No. 15-1182

IN THE

Supreme Court of the United States

SEQUENOM, INC.,

Petitioner,

v.

ARIOSA DIAGNOSTICS, INC., NATERA, INC., AND DNA DIAGNOSTICS CENTER, INC.,

Respondents.

On Petition for a Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

BRIEF OF *AMICUS CURIAE* BY THE CHARTERED INSTITUTE OF PATENT ATTORNEYS IN SUPPORT OF THE PETITIONER

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INTEREST OF AMICUS CURIAE[1]

The Chartered Institute of Patent Attorneys (CIPA) respectfully submits this brief *amicus curiae* in support of Petitioner, Sequenom, Inc.

CIPA is the professional and examining body for patent attorneys in the United Kingdom (UK). The Institute was founded in 1882 and was incorporated by Royal Charter in 1891. It represents over 2000 chartered patent attorneys, whether they work in industry or in private practice. Total membership is over 3500 and includes trainee patent attorneys and other professionals with an interest in intellectual property. Almost all chartered patent attorneys are members of the Institute of Professional Representatives before the European Patent Office (EPO). Most UK patent attorneys have substantial experience with the US patent system as a result of filing and prosecution of applications at the United States Patent and Trademark Office (USPTO) with the assistance of local counsel and many have experience of US litigation, again with the assistance of local counsel. CIPA's educational activities include organizing conferences, seminars and meetings on patent law, frequently with the assistance of US practitioners, publishing a monthly journal featuring articles on patent law and recent decisions, publishing books in-house on patent law, publishing through Sweet and Maxwell the *CIPA Guide to the Patents Acts* (now in its 8th Edition), the

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[1] No counsel for a party authored this brief in whole or in part, and no party directly or indirectly made monetary contribution to the preparation or submission of this brief. The parties in this case have mutually agreed to the filing of *Amicus* briefs.

European Patents Handbook and the *European Patents Sourcefinder*, and publishing other titles relating to trademarks and designs.

The range of patent-eligible subject matter in the United States is of fundamental concern to CIPA members and their clients, as is the harmonious development of patent law internationally. Patent protection is important for inventions in the life sciences, especially for pharmaceutical, biotechnological and medical testing inventions where research, product development and commercial activities depend upon broad and stable patent eligibility criteria. CIPA is concerned that expansive interpretations of recent decisions of this Court by the Federal Circuit and district courts and further downstream by the United States Patent and Trademark Office (USPTO) place undue burden and internationally discordant restrictions on long-established and widely accepted eligibility criteria. The situation affects many members of the UK (and international) public with applications undergoing examination by the USPTO.

SUMMARY OF THE ARGUMENT

The Federal Circuit's panel opinion applied an over-expansive interpretation of the *Mayo/Alice* test for judicial exclusion. It denied patent-eligibility and commensurate protection to a fundamental advance in the field of non-invasive maternal testing. The invention qualified as a matter of substance and not mere outward appearance as a patent-eligible process within 35 USC §101.

The need for further guidance from this Court is apparent from the reasoned opinions of Judges Linn, Lourie, Moore, Dyk and Newman who expressed concern or outright dissent about the expansive nature of the *Mayo/Alice* framework and outnumber Judges Reyna and Wallach who were the panel majority. Allowance of the petition and further guidance from this Court is preferable to leaving the law in a state of uncertainty and dispute and creating unnecessary difficulty and rejection for thousands, if not tens of thousands, of inventors with applications pending before the USPTO.

The right of a person who has made a breakthrough invention to receive commensurate protection was overlooked: *see The Telephone Cases*, 126 U.S. 1, 534-535 (1888). As in Europe, inventors of breakthrough inventions and inventors of incremental inventions should be placed on a level playing field as regards eligibility for patent protection.

Reconsideration is also needed to maintain international harmonisation in the law of patent-eligibility. The panel opinion and the present broad scope of the judicial exclusions represent an internationally discordant legal position irreconcilable with the provisions of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) administered by the World Trade Organization (WTO) and the consequential Directive 98/44/EC of the European Parliament.

