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A POTENTIAL ELIGIBILITY SAFE HARBOR FOR DIAGNOSTIC PATENTS CREATES MORE CONFUSION IN THE *ALICE/MAYO* TEST.

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Decisions by the Supreme Court interpreting the subject matter eligibility statute of the Patent Act[1] in cases implicating inventions in the medical field[2] have had a substantial impact on medical research.[3] Section 101[4] has traditionally been interpreted as stating that naturally existing substances and laws of nature are not patentable[5] while man-made inventions that employ laws of nature or naturally existing substances are patentable.[6] To verify if a patent claims an eligible subject matter, the Court has established a two-step test, also known as the *Alice/Mayo* test. The first step of the test focuses on whether the claim is directed to "a patent ineligible concept" and the second step verifies if the additional elements "transform the nature of the claim into a patent-eligible application."[7] This test has been particularly challenging for diagnostic inventions since they are usually based on discovered natural phenomena so closely linked to its utility that the "additional elements" are frequently conventional.[8] In fact, since *Mayo*,[9] diagnostic claims have frequently been found to be patent-ineligible under Section 101.[10] However, the development and production costs for diagnostic devices are considerable and, thus, patent protections are invaluable to

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1 35 U.S.C. § 101 (2018).

2 *See e.g.*, Mayo Collaborative Servs. v. Prometheus Labs., Inc. 566 U.S. 66 (2012); Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576 (2013).

3 *See e.g.*, Johnathon Liddicoat, Kathleen Liddell & Mateo Aboy, *The Effects of* Myriad *and* Mayo *on Molecular-Test Development in the United States and Europe: Interviews from the Frontline*, 22 VAND. J. ENT. & TECH. L. 785 (2020).

4 35 U.S.C. § 101.

5 Parker v. Flook, 437 U.S. 584, 593 (1978); *Mayo*, 566 U.S. at 70.

6 Diamond v. Chakrabarty, 447 U.S. 303, 307 (1980).

7 Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 573 U.S. 208, 217. (2014) (discussing *Mayo*, 566 U.S. 70–74) ("First, we determine whether the claims . . . are directed to one of those patent-ineligible concepts. If so, we . . . determine whether [] additional elements 'transform the nature of the claim' into a patent-eligible application.") (internal citations omitted).

8 *See e.g.*, *Myriad*, 569 U.S. at 583–84 (discussing the discovery of particular gene mutations associated with breast cancer used to identify persons with propensity to develop breast cancer); *Mayo*, 566 U.S. 66, 73–74 (discussing the discovery that presence of certain metabolites are associated with drug efficacy used to design customized patient treatment).

9 566 U.S. 66 (2012).

10 Athena Diagnostics Inc. v. Mayo Collaborative Servs., LLC, 927 F.3d 1333, 1352 (Fed. Cir. 2019) ("Since *Mayo*, we have held every single diagnostic claim in every case before us ineligible."); Warren D. Woessner & Robin A. Chadwick, *What's Left to Patent in the Life Sciences after* Myriad, Mayo, *and* Alice*?*, 101 J. PAT. & TRADEMARK OFF. 121, 123 (2019).

companies[11] and to research institutions that pursue them.[12] In *Illumina, Inc. v. Ariosa Diagnostics, Inc.*,[13] the Federal Circuit bucked this trend and upheld a challenged patent for a diagnostic invention. The holding stated that the claims with diagnostic utility[14] were valid because they were "directed to" a method of preparation of a sample that employed human-engineered parameters.[15] This holding was an extension of the precedent set in *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*,[16] a non-diagnostic patent case holding claims for production of cell lines were a patentable "method of preparation." Should this holding stand,[17] inventors may find an avenue to patent diagnostic inventions by focusing on innovations in the method of preparation of the sample. This holding, however, creates substantial challenges in understanding the two-step *Alice/Mayo* doctrine and is, potentially, in conflict with the Federal Circuit ruling in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.* [18]

