

United States Patent and Trademark Office
Madison Building
Madison
USA

By email: 2014_interim_guidance@uspto.gov

RE: Request for Comments Related to Patent Subject Matter Eligibility [Docket No.: PTO-P-2016-0041]

Dear Sir/Madam

The BIA (UK Bioindustry Association) is the UK trade association for innovative bioscience enterprises. BIA members include emerging and more established bioscience companies, pharmaceutical companies, academic research and philanthropic organisations, and service providers to the UK bioscience sector. Our members are international companies with a need to protect their IP globally, including in the United States.

Clear, predictable, and harmonized, intellectual property laws are essential for the smooth functioning of today's economy. Biomedical innovation, in particular, depends on a proper balance of economic incentives as well as legal certainty upon which billions of dollars are invested in our and future generations' health and wellbeing.

A consistent and harmonized patent eligibility framework allows inventors across the globe to determine, with predictability, whether to rely on patent protection (and therefore to disclose their inventions to the public) or, instead, withhold their discoveries and rely on trade secret as an alternative form of intellectual property protection. These two forms of protections are mutually exclusive – one cannot maintain a trade secret in one jurisdiction while obtaining a patent in another.

Court decisions over the past decade – *Bilski*, *Mayo*, *Myriad*, and *Alice* – have significantly impacted US patent eligibility law and created a schism between US and other international jurisdictions. The BIA and international biotechnology community has watched these developments with concern. The *Sequenom vs Ariosa* case provided an opportunity for the Supreme Court to provide a more refined guidance on patent eligibility. The BIA therefore decided to submit an *Amicus Brief* requesting that the Court review the decision of the Federal Circuit in that case. The BIA was joined in this brief by several other industry associations, illustrating the global importance of this issue: EuropaBio (the European Association for Bioindustries), AusBiotech, Swiss Biotech Association, HollandBIO, BIOTEC Canada, and Japan Bioindustry Association.

I attach the *Amicus Brief* as written evidence to your request for comments on the legal contours of eligible subject matter in the US patent system and hope it serves as a useful addition to the roundtables you recently held. The document demonstrates the view of the international biotechnology industry that there is a strong need for the US to reassess its approach to patents in this area.

Should you wish us to elaborate further on this matter or to speak to us directly we will be happy to do so. Please contact Martin Turner, Policy and Projects Manager, on mturner@bioindustry.org.

Yours faithfully,



Steve Bates OBE
Chief Executive, BIA
sbates@bioindustry.org

No. 15-1182

IN THE
Supreme Court of the United States

SEQUENOM, INC.,

Petitioner,

v.

ARIOSA DIAGNOSTICS, INC. *et al.*,

Respondents.

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

**BRIEF OF THE BIOINDUSTRY
ASSOCIATION JOINED BY EUROPABIO,
AUSBIOTECH, SWISS BIOTECH
ASSOCIATION, HOLLANDBIO,
BIOTECANADA, AND THE JAPAN
BIOINDUSTRY ASSOCIATION
AS *AMICI CURIAE* IN SUPPORT
OF GRANTING THE PETITION**

KONSTANTIN M. LINNIK

Counsel of Record

LANA A. GLADSTEIN

ISAAC A. HUBNER

NUTTER McCLENNEN & FISH LLP

Seaport West

155 Seaport Boulevard

Boston, MA 02210

(617) 439-2000

linnik@nutter.com

Counsel for Amici Curiae

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265049

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I. STATEMENT OF INTEREST OF *AMICI CURIAE*

The BioIndustry Association (BIA) is a United Kingdom trade association of over 300 member organizations working in research and development (R&D) and manufacturing in the bioscience sector.¹ BIA members include emerging and established biotechnology companies, pharmaceutical companies, academic research institutions, and philanthropic organizations. BIA members are responsible for over ninety per cent of biotechnology-based medicines currently in clinical development in the UK. They are at the forefront of innovative scientific developments targeting areas of unmet medical need.

BIA is joined in this brief by several other industry associations: **EuropaBio, AusBiotech, Swiss Biotech Association, HollandBIO, BIOTECanada, and Japan Bioindustry Association**. Each organization is briefly described below.