The panel opinion erred in not determining whether the claimed subject-matter fell as a matter of substance within the "process" category of §101, see *Diamond v. Chakrabarty*, 447 U.S. 303, 307 (1980). Instead, it focused unduly on the eligibility of cffDNA as isolated or amplified materials when these were only recited as elements of the claimed process. It gave insufficient weight to the series of acts recited in the claims and to the transformations that they produce: *Gottschalk v. Benson*, 409 U.S. 63, 70, 175 USPQ 673, 676, (1972), quoting *Cochrane v. Deener*, 94 U.S. 780, 788, 24 L. Ed. 139, (1877). It insufficiently considered the recited acts as an ordered combination and the benefits flowing from that combination. In applying the *Mayo/Alice* framework, the panel opinion applied the words "directed to" over-expansively, thereby bringing an unintendedly broad range of inventions within the scope of the exclusion framework. In the second step of analysis, the panel opinion applied the word "art" with undue generality and treated activity as "well known, routine and conventional" whereas in reality the steps were novel when applied to serum or

plasma from a maternal blood sample, that provenance setting the claimed process apart from all other processes, see *United States v. Adams*, 383 U.S. 39 (1966).

The present case, owing to the outstanding nature of the invention and its acknowledged novelty and inventive character, provides an appropriate vehicle for review of §101 eligibility.

ARGUMENT

I. The need for review by this court is plain from the concurring panel opinion and the concurrences and the dissent to the *en banc* petition and from the practical effects of decisions of this Court in incentivising or discouraging research in the life sciences

In his panel concurrence, Judge Linn summarised the merit of the invention and commented:

> It is hard to deny that Sequenom's invention is truly meritorious. Prior to the '540 patent, prenatal diagnoses required invasive methods, which "present[ed] a degree of risk to the mother and to the pregnancy" … In a groundbreaking invention, Drs. Lo and Wainscoat discovered that there was cell-free fetal DNA in the maternal plasma. The Royal Society lauded this discovery as "a paradigm shift in non-invasive prenatal diagnosis," and the inventors' article describing this invention

> has been cited well over a thousand times. The commercial embodiment of the invention, the MateniT21 test, was the first marketed non-invasive prenatal diagnostic test for fetal aneuploidies, such as Down's syndrome, and presented fewer risks and a more dependable rate of abnormality detection than other tests. …The new use of the previously discarded maternal plasma to achieve such an advantageous result is deserving of patent protection.

Similar views were expressed in the concurrence by Judges Lourie, Moore and Dyk denying *en banc* rehearng. In her dissenting opinion, Judge Newman commented:

> In the case at bar, the inventors are not claiming the scientific fact of the discovery of paternal DNA in the blood of a pregnant woman; they are claiming the discovery and development of a new diagnostic method of using this information. As the panel recognized, this is a "breakthrough," for this information can now be learned not only earlier in the gestation period than was previously available, but without the risks of the previously required invasive procedures of penetrating the amniotic sac.
>
> Precedent does not require that all discoveries of natural phenomena or their application in new ways or for new uses are ineligible for patenting; the Court has cautioned against

> such generalizations. Such caution takes hold for the case at bar. The new diagnostic method here is novel and unforeseen, and is of profound public benefit—"a significant contribution to the medical field," Panel Maj. Op. at 16—a "breakthrough," Panel Conc. Op. at 5. The panel's decision to withhold access to patenting, now endorsed by the *en banc* court's refusal to rehear the case, is devoid of support.

Judge Linn further observed that: "it is unclear how a claim to new uses for existing drugs would survive *Mayo*'s sweeping test."

CIPA shares these concerns for the reasons explained in the present Petition at pages 19-20. The European patent statute expressly provides that first and further medical uses for known substances are patent-eligible: Art. 54(4) and (5) EPC. Such discoveries are of profound importance to pharmaceutical and biotechnology industry, see also EPO Enlarged Appeal Board decisions G 5/83 *Second medical indication/EISAI* and G 2/08 *Dosage regime/ABBOTT RESPIRATORY* affirming the eligibility of second medical indications. The need for review to ensure that US law develops in an internationally harmonious, not discordant, manner is further apparent.