Illumina decided a claim of non-eligibility under Section 101 of two patents assigned to plaintiff-appellant Sequenom, U.S. Patents 9,580,751[19] and 9,738,931.[20] Both patents leverage the previously known fact that a pregnant person's blood plasma includes cell-free fetal DNA (cffDNA) along with the maternal DNA, and the inventors' discovery that most cffDNA is on the shorter end of the size distribution of total cell-free DNA obtained from the maternal blood plasma.[21] Specifically, the inventors discovered that cffDNA was almost always smaller than 500 base pairs and that a substantial portion was smaller than 300 base pairs.[22] Accordingly, the patents claim a method with a step for "selectively removing the DNA fragments greater than approximately"[23] a specified DNA size threshold — 500 base pairs in the '751 patent[24] and 300 base pairs in the '931 patent[25] — from the pregnant person's blood

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11 Johnathon Liddicoat, Kathleen Liddell & Mateo Aboy, *supra* note 3, at 811–12.

12 *Id.* at 809–810 (discussing Technology Transfer Offices of research institutions).

13 967 F.3d 1319 (Fed. Cir. 2020). The opinion is an August 3, 2020 re-issue and modification that supersedes the opinion issued on March 17, 2020 and reported at 952 F.3d 1367 (Fed. Cir. 2020) following a petition for rehearing filed by Defendant-Appellees. *See infra* notes 61–62 and accompanying text for a discussion of the modifications.

14 *Illumina*, 967 F.3d at 1327 (analysis of fetal chromosomal aberrations).

15 *Id.* at 1329 ("[M]ethods for preparing [a sample using] a specified human-engineered threshold . . . are 'directed to' more than merely natural phenomenon . . . . Accordingly, we conclude at step one of the *Alice/Mayo* test that the claims are not directed to a patent-ineligible concept.").

16 827 F.3d 1042, 1048 (Fed. Cir. 2016). *See infra* note 52–58 and accompanying text.

17 A rehearing en banc was denied. Illumina, Inc. v. Ariosa Diagnostics, Inc., 814 Fed.Appx. 601 (Fed. Cir. August 3, 2020). The author is currently unaware of any petition for certiorari to the Supreme Court.

18 788 F.3d 1371 (Fed. Cir. 2015). *See infra* note 61-69 and accompanying text for discussion.

19 Filed February 17, 2011.

20 Filed February 1, 2013.

21 Illumina, Inc. v. Ariosa Diagnostics, Inc., 967 F.3d 1319, at 1322–23 (Fed. Cir. 2020).

22 *Id.* at 1322.

23 '751 patent, claim 1 and '931 patent, claim 1.

24 '751 patent, claim 1.

25 '931 patent, claim 1.

plasma. This step enriches the amount of cffDNA in the sample,[26] making the sample more useful for detecting "a fetal chromosome aberration."[27] Plaintiff-appellants Illumina and Sequenom filed an infringement lawsuit against defendant-appellees Ariosa Diagnostics, Roche Sequencing Solutions, and Roche Molecular Systems, Inc in the district court for the Northern District of California.[28] The defendants moved for summary judgment by asserting that the claims were invalid under Section 101.[29] Judge Illston agreed with the defendants and held the claims were directed to ineligible subject matter.[30] The defendants filed a timely appeal to the Federal Circuit.[31] The question posed on appeal was whether the claims were indeed patent-ineligible under Section 101, which the panel reviewed under a *de novo* standard.[32]

Writing for the panel, Judge Lourie, who was joined by Judge Moore, reversed the district court's ruling and found that the patents are directed to patent-eligible subject matter. The court started by evaluating Section 101 which is the statute that enumerates the class of inventions and discoveries that may be patented.[33] Under this statute, laws of nature and natural phenomena are not patentable,[34] but their application may be.[35] However, not every application is patent-eligible. Applications employing "conventional steps specified at a high level of generality . . . cannot make [unpatentable subject matter] patentable."[36] The court employed the *Alice/Mayo* two-step test to distinguish patent-eligible applications of laws of nature from non-patentable ones.[37] The court explained the first step of the test as an examination of "whether the claims are 'directed to' a law of nature or natural phenomenon."[38] A claim that meets the patentability burden in this first step is ruled eligible.

