

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

10X GENOMICS, INC. and THE BOARD OF	)	
TRUSTEES OF THE LELAND STANFORD	)	
JUNIOR UNIVERSITY	)	
	)	
	)	
Plaintiffs,	)	C.A. No. 22-1117 (JHS)
	)	
v.	)	
	)	
PARSE BIOSCIENCES, INC.,	)	
	)	
Defendant.	)	

**10X'S SUPPLEMENTAL BRIEF
IN OPPOSITION TO PARSE'S MOTION TO DISMISS**

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I. INTRODUCTION

The Hearing confirmed that Parse has failed to meet its burden of proving, by clear and convincing evidence, the ineligibility of 142 patent claims across six Asserted Patents: each of the 82 claims of the '995, '207, and '357 Patents (the “ATAC-seq Patents”) and each of the 60 claims of the '981, '197, and '013 Patents (the “Brenner Patents”).

As a threshold matter, Parse has failed to show that the claims or claim elements it discusses are representative of all other claims in the Asserted Patents. This is fatal to Parse’s Motion. As discussed below, the Delaware district court regularly denies motions to dismiss under § 101 for failure to prove that the claims addressed are representative of all challenged claims. This is because, “from a procedural and practical perspective, a process in which a defendant seeks to have large groups of claims ruled subject matter ineligible after giving negligible attention to them strikes the Court as unfair and fraught with the potential for problematic decisionmaking.” *TriPlay, Inc. v. WhatsApp Inc.*, No. 13-1703-LPS, 2015 WL 1927696, at *6 (D. Del. Apr. 28, 2015), *report and recommendation adopted in relevant part*, 2015 WL 4730907 (D. Del. Aug. 10, 2015). And it is improper for Parse to rely on materials outside the pleadings—from prior litigations involving different patents for example—to try to prove representativeness. At a minimum, it is premature to address such highly technical issues on the pleadings for all 142 patent claims (most of which will no longer be at issue as the case proceeds) and without the benefit of fact and expert discovery and claim construction.

On the merits, Parse has failed to carry its burden of proving by clear and convincing evidence that each of the 82 claims of the ATAC-seq Patents is ineligible as directed to a natural phenomenon. It is undisputed that each of the claims requires engineered insertional enzymes and each of the claims requires contacting chromatin, which is found inside a cell’s nucleus.

And there can be no dispute from the prosecution history that the Patent Office determined that each of the claims recites an inventive concept. Indeed, no case has ever held that claims directed to a non-naturally occurring composition or a method using such composition is a natural phenomenon. And holding otherwise would be inconsistent with Supreme Court precedent. *See Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 594–95 (2013) (man-made cDNA not directed to patent ineligible natural phenomenon). Thus, Parse’s Motion invites legal error.

So too, Parse has failed to carry its burden of proving that each of the 60 claims of the Brenner Patents is directed to an abstract idea. Each of the claims of the Brenner Patents requires physical, concrete steps of generating tagged polynucleotides using a novel combinatorial multiplexed tagging approach that enabled researchers to differentiate previously undifferentiable pools of polynucleotides within a population of cells and to count each distinct polynucleotides within each cell in far fewer steps than was possible previously. This is not an abstract idea. And no case has ever held that a laboratory method of using a biological product is an abstract idea. Again, Parse’s Motion invites legal error.

Accordingly, 10x respectfully requests that the Court deny Parse’s Motion.

II. ARGUMENT

A. Parse Misstates the Law of § 101

Section 101 of the Patent Act provides: “Whoever invents or discovers any new and useful . . . composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.” 35 U.S.C. § 101. The Supreme Court has “long held that this provision contains an important implicit exception[:] Laws of nature, natural phenomena, and abstract ideas are not patentable.” *Mayo Collaborative Servs. v. Prometheus Lab’ys, Inc.*, 566 U.S. 66, 70 (2012) (internal quotation marks and brackets

omitted). “The rule against patents on naturally occurring things is not without limits, however, for ‘all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas,’ and ‘too broad an interpretation of this exclusionary principle could eviscerate patent law.’” *Myriad*, 566 U.S. at 589–90; *see, e.g., Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048 (Fed. Cir. 2016) (claims directed at “a new and improved way of preserving hepatocyte cells for later use” are patent eligible even if incorporating natural phenomena); *see also Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 967 F.3d 1319, 1327 (Fed. Cir. 2020) (use of “concrete process steps” to “exploit . . . a method for preparation of a mixture enriched in fetal DNA” is patent eligible even if incorporating natural phenomena).

1. Parse Bears the Burden of Proving That the 142 Challenged Claims in the Asserted Patents Are Invalid Under § 101

“[P]atents granted by the Patent and Trademark Office are presumptively valid. This presumption reflects the fact that the Patent and Trademark Office has already examined whether the patent satisfies ‘the prerequisites for issuance of a patent,’ including § 101.” *Cellspin Soft, Inc. v. Fitbit, Inc.*, 927 F.3d 1306, 1319 (Fed. Cir. 2019) (internal citations omitted); *see also* 35 U.S.C. § 282. Accordingly, defendants seeking to challenge the validity of the patent bear the burden of proving invalidity by clear and convincing evidence. *See id.*; *Bristol-Myers Squibb Co. v. Merck & Co., Inc.*, No. 15-560-GMS, 2016 WL 1072841, at *1 n.1 (D. Del. Mar. 17, 2016) (“Pursuant to Federal Rule of Civil Procedure 12(b)(6), and after having considered the pleadings in the light most favorable to the [plaintiff], the court concludes that [defendant] has not met its burden to prove by clear and convincing evidence that the ’999 Patent is invalid on its face for failing to cover patent-eligible subject matter under 35 U.S.C. § 101.”).

Notwithstanding the presumption of validity and its burden of proving ineligibility, Parse repeatedly sought to shift the burden to 10x at the Hearing, incorrectly asserting that it was 10x’s

burden to plead sufficient facts to prove that the Asserted Patents are valid.¹ But 10x need not plead facts in its Complaint to establish that its patents are not invalid. *Phonometrics, Inc. v. Hospitality Franchise Sys., Inc.*, 203 F.3d 790, 794 (Fed. Cir. 2000) (reversing district court’s dismissal of complaint under Rule 12(b)(6) and holding patent owner’s complaint was sufficient where patent owner’s complaint “allege[d] ownership of the asserted patent, name[d] each individual defendant, cite[d] the patent that is allegedly infringed, describe[d] the means by which the defendants allegedly infringe, and point[ed] to the specific sections of the patent law invoked.”); *see also Electric Storage Battery Co. v. Shimadzu*, 307 U.S. 5, 17 (1939) (noting that that the patentee need not plead “that the invention had not been in public use for more than two years before” filing the application despite it being a validity requirement at the time).

2. *Alice* Step One Requires Looking at the Claims in Their Entirety to Determine What the Claims Are “Directed To”

Resolving a § 101 issue begins with an *Alice* step one analysis of each claim in its “entirety to ascertain whether their character as a whole is directed to excluded subject matter.” *XY, LLC v. Trans Ova Genetics, LC*, 968 F.3d 1323, 1330 (Fed. Cir. 2020). This analysis has two elements: determining what concept underlies each claim as a whole, and whether that concept is directed to a patent ineligible exception to patenting such as a natural phenomenon or an abstract idea. As the Federal Circuit has explained, both elements are required: “At step one, therefore, it is not enough to merely identify a patent-ineligible concept underlying the claim; [courts] must determine whether that patent-ineligible concept is what the claim is ‘directed to.’”

¹ *See, e.g.*, Tr. at 8:17–23 (“There’s very little, precious little, in the patent complaint, which you would expect, that pleads an inventive advance or how the claims are directed.”); 27:23–28:3 (“They’re responsible for showing you where they possibly say this is an invention.”); 61:14–18 (“At a minimum they would need to re-plead and explain where their inventive concept is and all of that.”).

CellzDirect, 827 F.3d at 1050; *see also Illumina*, 967 F.3d at 1327 (claims found patent eligible where the inventors used “concrete process steps, not merely to observe the presence of the phenomenon that fetal DNA is shorter than maternal DNA, but rather to exploit that discovery in a method for preparation of a mixture enriched in fetal DNA.”); *XY*, 968 F.3d at 1332 (claims to “improve a laboratory technique for detecting, classifying, and sorting particles from an individual sample, so as to sort each population of particles ‘more accurately than in any other separation system’” were patent eligible even though the claims employ mathematical formulas with specific flow cytometry limitations). Yet that is exactly what Parse seeks to do here: identify an underlying concept of the claims without addressing the concrete steps that the patent claims are directed to which is the focus of the *Alice* step one inquiry.

Parse incorrectly relies on *CareDx, Inc. v. Natera, Inc.*, 40 F.4th 1371 (Fed. Cir. 2022) to assert in its Reply brief that “10x mischaracterizes the law, arguing that the ‘conventionality argument does not impact the natural phenomenon analysis at *Alice* step one’” based on *Illumina*, 967 F.3d at 1326, 1328. Parse Reply Br. (D.I. 20) at 4 (citing 10x Answering Br. (D.I. 14) at 11, 12). The question here under *Alice* step one is whether the patented concept set forth in the claims themselves is ***directed to*** a natural phenomenon or abstract idea. The answer to that is no and conventionality considerations are not relevant to that issue as the Federal Circuit made clear in an opinion authored by the same Judge who authored *CareDx*. “[W]hile such conventionality considerations may be relevant to the inquiry under *Alice/Mayo* step two, or to other statutory considerations such as obviousness that are not at issue [here], they do not impact the *Alice/Mayo* step one question whether the claims themselves are directed to a natural phenomenon.” *Illumina*, 967 F.3d at 1329. *CareDx* does not change that conclusion. In *CareDx*, the Federal Circuit addressed the specification’s characterization of conventionality in

assessing what the patented concept in the claims was. *CareDx*, 40 F.4th at 1378–79 (specification “is replete with characterizations of the claimed techniques in terms that confirm their conventionality”). The *CareDx* Court did not look to conventionality beyond the specification to determine whether that concept was directed to a natural phenomenon, which is what Parse urges the Court to do here.

3. *Alice* Step Two Applies Only if the Claims Are Directed to a Patent Ineligible Concept

Only if the claims are directed to a patent ineligible concept should the Court proceed to *Alice* step two. There, the Court must then search for an “inventive concept”—i.e., “an element or combination of elements that is ‘sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself.’” *Alice Corp. Pty. Ltd. v. CLS Bank Int’l*, 573 U.S. 208, 217–18 (2014). If *Alice* step two is reached, it is only then that the Court considers whether any elements are routine or conventional. *Illumina*, 967 F.3d at 1329.