Decisions of this Court incentivise or discourage investment in medical research. In 1974 Cohen and Boyer applied for a patent covering splicing genes to make recombinant proteins that was foundational to the biotechnology industry, see

Bera, The Story of the Cohen-Boyer patents, *Current Science*, **96**, 760,763 (2009). In 1980 this Court held in *Diamond v Chakrabarty* that a live human-made microorganism constitutes a "manufacture" or "composition of matter" under §101. That opinion paved the way for issue of US Patent 4468464 (August 1984) claiming a biologically functional recombinant plasmid capable of selection and replication in a prokaryotic cell and 4740470 (April 1988) claiming transformant cells comprising biologically functional circular recombinant DNA molecules. These patents earned over $255 million for Stanford and for the University of California system[2]. In contrast, as reported on page 6 of the present petition, bringing this invention to market as a viable medical test, clinically validating it and obtaining regulatory approvals cost Sequenom some $70 million, and price and market erosion from Ariosa's petition has prevented recovery of this investment. If the petition is dismissed, or if the panel opinion is affirmed, investment in medical and life science research will be discouraged as strongly as it was encouraged by the *Chakrabarty* decision, to the detriment of medical research and ultimately to patients.

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[2] Feldman, Lessons from the Commercialization of the Cohen-Boyer Patents: The Stanford University Licensing Program, http://www.iphandbook.org/handbook/chPDFs/ch17/ipHandbook-Ch%2017%2022%20Feldman-Colaianni0Liu%20Cohen-Boyer%20Patents%20and%20Licenses.pdf

II The *Mayo/Alice* framework needs reconsideration to place pioneering or breakthrough inventions and incremental inventions on a level playing field.

This case provides a paradigm example of the unwarranted disadvantages imposed by the *Mayo/Alice* framework on inventions underpinned by a fundamental discovery or breakthrough as compared to incremental inventions.

The present breakthrough came from insight that maternal plasma or serum previously discarded as medical waste might contain detectable amounts of previously unrecognized nucleotide sequences, experimental demonstration that this was indeed the case, and the proposal for processes to detect paternal DNA as a practical application of that discovery. The subject matter claimed in claims 1 and 21 represents a commensurate scope of protection.

However, under the *Mayo/Alice* framework as applied in the panel opinion, that advance is not enough. Whereas incremental inventors only have to make a single invention, for eligibility these pioneering inventors need to make two inventions. The return for the qualifying second invention is ashes: it is left open to others to find ways other than the second invention for performing the amplification and/or detection steps, after which those others can freely benefit from the fundamental discovery or breakthrough and the original inventors receive nothing.

No such disadvantage is imposed on inventors in Europe and there is no credible policy justification for such illogical and harsh treatment, which was not meted out to James Watt, Samuel Morse or Alexander Graham Bell. A better rule is in *The Telephone Cases*, 126 U.S. 1, 531 (1888):

> It may be that electricity cannot be used at all for the transmission of speech except in the way Bell has discovered, and that therefore, practically, his patent gives him its exclusive use for that purpose; but that does not make his claim one for the use of electricity distinct from the particular process with which it is connected in his patent. It will, if true, show more clearly the great importance of his discovery, but it will not invalidate his patent.

The continuing relevance of the rule in the *Telephone Cases* was affirmed by Justice Stevens in *Bilski v. Kappos*, 561 U.S. 593 (2010), where he said, also with reference to *O'Reilly v Morse*, 56 U.S. 62 (1853):

> One might think that the Court's analysis means that any process that utilizes an abstract idea is itself an unpatentable, abstract idea. But we have never suggested any such rule, which would undermine a host of patentable processes.

III The reasoning of the panel majority is irreconcilable with the obligations of the United States under Article 27 and Note 5 of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS).