The *Illumina* court found the claims eligible under the first step by noting that they were directed to "methods for preparing a fraction of cell-free DNA that is enriched in fetal DNA,"[39] and that these were patent-eligible applications of a discovered natural phenomenon.[40] Specifically, the court found that the discovery of the natural

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26 Illumina, Inc. v. Ariosa Diagnostics, Inc., 952 F.3d 1367, 1369 (Fed. Cir. 2020).

27 '751 patent, claim 12 and '931 patent, claim 1

28 Illumina, Inc. v. Ariosa Diagnostics, Inc., 356 F. Supp. 3d 925 (N.D. Cal. 2018).

29 *Id.* at 928.

30 *Id.* at 935.

31 *Illumina*, 952 F.3d at 1368.

32 *Id.* at 1370 ("We review a grant of summary judgment according to the law of the regional circuit. In the Ninth Circuit, a grant of summary judgment is reviewed *de novo*.") (internal citations omitted).

33 35 U.S.C. § 101 ("Whoever invents or discovers . . . my obtain a patent therefor.").

34 Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 70 (2012).

35 *Id.* at 71.

36 *Id.* at 82.

37 *Illumina*, 967 F.3d at 1324–25. *See also supra* note 6 and accompanying text.

38 *Illumina*, 967 F.3d at 1324–25 (citing Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 573 U.S. 208, 217 (2014)).

39 *Id.* at 1326.

40 *Id.* at 1329 ("claimed methods utilize the natural phenomenon that the inventors discovered").

phenomenon that maternal cell-free DNA and cffDNA have different size distributions[41] was exploited by the inventors in their use of size separation methods to prepare an enriched cffDNA sample.[42] To support this finding, the court noted that the size thresholds engineered to enrich the amount of cffDNA that remains in the mixture were "not dictated by any natural phenomenon."[43] The court further noted that the claimed process went beyond the mere detection of the natural phenomenon and was used to "change the composition of the mixture."[44] Thus, despite its diagnostic application, the panel found the claim eligible as directed to a method of preparation under step one.[45] The finding of eligibility under step one renders step two analysis unnecessary.[46]

Judge Reyna wrote a dissent from the panel's ruling, stating he would have held the claims patent-ineligible under the two-step *Alice/Mayo* test.[47] Judge Reyna notes that the claimed methods fail step one by because they consist of a manipulation of a naturally occurring sample without altering any naturally occurring substances.[48] Judge Reyna also challenged the majority's holding that a method of preparation should be analyzed differently from other diagnostic claims found invalid.[49] In doing so, Judge Reyna also challenged the analogy with *CellzDirect* by pointing to the distinction that the method in *CellzDirect* "went beyond applying a known laboratory technique" whereas the claims in *Illumina* "do not recite or recognize the creation of a new laboratory technique."[50] Judge Reyna further noted that the claimed method would also fail step two of the *Alice/Mayo* test because the size discrimination steps were conventional and routine and the specifically selected size thresholds were mere adaptations of the discovery to commercially available DNA separation methods predicated on the existence of existing testing kits and known laboratory techniques.[51] Finally, Judge Reyna noted the preemption concerns that these patents would raise.[52]

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41 *Id.* at 1325–26. The panel considered different formulations for a natural phenomenon without deciding a specific one.

42 *Id.* at 1326–27.

43 *Id.* at 1326.

44 *Id.* at 1326.

45 *Id.* at 1327–28.

46 *Id.* at 1329.

47 *Id.* at 1330 (Reyna, J., dissenting).