B. Parse Fails to Prove Representativeness Which Is Fatal to Its Motion

1. Parse Must Show That the Claims It Addressed in Its Motion Are Representative of All the Other Claims It Is Challenging, Which Is a Threshold Issue

Each claim of a patent is a separate invention. *See* 35 U.S.C. § 282. As a result, invalidity is assessed on a claim-by-claim basis including in a § 101 challenge:

Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim. The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity.

Id.; MPEP § 2106.07 (“The evaluation of whether the claimed invention qualifies as patent-eligible subject matter [under § 101] should be made on a claim-by-claim basis, because claims do not automatically rise or fall with similar claims in an application.”); *cf. Cellspin*, 927 F.3d at

1319 (presumption of validity applies to all grounds of invalidity, “including § 101”); *Berkheimer v. HP Inc.*, 881 F.3d 1360, 1365–66 (Fed. Cir. 2018) (arguments regarding patent eligibility of “claims 4–7 are not waived” where claim 1 was not representative); *Cronos Techs., LLC v. Expedia, Inc.*, No. 13-1538-LPS, 2015 WL 5234040, at *2–3 (D. Del. Sept. 8, 2015) (in the absence of an “indication that the parties have agreed that [the claim] is representative for purposes of the Court’s § 101 analysis, Defendants must provide at least *some* meaningful analysis for *each* of the challenged claims.”) (emphasis in original).

Where, as here, Parse relies on some claims as being representative of others for a § 101 analysis, that is a threshold issue, which Parse bears the burden of proving. *See, e.g., JSDQ Mesh Techs., LLC v. Fluidmesh Networks, LLC*, No. 16-cv-212-GMS, 2016 WL 4639140, at *2 (D. Del. Sept. 6, 2016) (denying motion to dismiss where defendant failed to meet “its burden to establish a representative claim,” which the Court characterized as a “preliminary matter”).

The Delaware district court regularly denies motions to dismiss under § 101 for failure to prove that the claims addressed are representative of all challenged claims. For example, in *Diogenes Ltd. v. DraftKings, Inc.*, the Court denied a motion to dismiss as to 27 claims in 7 patents because defendant “addressed only a very small number of asserted claims, none with any great specificity” and provided the court “almost no argument or way to meaningfully analyze” whether its assertions that the differences between the claims were minor and material were correct. No. 21-1695 (MN) (CJB), 2022 WL 3700902, at *4 (D. Del. Aug. 26, 2022). In so doing, the district court adopted Magistrate Judge Burke’s “spot on” “refusal to render ineligible all of the asserted claims based on Defendant’s paltry effort at showing representativeness” because “one could not use claim 1 as a cudgel to eliminate 27 other asserted claims across seven other patents” where “other claims include limitations that claim 1 does not.” *Id.* Similarly, in

TriPlay, Inc. v. WhatsApp Inc., the Court denied a motion to dismiss 42 patent claims where defendant failed to meet its burden of showing that the two claims it addressed were representative of the remaining 40 claims. 2015 WL 1927696, at *6, *report and recommendation adopted in relevant part*, 2015 WL 4730907 (D. Del. Aug. 10, 2015); *see also Cronos Techs.*, 2015 WL 5234040, at *2–3 (holding defendant failed to show the dependent claims were representative where defendant failed to “adequately articulat[e] why each of [the claim’s] dependent claims relates to the same abstract idea . . . [or] why each of the dependent claims fails to include an inventive concept.”); *Blix Inc. v. Apple, Inc.*, No. 19-1869-LPS, 2020 WL 7027494, at *4 (D. Del. Nov. 30, 2020) (“Apple and Blix dispute whether claim 17 is representative, and (particularly given the parties’ briefing) the Court is not in a position to conclude at this stage of the proceedings that all of the remaining claim limitations lack distinctive significance.”).

2. Parse Fails to Show Representativeness

10x and Parse disagree as to whether the few claims Parse addressed in its Motion are representative of all 142 claims of the Asserted Patents. 10x Answering Br. at 4–6; Parse Reply Br. at 2–3. This disagreement is itself a basis to deny Parse’s Motion. The Delaware district court has held that, at the motion to dismiss stage, disagreement over whether the claims analyzed in the motion are representative of all the asserted claims a defendant seeks to invalidate under § 101 may warrant denial of the motion. *See, e.g., Neustar, Inc. v. Prove, Inc.*, No. 20-1633-MN-CJB, D.I. 24 (D. Del. Apr. 29, 2021) (denying motion to dismiss “where the parties dispute whether the representative claims are in fact representative”); *Teladoc Health, Inc. v. Am. Well Corp.*, No. 20-1377-MN, D.I. 30 (D. Del. May 7, 2021) (same) (attached as Exhibit A and B to 10x’s Answering Brief, respectively); *see also* Order at 4, *F45Training Pty Ltd. v. Body Fit Training USA Inc.*, No. 20-01194-WCB, D.I. 41 (D. Del. May 12, 2021) (Judge

Stark’s § 101 Motions Pre-Hearing Checklist identifying “What claim(s) is/are representative” as the first item).²

Absent an agreement on representativeness, Parse “must provide at least *some* meaningful analysis for *each* of the challenged claims.” *Cronos Techs.*, 2015 WL 5234040, at *3 (emphasis in original); *see also Kaavo Inc. v. Cognizant Tech. Sols. Corp.*, No. 14-1192-LPS-CJB, 2016 WL 476730, at *16 (D. Del. Feb. 5, 2016) (denying motion to dismiss with respect to 10 of the 12 challenged claims and stating “[t]he Court is not prepared to take the significant step of finding such claims ineligible when they are addressed in such a cursory manner by the movant in the first instance”). Thus, Parse’s assertion that the Court need not read all the claims in a § 101 analysis invites legal error. *See* Tr. at 18:23–19:1 (“[Y]ou don’t need to read every single claim. There’s probably no Judge that’s reading every single claim like it’s part of, you know, they’re prepped.”).

Here, Parse fails to prove representativeness because its Motion does not address any patent claim in its entirety, let alone all the patent claims, even though each of the claims are distinct inventions. 10x Answering Br. at 9, 12–13 (each of the three ATAC-seq Patents is

² Counsel for Parse suggested at the Hearing that the Delaware practice of denying motions to dismiss where the parties do not agree a claim or claims are representative was a result of the “judicial emergency.” *See* Tr. at 67:11–22. These Orders, however, do not reference any “judicial emergency” (and none has been declared), and that is not the stated basis of these Orders. Rather, the Orders note the inefficiency of addressing patent claims that will no longer be at issue as the case progresses. D.I. 15-1, Exs. A & B. For example, under the District of Delaware Discovery Default Standard (Suppl. Wu. Decl., Ex. A), a plaintiff is required to identify those claims that will be asserted in the litigation with its infringement contentions. Suppl. Wu. Decl., Ex. A ¶ 4(c). Those claims are then further narrowed—either in the Court’s Scheduling Order or by party agreement—as claim construction nears. There is typically a final narrowing prior to trial where the plaintiff typically elects 10 claims or less to present to the factfinder. That same inefficiency applies here where Parse is asking the Court to review the eligibility of all 142 claims of the Asserted Patents, many of which will no longer be at issue as the case proceeds.

directed to different inventions and therefore needed to be analyzed separately at step one); 18–19 (each of the three Brenner Patents is directed to different laboratory inventions and that Parse’s analysis was deficient because it treated all three as the same without analyzing “the actual language of the claims”). For example, for the ATAC-seq Patents, the claims of the ’995 Patent are directed to a method for analyzing the biological cell, while the claims of the ’207 Patent are directed to a distinct method: a method for generating a sequence library. *See Illumina*, 967 F.3d at 1325 (methods of diagnosis claims are not representative of methods of preparation). The claims of the ’357 Patent are not directed to a method at all, and instead are directed to a composition of matter: a permeabilized cell nucleus.

At the Hearing (but not in its briefing), Parse urged the Court to “group” the patent families together. Tr. at 64:12–68:14. But Parse ignores that the claims within each of the Asserted Patents differ in meaningful ways. For example, Parse argued at the Hearing that the claims of the ATAC-seq Patents are not limited to the use of a bacterial insertional enzyme. Tr. 95:6–10, 97:22–98:2, 106:25–107:10, 117:7–25. But claims 11–12 of the ’995 Patent, claims 7–8, 23–29 of the ’207 Patent, and claims 11–12, 20–21, and 26–27 of the ’357 Patent, require a bacterial insertional enzyme as a claim element. Similarly, one of the Brenner Patents, the ’013 Patent, has dependent claims directed to a distinctive claim element—the number of different tag sequences, which goes to the scale of differentiation that the claimed method can achieve—which Parse never addresses. ’013 Patent, Claims 13–18.

Contrary to its Hearing arguments, Parse’s Reply asserts that its Motion “does not rely upon addressing only certain ‘representative’ claims, but rather addresses all of the claims.” Parse Reply Br. at 2 (citing Parse Opening Br. (D.I. 12) at 12–13, 17–20). This is incorrect. Parse did not address all 142 claims in its Motion, as the Court pointed out at the Hearing. *See*

Tr. at 64:9–65:14, 68:13–21. All Parse has done in its Motion is rely on individual claim elements to define all 142 claims. *See, e.g.*, Parse Opening Br. at 10–11. This fails because *Alice* step one requires looking at the character of the claim as a whole to determine what the claim is directed to; patent eligibility thus turns on each claim in its entirety and not individual claim elements of that claim. *See, e.g.*, *Illumina*, 967 F.3d at 1326; *XY*, 968 F.3d at 1328; *CellzDirect*, 827 F.3d at 1048–49. Nor has Parse shown that all 142 claims are directed to the same alleged abstract idea or natural phenomenon. *Cronos Techs.*, 2015 WL 5234040, at *2–3 (holding that courts should determine whether “all of the challenged claims relate to the same abstract idea”).

To the extent that Parse attempts to make new representativeness arguments in its supplemental brief, that is untimely and would prejudice 10x as it would not have an opportunity to meaningfully respond.

