 patent does not cover "all" use of "multiplex sequencing," followed by "analysis" of the results, "to observe the natural phenomenon." *Id.* at 25-26. It specifically requires creating "polymorphism profile[s]" by "obtaining a genotype of donor-specific polymorphisms or a genotype of subject-specific polymorphisms," and then using multiplex sequencing to detect and observe the proportion of each. C.A.J.A. 131.

The '652 patent thus claims a *specific way* to measure the natural correlation—by using specified tools to build profiles using a specified kind of genetic information (polymorphisms)—not *every* method for measuring the correlation. It also requires that the method be "greater than 56%" more sensitive than "current surveillance methods," *ibid.*, thus requiring improvement over the prior art. And respondents do not discuss the '497 or '607 patents, which are even more specific. Pet. App. 4a-8a.

The risk is not of "disproportionately tying up the use of the underlying natural laws." *Mayo*, 566 U.S. at 73. The risk is in discouraging investment in cutting-edge, life-saving diagnostics that require enormous investments to bring to market. The harm from the Federal Circuit's misreading of *Mayo* has gone on long enough.

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For the foregoing reasons, and those stated in the petition for a writ of certiorari, the Court should grant the petition or call for the views of the Solicitor General.

Respectfully submitted,

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