48 *Id.* at 1332 (Reyna, J., dissenting) ("[T]he claimed method steps do not alter those substances . . . and are, therefore, directed to a natural phenomenon."); *see also id.* at 1336.

49 *Id.* at 1333 (Reyna, J., dissenting) (citing Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 915 F.3d 743 (Fed. Cir. 2019), Genetic Techs. Ltd. v. Merial L.L.C., 818 F.3d 1369, 1375 (Fed. Cir. 2016), and Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (Fed. Cir. 2015)).

50 *Id.* at 1336 (Reyna, J., dissenting).

51 *Id.* at 1337-39 (Reyna, J., dissenting).

52 *Id.* at 1339 (Reyna, J., dissenting) ("Here, the claims are drafted in a manner that tie up future innovations premised upon the natural phenomenon because no skilled artisan would be entitled to rely on the natural phenomenon to isolate cff-DNA.").

The *Illumina* court appears to have extend the rule for "method of preparation" from *CellzDirect*[53] to diagnostic applications.[54] In *CellzDirect*, the patent-in-suit claimed a method to produce liver cell lines that are particularly resistant to freeze-thaw cycles[55] by subjecting cell lines to freeze-thaw cycles and selecting cells that display a desired resistance to the process.[56] The claim was invalidated in the district court under 35 U.S.C. § 101 as being directed to the natural phenomenon that certain cells survive freeze-thaw cycles.[57] The Federal Circuit reversed the district court by stating that the claim was, instead, directed to a technique to prepare the desired cells exploiting the inventors' discovery, thus constituting a patent-eligible subject matter under step one of the *Alice/Mayo* test.[58] The *Illumina* court analogized the cffDNA enrichment claims with the ones in *CellzDirect* in its "directed to" analysis under the step one of *Alice/Mayo* test by noting that both methods of preparation employed conventional technologies employed in an unconventional way.[59]

The sense that the *Illumina* court extended the precedent from *CellzDirect* to diagnostic applications is made stronger by the opinion's passage teaching a categorical doctrine of patent-eligibility for medical-related claims: "[W]e have consistently held *diagnostic claims unpatentable* . . . . In contrast, we have held that *method of treatment claims are patent-eligible* . . . . The *claims in this case do not fall into either category*, and we consider the claims under the *Alice/Mayo* test."[60] This explanation is a puzzling *dicta* for a case related to claims directed to a diagnostic test.[61] Tellingly, the superseded opinion used the word "bucket," a more categorical term,[62] and did not stress the human engineering aspects of the claims as much,[63] betraying perhaps an intention by the court of establishing a broad safe harbor for claims with

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53 827 F.3d 1042 (Fed. Cir. 2016).

54 *Cf. Illumina*, 967 F.3d at 1328 ("In our view, *CellzDirect*, while not directly on point, is instructive.").

55 *CellzDirect*, 827 F.3d at 1046.

56 *Id.* at 1046.

57 *Id.* at 1048.

58 *Id.* The *CellzDirect* opinion also made an alternative finding of validity by stating that the claimed freeze-thaw cycles would also be considered unconventional under step two of the *Alice/Mayo* test, had it not survived step one. *Id.* at 1050–51.

59 *Illumina*, 967 F.3d at 1328.

60 *Illumina*, 967 F.3d at 1325 (emphasis added).

61 *E.g.*, '751 patent, claim 1 ("A method . . . useful for analyzing a genetic locus involved in a fetal chromosomal aberration.").

62 Illumina, Inc. v. Ariosa Diagnostics, Inc., *952 F.3d 1367*, 1371 (Fed. Cir. 2020) ("The claims in this case do not fall into either *bucket*." (emphasis added)).