3. Parse’s Reliance on Extrinsic Materials Is Improper, and Cannot Show Representativeness for a Rule 12(b)(6) Motion to Dismiss

Rather than analyze the language of each of the claims, Parse attempts to rely on materials extrinsic to the complaint to show representativeness.³ *See* Tr. at 33:24–34:3 (“Helpfully 10x said let’s use the [’]981 patent, which I handed up to you, so you have a physical copy of it to be helpful, has been exemplary. Because they’re the same.”); 34:18–19 (“Everyone’s comfortable grouping them, that’s what they did in the briefing, that’s what we did.”); 64:25–65:13 (“The Court: So you want them all grouped together? Mr. Reines: Just like they did.”). It is improper for Parse to rely on extrinsic statements made by 10x in a separate

³ For the ATAC-seq Patents, Parse rested on its position in its briefs. *See* Tr. at 96:1–16. As 10x pointed out at the Hearing, Parse’s oversimplification of the claims does not prove representativeness. Tr. at 48:18–50:10, 70:11–17.

litigation involving different patents with different claim language⁴ against Celsee, who is not a party to this litigation to support a Rule 12(b)(6) motion to dismiss.

The Federal Circuit has held that on a motion to dismiss in patent infringement cases, the Court considers only the pleadings and documents intrinsic to the pleadings such as the asserted patents and the prosecution history of those patents before the United States Patent Office. *CODA Development S.R.O. v. Goodyear Tire & Rubber Co.*, 916 F.3d 1350, 1360 (Fed. Cir. 2019); *In re Bendamustine Consolidated Cases*, No. 13-2046-GMS, 2015 WL 1951399, at *1 (D. Del. Apr. 29, 2015) (the asserted patents and file histories are “integral to or explicitly relied upon in the complaint”); *see also* Tr. at 61:16–17 (conceding that the asserted patents are part of the complaint).

Although the Court may take judicial notice of government records or public documents that contain undisputed facts, *see CODA*, 916 F.3d at 1360, the content of *Celsee* litigation documents are not subject to judicial notice. *See, e.g., Atleisure, LLC v. Sunvilla Corp.*, No. 1:20-4662-TWT, 2021 WL 2449855, at *3 (N.D. Ga. May 5, 2021) (“Here, the Defendant asks the Court to judicially notice the contents of earlier pleadings and filings [from other litigations] for the truth of the matter asserted, which the Court cannot do. . . . This statement, made by the Plaintiff to oppose a summary judgment motion, is by its very nature disputable and therefore not amenable to judicial notice. Any statement of fact made by the Plaintiff in the course of earlier litigation through declarations, briefs, and other filings cannot be noticed by the Court, though the existence of such filings will be.”).

⁴ The ’013 Patent asserted here was not asserted in the *Celsee* litigation; and the ’459 Patent asserted in that litigation is not asserted here. *See* Walter Decl. Ex. 6 (D.I. 13-6) at 1.

Even if the Court were to consider such extrinsic materials in resolving Parse's Rule 12(b)(6) Motion, the procedural and substantive posture in the *Celsee* litigation is significantly different than here. There, 10x was opposing Celsee's motion for summary judgment, not a motion to dismiss under Rule 12(b)(6), based on invalidity for lack of written description under 35 U.S.C. § 112, not patent ineligibility under 35 U.S.C. § 101. The legal test for validity under 35 U.S.C. § 112 is different than the test for ineligibility under 35 U.S.C. § 101; groupings for a particular feature of patent claims under 35 U.S.C. § 112 for purposes of determining whether they were adequately described in the written description have no bearing on the § 101 analysis here which focuses on whether the claim as a whole is directed to an abstract idea. Thus, 10x's discussion of certain aspects of the claims relevant to the § 112 issues raised by Celsee—namely tagging with the first and second tags, *see* Tr. at 19:12–20:3; Parse slides 24 & 26—was in no way a concession that the patent claims are directed solely to methods of tagging under § 101. As 10x explained in its briefing, the Brenner Patents' method claims are directed to more than just methods of tagging. 10x Answering Br. at 16–19. As is clear from the claim preambles, the claims are directed to application of 10x's novel combinatorial, multiplexed tagging to prepare samples that can then be used for analysis and/or counting. Parse does not meaningfully address these claim elements so as to warrant invalidating 142 claims.

Moreover, the *Celsee* litigation statements cannot replace the required analysis of whether the elements addressed by Parse are representative of each asserted claim Parse seeks to invalidate for § 101 purposes. *Diogenes*, 2022 WL 3700902, at *4 (“Although the Federal Circuit has made clear that courts ‘may treat a claim as representative in certain situations,’ those situations do not extend to the one here – where Defendant offers arguments that are conclusory and unexplained at best and Plaintiff . . . offered meaningful argument as to the distinctive

differences between claims.”). Notably, Parse does not even attempt to establish the elements of judicial estoppel as to the *Celsee* statements or provide context for those statements. Parse also fails to establish that those statements are inconsistent with 10x’s current positions or that the *Celsee* Court accepted the statements as true. And Parse provides no evidence of bad faith. *See, e.g., Sequoia Tech., LLC v. Dell Inc.*, No. 18-1127-LPS-CJB, 2021 WL 2010448, at *3 (D. Del. May 20, 2021) (slip op.) (appeal filed) (adopting Magistrate Judge’s Report and Recommendation denying judicial estoppel as to inconsistent positions regarding narrower construction because there was no “indication of bad faith on [defendant] Red Hat’s part or any affront to the integrity of the courts from permitting Red Hat to press its current [narrower claim construction] position.”); *Amgen Inc. v. Sanofi*, No. 14-1317-RGA, 2019 WL 259099, at *4–6 (D. Del. Jan. 18, 2019) (declining grant of summary judgment to plaintiffs’ judicial estoppel argument because defendants’ arguments were not “irreconcilably inconsistent” as prior representations did “not address the exact same factual matters that are at issue in [the current] case.”). Thus, the *Celsee* statements are not binding or relevant to the § 101 challenge here on the pleadings.

Similarly, 10x’s statements made in a different case brought by Becton-Dickinson involving unrelated patents held by a different party are not properly considered here in resolving a Rule 12(b)(6) motion to dismiss. The Fodor Patents are not even part of the record here (as the Court noted in its questioning, Tr. at 21:19–25), let alone part of the Complaint.⁵ Yet Parse essentially asks the Court not only to review the patent claims at issue here but to compare them

⁵ Parse asks the Court to consider extrinsic materials in other litigation about other patents while at the same time suggesting that the Court should ignore the intrinsic evidence of statements by the Patent Office about the Asserted Patents that confirm their inventiveness. Parse Reply Br. at 5. This is improper.

with other patent claims of the Fodor Patents not at issue to conclude that statements about the subject matter of those other patents are sufficiently similar to be pertinent here. All Parse stated was that the Fodor claims “are remarkably similar,” which merely confirms that the Fodor claims are not the same as the 10x claims asserted here. Thus, there is no merit to Parse’s argument that 10x’s grouping of the Fodor claims requires grouping of the patent claims here.

C. Parse Fails to Prove Each of the 142 Claims of the Asserted Patents Are Patent Ineligible Under § 101

1. Background of the Technology

Both parties discussed the technology of the Asserted Patents at the Hearing. *See, e.g.*, Tr. at 9:22–13:4, 36:16–39:22. Generally, the Asserted Patents are directed to compositions and laboratory methods that can be used to uncover genetic information that then can be used to better understand the genetic underpinnings of human life and diseases, such as cancer. ’981 Patent, Claim 1 (“A method of analyzing nucleic acids from a plurality of single cells . . .”); ’013 Patent, Claim 1 (“A method for multiplexed analysis of nucleic acids from single cells . . .”); ’197 Patent, Claim 1 (“A method of counting nucleic acids in a sample . . .”); ’995 Patent, Claim 1 (“A method for analyzing a biologic sample . . .”); ’207 Patent, Claim 1 (“A method for generating a sequencing library from a plurality of cells . . .”); ’357 Patent, Claim 1 (“A composition comprising: a permeabilized cell nucleus comprising . . . an insertional enzyme complex . . .”).

Each human cell contains genetic information in its chromosomes, which is made up of deoxyribonucleic acids (“DNA”). *See* ’995 Patent at 8:63–9:14, 13:29–35.

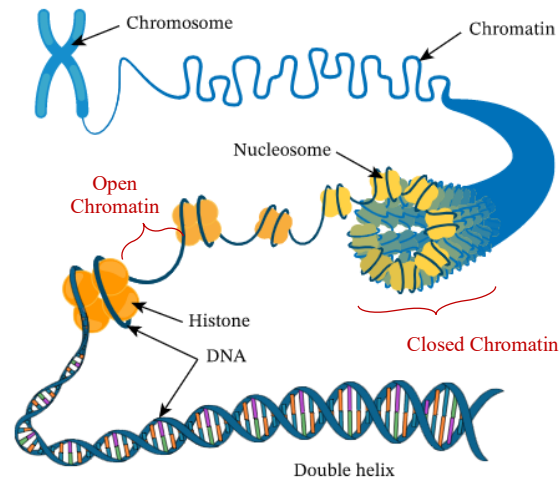


Figure 1: An illustration showing the organization of genetic information in a human cell.

DNA, in turn, is made up of units of nucleic acids (or “nucleotides”; a chain of nucleotides such as DNA is a “polynucleotide”) with different nucleobases called adenine, cytosine, guanine, and thymine, and thus the nucleic acids are often shorthand as A, C, G, and T. *See, e.g.,* Parse slide 10. The sequence of the nucleic acids—the DNA sequence—provides information that the cell uses to make proteins that constitute much of what is in living organisms, including cells, tissues, enzymes, and antibodies. *See* Tr. at 102:21–103:6. Specifically, DNA is the cell’s file copy; when the cell is ready to make proteins, the DNA is copied or “transcribed” into a different polynucleotide called messenger RNA (“mRNA”) that acts as the working copy, the sequence of which can be “translated” into a protein. *See* Tr. at 102:14–20. The nucleic acid sequences (i.e., the DNA or RNA sequences) used to make proteins are sometimes called “protein-coding genes.” *See* Tr. at 102:21–103:6.

The DNA in humans is very long, and only a very small percentage is used to code for proteins. About 98% of our genome is non-coding DNA that can help with, for example, organizing the DNA within the cell or can help with turning on or off the genes that do code for

proteins.⁶ For example, cells may be able to control gene activity without changing the DNA sequence by modifying the compounds surrounding the non-coding DNA. Such modifications are called “epigenetic” features. ’995 Patent at 1:24–31. As shown in the figure above, one such epigenetic feature is wrapping DNA around compounds called histones to form nucleosomes that are not readily accessible for transcription into mRNA and thus cannot be used to make proteins. Tr. at 102:3–103:6; ’995 Patent at 12:54–63. Only areas that are not tightly wound into a nucleosome—areas of open chromatin—are open and available to be transcribed into mRNA and translated into proteins. Tr. at 102:3–103:6.