Any administrative or judicial interpretation of the provisions of any statute, including 35 USC §101, which places the U.S. in a position where it does not meet the obligations of an international agreement by which it is bound is *prima facie* incorrect and requires reconsideration, see *Murray v. Schooner Charming Betsy*, 6 U.S. (2 Cranch) 64, 118 (1804). It is submitted that the panel opinion falls into that category.

Article 27.1 of TRIPS entitled "Patentable Subject Matter" provides a complete code for patent-eligibility which WTO member countries including the U.S. have agreed to respect. It requires patents to be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application. In that situation, patent rights should be enjoyable without discrimination as to the field of technology. In negotiating TRIPS, care was taken to ensure consistency with U.S domestic law. Thus, Article 27 is to be read with note 5 which provides that the term "capable of industrial application" may be deemed to be synonymous with the term "useful".

Exclusions are covered by Articles 27.2 and 27.3. They include the protection of *ordre public* or morality, protection of human or plant life or health, and avoidance of serious prejudice to the environment. Other exclusions also exist, but there is no provision for the exclusion of natural products or processes involving natural products.

Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, Official Journal L 213, 30/07/1998 P. 0013 – 0021 draws attention in its early recitals to the facts that biotechnology and genetic engineering are increasingly important in a broad range of industries, that such research and development requires considerable high-risk investment, and that effective protection is essential to maintain and encourage investment in biotechnology. Recital 13 directs attention to the TRIPS Agreement and Article 1 recognises the obligations of Member States.

Article 2(a) of the Directive defines "biological material" to mean any material containing genetic information and capable of reproducing itself or being reproduced in a biological system. Self-evidently cffDNA falls within that definition. Article 3(1) provides that inventions which are new, involve an inventive step and are susceptible of industrial application shall be patentable even if they concern a product consisting of or containing biological material or a process by which biological material is produced, processed or used. The subject matter

claimed in claims 1 and in more detail in claim 21 plainly falls within that Article. Article 5(2) provides that an element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.

An application to the European Court for annulment of the Directive was rejected in *Kingdom of the Netherlands v Council of the European Union*, European Court, Case 377/97 (2001). Subsequently in *Monsanto Technology v Cefetra BV*, European Court (Grand Chamber), Case C-428/08 (2010) the ECJ pointed out that Article 1(1) of the Directive requires member states to protect biotechnological inventions under their national patent laws and to make adjustments in accordance with the provisions of the Directive. Accordingly the harmonization effected by Article 9 of the Directive (which refers to scope) should be regarded as exhaustive and precludes national legislation from producing a different effect. It will be apparent that the same argument is equally applicable to Articles 2, 3 and 5 and is consistent with the ruling in the *Kingdom of the Netherlands* case.

The EPO incorporated the provisions of Articles 2, 3 and 5 of the Directive into the Implementing Regulations to the EPC without modification as EPC 2000 rules 26 - 29, see also the *EPO Examination Guidelines* G II, 5.2. These rules now provide legislative authority for the patent-

eligibility under the EPC of claims to isolated nucleotide sequences covering naturally occurring genes, and the resulting patents can be brought into effect in all EPC contracting states. In T 1213/05 *Breast and ovarian cancer/UNIVERSITY OF UTAH* opponents objected that the sequences of nucleic acid probes claimed which comprised partial DNA sequences of the human BRCA1 gene and occurred in nature were a discovery rather than an invention. However, the Appeal Board held that these probes were isolated elements of the human body as defined in Rule 29(2) EPC (formerly r. 23e(2)) and thus patentable subject-matter. Accordingly, the subject-matter of claims 1 to 3 was not excluded under a. 52(2)(a) EPC from patent-eligibility as being mere discoveries, see also T 272/95 *Relaxin/HOWARD FLOREY INSTITUTE*.

