No. 24-1129

United States Court of Appeals for the Federal Circuit

GUARDANT HEALTH, INC.,

Appellant

v.

UNIVERSITY OF WASHINGTON,

Appellee

Appeal from the United States Patent and Trademark Office, Patent and Trial Appeal Board in No. IPR2022-00817

APPELLEE UNIVERSITY OF WASHINGTON'S COMBINED PETITION FOR PANEL REHEARING AND REHEARING EN BANC

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Dated: March 16, 2026

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 2024-1129

Short Case Caption Guardant Health, Inc. v. University of Washington

Filing Party/Entity University of Washington

Instructions:

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Date: 11/21/2023

Signature: /s/ Ralph Wilson Powers III

Name: Ralph Wilson Powers III

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
University of Washington	TwinStrand Biosciences, Inc.	

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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).

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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)?

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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

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INTRODUCTION

The panel decision adopts a sweeping rule: when two claim elements appear together in a single prophetic prior-art embodiment, their combination is obvious as a matter of law—regardless of how sparse the description of the combination, regardless of evidence that a skilled artisan would lack motivation to implement such a combination, and regardless of evidence that the artisan would lack any expectation of success. Op. 9, 13. That rule defies precedent and logic alike.

Below, Guardant argued that the University of Washington's DNA sequencing patent would have been obvious based on two prior-art references. Guardant's theory depended on combining a particular method of DNA amplification (rolling circle replication, or "RCR") with a particular method of DNA sequencing (SMRT sequencing). RCR and SMRT sequencing are mentioned together "once"—in passing—in one of the references. Op. 6. The Board correctly rejected Guardant's theory that a skilled artisan would combine RCR and SMRT sequencing based on a mountain of evidence showing that the combination was unworkable. Appx30-45.

The panel did not dispute the Board's account of that evidence. Instead, it deemed the evidence irrelevant. The panel held that, because RCR and SMRT sequencing are mentioned together in a prophetic prior-art embodiment,

considerations of motivation to combine and reasonable expectation of success simply do not matter.

That holding cannot be reconciled with *Impax Laboratories Inc. v. Lannett Holdings Inc.*, 893 F.3d 1372 (Fed. Cir. 2018), which affirmed a finding of no motivation to combine and no reasonable expectation of success *even though* the prior art "expressly disclosed" the claimed combination. *Id.* at 1379. Nor can it be squared with settled law requiring courts to consider not just "[e]vidence suggesting reasons to combine" but also "evidence suggesting reasons not to combine." *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1363 (Fed. Cir. 2017). The University discussed both cases at length in its briefing—but the panel ignored them.

The panel's rule also does not make sense. A reference's passing disclosure of a hypothetical combination of elements—without describing why or how one would combine them—does not dispositively prove skilled artisans *would* pursue the combination. And it certainly does not prove the artisan *could* successfully do so using only ordinary skill. A reference that discloses a rocket engine and says it could theoretically be attached to a Buick does not render obvious a car capable of space travel.

The panel remarked that an obviousness analysis does not require a patent challenger "to re-do the work already done in [a] prior art reference." *General*

Elec. Co. v. Raytheon Techs. Corp., 983 F.3d 1334, 1352 (Fed. Cir. 2020). True. But that statement presupposes that the reference actually *did the work* to explain *why* the combination would be pursued and—even more critically—*how* it would be accomplished. The panel's rule leaves no room for that inquiry. Under the panel's reasoning, the mere presence of the combination in the prior art—no matter how unexplained, unworkable, or implausible—renders motivation to combine *and* reasonable expectation of success categorically irrelevant. That is particularly illogical vis-à-vis reasonable expectation of success. Just because the prior art proposes combining two things does not conclusively prove that skilled artisans would expect the combination to work—particularly where, as here, the patentee adduces voluminous evidence showing it would not.

The panel's rule collapses obviousness into anticipation, invites hindsight bias, and threatens to foreclose patent protection for inventions that the art merely speculated about but could not actually achieve. Rehearing should be granted.

POINTS OF LAW OR FACT OVERLOOKED OR MISAPPREHENDED BY THE COURT

The panel failed to address *Impax*, whose holding conflicts with the panel's reasoning in this case.

RULE 40(C) STATEMENT OF COUNSEL

Based on my professional judgment, I believe the panel decision is contrary to the following precedents of this court: *Impax* and *Arctic Cat*.

I further believe this appeal requires an answer to the following precedent-setting question of exceptional importance:

Whether the presence of two claim elements together in a prior-art embodiment, standing alone, dispositively proves that the combination of those elements would be obvious—notwithstanding the level of detail in the disclosure and notwithstanding any contrary evidence demonstrating that a skilled artisan would lack a motivation to combine the elements or a reasonable expectation of success in doing so.

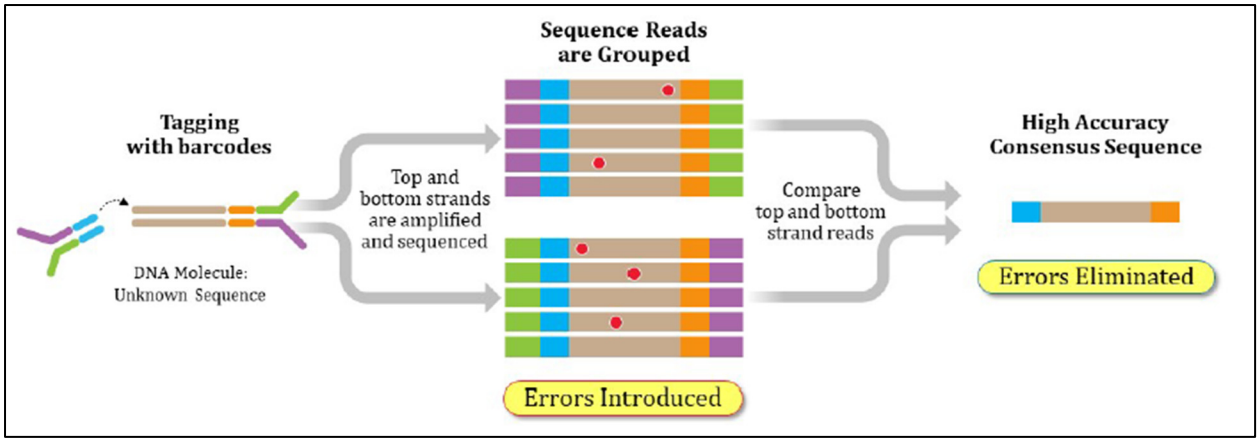
/s/ William H. Milliken
William H. Milliken