Cancers can form when normal cells have been changed to produce cancer-related proteins or have lost their ability to produce needed proteins to, for example, regulate cell growth. Such cancerous cells can have a different DNA sequence than healthy cells or can have different epigenetic features controlling what parts of the DNA are used to make proteins. ’995 Patent at 21:16–40, 21:59–22:17. Moreover, as a cancer progresses, different cancerous cells can be more or less differentiated from healthy cells. Thus, it is important to have compositions and methods that can be readily used to determine the epigenomic features for each of those cells, which is the focus of the ATAC-seq Patents (’995 Patent at 21:16–40), as well as methods to differentiate the DNA or RNA sequences from within a population of cells, for example, from a biopsy that may contain tens of thousands of cells, both healthy and cancerous, which is the focus of the Brenner Patents (’981 Patent at 6:33–7:22, 15:36–50).

⁶ See, e.g., Chelsea Toledo & Kirstie Saltsman, *Genetics by the Numbers*, Nat’l Institute of General Medical Science, <https://nigms.nih.gov/education/Inside-Life-Science/Pages/Genetics-by-the-Numbers.aspx#:~:text=3.2%20billion&text=That's%20how%20many%20base%20pairs,day%20C%20for%20about%2050%20years!> (June 12, 2012).

2. The 82 Claims of the ATAC-Seq Patents

a. The Problem Solved by the ATAC-Seq Patents

The inventors of the ATAC-seq Patents solved problems associated with determining what areas of the genome are available for transcription and translation into proteins—namely regions of open chromatin. Tr. at 104:14–105:6. The prior methods of analyzing areas of open chromatin involved a very complex 44-step process that few people could reproducibly perform and required very large amounts of sample and a long period of time to complete. Tr. at 103:12–104:13. The inventors determined that the engineered insertional enzyme could, in fact, be introduced into the cell nucleus and be used to tagment the areas of open chromatin, and only those areas—a process that had never been performed before. *See* Tr. at 107:11–108:1. Thus, the scientists had discovered a new use for a known, man-made material, that vastly simplified the prior art methods—reducing the 44-step process to a two-step process. Tr. at 103:12–104:13. The inventors’ novel ATAC-seq “offers substantial advantages over existing technology due to its speed, simplicity, and low input cell number requirement.” Walter Decl. Ex. 1 (D.I. 13-1) at 6; *see also* Tr. at 103:12–104:21. Each of the claims of the ATAC-seq Patents is directed to such new uses and associated compositions. *See* ’995 Patent, ’207 Patent, ’357 Patent.

The inventors started their work with a bacterial insertional enzyme called Tn5 transposase. Tr. at 106:25–107:3. In nature, bacteria (which are simple, single-cell organisms that, unlike human cells, do not have a nucleus) use transposases to cut pieces of bacterial DNA and transpose that piece of DNA (sometimes called a “transposon”) from one part of the bacterial genome to another.⁷ *See* Tr. at 73:3–20. Scientists had engineered insertional enzymes

⁷ 10x notes that Parse’s counsel and its briefing mistakenly referred to a “transposase” as a “transposon” at the Hearing. *See, e.g.*, Parse Opening Br. at 1; Tr. at 73:3–4. A transposase is an

such as transposases to be different than naturally occurring transposases—scientists had engineered the enzymes with DNA tags. *See* Tr. at 75:8–21. As Parse admitted at the Hearing, these engineered insertional enzymes are not found in nature—they are man-made. *See* Tr. at 75:5–21.

Prior to the ATAC-seq Patents, scientists had used these engineered enzymes on isolated pieces of DNA, for example, pieces of human DNA that had been removed from the nucleus and the cell and stripped from its chromatin context, to fragment the isolated DNA and add the DNA tag on each fragment (a process sometimes called tagmentation). *See* '995 Patent at 14:31–38; Tr. at 76:5–20 & Parse Slide 53 (citing the same passage in the '207 Patent at 14:36–42). Although engineered insertional enzymes having sequencing adaptor molecules had been used to tagment *isolated* DNA fragments, prior to the ATAC-seq Patents, such engineered insertional enzymes had not been introduced *into a cell nucleus* to perform tagmentation *inside* the cell nucleus to interrogate areas of open chromatin. *See* Tr. at 106:8–107:20.

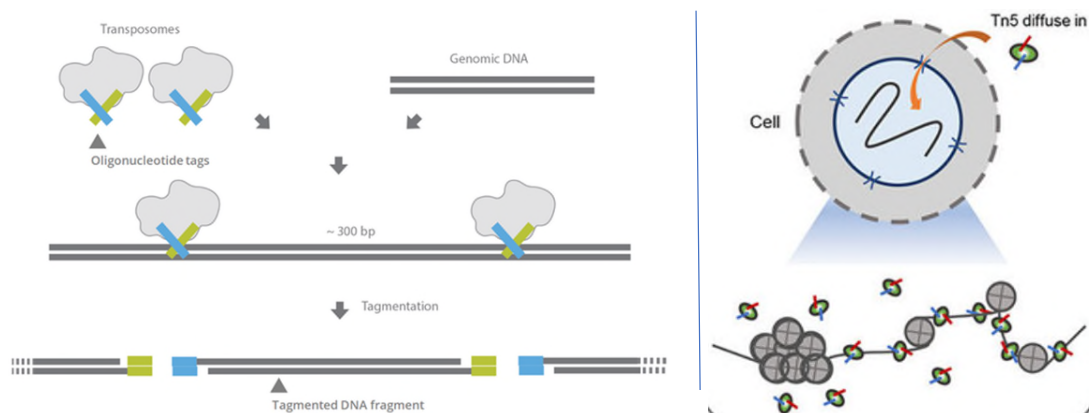


Figure 2: An illustration of the prior art method of using engineered transposase to tagment isolated genomic DNA (left) (*see also* Parse Slide 51) and the novel method of using engineered transposase inside the cell nucleus to interrogate areas of open chromatin (right)

enzyme whereas a transposon is the piece of DNA that the transposase can insert into another portion of DNA.

b. Alice Step One

Under *Alice* step one, the claims of the ATAC-seq Patents are not directed to a natural phenomenon. Each of the claims requires engineered insertional enzymes and each of the claims requires contacting chromatin, which is found inside a cell's nucleus. Specifically, the claims of the '995 and the '207 Patents are directed to new (and different) applications for an insertional enzyme complex—which is undisputedly man-made and thus not found in nature—that involves manipulating the complex into the nucleus of a cell and tagmenting the DNA found in open chromatin to generate tagged DNA fragments—a non-natural process. *See Nat. Alts. Int'l, Inc. v. Creative Compounds, LLC*, 918 F.3d 1338, 1345–46 (Fed. Cir. 2019) (new use of a compound, even if the use is dependent on the body's natural process processing the compound, is not “directed to” a natural phenomenon). The '357 Patent is directed to novel *compositions* that comprise a man-made insertional enzyme complex that has been manipulated—again by man—into the nucleus of a cell that has been permeabilized—by man. *See Myriad*, 569 U.S. at 594–95.

For example, in the '995 Patent:

1. A method for analyzing a biological sample, comprising:
 - (a) contacting chromatin of a genome region of said biological sample with an **insertional enzyme complex to produce tagged nucleic acid molecules, wherein said insertional enzyme complex does not comprise an antibody specific to a protein that is part of said chromatin; and**
 - (b) performing a nucleic acid assay on said **tagged nucleic acid molecules or derivatives thereof, to provide sequence information of said tagged nucleic acid molecules or derivatives thereof.**
2. The method of claim 1, further comprising **generating a representation of epigenetic features of said genome region at least in part by mapping said sequence information to said genome region.**

'995 Patent, Claims 1 & 2 (emphases added); 10x Answering Br. at 9.

And it is that use of man-made materials that was found to be inventive by the Patent Office, which stated in its Notice of Allowance⁸:

The claims are deemed to be in condition for allowance because **no prior art was found teaching or suggesting a method for analyzing a biological sample comprising contacting chromatin** of a genome region of said biological sample with an insertional enzyme complex to produce tagged nucleic acid molecules, wherein **said insertional enzyme complex does not comprise an antibody specific to a protein that is part of said chromatin**; and performing a nucleic acid assay on said tagged nucleic acid molecules or derivatives thereof, to provide sequence information of said tagged nucleic acid molecules or derivative thereof. **Rather the art supports techniques which involves the use of insertional complex that comprises an antibody specific to a protein that is part of the chromatin**, such as via chromatin immunoprecipitation) as a main tool for investigating transposition in epigenetic studies. See for example Park et al., Nature 10, 669-680, 2009; see entire reference especially Figure 1 (citation made of record on IDS filed 7/24/2018) and Jelinek et al (US 20160115474, effective filing date May 2013) both of which requires transpososome-antibody complex associated with chromatin for subsequent analysis.

Wu Decl. (D.I. 15-1) Ex. 1, Notice of Allowability at 2–3 (emphases added).

The same is true for the '207 Patent claims:

1. A method for generating a sequencing library from a plurality of cells, comprising:
 - a) lysing a plurality of cells to provide a plurality of cell nuclei, wherein the plurality of cell nuclei comprises chromatin;
 - b) **contacting a cell nucleus of the plurality of cell nuclei with a transposase complex such that polynucleotides of the cell nucleus are tagmented at regions of open chromatin to produce a plurality of tagged fragments**; and
 - c) performing one or more nucleic acid reactions **on the tagged fragment to produce a sequencing library**.

⁸ The back and forth between a patent applicant and the Patent Office is referred to as the “prosecution history.” The prosecution history includes the submissions by the patent applicant and the responses by the patent examiner, including rejections, amendments, interviews, and the notice of allowance. The notice of allowance is a statement by the patent examiner that typically includes the patent examiner’s opinion on what the closest prior art is to the allowed claims and why the claims are novel and non-obvious over that prior art.