63 Examples of inclusions from the modification of *Illumina* include "claimed size thresholds are *human-engineered parameters* that optimize the amount of maternal DNA that is removed from the mixture and the amount of fetal DNA that remains in the mixture," 967 F.3d at 1326, and "methods of preparation include size discrimination of the DNA based on *size parameters that the inventors selected* to balance the need to remove enough longer maternal DNA fragments to enrich the sample but also leave behind enough shorter fetal DNA fragments to allow for testing," *id.* at 1322-23 (inclusions denoted by emphasis).

diagnostic utility so long as the diagnostic invention method included an inventive sample preparation step that is not derived from the discovery itself.[64] This rule readily distinguishes *Illumina* from the cases cited by the panel as precedential unpatentable diagnostic claims,[65] where the patents attempted to claim the use of a discovered biological marker for diagnosis. As such, *Illumina* sets a potential safe harbor for diagnostic methods that include an innovative sample preparation step.

However, it is unclear that this categorization can be reconciled with Federal Circuit precedent from *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*,[66] a case invalidating a patent that covered remarkably similar subject matter issues and was owned by the same party. The challenged patent in *Ariosa*, was also for a method preparing an enriched sample of a type of cffDNA to be used for diagnostics. There, the claimed method employed a DNA amplification step to enrich paternally inherited cffDNA present in the maternal blood plasma.[67] The opinion written by Judge Reyna, a dissenter in *Illumina*, found that the patent did not pass step one of the *Alice/Mayo* test because it was directed to the presence of paternal cell-free DNA itself in maternal plasma.[68]

Given the similarities among the inventions, one wonders if the *Illumina* panel would have considered the claims in *Ariosa* in the category of a method of preparation.[69] The distinction between both cases is in the step one analysis of the *Alice/Mayo* test. According to the *Illumina* panel, the invalidated claims in *Ariosa* "were directed to detecting a natural phenomenon after a sample has been prepared or extracted,"[70] even though the *Ariosa* claims recite a DNA amplification step which is used to prepare the sample.[71] Perhaps the relevant distinction is in the specificity of the sample preparation step. The presence of a threshold in *Illumina* makes the step unconventional, in contrast with the conventional DNA amplification step in *Ariosa* recited in general terms.[72] However, the conventionality of a claim limitation

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64 *Illumina*, 967 F.3d at 1326; *cf.* Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc., 827 F.3d 1042, 1052 (Fed. Cir. 2016) ("[The crux of the defendant's] argument seems to be that, once it was discovered that hepatocytes could survive multiple freeze-thaw cycles, it would have been a simple task to repeat the known free-thaw process . . . . [P]atent-eligibility does not turn on the ease of execution or obviousness of the application.").

65 *Illumina*, 967 F.3d at 1325 (citing Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 915 F.3d 743 (Fed. Cir. 2019); Cleveland Clinic Found. v. True Health Diagnostics LLC, 859 F.3d 1352 (Fed. Cir. 2017); Cleveland Clinic Found. v. True Health Diagnostics LLC, 760 F. App'x 1013 (Fed. Cir. 2019)).

66 788 F.3d 1371 (Fed. Cir. 2015).

67 *Id.* at 1373.

68 *Id.* at 1376.

69 *Ariosa* was conspicuously omitted from the list of cases ruling diagnostic patents ineligible. *See supra* note 65.

70 Illumina, Inc. v. Ariosa Diagnostics, Inc., 967 F.3d 1319, 1327 (Fed. Cir. 2020).

71 *See Ariosa*, 788 F.3d at 1373.

72 *Compare Illumina*, 967 F.3d at 1323 ("selectively removing the DNA fragments greater than approximately 300 base pairs") with *Ariosa*, 788 F.3d at 1373 ("amplifying a paternally inherited nucleic acid").

should not affect the "directed to" analysis in the *Alice/Mayo* test.[73] Judge Reyna's dissent in *Illumina* points precisely to this doctrinal challenge by stating that the majority "conflates the *Alice/Mayo* step-one analysis with the step-two analysis."[74]