Counsel for Appellee University of Washington

BACKGROUND

This is an appeal from an inter partes review of the University of Washington's U.S. Patent No. 10,760,127, which describes a breakthrough method of high-fidelity DNA sequencing. The invention allows researchers to distinguish signal from noise in DNA sequencing data to detect ultra-rare genetic mutations—in turn enabling superior diagnosis and treatment of life-threatening conditions.

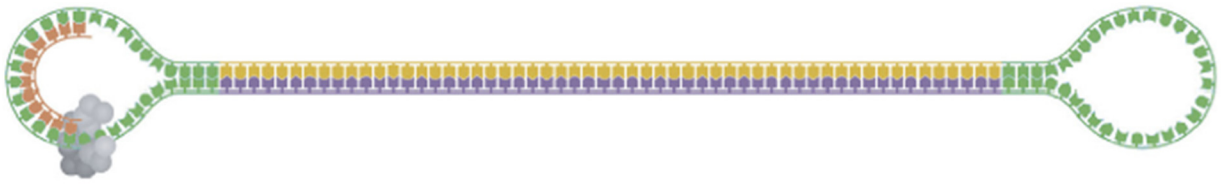
As relevant here, the claims require "amplifying" DNA templates—making copies of tagged strands of target DNA—before sequencing the amplified copies. Appx87(37:37-52). Because mistakes arise in both amplification and sequencing, Appx69(1:60-2:7), sequencing many copies of a given strand improves accuracy by imposing redundancy. *E.g.*, Appx69(2:17-26). The invention further enables *relating* sequence reads by family (i.e., confirming that a particular read is derived from a particular DNA strand) and *distinguishing* "top" strands from "bottom" strands within a family. Appx76-77(15:22-17:12). Because the top and bottom stands of a DNA molecule are complementary, sequence reads from the two strands operate as a cross-check on one another. Appx76-77(16:59-17:12). In this way, the invention enables distinguishing between errors and true mutations. *Id.* The following schematic provides an overview of the process:



A. The proceedings below

After the University sued Guardant for infringing the '127 patent—a suit that eventually led to a finding of willful infringement and an eight-figure damages award—Guardant filed an IPR. Guardant argued that the claims would have been obvious over Travers '075 and Travers 2010, two references authored by employees of Pacific Biosciences (PacBio). The references are "mainly directed to" a PacBio DNA sequencing method called "SMRT sequencing." Op. 5-6 & nn.1-2.

Unlike the '127 patent, SMRT sequencing does not use a template amplification step. Appx1587. It employs topologically circular DNA templates called "SMRTbells":



Appx1585. These SMRT bells are sequenced in extremely narrow wells arrayed on a "zero-mode waveguide" (ZMW) chip. Appx4221. The circular nature of the SMRTbell allows for repeatedly sequencing "around the circle" of the target DNA, achieving sequencing redundancy *without* amplification. Appx427. This lack of a template amplification step is widely recognized as an "advantage" of SMRT sequencing. Appx431-432 (collecting evidence).

Because SMRT sequencing does not employ template amplification as required by the '127 patent claims, Guardant's obviousness argument relied on a hypothetical modification to SMRT sequencing that is not mentioned in Travers 2010 at all and is "only mentioned once" in Travers '075. Op. 6; Appx183-185. Travers '075 ¶122 states that SMRTbells may be subjected to rolling circle replication to produce concatemer molecules that may then be "employed directly" in SMRT sequencing. Appx1532-33(¶122). But neither that paragraph nor anywhere else in the Travers references explains *why* or *how* this would be done.

Despite Travers having invited future researchers to perform SMRT sequencing of RCR concatemers, no one ever took him up on the offer. There is no evidence that *anyone* has *ever* used an RCR step in SMRT sequencing in the fifteen years since the method was developed. That is for good reason. As the University explained, citing over 100 paragraphs of supporting expert testimony, a skilled artisan would not have tried that and would not have expected it to work.

Appx425-472; Appx3424-3493(¶¶96-210). Adding an RCR amplification step to SMRT sequencing would create several intractable technical problems that would have rendered the method unworkable.

Most fundamentally, sequencing an RCR concatemer (a large star-shaped structure) using the PacBio method (designed for long, narrow SMRTbells) would have produced unreadable sequencing data. Appx438-442; Appx3442-3447(¶¶128-137). Additionally, the RCR concatemers would have varied significantly in size. Those most likely to find their way into a ZMW well for sequencing would have been small and incomplete, further compromising the quality of the sequencing data. Appx442-462; Appx3447-3468(¶¶138-169). And larger RCR concatemers that *did* have sufficient redundancy would be too bulky to fit into the ZMW wells. Appx3468-3491(¶¶170-205). In short, despite what Travers suggested might be possible, SMRT sequencing RCR concatemers was doomed to fail.

The Board found that the approach proposed in ¶122 would have presented insurmountable problems that would have "dissuaded" a skilled artisan from trying it. Appx37; *see* Appx30-45. And, "even if a skilled artisan would have pursued" that approach, she would not have expected success in implementing it. Appx37-38. Quite the contrary: the skilled artisan would have thought the approach "futil[e]." Appx37; *see* Appx30; Appx45. So the Board found the claims not unpatentable.