The *Case Law of the Boards of Appeal of the European Patent Office*, 7th Ed. 2013, explains at page 15 that discoveries, scientific theories and mathematical methods excluded under art. 52(2)(a)-(d) EPC share the common feature that they do not aim at any direct technical result but are rather of an abstract and intellectual character and that:

> If a new property of a known material or article is found out, that is mere discovery and unpatentable because discovery as such has no technical effect and is therefore not an invention within the meaning of Art. 52(1) EPC. If, however, that property is put to practical use, then this constitutes an invention which may be patentable. To find a

> previously unrecognised substance occurring in nature is also mere discovery and therefore unpatentable. However, if a substance found in nature can be shown to produce a technical effect, it may be patentable…."

It is submitted that this statement encapsulates the proper bounds of the exclusion under TRIPS Art. 27 and any difference in U.S. law rises from over-expansive interpretation of *Mayo, Myriad* and *Alice*.

It follows that no European court or other judicial authority could treat cffDNA taken from a sample of maternal plasma or serum or its amplification product in the dismissive manner set out by the panel majority. Such dismissal of the process claimed in claims 1 and 21 as set out by the panel majority would contravene Article 3(1) of the Directive, and the conclusory objection of lack of patent eligibility made by the panel majority could not validly arise in the EPO or in any national court or IP Office of any EU contracting state.

The above position is unaffected by the decision of the High Court of Australia in *Yvonne D'Arcy v Myriad Genetics*, [2015] HCA 35 where the majority recognised that the decision to accord or refuse patentability to a particular class of claims could have implications for Australia's obligations under international law [31]. The law of other countries was taken into account, noting the practice in the Patent Offices of most of Australia's regional trading partners including China, Japan, Korea,

Singapore and India to grant patents for isolated nucleic acids, particularly if the claim demonstrated that they were not mere discoveries. The majority concluded that the Court was not concerned with "gene patenting" generally, but with the limited issue whether the particular invention as claimed in Claims 1 to 3 of the Australian patent fell within established applications of the concept of "manner of manufacture" [37].

Although the *D'Arcy* decision acknowledged that different opinions about the meaning of "invention" within Art. 27 could be reached in different jurisdictions where delineation of boundaries was difficult, the present invention which is a multi-step technical process where substances are isolated and transformed by the hand of man, giving results of medical and economic utility, creates no such difficulty. Accordingly the *D'Arcy* decision does not point away from the existence of the TRIPS conflict referred to above.

The present case is an example of an internationally discordant, not harmonious, result, contrary to TRIPS Article 27. Eligibility of the corresponding European patent was never disputed and it was held nonobvious for solving the technical problem of detecting fetal nucleic acid with higher sensitivity, see Appeal decision T 146/07 *Prenatal diagnosis/ISIS*. It is wrong that a patent that survived validity challenges in Europe should be held ineligible for consideration in the U.S.

IV The panel opinion should have considered whether the claimed method falls as a matter of substance and not mere outward appearance within 35 USC §101 before considering judicial exceptions.

The first question to be considered here was whether the method described and claimed was as a matter of substance and not mere outward form a "process" within the meaning of §101, see *Gottschalk v Benson,* 409 US 63, 64 (1972), *Diamond v Chakrabarty,* 447 U.S. 303, 307 (1980), *Diamond v Diehr,* 450 U.S. 175, 176 (1981), *J. E. M. AG Supply, Inc. v. Pioneer Hi-Bred International, Inc.*, 534 US 130 (2001), *Bilski v Kappos*, 561 U.S. 593 (2010), and *Association for Molecular Pathology v. Myriad Genetics*, (569 U.S. ___ June 13, 2013), see also an amicus brief filed by the New York Intellectual Property Law Association in the *Myriad Genetics* case[3].

It was said in *Chakrabarty* at p.446 that although Congress contemplated that the patent laws would be given wide scope that was not to suggest that § 101 has no limits, or that it embraces every discovery. The counterpart question that needs to be answered here is how the limits on the judicial

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[3] http://www.americanbar.org/content/dam/aba/publications/supreme_court_preview/briefs-v2/12-398_resp_amcu_nyipla.authcheckdam.pdf at pages 9-10, (accessed 23 February 2016)

exceptions should be defined and how they are to be reconciled with the plain text and meaning of the statute.