2. The method of claim 1, further comprising **sequencing the sequencing library to produce a plurality of sequence reads.**

19. The method of claim 2, further comprising analyzing the sequence **reads to generate an epigenetic map representing one or more epigenetic features of the polynucleotides of the cell nuclei.**

22. The method of claim 1, **wherein the transposase complex does not comprise an antibody specific to a protein that is part of chromatin.**

'207 Patent, Claims 1, 2, 19, & 22 (emphases added); 10x Answering Br. at 12.

The Patent Office confirmed the claims do not cover the prior art, as the '207 Patent pending claims are directed to using transposase to tagment all the open chromatin regions in a nucleus. Wu Decl. Ex. 2, Office Action at 5. The Patent Office explained:

While the art teaches various aspect [sic] of the instant invention, the prior art does not teach contacting the cell nucleus of the plurality of cell nuclei with a transposase complex such that polynucleotides of the cell nucleus are tagmented at regions of open chromatin to produce a plurality of tag fragments in combination with the additional steps.

Id. The Patent Office then allowed the claims. Wu Decl. Ex. 2, Notice of Allowability at 1.

The claims of the '357 Patent are directed to novel, non-natural compositions:

16. A composition comprising:

a permeabilized cell nucleus comprising:

- (a) **an insertional enzyme complex comprising a transposase enzyme;** and
- (b) **a plurality of tagged nucleic acid fragments**, wherein each tagged nucleic acid fragment comprises a first sequencing adapter and a second sequencing adapter

wherein each tagged nucleic acid fragment is derived from a region of open chromatin.

'357 Patent, Claim 16 (emphases added); 10x Answering Br. at 13.

The Patent Office made clear that such man-made compositions with a “plurality of DNA or fragments derived from open chromatin regions” was a non-conventional inventive concept.

Wu Decl. Ex. 3, Office Action at 7 (the prior art does not “expressly teach plurality of DNA or

fragments derived from open chromatin regions as recited in the [pending] claims”). The Patent Office allowed the claims on this basis:

Applicant’s amendment and arguments were found persuasive to obviate the rejections of the prior Office action. The closest prior art has already been made of record. While the teaching of Jouvenot (US 20110306042; citation previously made of record) discloses a permeabilizing cell membrane such that the structure of genomic DNA of the cells including nucleosomal or chromatic structure are not disrupt [sic] [0055], the prior art either alone or in combination, do not teach or suggest a composition comprising a cell nucleus comprising a plurality of polynucleotide molecules and an insertional enzyme complex comprising an insertion enzyme and an insert element comprising a predetermine [sic] sequence. **No prior art either alone or in combination teach the composition further comprising open chromatin regions. Thus, the claimed invention comprising the combination of components which make up the composition is deemed to be novel and non-obvious over the teachings of the prior art.**

Id., Notice of Allowability at 2 (emphasis added).

c. *Alice* Step Two

The Court need not reach *Alice* step two because each of the ATAC-seq Patent claims is not directed to a patent-ineligible concept. But in the event the Court nonetheless were to reach step two, the claimed inventions recite inventive concepts that are “significantly more” than the allegedly ineligible concept itself. *See Alice*, 573 U.S. at 217–18 (quoting *Mayo*, 566 U.S. at 72–73)). As discussed above and in 10x’s Answering Brief, each of the ATAC-seq Patent claims are non-conventional improvements over prior transposase compositions and prior methods of using transposase, as the ATAC-seq Patents themselves state and the Patent Office itself determined in allowing each of the ’995, ’207, and ’357 Patent claims to issue, as discussed above, which Parse simply ignores. *Supra* at 21–23. For example, the ATAC-seq Patents state that even where previously known materials are employed, the specification states that they would have to be “adapted for use herein” in a non-conventional way as the materials had never been manipulated into a cell nucleus, let alone been used to interrogate open chromatin. *See* ’995 Patent at 14:31–

38; *supra* at 21–23. And the claimed inventions’ vastly improved method to generate epigenetic maps, reduced the number of required steps from over 40 to just two, and permitted the use of much smaller samples down to even a single cell. ’995 Patent at 29:6–21. Thus, the evidence intrinsic to the Complaint establishes that the claimed inventions are not “well-understood, routine, [or] conventional.” *Alice*, 573 U.S. at 225. Further, whether claim elements or their combination are well-understood, routine, or conventional to a person of ordinary skill in the art is a question of fact. *Berkheimer*, 881 F.3d at 1368. At best, Parse raises factual disputes as to what was routine and conventional at the time, which must be resolved in 10x’s favor on a motion to dismiss.

d. Parse’s Motion Asks This Court to Make New Law That a Non-Naturally Occurring Composition or Method Is a Natural Phenomenon

Parse’s argument that the 82 claims of the ATAC-seq Patents are invalid under § 101 as natural phenomena asks this Court to make new law. It is undisputed that the insertional-enzyme complex contains human-engineered tags that are not naturally occurring. *See* Tr. at 75:5–21 (regarding engineered transposons); 90:6–10 (regarding engineered transposase). The insertional-enzyme complex such as the transposases engineered with tags simply do not occur in nature but for humans creating them. *See id.* No case holds that a composition patent directed to a non-naturally occurring composition or method using such composition is a natural phenomenon. If anything, that would be contrary to Supreme Court law. In *Myriad*, the Supreme Court held that claims to DNA that had been modified only slightly to remove the non-coding regions from a protein-coding gene (called copy DNA or “cDNA”) were patent eligible and not directed to natural phenomenon. *Myriad*, 569 U.S. at 594–95. Similarly, no case holds that claims to a non-natural product, such as engineered transposases that have been introduced into a cell nucleus, or the use of such non-natural product as described in the ATAC-seq Patents,

are patent ineligible because the claims are directed to a natural product or a natural phenomenon.

Recognizing the weakness of its position, Parse’s fallback argument is that the ATAC-seq Patents are directed to an alleged natural phenomenon “that a transposon [sic, transposase] will, in fact, interrogate the open chromatin,” and that the ATAC-seq Patents “just plopped that on to the tagmentation process.” Tr. at 81:21–25, *see also* Parse Opening Br. at 3 (“What then is allegedly new in the Buenrostro patents? If anything at all, it is only a natural phenomenon, namely the ability of the transposase to perform tagmentation on so-called ‘open chromatin.’”); Parse Reply Br. at 1 (“10x does not deny that the discovery that transposons [sic, transposase] would work with open chromatin is not an invention, but a natural phenomenon.”); Tr. at 122:19–24 (“I mean, the bottom line is, we all agree all this is, is prior art tagmentation used with open chromatin. And that last bit, using with open chromatin, it’s just the natural phenomenon that in fact transposase will work on open chromatin. That’s not patent eligible.”). Parse then argued that “it doesn’t matter [how] groundbreaking the discovery is . . . you can’t patent it by tacking that discovery and just packing on routine and conventional steps. No matter how groundbreaking.” Tr. at 87:3–8.

This fails. The Federal Circuit has made clear that a new method of using a product, even if such use implicates a natural phenomenon or the use of a natural product, is patent eligible under § 101. *Nat. Alts. Int’l*, 918 F.3d at 1345 (“[T]he natural ability of the subject matter to *undergo* the process does not make the claim directed to that natural ability.”) (internal quotation omitted) (emphasis in original). Similarly, the Supreme Court and the Federal Circuit have long held that the use of conventional techniques in a new way is also patent eligible. *See*

Illumina, 967 F.3d at 1328–29; *Eibel Process Co. v. Minn. & Ontario Paper Co.*, 261 U.S. 45, 54–56 (1923).

e. Parse’s Other Arguments Fail

Parse attempts to argue that the Court should ignore the Patent Office’s findings that the claims are directed to a non-conventional inventive concept, and give the prosecution history “no weight.” *See* Parse Reply Br. at 5. The law is otherwise. Unlike Parse’s attempts to rely on extrinsic evidence from other litigations involving different patents, it is entirely proper to resolve patent eligibility challenges under § 101 “based on the sources properly considered on a motion to dismiss, such as the complaint, the patent, and materials subject to judicial notice” such as prosecution histories. *See Aatrix Software, Inc. v. Green Shades Software, Inc.*, 882 F.3d 1121, 1128 (Fed. Cir. 2018); *Data Engine Techs. LLC v. Google LLC*, 906 F.3d 999, 1008 n.2 (Fed. Cir. 2018) (“On a motion for judgment on the pleadings . . . the court may consider ‘matters of public record.’ Prosecution histories constitute public records.”) (citations omitted). Thus, although the fact that the Patent Office allowed the patent to issue does not itself preclude a finding of ineligibility, the specific findings the patent examiner (a skilled artisan) made during the prosecution of the patent application—including those related to inventiveness that are directly relevant to the § 101 inquiry—can be considered by the Court on a Rule 12(b)(6) motion.

Further, the cases cited by Parse are inapposite because the ’995 and ’207 Patents recite laboratory methods that do more than detect or screen for a natural phenomenon. *See, e.g., Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1377 (Fed. Cir. 2015) (finding eligible methods of detection directed to the “discovery of the presence of [naturally-occurring] cfDNA in maternal plasma or serum”); *INO Therapeutics LLC v. Praxair Distribution Inc.*, 782 F. App’x 1001, 1008 (Fed Cir. 2019) (finding eligible methods of treatment “focused on

screening for a natural law”); *Cleveland Clinic Found. v. True Health Diagnostics LLC*, 760 F. App’x 1013, 1018–19 (Fed. Cir. 2019) (finding eligible methods of detection “directed to the patent-ineligible natural law that blood MPO levels correlate with risk of atherosclerotic CVD”). And certainly none of the cases hold that a composition containing a non-naturally occurring component—as is claimed in the ’357 Patent—is patent ineligible. *See Myriad*, 569 U.S. at 595.

3. The 60 Claims of the Brenner Patents

a. The Problem Solved by the Brenner Patents

The inventors of the Brenner Patents addressed problems associated with methods for analyzing nucleic acid sequences within a sample containing a population of cells, such as a sample from a needle biopsy that contains tens of thousands of cells. Each cell within that population of cells may have different nucleic acid sequences; pooled together, that population may contain millions of nucleic acid sequences. Tr. at 42:25–43:5. Prior methods relied on bulk analyses that provided aggregated results over the entire population but did not provide information about cell-to-cell variability within that population; researchers were not able to efficiently analyze the nucleic acid sequences within each individual cell within a population of cells. Tr. at 36:10–33:3.