B. The panel's decision

1. Guardant appealed, arguing that the Board erred in requiring a showing of motivation to combine and reasonable expectation of success because the amplification and sequencing steps at issue were both disclosed in ¶122 of Travers '075. BBr. 35-49. Guardant also attacked the Board's factual findings. BBr. 49-72.

In response, the University showed—relying on *Impax*—that Guardant's legal argument was wrong. RBr. 40-44. And the University showed that the Board's factual findings enjoyed substantial-evidence support. RBr. 48-67.

2. The panel did not disturb the Board's extensive findings that Travers' ¶122 embodiment would have produced a "a jumbled mess" of sequencing data that would have rendered it utterly "unworkable." Appx31; Appx38. Instead, the panel held that those findings were categorically irrelevant.

In the panel's view, because ¶122 "expressly discloses performing" amplification and sequencing and "the Petition did not rely on modifying these two steps to arrive at the claimed invention," nothing else matters. Op. 2. Relying on *General Electric*, the panel held that, "[w]hen the disputed elements of a claim are disclosed in a single embodiment in a single reference, no finding regarding a motivation to combine to arrive at those claimed elements is required." Op. 9. The

panel further held that, in such a circumstance, the challenger need not prove reasonable expectation of success either. Op. 13.

In so holding, the panel incorrectly stated that the University had not "cited a case that requires a party to demonstrate a reasonable expectation of success in combining two elements to arrive at the claimed invention when those elements are disclosed in a single embodiment of a single prior art reference." Op. 13. That is wrong: *Impax* is exactly such a case.

Having concluded that motivation to combine and reasonable expectation of success were immaterial, the panel vacated and remanded. This petition followed.

ARGUMENT

I. The panel decision conflicts with foundational principles of obviousness law.

The University showed, and the Board found, that applying SMRT sequencing to an RCR concatemer would have been "unworkable" and "futil[e]," resulting in "unsequenceable" DNA templates. Appx22; Appx30-31; Appx37; Appx45. Indeed, Travers '075 itself teaches methods of "*prevent[ing] concatemerization*." Appx36 (quoting Appx1350(¶105)). And—with the sole exception of Travers '075 ¶122—the prior art as a whole uniformly taught that SMRT sequencing *does not use amplification*. *See* Appx22; Appx24; Appx431-432; Appx1587. In short, a skilled artisan simply would not have tried the

hypothetical approach passingly mentioned in ¶122. Appx36-37. And, even if the skilled artisan had done so, she would not have expected it to work. Appx37.

The panel disputed none of this. Instead, the panel said none of it matters. On the panel's logic, the presence of two elements together in one prior-art embodiment makes motivation to combine and reasonable expectation of success irrelevant—the combination is obvious, period. Op. 9-14. Or, stated equivalently, such a showing *conclusively proves* that a skilled artisan would be motivated to combine the elements *and* would reasonably expect success in doing so.

That holding defies precedent. It is established law that the prior art's passing reference to a combination of elements does not itself dispositively establish a motivation to combine those elements or a reasonable expectation of success in doing so. *Infra* § I.A. It is equally established that an obviousness analysis must consider the whole record, *including* evidence undermining motivation to combine and reasonable expectation of success. *Infra* § I.B. The panel decision flouts those principles. And, if permitted to take root, it threatens to wreak havoc with the law of obviousness—"the most important and most litigated of the conditions of patentability." *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1074 n.2 (Fed. Cir. 2016) (Dyk, J., dissenting).

A. The panel decision defies *Impax* and invites hindsight reconstruction.

1. The panel decision is flatly contrary to *Impax*. The claims there required a nasal formulation of zolmitriptan. 893 F.3d at 1375. A single prior-art reference, Chauveau, disclosed formulations of active ingredients with capryl caproyl macrogol glycerides and stated that the "nasal route" was the "preferred" mode of administration. *Id.* at 1379. Chauveau also disclosed that the active substance may be "a triptan, such as sumatriptan or zolmitriptan." *Id.* The reference thus "expressly disclosed using zolmitriptan in a nasal spray." *Id.* No "selection from a large list of elements," Op. 14, was required; the reference disclosed a zolmitriptan formulation as a standalone embodiment and stated that the "preferred" route of administration was nasal. *Impax*, 893 F.3d at 1379.

Yet—despite Chauveau's "express mention of zolmitriptan in connection with nasal formulations"—this Court affirmed the district court's finding that a skilled artisan "would not have been motivated to make nasal formulations of zolmitriptan or had a reasonable expectation of success in doing so." *Id.* at 1378-79. That was because the patentee presented evidence that "it would have been absolutely counterintuitive to make a nasal spray" formulation of zolmitriptan. *Id.* at 1380, 1382. Such a formulation would fail to result in zolmitriptan's active metabolite, which was thought necessary for efficacy. *Id.* So, the district court—

properly accounting both for "what Chauveau discloses and the state of the prior art as a whole"—permissibly found the formulation non-obvious. *Id.* at 1382.

Impax formed the centerpiece of the University's response to Guardant's legal argument. RBr. 40-44. The case could hardly be more on point. Chauveau's passing—albeit "express"—mention of zolmitriptan nasal sprays did not render them obvious given evidence that skilled artisans viewing the art as a whole would have found that approach "counterintuitive" and unlikely to succeed. 893 F.3d at 1380. Similarly, Travers '075's passing—albeit express—mention of SMRT sequencing RCR concatemers does not render it obvious given evidence that skilled artisans viewing the art as a whole would have viewed that approach "unworkable" and "futil[e]." Appx31; Appx37-38. Yet the panel did not so much as cite *Impax*. That oversight alone justifies rehearing.