EuropaBio is the European Association for Bioindustries, with the mission is to create an innovative and dynamic biotechnology-based industry in Europe. EuropaBio has 60 corporate members and seventeen national biotechnology association members, who in turn represent more than 1800 small and medium sized biotech companies in Europe. Members of EuropaBio are involved in research, development, testing, manufacturing and

1. All parties have agreed to mutual blanket consents to all amicus briefs filed in support of either (or no) side. No person other than *amici curiae*, its members, or its counsel has made a monetary contribution to the brief's preparation and submission.

commercialization of biotechnology products in human and animal health care, diagnostics, bio-informatics, chemicals, crop protection, agriculture, food and environmental products and services.

AusBiotech is Australia's biotechnology organization, working on behalf of over 3,000 members in the life sciences, including therapeutics, medical technology (devices and diagnostics), food technology and agricultural, environmental, and industrial sectors. AusBiotech is dedicated to the development, growth and prosperity of the Australian biotechnology industry, by providing initiatives to drive sustainability and growth, outreach, and access to markets, and representation and support for members nationally and around the world.

BIOTECCanada is the Canadian national industry association with over 200 members located Canada-wide, reflecting the diverse nature of Canada's health, industrial, and agricultural biotechnology sectors. BIOTECCanada's mission is to support the growth and commercialization of Canadian biotechnology innovation for a global marketplace.

HollandBIO is the Netherlands' biotech industry organization. The Netherlands is home to a vibrant, dense biotechnology cluster of more than 1150 life science companies and research organizations, all operating within a 120-mile radius. HollandBIO connects, supports and represents many in this tight-knit community in order to promote economic growth, better health and greater sustainability.

Swiss Biotech Association represents the interests of the biotech sector, supports the entrepreneurship of biotech companies, and generates value for them through the development of optimal framework conditions for the biotech sector, networking of stakeholders at national and international levels, dissemination of accomplishments in biotechnology, and collaboration with strategic partners.

The Japan Bioindustry Association (JBA) has over 300 members, including private and public organizations, universities, public research institutes involved in researching, developing or commercializing biotechnology, pharmaceutical, and medical technologies as well as food, cosmetics, and related industries. The mission of JBA is to promote advancement of life science technologies through cooperation of industry, academia, and government.

Collectively, our organizations represent the many voices of life sciences, biotechnology, and pharmaceutical enterprises from around the world. The issues raised in this case are of great importance to the members of our organizations. Many of our members are small and medium size enterprises. For these enterprises, their ability to raise R&D funding or attract larger companies to collaborate heavily depends on the strength of their intellectual property, primarily in the form of patents. Lack of patent protection severely hinders, if outright not rendering impossible, their ability to bring to life new and improved diagnostics and therapies.

Many of our members operate, or plan to operate, directly or indirectly in the US, and thereby create jobs in and bring new and improved technologies to the US. Not surprisingly, startups and fledging businesses rely

on the US market projections for securing R&D funding, as the US accounts for 47% of the global biotechnology market.² This is directly reflected by patent statistics. According to the USPTO, approximately 50% of all US patent applications are filed by foreign entities.³

Our members believe that a clear, predictable, and effective patent system is vital to innovation and healthcare, not just in the US, but globally. Our members are concerned that the Federal Circuit's decision in this case—without further guidance from the Supreme Court—discourages disclosure and development of new diagnostic and therapeutic methods and thereby puts at risk the future development of much-needed diagnostics and life-saving medicines.

II. INTRODUCTION AND SUMMARY OF ARGUMENT

Clear, predictable, and harmonized, intellectual property laws are essential for the smooth functioning of today's economy. Biomedical innovation, in particular, depends on a proper balance of economic incentives as well as legal certainty upon which billions of dollars are invested in our and future generations' health and well-being.

2. EvaluatePharma, *Pharmaceutical & Biotech Sales Analysis by Country* (May 2014), available at <http://info.evaluategroup.com/rs/evaluatepharmaltd/images/EvaluatePharma%20-%20Pharmaceutical%20%26%20Biotech%20Sales%20Analysis%20by%20Country%20-%20Report.pdf>.

3. US Patent and Trademark Office, *U.S. Patent Statistics, Calendar Years 1963-2014* (Jun. 2015), available at http://www.uspto.gov/web/offices/ac/ido/oeip/taf/us_stat.pdf.

A consistent and harmonized patent eligibility framework allows inventors across the globe to determine, with predictability, whether to rely on patent protection (and therefore to disclose their inventions to the public) or, instead, withhold their discoveries and rely on trade secret as an alternative form of intellectual property protection. These two forms of protections are mutually exclusive—one cannot maintain a trade secret in one jurisdiction while obtaining a patent in another.