However, there was a need to analyze biological samples that contain a population of cells on an individual cell level. *Id.* Understanding which cells are making (or expressing) which proteins—and how much of that protein—are important keys to understanding the biological processes that underpin various diseases such as cancer and how our body successfully or unsuccessfully responds to those diseases and to treatments for those diseases. For example, consider a population of cells from a liver biopsy. A normal liver cell contains the mRNA used to make normal liver cell proteins. But if a liver cell is cancerous, it contains a different mRNA used to make abnormal liver cell proteins. And various immune cells in that

population contain yet another set of mRNA used to make immune cell proteins. The amount of mRNA within each cell as well as the levels of protein expression also change based on cell interactions within the population.

Using prior methods for analyzing nucleic acid sequences within a population of cells, it was not possible to differentiate which cell any particular nucleic acid sequence came from (and thus which proteins that cell was producing) and to determine which sequences were original to that cell (and thus how much protein that cell was making) or, for example, just artifacts of the sequencing process. And, because it was also impossible to differentiate between different types within a sample, it was also impossible to quantify the relative numbers of such different cell types. As a consequence, researchers were unable to discern critical information about cell-to-cell variability. Tr. at 36:10–33:3.

The Brenner Patents solved this problem of differentiating possibly millions of polynucleotides, such as mRNA, using a novel multiplex tagging approach that the inventors termed “MID,” where there is a first tag that is associated with the single cell in the sample from which the sample polynucleotide was derived, and a second tag that distinguishes the sample polynucleotide from other sample polynucleotides derived from the same cell. *See* ’981 Patent, Claim 1. This approach is termed “combinatorial” meaning that by combining building blocks in different ways a huge number of chemically different tags can be created. Using such methods, it was possible to differentiate between vast numbers of otherwise indistinguishable mRNA sequences in a sample in order to analyze the different mRNA and to count the number of different mRNA from each cell. This allows measurement of the amount of mRNA in each cell, which indicates how much of the corresponding protein that cell is making *e.g.*, normal liver proteins versus abnormal liver proteins.

The Brenner Patents also disclose a novel method for copying or “reflecting” the multiplexed tags across the length of the polynucleotide—a technique that can be useful when the polynucleotide sequence is long. The inventors termed that method the “reflex method.” The Brenner Patents disclose *both* methods of analysis and counting through combinatorial multiplex tagging and reflex methods, shown in Figure 5 of the Brenner patents, copied below.⁹

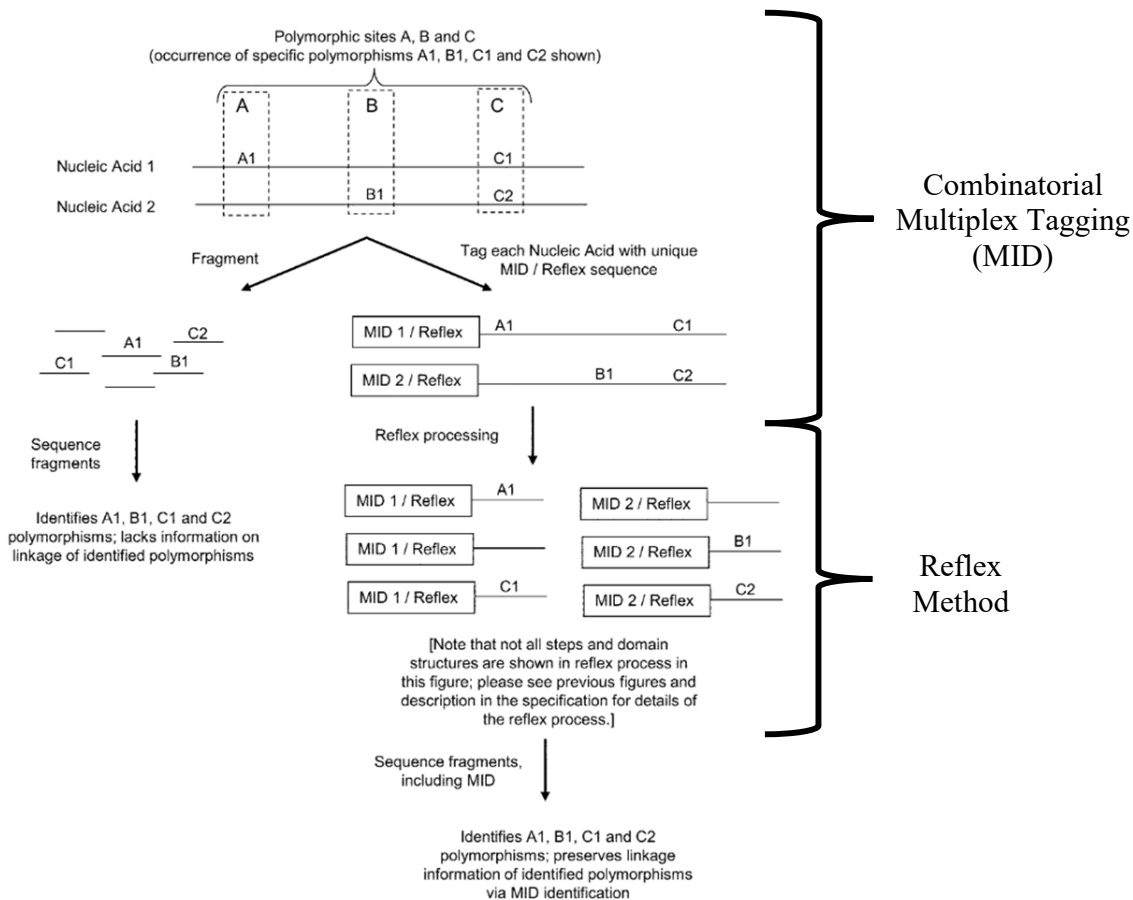


Figure 5 of the Brenner Patents

The Brenner Patent claims to methods that include a physical step of generating combinatorially-tagged polynucleotides are not directed to an abstract idea. Parse’s focus on the

⁹ Thus, Parse’s repeated suggestion at the Hearing that the Brenner Patents are directed only to a reflex method is not only irrelevant—it is wrong. Equally irrelevant and erroneous were Parse’s suggestions that 10x had expanded its claims in the Brenner Patents beyond what it had invented and disclosed. *See* Parse Opening Br. at 5; Tr. at 13:22–25.

reflex method at the Hearing is a red herring. *See* Tr. at 18:17–22, 28:4–9. The word “reflex” does not appear in any of the patent claims in the Brenner Patents. The question here is not whether the reflex method is an abstract idea; it is whether the sixty claims asserted in the Brenner Patents are *each* directed to an abstract idea under the law of 35 U.S.C. § 101. The answer to this question is no.

b. *Alice* Step One

Under *Alice* step one, none of the claims of the Brenner Patents is directed to an abstract idea. Each of the claims requires physical, concrete steps of generating tagged polynucleotides using a novel combinatorial multiplexed tagging approach that enabled researchers to differentiate previously undifferentiable pools of polynucleotides within a population of cells and to count each distinct polynucleotide within each cell—a feat that previously was not possible. *See Illumina*, 967 F.3d at 1328; *CellzDirect*, 827 F.3d at 1048–49.

For example, in the ’981 Patent:

1. A **method of analyzing nucleic acids from a plurality of single cells**, the method comprising:
 - (a) providing a sample comprising a plurality of single cells, wherein each single cell of the plurality of single cells comprises a plurality of sample polynucleotides;
 - (b) **generating a plurality of tagged polynucleotides from the plurality of sample polynucleotides, wherein each tagged polynucleotide comprises:**
 - (i) a sequence from a sample polynucleotide of the plurality of sample polynucleotides; and
 - (ii) **a multiplex identifier (MID) sequence** comprising:
 - I. **a first tag sequence associated with the single cell from which the sample polynucleotide is derived, wherein the first tag sequence is a different sequence for different single cells in the plurality of single cells; and**
 - II. **a second tag sequence distinguishing the sample polynucleotide from other sample polynucleotides derived from the same single cell;**

- (c) sequencing the plurality of tagged polynucleotides to obtain a plurality of identified polynucleotide sequences;
- (d) **using the first tag sequence to correlate the identified polynucleotide sequence with the single cell from which the identified polynucleotide sequence is derived;** and
- (e) **using the second tag sequence to correlate the identified polynucleotide sequence with the sample polynucleotide from which the identified polynucleotide sequence is derived.**

'981 Patent, Claim 1 (emphases added). Thus, claim 1 of the '981 Patent is directed to methods of analyzing nucleic acids within a population of cells that require not only the physical step of “generating a plurality of tagged polynucleotides” comprising “a multiplex identifier (MID) sequence” comprising combinatorial tags to distinguish not only the cell the polynucleotide is from but also from other polynucleotides within that cell, but also the physical step of “sequencing the tagged polynucleotides.” Several of the dependent claims add additional physical, non-abstract steps, including “amplifying the tagged polynucleotides prior to the sequencing step” (claim 2) and generating the tagged nucleotides “through at least one ligation reaction” (claim 5) or “through PCR or linear amplification of the plurality of sample polynucleotides using an adaptor sequence comprising the MID sequence and an amplification primer” (claim 6). Parse fails to explain, let alone meet its burden of demonstrating, how these additional physical steps are directed to an abstract idea.

The specification explains that combinatorially tagging the same polynucleotide with a first and second tag sequence provides a “correlation between a polynucleotide and its source” so that researchers can know, for example, how many individual polynucleotides are in each single cell within a sample. '981 Patent at 6:38–51. This concrete application was explicitly claimed in the '197 and '013 Patents. For example, the '197 Patent claims:

1. A **method of counting nucleic acids in a sample**, the method comprising:
 - (a) providing a sample comprising a plurality of cells, wherein a cell of the plurality of cells comprises a plurality of sample polynucleotides;

- (b) **generating a plurality of tagged polynucleotides from the plurality of sample polynucleotides** of said cell and a plurality of oligonucleotide tags, wherein a tagged polynucleotide of the plurality of **tagged polynucleotides comprises**:
 - (i) a sample sequence from a sample polynucleotide of the plurality of sample polynucleotides;
 - (ii) **a first tag sequence distinguishing said sample polynucleotide from sample polynucleotides from other cells**; and
 - (iii) **a second tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell**;
- (c) sequencing the tagged polynucleotide to determine the sample sequence, the first tag sequence, and the second tag sequence; and
- (d) **using the first tag sequence and the second tag sequence to count a number of sample polynucleotides in said plurality of sample polynucleotides of said cell.**

'197 Patent, Claim 1 (emphases added).