Impax is not just binding circuit precedent; it makes eminent sense. That a prior-art reference passingly suggests a given course without describing how to implement it does not, without more, prove those in the field could implement it using only ordinary skill, without doing the difficult work of invention. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007) (even if a skilled artisan would have found it obvious to apply a known technique to a particular problem in the way claimed, the invention is not obvious if the technique's "actual application is beyond his or her skill"). Chief Judge Moore made this very point at oral

argument: many references offer only "wish lists" or "grandiose claim[s]" of combinations without explaining how to execute them. Such descriptions do not "really disclos[e]" the combination. Oral Arg. 34:02-35.

2. As Chief Judge Moore's observation illustrates, the panel's rule is particularly illogical vis-à-vis the reasonable-expectation-of-success requirement. *See* Op. 13. Even if the presence of two elements together in a prior-art embodiment suffices to prove motivation to combine, it decidedly should not suffice to prove reasonable expectation of success. *Cf. Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1344 (Fed. Cir. 2021) (finding of motivation to combine "does not necessarily imply that the challenger has also met its burden of showing a reasonable expectation of success"). The prior art is full of speculation, musings, and implausible proposals. Just because someone proposes a combination does not, as a matter of law or logic, mean skilled artisans would reasonably expect it to work. *Cf. In re Swartz*, 232 F.3d 862, 863-64 (Fed. Cir. 2000) (affirming rejection of claims to cold fusion for lack of utility and enablement).

The reasonable-expectation-of-success inquiry operates as a critical bulwark against hindsight bias. *See, e.g.*, *University of Strathclyde v. Clear-Vu Lighting LLC*, 17 F.4th 155, 165 (Fed. Cir. 2021); *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1363 (Fed. Cir. 2009). The panel's rule would jettison that requirement merely because a given combination happens to appear in a single

prior-art embodiment—no matter how meager the discussion of its implementation or how problematic it would prove. That contravenes this Court's precedent, blurs the line between anticipation and obviousness, and invites the sort of hindsight reconstruction this Court has decried. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070-71 (Fed. Cir. 2012) ("hindsight claims of obviousness" that "merely throw metaphorical darts at a board in hopes of arriving at a successful result" should be "reject[ed]"). That danger is heightened in an era when automated tools can generate countless hypothetical combinations untethered from technical feasibility. *See generally* USPTO Request for Comments Regarding the Impact of the Proliferation of Artificial Intelligence on Prior Art, 89 Fed. Reg. 34,217 (April 30, 2024). The Court should not invite that result.

B. The panel decision defies the precept that an obviousness analysis must consider the prior art as a whole—including evidence suggesting reasons not to combine.

It is black-letter law that "[e]vidence suggesting reasons to combine cannot be viewed in a vacuum apart from evidence suggesting reasons not to combine." *Arctic Cat*, 876 F.3d at 1363. "Even a single reference" can include statements "suggesting a combination and others critiquing or otherwise discouraging" it. *Id.* at 1360. And "it is error to fail to consider the entirety of the art." *Id.*

The panel made exactly that error here. Even assuming ¶122 suggested SMRT sequencing an RCR-amplified concatemer, the obviousness analysis cannot not ignore the ample contrary evidence. It is relevant that canonical SMRT sequencing did not involve amplification (an art-recognized advantage of the process). Appx22. It is relevant that implementing ¶122's approach would entail myriad technical problems. Appx30-45. It is relevant that that Travers '075 recommends "prevent[ing] concatem[e]rization" before sequencing. Appx36. And it is relevant that—so far as this record shows—no one has *ever* attempted to apply SMRT sequencing to an RCR concatemer since Travers' 075 published. Appx589.

The panel's rule would have the factfinder ignore all this evidence. Under the panel's reasoning, any combination—no matter how fraught with problems—is obvious *as a matter of law* so long as it is mentioned in one embodiment of a prior-art reference. That holding contravenes decades of obviousness precedent. *See Arctic Cat*, 876 F.3d at 1360; *Application of Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965) (obviousness analysis may not "pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests").

Indeed, the panel's holding contravenes the panel's own observation that the prior art must be considered "for all that it teaches." Op. 14. To be sure, the embodiment disclosed in ¶122 is relevant to the analysis. But so are the numerous

teachings catalogued above that point decisively *away* from that proposal. Relevant, too, is Travers' failure to "teach" *anything* of substance regarding the ¶122 embodiment. Travers does not say why one would do this or how it would be done. It does not explain how to surmount the "multitude of technical issues" the Board identified. Appx45. Willful blindness to such evidence flies in the face of both fundamental evidentiary principles and basic obviousness law.

II. The panel's attempt to justify its holding fail.

The panel appeared to believe that its categorical rule necessarily followed from this Court's post-*Impax* decision in *General Electric*. Op. 9. Not so.

General Electric held that—on the particular facts there, where the elements in question appeared in one reference *and* the patentee presented no evidence tending to undercut motivation to combine—the Board erred in requiring evidence of a separate motivation. 983 F.3d at 1352. *General Electric* does not stand for a categorical rule that the presence of two elements together in a single prior-art embodiment renders motivation to combine and reasonable expectation of success irrelevant. If it did, it would squarely contradict *Impax* (which would in any event underscore—not undermine—the need for en banc review). *See* IOP #13(2)(a).[1]

[1] Nor does *Realtime Data, LLC v. Iancu*, 912 F.3d 1368 (Fed. Cir. 2019) (cited at Op. 11-12) stand for such a rule. That case holds only that a challenger need not prove a motivation to combine Reference A with Reference B if Reference A by itself discloses every claim limitation.