A second challenge to the Federal Circuit categorization is that, much like the sample preparation steps in *CellzDirect* and in *Illumina*, the DNA amplification step in *Ariosa* does not follow directly from the discovery.[75] The natural phenomenon that paternal DNA is present in the maternal DNA does not dictate the parameters of the DNA amplification step.[76] There is, thus, a tension in the *Illumina* panel's assertion that a preparation step using engineered processes not dictated by the natural discovery makes a claim patent-eligible.[77] This doctrinal tension is one that researchers and inventors are likely to find confusing, since it is not meaningful to distinguish the size separation step in the *Illumina* claims from the DNA amplification step in the *Ariosa* claims from an innovation standpoint. Conventional amplification methods require some engineering that parallels the choice of the size threshold for a size selection.[78] In fact, both methods for DNA enrichment of cell-free DNA are viable alternatives available to researchers seeking to enrich cffDNA.[79] Thus, It is unclear to a researcher why only one of these two options makes a diagnostic test *unconventional* patent-eligible subject matter under 35 U.S.C. § 101.

This discussion regarding the differences between *Illumina* and *Ariosa* decisions illuminates the doctrinal difficulties of applying the two-

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73 In the *Alice/Mayo* test, the "directed to" analysis is performed in step one, Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 573 U.S. 208, 217 (2014), while the analysis of whether claim limitations are conventional applications of technology is performed in step two, *id.* at 222.

74 *Illumina*, 967 F.3d at 1333 (Reyna, J., dissenting).

75 *See id.* at 1326. *See also supra* notes 40–44 and accompanying text.

76 Conventional DNA amplification of a target DNA is a biomolecular process based on synthesizing DNA primers based on the target DNA sequence and the length of the DNA sequence. *See e.g.*, Wojciech Rychlik, *Selection of Primers for Polymerase Chain Reaction*, 3 MOLECULAR BIOTECHNOLOGY 129 (1993). Amplification of paternal DNA would require additional engineering choices beyond the mere knowledge that paternal DNA is present, such as the choice of a target sequence in the paternal DNA and the choice of the primers. *See e.g.*, U.S. Patent 6,258,540 (filed Mar. 4, 1998), *invalidated by Ariosa*, 788 F.3d at 1319 (providing chosen target sequences and primers in the detailed description of the embodiments). Arguably, the size threshold discussed in *Illumina* is determined by the discovered DNA size distribution since the primers used for DNA amplification are determined by the discovered paternal DNA.

77 *Illumina*, 967 F.3d at 1326–27.

78 Compare *E.g.* Rychlik, *supra note* 76, at 129 (discussing the choice of primers for a successful polymerase chain reaction based on a thermodynamic model of DNA binding) with *Illumina*, 967 F.3d at 1328 (discussing the choice of a size threshold based on a size distribution model).

79 See e.g., Ping Hu et al., *An enrichment method to increase cell-free fetal DNA fraction and significantly reduce false negatives and test failures for non-invasive prenatal screening: a feasibility study*, 17 J. TRANSLATIONAL MED., no. 124, 2019, at 6 ("[S]everal attempts have been reported for fetal DNA enrichment . . . [One study] reported a PCR-based enrichment method to selectively amplify the fetal cfDNA . . . [Another study] reported a size-based method . . . . These works all focused on the size difference of the cffDNA in maternal plasma.").

steps *Alice/Mayo* test. The "directed to" analysis of the first step bleeds into the conventionality of the "additional elements" of the second step. This challenge is not exclusive to the field of medical diagnostics, or even to biomedical-related inventions. For example, dissenting from a holding invalidating a mechanical engineering patent, Judge Newman noted that that decision "collapses the *Alice/Mayo* two-part test to a single step."[80] In a similar vein, the *Illumina* court further complicated the *Alice/Mayo* test while attempting to create a clear doctrine for patent eligibility of diagnostic inventions. And perhaps, that confusion can only be solved by the Supreme Court or Congress.

80 Am. Axle & Mfg., Inc. v. Neapco Holdings LLC, 967 F.3d 1285, 1304 (Fed. Cir. 2020) (Moore, J., dissenting).