The present case exemplifies an unduly broad interpretation and application of this Court’s prior decision in *Mayo Collaborative Servs. v. Prometheus Labs.*, 132 S. Ct. 1289 (2012). Since *Mayo*, the ever-expanding doctrine of “judicial exceptions” has rampantly infected the US patent system. Meritorious inventions are too often shackled up to a “judicial exception” and, on that basis, are now routinely denied patent protection in the US despite the express language of 35 U.S.C. § 101 (2012).⁴ All the while, the same inventions remain soundly patent-eligible in other jurisdictions. The Federal Circuit’s interpretation of the Supreme Court’s precedent is so broad that, in effect, it excludes from patent protection any readily conceivable invention based on a discovery of a naturally occurring phenomenon or a “law of nature”—a typical invention in diagnostics and personalized medicine.

This erosion of patent eligibility in the US creates a schism among jurisdictional patent eligibility standards in

4. *Id.* states: “Inventions patentable. Whoever invents or discovers *any* new and useful process, machine, manufacture, or composition of matter, or *any* new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.” (Emphasis added).

a world that is increasingly interdependent. It undercuts long-standing efforts, led and supported by the US, to harmonize patents laws and harms one of our common objectives—to promote progress in biomedical science. As this Court recognized in *Mayo*, “all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas,” and as a result “too broad an interpretation” of these implicit exclusions from eligibility could “eviscerate patent law.” *Mayo Collaborative Servs.*, 132 S. Ct. at 1293. Judge Dyk echoed this concern stating that “a too restrictive test for patent eligibility under 35 U.S.C. § 101 with respect to laws of nature (reflected in some of the language in *Mayo*) may discourage development and disclosure of new diagnostic and therapeutic methods in the life sciences, which are often driven by discovery of new natural laws and phenomena.” *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 809 F.3d 1282, 1286 (Fed. Cir. 2015; denial of reh’g en banc; Dyk, T., concurring).

The US is a world leader in biomedical innovation and a stalwart champion of strong intellectual property rights, setting the example for many to follow. The Federal Circuit’s decision, if left unaddressed, will mark a significant setback leading to further “unintended consequences” and incompatible outcomes across jurisdictions.

Accordingly, the *amici curiae* respectfully urge the Court to grant certiorari in order to provide a more refined guidance on patent eligibility. Our common objective is to make results more predictable and uniform across jurisdictions while maintaining a proper balance of rewards inherent in a well-functioning intellectual property rights system.

III. ARGUMENT

A. The Federal Circuit's Application of *Mayo* Leads To Outcomes Inconsistent Across Jurisdictions

In determining that Sequenom's claims are directed to patent-ineligible subject matter, the Federal Circuit based its decision on the Supreme Court's two-step approach, which was first enunciated in *Mayo* and subsequently applied in *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013) and *Alice Corp. Pty. Ltd. v. CLS Bank*, 134 S. Ct. 2347 (2014). *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1375 (Fed. Cir. 2015). Judge Linn characterized the original panel's holding as an unintended consequence of *Mayo*. *Id.* at 1380 (Lynn, R., concurring). In a similar vein, Judge Dyk noted that the Federal Circuit was "bound by the language of *Mayo*, and any further guidance must come from the Supreme Court, not [the Federal Circuit]." As Judge Dyk stated, the "language of *Mayo* is clear ... Patent claims directed to laws of nature are ineligible under 35 U.S.C. § 101 when, (*apart* from the natural laws themselves) [they] involve well-understood, routine, conventional activity previously engaged in by researchers in the field." *Id.* (emphasis added).

But this Court's precedent does not dictate such an outcome. The precedent does not require that an invention that *specifically* applies a newly discovered law of nature or natural phenomenon must be separately patentable, *apart* from the new discovery itself. A blanket exclusion denying patent protection to meritorious inventions merely because they are based upon a discovery of something that occurs in nature is unwarranted.