Moreover, even the broadest possible reading of *General Electric* would not support the panel's holding as it concerns reasonable expectation of success. RBr. 46 & n.9. *General Electric* expressly declined to address the reasonable-expectation-of-success requirement because the challenger had indisputably proven that below: "the Board did not adopt Raytheon's argument that GE did not show a reasonable expectation of success in combining Wendus and Moxon." 983 F.3d at 1352. If anything, the quoted language suggests that the *General Electric* court believed that a showing of reasonable expectation of success *was* required—*even though* the relevant elements appeared in one prior-art embodiment.

On appeal, Guardant repeatedly cited *General Electric* for the proposition that it was not required to "re-do the work already done" in Travers '075. *E.g.*, BBr. 5; *see* Op. 10. But that framing elides a critical point: Travers '075 *did no work* to show how RCR amplification and SMRT sequencing would be successfully combined. *See* Op. 6.

Nor does *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359 (Fed. Cir. 2016) (cited at Op. 13) address the question here. The panel cited *Intelligent Bio-Systems* for the proposition that "[t]he reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention," *id.* at 1367—apparently implying that this requirement comes into play *only* when a combination of references is at

issue. But that does not follow. *Intelligent Bio-Systems* addressed a combination of references, *id.*, so naturally it framed its analysis in terms of whether there was a reasonable expectation of success "combining references." The case says nothing about whether a reasonable expectation of success need be shown when the relevant disclosures appear in one prior-art embodiment.

Impax, in contrast, squarely answers that question in the affirmative. 893 F.3d at 1378, 1380; *contra* Op. 13. And the University is aware of no case—from this Court or any other—that holds otherwise. *See* Oral Arg. 35:25-30 (Chief Judge Moore making this point).

* * *

An aspirational, unexplained disclosure of two elements together in the prior art does not dispositively prove that combining those elements would have been obvious. The panel's contrary holding defies precedent and invites hindsight reconstruction. The panel—or, failing that, the en banc Court—should grant rehearing and affirm the decision below.

CONCLUSION

The petition should be granted.

Dated: March 16, 2026

Respectfully submitted,

/s/ William H. Milliken

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ADDENDUM

NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

GUARDANT HEALTH, INC.,
Appellant

v.

UNIVERSITY OF WASHINGTON,
Appellee

2024-1129

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2022-00817.

Decided: January 23, 2026

E. JOSHUA ROSENKRANZ, Orrick, Herrington & Sutcliffe LLP, New York, NY, argued for appellant. Also represented by SAMANTHA MICHELLE LEFF; TRAVIS JENSEN, Menlo Park, CA; RAGHAV KRISHNAPRIYAN, ELIZABETH MOULTON, San Francisco, CA; SONJA ROCHELLE GERRARD, JAD ALLEN MILLS, MICHAEL T. ROSATO, Wilson, Sonsini, Goodrich & Rosati, PC, Seattle, WA; RICHARD TORCZON, Washington, DC.

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PLLC, Washington, DC, argued for appellee. Also represented by RICHARD CRUDO, DAVID HOLMAN, BYRON LEROY PICKARD, RALPH WILSON POWERS, III.

Before MOORE, *Chief Judge*, HUGHES and STOLL, *Circuit Judges*.

STOLL, *Circuit Judge*.

Guardant Health Inc. appeals the final written decision of the Patent Trial and Appeal Board holding claims 1–30 of the University of Washington's U.S. Patent No. 10,760,127 not unpatentable under 35 U.S.C. § 103. On appeal, Guardant challenges the Board's decision requiring a motivation to combine and a reasonable expectation of success where the elements of amplification followed by sequencing were disclosed together in a single embodiment in a single reference. Guardant also asserts that substantial evidence does not support the Board's findings of no motivation to combine or reasonable expectation of success. We determine that the Board erred by requiring Guardant to show that a skilled artisan would have had a motivation to combine the steps of amplification followed by sequencing and would have had a reasonable expectation of success in performing the amplification and sequencing steps because the prior art reference expressly discloses performing those steps in sequence and the Petition did not rely on modifying these two steps to arrive at the claimed invention. Thus, we vacate the Board's unpatentability determination and remand for further proceedings consistent with this opinion.

BACKGROUND

I

The '127 patent is directed to a method for reducing the error rate in massively parallel DNA sequencing using Duplex Consensus Sequencing (DCS). U.S. Patent

No. 10,760,127 Title, Abstract, col. 17 ll. 3–10. The specification explains that massively parallel DNA sequencing has been used for clinical applications such as prenatal screening for aneuploidy and early detection of cancer and monitoring its response to therapy with nucleic acid-based serum biomarkers. The specification further states that massively parallel DNA sequencing has the "unique ability to detect minor variants within heterogenous mixtures." '127 patent col. 1 ll. 32–41. According to the specification, however, this type of sequencing has limitations, including errors that may occur during sample preparation and sequencing. These errors create "a practical limit of detection" leading to "approximately 1% of bases" being incorrectly identified. *Id.* at col. 1 l. 60–col. 2 l. 8. The specification goes on to state that "[t]his background level of artifactual heterogeneity establishes a limit below which the presence of true rare variants is obscured." *Id.* at col. 2 ll. 8–10. The specification then states that "[i]t would be desirable to develop an approach for tag-based error correction, which reduces or eliminates artifactual mutations arising from DNA damage, PCR errors, and sequencing errors; allows rare variants in heterogenous populations to be detected with unprecedented sensitivity; and . . . capitalizes on the redundant information stored in complexed double-stranded DNA." *Id.* at col. 2 l. 63–col. 3 l. 2.

The '127 patent then discloses the use of DCS for lowering the error rate of sequencing. The specification discloses that DCS involves: (1) "ligating [i.e., attaching] a double-stranded target nucleic acid molecule to at least one [single molecule identifier (SMI)] adaptor molecule to form a double-stranded SMI-target nucleic acid complex;" (2) "amplifying [i.e., copying] the double stranded SMI-target nucleic acid complex;" and (3) "sequencing [i.e., determining the linear sequence of] the amplified SMI-target nucleic acid products." *Id.* at col. 3 ll. 18–27.