The '013 Patent claims:

1. A **method for multiplexed analysis of nucleic acids from single cells**, the method comprising:
 - (a) providing a sample comprising a plurality of cells, wherein a single cell of the plurality of cells comprises a plurality of sample polynucleotides;
 - (b) **performing combinatorial tagging to generate a plurality of tagged polynucleotides from said plurality of sample polynucleotides** and a plurality of oligonucleotide tags, wherein a tagged polynucleotide of the plurality of tagged polynucleotides is generated by:
 - (A) providing an extension product by primer extension using a first oligonucleotide tag and a sample polynucleotide of said plurality of sample polynucleotides, and
 - (B) ligating a second oligonucleotide tag to said extension product, and wherein said tagged polynucleotide of **the plurality of tagged polynucleotides comprises**:
 - (i) a sample sequence corresponding to said sample polynucleotide of the plurality of sample polynucleotides;
 - (ii) **a first tag sequence distinguishing said sample polynucleotide from sample polynucleotides from other cells**; and

- (iii) **a second tag sequence distinguishing said sample polynucleotide from other sample polynucleotides from said cell;**
- (c) amplifying said tagged polynucleotide, thereby generating a plurality of amplified polynucleotides corresponding to the tagged polynucleotide; and
- (d) sequencing said plurality of amplified polynucleotides to determine sequences of the amplified polynucleotides corresponding to the sample sequence, the first tag sequence, and the second tag sequence of the tagged polynucleotide; and
- (e) using the sequences determined in step (d) **to count sample polynucleotides for multiple different sample polynucleotides of multiple different single cells of said plurality of cells.**

'013 Patent, Claim 1 (emphases added).

Moreover, Parse fails to explain, let alone meet its burden of demonstrating, how the physical steps of the claimed method, including “providing an extension product by primer extension,” “ligating . . . to said extension product,” “amplifying said tagged polynucleotide, thereby generating a plurality of amplified polynucleotides,” and “sequencing,” are directed to an abstract idea. Similarly, Parse fails to explain how the dependent claims of the '197 and '013 Patent that specify the physical steps necessary to make the tagged polynucleotides ('197 patent, claims 8-11; '013 claims 3-5, 8-9) or the physical steps of “hybridizing said tagged polynucleotide to a solid support” ('197 Patent, claims 21-22; '013 Patent, claims 20-21), “generating said plurality of amplified polynucleotides using polymerase chain reaction (PCR)” ('013 Patent, claim 11) are directed to an abstract idea.

For each of the Brenner Patents, tagging each polynucleotide with a first tag sequence and a second tag sequence is not merely labeling a polynucleotide. Nor is it routine or conventional, as the Patent Office made clear in allowing the '981 Patent:

The following is an examiner's statement of reasons for allowance: The 35 USC 102 rejection is hereby withdrawn. The closest prior art, Linnarsson (WO 2010/117620), does not teach or suggest generating a plurality of tagged

polynucleotides comprising an identifier sequence of instant claim 1(ii). The claimed identifier sequence comprises a first tag sequence, which distinguishes each single cell in a sample of plurality of cells, and a second tag sequence, which distinguishes a sample polynucleotide from other sample polynucleotides derived from a single cell, which is not taught by Linnarsson.

Wu Decl. Ex. 4, Notice of Allowability at 2. The Patent Office also stated in allowing the '013

Patent claims to issue that the claimed invention had not been taught in the prior art:

The claims are allowed for the reason that a thorough search demonstrated the prior art does not teach or fairly suggest Applicants' claimed method of combinatorial tagging polynucleotides from single cells in which a sample polynucleotide of a plurality of sample polynucleotides comprises a first tag sequence which distinguishes the sample polynucleotide from the sample polynucleotides from other cells and a second tag sequence which distinguishes the sample polynucleotide from other sample nucleotides.

Wu Decl. Ex. 5, Notice of Allowability at 3.

Each of the '981, '197, and '013 Patents claims different laboratory methods with novel, physical steps, and thus are not directed to an abstract idea. *See Illumina*, 967 F.3d at 1328; *CellzDirect*, 827 F.3d at 1048–49.

c. Alice Step Two

Because each of the Brenner Patent claims is not directed to an abstract idea, the Court need not reach *Alice* step two. But in the event the Court were to reach step two, the claimed laboratory inventions recite inventive concepts that are “significantly more” than an abstract idea itself. *Alice*, 573 U.S. at 217–18 (quoting *Mayo*, 566 U.S. at 72–73). As discussed above, the Patent Office allowed the claims because of their unconventional tagging of a single polynucleotide with a first and second tag sequence. *Supra* at 30–32. Further, the statement in the Brenner Patents that the “practice of the present invention *may employ*, unless otherwise indicated, conventional techniques and descriptions of organic chemistry, polymer technology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology” ('981 Patent at 13:32–36 (emphasis added)) is merely a statement that techniques

such as joining or ligating polynucleotides together were known, not an admission that the claimed invention employing those techniques was routine or conventional. *See Illumina*, 967 F.3d at 1328; *CellzDirect*, 827 F.3d at 1048–49. What was not known, as the Patent Office noted, were the claimed methods using tagging of a single polynucleotide with a first and second tag sequence.

Parse incorrectly attempts to rely on statements made at *Alice* step one in a natural-phenomenon case to support its step two abstract-idea arguments to patents directed to measurement techniques. In *CareDx, Inc. v. Naterra, Inc.*, the Federal Circuit found ineligibility at *Alice* step one, holding that the claimed method of detection “appl[ies] conventional measurement techniques to detect a natural phenomenon.” 40 F.4th at 1378. The Federal Circuit distinguished that case from cases, like here, involving “a method of preparation of a new measurement technique.” *Id.* at 1377. Moreover, whether claim limitations are well-understood, routine, or conventional to a person of ordinary skill in the art is a question of fact. *Berkheimer*, 881 F.3d at 1368. Thus, Parse’s arguments fail because at best, they raise factual disputes as to what was routine and conventional at the time of the invention, which must be resolved against Parse on a motion to dismiss. *See infra*, § II.D.

Parse criticizes the Brenner patents for not stating their inventive concepts in a single place in the patents or explaining why particular embodiments are inventive. Tr. at 22:4–11; Parse Opening Br. at 17–19; Parse Reply Br. at 5, 9. In so doing, Parse confuses the law on patent eligibility under § 101 with the law of § 112 as to whether there is sufficient written description (a different and unrelated ground for invalidity). But in any event, the law does not require that issued patents, which are presumed to be valid, state their inventive concepts in a particular place. *See Berkheimer*, 881 F.3d at 1370 (identifying statements in the detailed

description of the preferred embodiments as disclosing the inventive concept described in the specification and claimed in the challenged claims). Nor does the support for the claims have to be found in the summary of the invention as Parse suggests. *See* Tr. at 18:17–22, 22:4–11; *Berkheimer*, 881 F.3d at 1370 (identifying statements in the detailed description of the preferred embodiments as disclosing the inventive concept described in the specification and claimed in the challenged claims). Rather, all that is required is that the disclosure provide sufficient guidance for a person of ordinary skill in the art to make and use the claimed invention under 35 U.S.C. § 112; there is no requirement that the patent expressly teach or disclose why the claimed invention is inventive. *See Progressive Cas. Ins. Co. v. Safeco Ins. Co.*, No. 10-cv-1370, 2010 WL 4698576, at *4–5 (N.D. Ohio Nov. 12, 2010) (“Accordingly, plaintiff is not required to point to any specific facts [regarding § 101 eligibility] to trigger the presumption of validity.”); *see also Berkheimer*, 881 F.3d at 1370. That support can be found anywhere in the patent specification, including outside the Summary of the Invention. *See Berkheimer*, 881 F.3d at 1370.

d. Parse’s Motion Asks the Court to Make New Law That a Method of Analyzing Nucleic Acids Based on Tagging Is an Abstract Idea

Parse’s argument that the 60 claims of the Brenner Patents are invalid under § 101 as abstract ideas asks this Court to make new law. Patent claims found to be ineligible as abstract ideas are typically directed to computer implementation methods and technology relating to use of a computer. *See, e.g., Alice*, 573 U.S. at 219–21 (discussing patents and ideas related to “mathematical formula[s],” “computing,” “algorithms,” and “generic computer implementation” are patent ineligible as abstract ideas); *Intell. Ventures I LLC v. Cap. One Bank (USA)*, 792 F.3d 1363, 1366–68 (Fed. Cir. 2015) (similar). Indeed, the only cases that Parse cites to support its

argument focused on software patents where the use of a computer did not make the idea non-abstract. *See* Parse Opening Br. at 16.

That is not the case here, where the Brenner Patents do not use a computer to implement the claimed invention. *See, e.g., Alice*, 573 U.S. at 218–21 (discussing intermediated settlements and implementation by computers as directed to an abstract idea like that of *Bilski v. Kappos*, 561 U.S. 593 (2010), where hedging was found to be an unpatentable abstract idea). Rather, the Brenner Patents are directed to methods of analysis of nucleic acids and methods of counting nucleic acids. Parse cites to no case holding—and we have found none—that patent claims to a laboratory method of using a biological product are abstract ideas. The only case even coming close to such an argument is *Boehringer Ingelheim Pharmaceuticals Inc. v. Mylan Pharmaceuticals Inc.*, in which the district court considered whether claims to a method of using a particular type of inhibitor called a DPP-IV to treat type 2 diabetes mellitus were directed to the “abstract idea” of “administering the DPP-IV inhibitor to the target patient population.” 803 F. App’x 397, 398–99 (Fed. Cir. 2020). After the district court held the claims invalid as being directed to an abstract idea, the Federal Circuit reversed, holding that “the claims are directed to a particular method of treatment under step one [of *Alice*] and are therefore patent eligible.” *Id.* at 400. Even though the ability of the inhibitor to treat was based on the ability of the inhibitor to be metabolized in the liver rather than in the kidney, this did “not make the claim ‘directed to’ that natural ability.” *Id.* at 400–01 (quotation omitted).