Unquestionably, *Mayo*, *Myriad* and *Alice* prescribe that patent protection is not available if the inventor “claims” a “judicial exception” (a law of nature, a natural phenomenon, or an abstract idea). *See, e.g., Mayo Collaborative Servs.*, 132 S. Ct. at 1297. It is also clear that the claim language is not to be interpreted literally. Instead, this Court instructs one to look at the *substance* of what the inventor attempts to claim. *Id.* One needs to determine whether the inventor has added “significantly more” to the claims, that is “enough” to transform a patent-ineligible discovery into a patent-eligible application of that discovery. *Id. at 1294.*

It is critical, therefore, for this Court to delineate with clarity and predictability when a discovery becomes sufficiently transformed to become patent-eligible. A sweeping interpretation requiring the inventor to come up with an “inventive concept” beyond a *novel application* of the discovery has led to aberrant results, as here, where even an acknowledged ground-breaking meritorious invention is denied patent protection in the US—while remaining soundly patent-eligible elsewhere—merely because it originates from a discovery of a natural phenomenon.

A side-by-side comparison with other jurisdictions may be instructive for interpreting 35 U.S.C. § 101 (2012) and clarifying the *Mayo* framework. Similar to the US, laws of nature and natural phenomena are not patentable in other jurisdictions. Yet, patent eligibility determinations differ drastically when the US is compared to the rest of the world, contrary to the aims of a number of international laws and treaties. Which begs the question: “Does the problem lie with the analytical legal framework rather than the merits of the inventions?”

As Justice Breyer pointed out in his book “*The Court and The World*,” our economic relations are intensely interdependent. “To find answers today, the Court must increasingly consider foreign and domestic laws together, as if they constituted part of a broadly interconnected legal web.”⁵ “The Court has increasingly sought interpretations of domestic law that would allow it to work in harmony with related foreign laws, so that together they more effectively achieve common objectives.”⁶

To that end, provided below are side-by-side comparisons of Sequenom’s US claims and their European, Australian, Canadian, and Japanese counterparts as specific examples illustrating the disparity in the application of subject matter eligibility jurisprudence.

1. Europe

Like in the US, laws of nature and natural phenomena are not patent-eligible in Europe.⁷ Article 52(2) of the European Patent Convention (EPC) states, “[t]he following in particular shall not be regarded as inventions...: (a) discoveries, scientific theories and mathematical methods...” *Id.* Similarly, national laws of many EPC member nations have analogous exclusions. For example, UK and German national patent statutes

5. Stephen Breyer, *The Court and The World: American Law and New Global Realities* (2015), at 91.

6. *Id.* at 92.

7. Article 52, European Patent Convention, *available at* <https://www.epo.org/law-practice/legal-texts/html/epc/2013/e/ar52.html>

exclude from the term “invention” “discoveries, scientific theories and mathematical methods.”⁸

In the UK, for instance, as held by The Patents Court of the High Court of England and Wales in *CFPH LLC’s Applications* [2005] EWHC 1589:

It is well-settled law that, although you cannot patent a discovery, you can patent a useful artefact or process that you were able to devise once you had made your discovery. ***This is so even where it was perfectly obvious how to devise that artefact or process, once you had made the discovery.*** (Emphasis added.)⁹

Likewise, in Germany, the Federal Court of Justice, the nation’s highest court, recently confirmed “[u]nder Art. 52 (2) (A), (3) EPC, a discovery as such is not patent eligible, just like a scientific theory or a mathematical method.”¹⁰ The court, however, explained that:

8. See UK Patent Act 1977, Section 1(2)(a), available at <http://www.legislation.gov.uk/ukpga/1977/37> and Section (1)(3) of the German Patent Act, available at http://www.wipo.int/wipolex/en/text.jsp?file_id=126258.

9. Available at <http://www.bailii.org/ew/cases/EWHC/Patents/2005/1589.html>. Also see United Kingdom Intellectual Property Office, *Manual of Patent Practice*, at Section 1.27 (citing *CFPH LLC’s Applications* at Paragraph 34), updated Apr. 14, 2016, available at <https://www.gov.uk/guidance/manual-of-patent-practice-mopp/section-1-patentability>.

10. See Appendix A. *Certified English Translation of BGH X ZR 141/13*, at paragraph 50. BGH X ZR 141/13 *Rezeptortyrosinkinase* (Bundesgerichtshof, Jan. 19, 2016), original decision in German available at <http://www.rechtsprechung-im-internet.de/jportal/portal/t/1mhh/page/bsjrsprod.psml?doc.id=KORE313052016>.