Claim 1 is illustrative of the claims on appeal and recites:

> 1. A method of sequencing DNA comprising:
>
> a) attaching adapters to double-stranded DNA fragments to generate a plurality of partially-complementary, asymmetrical double-stranded adapter-DNA molecules, wherein the adapters comprise barcodes selected from a plurality of distinct barcode sequences;
>
> b) *amplifying original strands of at least a portion of the double-stranded adapter-DNA molecules to produce first and second strand copies*;
>
> c) *sequencing a plurality of first and second strand copies to obtain first and second strand sequence reads for at least a portion of the adapter-DNA molecules*; and
>
> d) for at least some of the adapter-DNA molecules comprising barcodes—
>
> confirming the presence of at least one sequence read derived from each of the original first and second strands of the adapter-DNA molecules;
>
> comparing at least one of the confirmed first and second strand sequence reads to a reference sequence; and
>
> analyzing one or more correspondences between at least one of the confirmed first and second strand sequence reads and the reference sequence to identify a sequence variation.

Id. at col. 37 ll. 31–52 (emphases added to highlight the claim limitations in dispute). Limitation 1.b, which involves "amplifying," and limitation 1.c, which involves "sequencing," are relevant on appeal.

II

The claims were challenged as unpatentable under 35 U.S.C. § 103 in light of four prior art references, though

not all four are relevant on appeal. We describe only the two prior art references necessary to address Guardant's challenges on appeal. The obviousness ground at issue on appeal is Travers '075[1] in view of Travers 2010.[2] We describe each reference below.

TRAVERS '075

Travers '075 is a patent application publication directed to compositions and methods for nucleic acid sequencing assigned to PacBio. J.A. 1501. Travers '075 mainly teaches Single Molecule Real Time (SMRT™) sequencing. J.A. 1522 ¶ 43. SMRT sequencing uses a nucleic acid synthesis complex comprising a polymerase enzyme, a template sequence, and a primer sequence, which is complementary to a portion of the template sequence. J.A. 1522 ¶ 43. This complex is immobilized within a confined illumination volume, or wells, which are part of a zero mode waveguide (ZMW) array. *Id.*; J.A. 1535 ¶ 141. The complex is surrounded by a reaction mixture containing the four different nucleotides (A, G, T, and C), each of which is labeled with a spectrally distinguishable fluorescent label attached to its terminal phosphate group. J.A. 1522 ¶ 44. The fluorescent label of the free nucleotides provides a short signal while a nucleotide incorporated by the polymerase in a primer extension provides a longer signal. *Id.* This technique allows the identity of each base to be detected in real time. J.A. 1522 ¶ 45.

One of the exemplary embodiments in Travers '075 teaches a circular template comprising a double-stranded

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1 U.S. Patent Application No. 2009/0298075 A1.

2 Kevin J. Travers et al., *A Flexible and Efficient Template Format for Circular Consensus Sequencing and SNP Detection*, 38 Nucleic Acids Research e159 (2010). Travers 2010 was authored by Pacific Biosciences (PacBio) employees.

portion linked by two single stranded portions. J.A. 1504 Fig. 2B; J.A. 1523 ¶ 50. Travers '075 teaches the application of the SMRT sequencing process to the circular template. J.A. 1505 Fig. 3B; J.A. 1523–24 ¶ 55.

Even though Travers '075 is mainly directed to SMRT sequencing, paragraph 122 discloses an embodiment in which replication occurs followed by SMRT sequencing as follows:

> Although the constructs of the invention are described primarily, and preferably, for use directly as templates for, e.g., sequencing applications, it will be appreciated that these structures may also serve as intermediate structures in the preparation of templates that provide for sequence redundancy in line with that provided by such constructs. For example, the structurally circular nucleic acid segments described herein, *may be used as templates in a rolling circle replication process* to produce concatemer molecules that include repeating copies of both the sense and antisense strands of the originating double stranded segment included within the circular nucleic acid. These replicated products *may then be employed directly as template molecules in a template dependent sequencing process* . . . .

J.A. 1532–33 ¶ 122 (emphases added).

Rolling circle replication (RCR) is only mentioned once in Travers '075—i.e., in paragraph 122—making this the sole disclosure of sequentially performing RCR amplification followed by sequencing.

TRAVERS 2010

As in Travers '075, Travers 2010 teaches the same SMRT sequencing method, using a SMRTbell template, similar to the circular template in Travers '075, for SMRT sequencing. J.A. 1585. Like the circular template in

Travers '075, the SMRTbell template taught by Travers 2010 has a double-stranded region flanked by two hairpin loops or single-stranded regions. *Id.* According to Travers 2010, "this format resembles a linear double-stranded molecule, and yet it is topologically circular." J.A. 1583, Abstract. Like Travers '075, Travers 2010 teaches applying the SMRTbell template to SMRT sequencing. J.A. 1585. Travers 2010 states that the SMRT sequencing process "does not depend on amplification." J.A. 1587.

III

Guardant petitioned for inter partes review of claims 1–30 of the '127 patent based on the combination of Travers '075 and Travers 2010. Guardant referred to Travers '075 and Travers 2010 collectively as the Travers Publications in its Petition. In its Petition, Guardant argued the Travers Publications disclose limitation 1.b, which involves "amplifying," and limitation 1.c, which involves "sequencing," and thus render claim 1 obvious. J.A. 183–85. Regarding limitation 1.b, Guardant cited paragraph 122 of Travers '075's disclosure of "rolling circle replication" of SMRT bell templates as evidence that Travers '075 discloses the amplification step. J.A. 183–84. Guardant argued that the sequencing step taught by limitation 1.c was also disclosed by paragraph 122 of Travers '075, where the products of RCR amplification are then employed in a sequencing process. J.A. 184–85. The Board instituted review. J.A. 333–55.