If claimed subject matter falls as a matter of substance and not mere outward form within one of the statutory categories, then the *Mayo/Alice* framework should apply only as a check for a *de minimis* situation. As set out in *Chakrabarty* at 447, courts "should not read into the patent laws limitations and conditions which the legislature has not expressed." quoting *United States v. Dubilier Condenser Corp*., 289 U. S. 178, 289 U. S. 199 (1933). Any broader interpretation of the judicial exceptions invokes the very limitations and conditions that *Dubilier Condenser* explains are impermissible.

The problems that can arise through failure to give attention to the wording of the statute are exemplified by *University of Utah v Ambry Genetics* (2014) where the Federal Circuit held ineligible a claim to a pair of single-stranded DNA primers on the ground of identity to the natural sequences by supposed analogy with the holding in *Myriad*. However, the decision is clearly erroneous because what was claimed was not a single substance but a composite article straightforwardly falling within the eligible “composition of matter” category defined in *Chakrabarty,* 447 U.S. at 308, citing *Shell Development Co. v. Watson*, 149 F.Supp. 279, 280 (DC 1957).

Under §101, the panel majority here repeated the error by considering only matters of outward form and not underlying substance, the entirety of its holding appearing below:

> The claims of the '540 patent that are at issue in this appeal are method claims. Methods are generally eligible subject matter. In this case, the asserted claims of the '540 patent are directed to a multistep method….

The panel majority thereafter focused its entire attention on the judicial exceptions and not the statute. In consequence of that error, the panel majority omitted to consider either the full contribution of each step individually as an aspect of an eligible process or their combined contribution as an ordered combination. When applying the *Mayo/Alice* framework, that decision fell into two significant legal and factual errors. Firstly it was confused as to what the claimed subject matter was "directed to" and applied those words in an over-expansive manner. At one point it correctly acknowledged that the claims are directed to a multi-step method. Then it took the inconsistent position that the claims are directed to naturally occurring phenomena. It consequently confused individual phenomena with the process as an ordered combination, and it over-focussed on the status of those phenomena as compositions of matter or manufactures rather than as elements of the claimed process. Secondly when considering the transformative nature of additional elements in the second stage of the analysis, it over-generalized the word "art" in the criteria "already well known in the art" and "well-understood, routine, and

conventional" so as to cover elements that were known but only in different arts, contexts, or processes.

Consequently, the panel majority did not give adequate weight to the transformative nature of the claimed elements as an ordered combination. The result eviscerated the holding in *Diamond v. Diehr* at p. 189, *i.e.,* that a new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made.

V Sequenom's method claims are eligible as a matter of substance under the "process" category of 35 USC §101 and are neither "directed to" matter that is naturally occurring nor lacking in transformative additional features.

Under the §101 category of "process," the relevant question is whether the maternal serum or plasma, or the nucleic acid within it, has been transformed or made into a different state or thing: *Cochrane v. Deener*, 788, quoted with approval in *Parker v. Flook*, 59, *Diamond v. Diehr*, 185, *Bilski v. Kappos*, 561 U. S. ___, ___ (2010) and *Association for Molecular Pathology v. Myriad Genetics.* In holding that the claimed method begins with a natural phenomenon, the panel opinion erroneously applied to a claim falling within the category "process" legal criteria proper only to the categories "composition of matter" and "manufacture".

The eligibility of the claimed subject-matter is apparent from the following discussion.

A Deriving a paternally inherited nucleic acid from the maternal serum or plasma of a pregnant female was a transformation or reduction of that nucleic acid to a different state or thing and was neither a well-understood, routine, conventional activity previously engaged in by researchers in the relevant field nor a mere recitation of a law of nature.