The *Tangelo* case cited by Parse is inapposite. *See* Parse Opening Br. at 16, (citing *Tangelo IP, LLC v. Tupperware Brands Corp.*, No. 18-692-RGA, 2018 WL 6168083, at *4 (D. Del. Nov. 26, 2018)). The claims in *Tangelo* were “directed to the abstract idea of using an identifier to allow a reader of a printed publication to access related information not in a printed

publication,” that lacked an inventive concept because the claims “merely appl[y] the abstract idea . . . in a generic computer environment.” *Tangelo*, 2018 WL 6168083, at *2, *4. That is far from the case here, where the use of combinatorial, multiplex identifier tags is used to help differentiate all the polynucleotides within a population of cells in a way that had never been done before. And, as Parse admits, no case holds that tagging is, in and of itself, an abstract concept under *Alice* step one. Tr. at 56:4–8.

e. Parse’s Other Arguments Fail

As is common practice before the Patent Office, the different inventions disclosed in the Brenner Patent specification were pursued in different patent applications. There is nothing untoward about such a practice, as Parse repeatedly implied. *See, e.g.*, Tr. at 9:3–21. Not only is filing multiple applications explicitly allowed under the Patent Statute, it may be **required** by the Patent Office in some circumstances under a restriction requirement. 35 U.S.C. §§ 120 & 121; MPEP § 803. That is what occurred here. For example, the Patent Office issued a restriction requirement in the parent application to the asserted Brenner Patents, U.S. Patent Application No. 13/387,343 (which issued as U.S. Patent No. 8,298,767) and required the applicant to restrict the claims to either methods of analysis or to kits. *See generally* Suppl. Wu Decl., Ex. B; Suppl. Wu Decl., Ex. C. Nevertheless, Parse attempts to argue that 10x improperly obtained each set of patents from the Patent Office because each patent is directed at a different inventive embodiment disclosed in the specification. *See* Tr. at 9:11–21 (characterizing the different asserted claims as “different attempts to state what their right is. And so by multiplying it out, they get more claims.”), 29:12–16 (“They’re just different bites at the apple of trying to state what their right is.”).

This fails. Seeking patent protection for different inventions disclosed in a parent application in different children applications is a common practice and is not evidence of

invalidity. *See, e.g., Plantronics, Inc. v. Aliph, Inc.*, 724 F.3d 1343, 1351 (Fed. Cir. 2013) (stating restriction requirement to split four patentably distinct inventions in application did not surrender claim scope of claims patent owner elected to pursue); *UCB, Inc. v. Watson Labs. Inc.*, 927 F.3d 1272, 1279 (Fed. Cir. 2019) (stating Patent Office restriction requirement and patent owner's election in response to choose between two groups of claims did not surrender claim scope of polyisobutylene because election did not give up scope of non-silicate and non-acrylate adhesives). Parse also suggests a patent examiner allowed multiple Brenner patents because "the patent examiner is not an attorney who will let them [obtain multiple patents]." Tr. at 14:12–13. Parse's self-serving criticism of patent examiners and the Patent Office, which is a federal agency, has no place in a § 101 analysis and should be rejected. *See, e.g., Wanker v. United States*, 146 Fed. Cl. 582, 592 n.2 (2020) (denying Rule 12(b)(6) motion to dismiss under § 101, noting "[i]ssued patents received the benefit of a 'presumption recogniz[ing] the deference that is due to a qualified government agency presumed to have done its job correctly.'"); *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999) ("The 'presumption of validity under 35 U.S.C. § 282 carries with it a presumption that the Examiner did his duty and knew what claims he was allowing.'").

D. Parse's Belated Attempt to Inject New Disputed Factual Issues into the Record Confirms That Its Motion Should be Denied

On the same day that the Supplemental Briefs were originally due on December 13, 2022 and months after Parse's Motion was filed, counsel for Parse advised that it may rely on two references that are not in the record for this Rule 12(b)(6) Motion, and that it did not cite in its Motion briefing or at the Hearing. *See* Suppl. Wu Decl., Ex. D (asserting that Parse "may rely on these two cited references to address 10x's arguments about the claimed tagging as the alleged inventive concept," citing U.S. Patent Application Publication No. 2007/0020640 to

Megan L. McCloskey et al. (“McCloskey II”) and Roche 454 Sequencing, *Technical Bulletin, Genome Sequencer FLX System, Using Multiplex Identifier (MID) Adaptors for the GS FLX Titanium Chemistry – Basic MID Set* (“Roche 454 Technical Bulletin”). Parse’s belated attempt to inject these new references—and thus new disputed facts—into the record confirms that its Motion should be denied.¹⁰

To the extent that the Court nonetheless considers Parse’s new arguments, at best, the new references raise factual disputes as to what they disclose and whether they show that certain claim elements were routine or conventional. What a reference discloses is a question of fact, and one that is disputed here. *See, e.g., Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617 F.3d 1296, 1303 (Fed. Cir. 2010). So too whether any element is conventional or routine is a question of fact, which is also disputed here: “[t]he mere fact that something is disclosed in a piece of prior art, for example, does not mean it was well-understood, routine, and conventional.” *Berkheimer*, 881 F.3d at 1369 (“Whether something is well-understood, routine, and conventional to a skilled artisan at the time of the patent is a factual determination.”). Such factual disputes are fatal to Parse’s Motion. As *Cronos* stated, the question presented here is: “is there **any** set of facts that could be proven relating to questions of preemption, questions of patentability, or whether the claims ‘solve a technological problem,’ that would result in a determination that one or more of the claims are patent eligible?” 2015 WL 5234040, at *6 (emphasis in original). If so, the Motion to dismiss must be denied. *See id.* at *10–11.

¹⁰ Parse’s attempt to inject new arguments relying on new materials is untimely and prejudicial to 10x as it would have no opportunity to respond. Parse had ample time to address these materials in its briefing and at the Hearing but failed to do so. As such, any arguments should be considered waived.

Delaware district courts regularly deny Rule 12 motions to dismiss, including those brought under § 101 where there are factual disputes. *See Guada Techs LLC v. Vice Media, LLC*, 341 F. Supp. 3d 390, 399–400 (D. Del. 2018) (“Here, there exists a factual dispute as to whether the purported inventive concepts were ‘well-understood, routine and conventional’ in 2002” denying motion to dismiss at Alice step two); *Nielsen Co. (US), LLC v. HyphaMetrics, Inc.*, No. 21-cv-1591-CJB, 2022 WL 3211915, at *6 (D. Del. Aug. 9, 2022) (slip op.) (denying motion to dismiss where the complaint and a declaration “taken together with the specification of the [patent] and the content of [the claim], create a material factual dispute as to patent eligibility”); *NICE Ltd. v. CallMiner, Inc.*, No. 18-cv-2024-RGA, 2020 WL 1502290, at *11 (D. Del. Mar. 30, 2020) (denying motion to dismiss where “there is a factual dispute about whether the invention ‘describes well-understood, routine, and conventional activities.’”); *see also Belcher Pharms., LLC v. Int’l Medication Sys., Ltd.*, 379 F. Supp. 3d 326, 333–34 (D. Del. 2019) (denying motion to dismiss because defendants’ arguments regarding patent infringement and invalidity “implicate factual disputes.”); *Aperture Net LLC v. Cambium Networks, Inc.*, No. 21-cv-298-RGA, 2022 WL 605740, at *3 (D. Del. Feb. 1, 2022) (“factual questions” raised by defendant were “not appropriate for resolution at the motion to dismiss stage”).

Moreover, Parse’s attempt to rely on the two references cannot meet its burden here. Neither reference is directed to the same invention as the Brenner Patents. As discussed above, the Brenner Patents are directed to the problem of analyzing nucleic acids in a population of cells at a single cell level to understand, for example, cell-to-cell variability within that population, and of counting the different nucleic acids within each single cell in a population of cells, neither of which were possible based on prior methods. Dr. Brenner and his co-inventors solved these problems through the novel use of combinatorial multiplexed tags where one tag could be used

to identify the single cell a polynucleotide is from, and a second tag could be used to distinguish the polynucleotides within that single cell. In contrast, McClosky II and the Roche 454 Technical Bulletin are directed to methods that solved a different problem altogether—identifying what sample the polynucleotide is from (i.e., sample indexing).

Roche 454 Technical Bulletin describes how to use Roche’s 454 Sequencer to perform “General (e.g., Shotgun) library preparation” for sequencing using tags that Roche called “Multiplex Identifiers (MID).” Roche 454 Technical Bulletin at 2. Shotgun sequencing refers to a technique that is used to sequence long strands of polynucleotides. Traditional sequencing machines can sequence only polynucleotides that are made up of a few hundred nucleosides or less. To obtain the sequence of a polynucleotide that contains thousands of nucleotides, researchers used the “shotgun” sequencing method, which required making several copies of the polynucleotide (or amplifying the polynucleotide), breaking each copy into random smaller pieces (or fragments) where each copy ideally is fragmented differently (like how a shotgun shell breaks apart after it is fired from a shotgun) to generate a “library” of fragments, sequencing the smaller fragments, and piecing the fragments together based on the overlap between the fragments to obtain the sequence of the long polynucleotide. Such methods were costly, and some researchers would try to run several such experiments in parallel on a single machine. In order to do so, each of the sample polynucleotides must be tagged such that the library of fragments created by the shotgun method could be associated with the correct sample polynucleotide. Roche provided a set of ten tags that it called “Multiplex Identifier (MID)” that can be used as “specific library-identifying sequence.” *Id.* at 3. Thus, despite the similarity in name, Roche’s Multiplex Identifier (MID) in the Roche 454 Technical Bulletin—used to associate library sequences to its corresponding polynucleotide—is not the same as the

combinatorial multiplex identifier tag in the Brenner Patents—used to distinguish the single cell from which the polynucleotide came and to distinguish the polynucleotides from within the same single cell from each other. Moreover, the Roche 454 Technical Bulletin does not disclose how to use the Roche MID to analyze polynucleotides on a single cell basis within a population of cells or to count the polynucleotides in a single cell within a population of cells.

Similarly, McCloskey II is directed to methods to “verify[] the authenticity of PCR products” by distinguishing sample DNA from contaminants. McCloskey II, at [0003–0004]. This means nothing more than tagging the sample of interest so that the sample’s identity and the date the test was run can be tracked and distinguished from contaminants. *Id.* at [0005]. McCloskey II, however, is not directed to the analysis of the polynucleotides in a single cell within a population of cells and the counting of polynucleotides in a single cell within a population of cells.

III. CONCLUSION

For the foregoing reasons and the reasons set forth in 10x's Answering Brief and at the Hearing, 10x respectfully requests that the Court deny Parse's Motion.

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December 15, 2022

CERTIFICATE OF SERVICE

I hereby certify that on December 15, 2022, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on December 15, 2022, upon the following in the manner indicated:

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