In its Patent Owner Response, UW argued that Guardant failed to show that a skilled artisan would have had a motivation to modify the SMRT sequencing process with the RCR amplification step disclosed in Travers '075 with a reasonable expectation of success. J.A. 426–66. UW also argued that Travers '075 did not enable RCR amplification followed by SMRT sequencing. J.A. 466–68.

In its Final Written Decision, the Board determined that Guardant did not demonstrate by preponderant evidence that a skilled artisan would have had a reason to combine, or a reasonable expectation of success in performing RCR amplification followed by SMRT sequencing. J.A. 21–22. Specifically, the Board found that a skilled artisan would not have modified the Travers Publications to perform RCR amplification followed by SMRT sequencing because it would render the SMRT sequencing on ZMWs disclosed in the Travers Publications unworkable. J.A. 45. The Board did not reach the issue of whether Travers '075 enabled RCR amplification followed by SMRT sequencing.

Guardant appeals. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

"We review the Board's legal conclusions de novo and its factual findings for substantial evidence." *Univ. of Strathclyde v. Clear-Vu Lighting LLC*, 17 F.4th 155, 160 (Fed. Cir. 2021). "The substantial evidence standard asks 'whether a reasonable fact finder could have arrived at the agency's decision,' and 'involves examination of the record as a whole, taking into account evidence that both justifies and detracts from an agency's decision.'" *OSI Pharms., LLC v. Apotex, Inc.*, 939 F.3d 1375, 1381–82 (Fed. Cir. 2019) (quoting *In re Gartside*, 203 F.3d 1305, 1312 (Fed. Cir. 2000)).

Obviousness is a legal question based on underlying findings of fact. *Strathclyde*, 17 F.4th at 160. A claim is unpatentable as obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art." 35 U.S.C. § 103(a).[3] The inquiries of whether the prior art discloses a claim limitation, whether a skilled artisan would have been motivated to modify or combine teachings in the prior art, and whether she would have had a reasonable expectation of success in doing so are questions of fact, reviewed for substantial evidence. *Strathclyde*, 17 F.4th at 160.

On appeal, Guardant asserts that the Board erred by requiring a motivation to combine and a reasonable expectation of success because the amplification and sequencing steps are both taught by paragraph 122 of Travers '075. We address these issues in turn.

I

Guardant argues that the Board erred when it required Guardant to show a persuasive motivation to modify Travers to perform RCR amplification before SMRT sequencing when those steps are disclosed in Travers '075. According to Guardant, a motivation to combine the steps was not required because the two steps were disclosed in a single embodiment in a single prior art reference. We agree. When the disputed elements of a claim are disclosed in a single embodiment in a single reference, no finding regarding a motivation to combine to arrive at those claimed elements is required. Our case law supports this conclusion. In *General Electric Co. v. Raytheon Technologies Corp.*, for example, we held that it is error to "require a motivation to combine each element of the claim—even those present together in a reference." 983 F.3d 1334, 1352 (Fed. Cir. 2020). We reasoned that such an approach "unduly

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[3] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. § 103, effective March 16, 2013. Because the '127 patent has an effective filing date before March 16, 2013, the pre-AIA version of § 103 applies.

dissects prior art references into collections of individual elements, requiring a party showing obviousness to re-do the work already done in the prior art reference." *Id.*

The Board erred when it required Guardant to show that a skilled artisan would have been motivated to combine the steps of performing RCR amplification followed by SMRT sequencing because both steps were expressly disclosed in a single embodiment in Travers '075 paragraph 122. It is undisputed that the claimed method requires the amplification step to occur before the sequencing step, and that the sequencing step requires sequencing the amplified adapter-DNA products from the amplification step. J.A. 10. The parties do not dispute that the RCR process taught by Travers '075 is a type of amplification process. Appellant's Br. 35; Appellee's Br. 25. The parties also do not dispute that the SMRT sequencing process is a type of sequencing process. Appellant's Br. 35; Appellee's Br. 25–26. The parties do not dispute that paragraph 122 of Travers '075 teaches amplification followed by sequencing. As such, there is no need to show that a skilled artisan would have been motivated to modify a reference to perform two claim steps one after the other when the reference itself already discloses those limitations together in the same sequence required by the claims.

UW argues that Guardant never presented an argument solely relying on Travers '075 before the Board, and thus the Board did not err in requiring that Guardant show a motivation to combine. Appellee's Br. 33–38. We disagree. In its Petition, Guardant cited the embodiment in paragraph 122 of Travers '075 that expressly teaches the steps of amplification followed by sequencing. Regarding claim limitation 1.b, Guardant's Petition specifically stated: "Travers['075] further describes amplification of template molecules prior to redundant sequencing. For example, Travers['075] explains that 'rolling circle replication' of SMRTbell templates produces concatemer molecules comprising 'repeating copies of both the sense

and antisense strands of the originating double stranded segment.'" J.A. 183–84 (quoting Travers '075 J.A. 1532–33, ¶ 122). The Petition also cited Figures 1 and 4 of Travers 2010, but Figures 1 and 4 are not directed to RCR or any other amplification process. J.A. 184; J.A. 1585, 1588. Instead, these figures illustrate and disclose the details regarding sequencing of the SMRTbell template. With respect to limitation 1.c, Guardant's Petition stated: "Travers['075] discloses that either SMRTbell templates or replication products therefrom (i.e., concatemers) may be sequenced using the disclosed template-dependent sequencing process." J.A. 184 (citing Travers '075 J.A. 1532–33, ¶ 122). The Petition also cited Travers 2010 for its teaching regarding SMRT sequencing. J.A. 166, 175–76.