The relevant field or art is defined (Patent 1: 6-7) as prenatal detection using non-invasive techniques. Conventional activity of those working in that field is explained (Patent 1: 12-37), further activities (Patent 1: 38-46) belonging to other fields and not being relevant to the §101 enquiry. It is undisputed that conventional activity did not include transforming paternal DNA obtained from the serum or plasma of a pregnant female to a state where it could subsequently be amplified.

Conversion of the maternal serum or plasma into paternal DNA is a technical process carried out by the hand of man as explained (Patent 2: 26-42) with reference to the examples (see also the reference in claim 21 to separation of a maternal blood sample into a cellular and a non-cellular fraction). In Example 1 the samples were twice centrifuged to remove cellular material, heated at 95°C for five minutes and subjected to a further

stage of centrifugation. A clear supernatant was collected which contained the nucleic acid in a degree of purity in which it could be amplified. In Examples 2-4, the DNA is extracted using a column. The resulting purified or extracted nucleic acid is both the result of a technical process and has new utility (capacity for amplification).

The paternal DNA was not being claimed as a new substance. The panel opinion failed to give weight to the contribution that the human activities defined in the first element of the present claims make to §101 eligibility.

B Amplifying nucleic acid of the specified provenance was also not a well-understood, routine, conventional activity previously engaged in by researchers in the field of non-invasive prenatal detection. The panel opinion confused what was conventional in that field with what was conventional in different scientific fields, for example the cancer detection. Its finding that the product of amplification was a mere natural phenomenon was both a legal and a factual misclassification.

As previously explained, paternal nucleic acid from maternal serum or plasma had not previously been amplified either within the field of non-invasive prenatal detection or within any other field of medical or scientific endeavour. Amplification is a technical process in which a relatively short region of

nucleic acid present in the original sample is selected using so-called "primers" and multiple copies of the selected region are produced by enzymatic chemical synthesis from individual monomeric nucleotides.

The naturally occurring phenomenon properly defined is the existence of cffDNA in maternal blood. The resulting synthetic oligonucleotides differ from that phenomenon in that (a) they are of defined length and defined starting and end positions differing from the naturally-occurring nucleotides in cffDNA, (b) they are the result of enzymatic chemical synthesis and not a natural occurrence in their defined form, and (c) they occur in a concentration 1000-1,000,000 times that of the original cffDNA as acknowledged in the panel opinion. They are therefore a newly created article in a new form (higher oligonucleotide concentration), with new provenance and with new utility (detectability), all of which are attributes of eligibility as a "manufacture" under the criteria in *Hartranft v. Wiegmann*, 121 U. S. 609, 121 U. S. 615 (1887), quoted with approval in *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U. S. 1, 283 U. S. 11 (1931), *Diamond v. Chakrabarty*, 308 and *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. ___, 133 S.Ct. 2107 (2013). The real and tangible oligomer sequences in their amplified form have also become for every practical purpose a new thing commercially and analytically: *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95 (C.C.S.D.N.Y. 1911) (adrenalin), *Kuehmsted v. Farbenfabriken of Elberfeld Co.*, 179 F. 701 (7th Cir. 1910) (aspirin), *Merck & Co. v. Olin*

Mathieson Chem. Corp., 253 F.2d 156 (4th Cir. 1958) (vitamin B12).

If this Court does not recognise the contribution of the amplification step to process-eligibility and affirms the holding of the panel opinion that the claimed method begins and ends with a natural phenomenon, these long-standing precedents will be further questioned and the pharmaceutical and related industries will be further damaged, not only in the U.S., but also world-wide.

C The detection step which is the third element of the claimed method also makes a hitherto unacknowledged contribution to process-eligibility.

Detection of the amplified paternal nucleic acid of the present provenance was a further new activity within the field of non-invasive prenatal detection and was not a well-understood, routine, conventional activity previously engaged in by researchers in that field. It is undisputed that similar methods were used in relation to maternal DNA of different provenance (e.g. obtained by amniocentesis), but what was well-understood, routine and conventional activity previously engaged in by researchers in relation to these nucleic acids of different provenance is not material to the present §101 enquiry because that does not constitute an element of the present process considered as an ordered combination.