The Petition, however, did not rely on modifying Travers '075 or Travers 2010 to perform RCR replication of SMRTbell templates followed by SMRT sequencing and the Board abused its discretion to the extent it found otherwise.[4] As such, the Board erred in requiring Guardant to provide a motivation to so modify the Travers Publications. Our decision in *Realtime Data, LLC v. Iancu*, 912 F.3d 1368 (Fed. Cir. 2019), is instructive. There, the petitioner argued that all the elements of challenged claim 1 were disclosed in a single prior art reference, O'Brien. *Realtime Data*, 912 F.3d at 1371. The petitioner alternatively argued that the claims would have been obvious in view of O'Brien combined with a secondary prior art reference—which did not disclose all elements of the claim on its own. *Id.* The Board agreed that O'Brien taught every limitation of the challenged claims and determined that the claims thus would have been unpatentable under both references. *Id.* at 1371–72. The patent owner appealed, arguing that

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[4] The Board never explicitly found that the Petition relied on modifying Travers '075 or Travers 2010.

the Board erred in determining a skilled artisan would have been motivated to combine the references. *Id.* at 1372. We held that the Board was free to conclude that O'Brien alone disclosed every element of the challenged claims. *Id.* at 1373. We further determined that, because the Board did not rely on the secondary reference as disclosing any particular claim element or teaching, there was no obligation for the Board to combine the references and no need to show a motivation to combine. *Id.*

Here, the Petition asserted that Travers '075 expressly disclosed performing amplification followed by sequencing by quoting paragraph 122 of Travers '075. As discussed, paragraph 122 of Travers '075 itself teaches not only limitations 1.b and 1.c, but the specific order of amplification followed by sequencing. Like *Realtime Data*, a single embodiment in Travers '075 teaches both the amplification and sequencing steps of claim 1, while Travers 2010 only teaches the sequencing step. And similar to *Realtime Data*, Guardant did not need to show a motivation to combine when relying on only the single reference. Accordingly, the Board erred here by treating the Petition as if it were relying on modifying the SMRT sequencing as disclosed in the Travers Publications by performing RCR amplification sequencing as disclosed in Travers '075.

We do, however, acknowledge that the Petition here could have been clearer. While the Petition relies on paragraph 122 of Travers '075, it also cites other parts of Travers '075 and Travers 2010 without expressly stating that it is presenting alternative theories or explaining how these different cites support its position. Despite these additional cites, however, the main theory in the Petition is that the steps of amplification followed by sequencing are taught by paragraph 122 of Travers '075 alone.

II

Guardant also argues that substantial evidence does not support the Board's finding that a person of ordinary

skill in the art would not have had a reasonable expectation of success in first performing RCR replication of SMRTbell templates and then performing SMRT sequencing. Like our conclusion regarding motivation to combine, however, we conclude that the Board erred by requiring Guardant to show that a skilled artisan would have had a reasonable expectation of success in performing RCR replication of SMRTbell templates followed by SMRT sequencing because Guardant's Petition relies on paragraph 122 of Travers '075 as disclosing these steps in sequence.

We have explained that "[t]he reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). And neither the Board nor UW has cited a case that requires a party to demonstrate a reasonable expectation of success in combining two elements to arrive at the claimed invention when those elements are disclosed in a single embodiment of a single prior art reference. UW cites *In re Stepan Co.*, 868 F.3d 1342 (Fed. Cir. 2017), to argue that Guardant had the burden to show that a skilled artisan would have been motivated to arrive at the claimed invention with a reasonable expectation of success:

> Whether a rejection is based on combining disclosures from multiple references, combining multiple embodiments from a single reference, or selecting from large lists of elements in a single reference, there must be a motivation to make the combination and a reasonable expectation that such a combination would be successful, otherwise a skilled artisan would not arrive at the claimed combination.

Stepan, 868 F.3d at 1346 n.1; *see also* Appellee's Br. 43–44. This quote is inapposite, however, because it addresses combinations. In other words, *Stepan* is distinguishable

from the present case because, here, the elements of the challenged claim are expressly taught by Travers '075. Travers '075 discloses performing RCR amplification followed by SMRT sequencing in a single embodiment. There is no combination of references, combination of multiple embodiments in a single reference, or selection from a large list of elements.

UW also argues that Travers '075 only provides a "passing mention" of performing RCR amplification prior to SMRT sequencing. Appellee's Br. 49. But a reference is prior art for all that it teaches, including less preferred embodiments. *See In re Inland Steel Co.*, 265 F.3d 1354, 1361 (Fed. Cir. 2001) (explaining that all disclosures of the prior art, including unpreferred embodiments, must be considered); *see also Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989) ("Even if a reference discloses an inoperative device, it is prior art for all that it teaches." (citation omitted)).

III

As an alternate ground for affirmance, UW asserts that the Board's fact findings are sufficient for this court to affirm the Board's final written decision on the basis that paragraph 122 of Travers '075 is not enabled. Appellee's Br. 67–68. Specifically, UW argues that "Travers '075 does not enable the sequencing of an RCR concatemer using PacBio's SMRT sequencing," and therefore because paragraph 122 is not enabled, it cannot be relied on for disclosing amplification followed by sequencing. Appellee's Br. 67. The Board did not reach this issue. As an appellate court, we will not address this issue in the first instance. *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1339 (Fed. Cir. 2010) ("A federal appellate court does not consider an issue not passed upon below." (quoting *Singleton v. Wulff,* 428 U.S. 106, 120 (1976))). Rather we remand the case for consideration of this issue by the Board in the first instance.

CONCLUSION

We have considered the parties' remaining arguments, and we find them unpersuasive. We vacate the Board's decision and remand the case to the Board for further proceedings consistent with this opinion.

VACATED AND REMANDED

COSTS

Costs to Appellant.

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: 2024-1129

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