Detection is a technical process, *see e.g.*, Example 1 of the patent where the amplified PCR products were analysed by agarose gel electrophoresis and ethidium bromide staining and PCR results were scored before the foetal sex was revealed to the investigator (Patent 5: 23-26). The remaining examples employ more sophisticated quantitative detection methods. As explained (Patent 1: 57 onwards), the new method enables those working in non-invasive prenatal detection to detect genes which confer a disease phenotype including foetal Rhesus D, ß-thalassaemia, paternity, (Patent 3: 11-24), chromosomal aneuploidies including Down's syndrome and pre-eclampsia. Attention is also directed to claim 21 where detection is followed by the provision of a diagnosis based on the presence and/or quantity and/or sequence of the foetal nucleic acid.

D The panel opinion erred in discounting the new utility of the ordered combination of claimed elements considered as affirmative evidence of eligibility and, instead, erroneously concluded that the claimed method of detecting paternally inherited cffDNA is not new and useful.

The panel opinion that the presently claimed method was not new and useful would be greeted with incredulity by the multitude of mothers who have benefitted from Sequenom's Maternit21 test and Ariosa's Harmony prenatal test and by the doctors and nurses who treat them. Amongst the

new and useful properties, there may be mentioned the non-invasive character of the claimed method and its ability to detect genetic deformities as early as 7 weeks of gestation (Patent: 3: 60-62).

New and useful result has long been accepted as evidence of unobviousness under §103, and since "new and useful" comprise a core context of § 101, such evidence of new utility should also be recognized as powerful evidence of §101 eligibility. It was said in *Evans v Eaton*, 20 US 356, 399 (1822):

> That a new modus operandi, by a new combination of old instruments or machines, so as to produce either a new effect, or an old effect in a new way, is the proper subject matter of a patent, appears from numerous authorities, and may be considered as a settled principle of the patent law. It was on this principle that Watt's patent for his improvements on the steam engine, which made so much noise in Westminster Hall, and produced such important effects, was finally supported and established.

The principle is aptly summarised by Justice Bradley in *Webster Loom Co. v. Higgins*, 105 U.S. at 591:

> "It may be laid down as a general rule, though perhaps not an invariable one, that if a new combination and arrangement of known elements produce a new and beneficial result, never attained before, it is *evidence* of invention." (emphasis added)

That opinion was cited with approval in *Washburn & Moen v Beat'Em All Barbed Wire,* 143 US 275 (1892), *Carnegie Steel v Cambria Iron,* 185 US 40 (1902), *Expanded Metal v Bradford* 214 U.S. 366 (1909) and *Goodyear Tire & Rubber Co. v. Ray-O-Vac Co.*, 321 U.S. 275 (1944). Similarly, in *KSR*, 550 U.S. at 416, the Court observed of the *Adams* invention:

> "The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams's design was not obvious to those skilled in the art."

That the claimed combination of starting material and method steps produced a new and beneficial test for foetal abnormalities and the like is affirmative evidence of invention, which evidence could not and should not have been disregarded when considering eligibility of the "ordered combination" under § 101.

VI. This case provides an appropriate vehicle for this Court to review the scope of the judicial exclusions and in particular the scope of the *Mayo/Alice* framework.

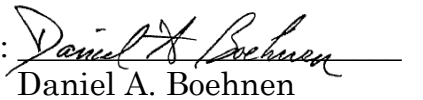
It is difficult to see how there could easily be a better case than this to clarify the misdirection being followed by the *Mayo/Alice* framework. The invention was made at Oxford University which is one of the leading research universities of the world. The invention has received great worldwide acclaim. The patent has been held to claim ineligible subject

matter but, on the materials before, the court there is little question that subject matter is inventive, and no other objection is before the Court.

CONCLUSION

For the reasons stated above, the judgment of the Federal Circuit should be reconsidered and reversed.

Respectfully submitted

By: 

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