Contrary to the decision of the US Supreme Court [in Mayo], however, a technical teaching which teaches the use of a discovery to achieve a certain object, is patent eligible under European–and German–law, regardless of whether the teaching comprises an “inventive surplus” that goes beyond the purposeful use of the discovered law of nature. This is because all technical activities rely on a purposeful use of laws of nature.¹¹

Furthermore, the European Patent Office (EPO), charged with administering the EPC, has long-recognized that, when an idea or concept underlying the invention resides in a discovery, it does not necessarily mean that the claimed invention is directed to the discovery as such.¹² Accordingly, the EPO Guidelines¹³ differentiate a mere discovery from a *practical application* of that discovery, as follows:

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). If, however, that property is put to practical use,

11. *Id.* (emphasis added).

12. G2/88, OJ 1990, 93, available at http://archive.epo.org/epo/pubs/oj1990/p093_185.pdf.

13. EPO, *EPO Guidelines for Examination*, available at http://www.epo.org/law-practice/legal-texts/html/guidelines/e/g_ii_3_1.htm (emphasis added).

then this constitutes an invention which may be patentable.¹⁴

Therefore, it is instructive to compare Sequenom's European patent and its US counterpart, held ineligible by the Federal Circuit. *Ariosa Diagnostics*, 788 F.3d at 1380. As seen from the table below, European claims 1 and 18 are substantially identical to US claims 1 and 21.¹⁵ The EPO has twice affirmed claims 1 and 18 as novel and inventive.¹⁶ Subject matter eligibility was never at issue for the European patent. *Ariosa Diagnostics*, 809 F.3d at 1286. Consistent with the EPC and various national

14. The EPO Guidelines further state: "... ***However, if a substance found in nature can be shown to produce a technical effect, it may be patentable. An example of such a case is that of a substance occurring in nature which is found to have an antibiotic effect.***" *Id.* (emphasis added).

15. Consistent with Sequenom's Petition, claim 21 is presented as a representative claim and incorporates all elements of claim 1 by reference. See *Petition for Certiorari, Sequenom, Inc. v. Ariosa et al.*, No. 15-1182, at 3. The Patent Trial and Appeal Board (PTAB) of the USPTO considered the patentability of US Patent No. 6,258,540 in an *inter partes* review proceeding (*Ariosa Diagnostics v. Isis Innovation Limited*, IPR 2012-00022, Paper 166 (PTAB, Sept. 2, 2014). While the PTAB found claim 1 and certain other claims unpatentable under 35 U.S.C. § 102(b), the PTAB has maintained claim 21 as patentable despite challenges under both 35 U.S.C. §§ 102, 103 (2012). *Id.* at 3. The PTAB's decision is pending appeal which is currently stayed in view of the present case. Both claims are reproduced in the tables below with their counterparts when available.

16. EP '963 patent was challenged but survived a third-party opposition and an appeal of that decision at the EPO. See *Decision of the Boards of Appeal of The EPO*, Case No. T 0146/07 - 3.3.08 (December 13, 2011), available at <http://www.epo.org/law-practice/case-law-appeals/recent/t070146eu1.html>.

laws, claims like Sequenom’s European claims are patent-eligible throughout Europe.

Table 1. Comparison of US and European Clams

US 6,258,540	EP 994 963 ^{17, 18}
1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.	1. A detection method performed on a maternal serum or plasma sample from a pregnant female, which method comprises detecting the presence of a nucleic acid of foetal origin in the sample, wherein said nucleic acid is a paternally inherited sequence which is not possessed by said pregnant female.

17. Under Article 2(2) EPC, a European patent shall, in each of the contracting states for which it is granted, have the effect of a national patent granted by that state, unless otherwise provided in the EPC. Article 2, European Patent Convention, *available at* <https://www.epo.org/law-practice/legal-texts/html/epc/2013/e/ar2.html>.

18. EP '963 has been “validated” under the EPC procedures in Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Monaco, Netherlands, Portugal, Spain, Sweden, Switzerland and the United Kingdom. Consequently, the patent claims in these countries are the same as EP '963. *See* http://worldwide.espacenet.com/publicationDetails/inpadocPatentFamily?CC=EP&NR=0994963A1&KC=A1&FT=D&ND=3&date=20000426&DB=&locale=en_EP.

<p>21. A method of performing a prenatal diagnosis, which method comprises the steps of:</p> <p>(i) providing a maternal blood sample;</p> <p>(ii) separating the sample into a cellular and a non-cellular fraction;</p> <p>(iii) detecting the presence of a nucleic acid of foetal origin in the non-cellular fraction according to the method of claim 1;</p> <p>(iv) providing a diagnosis based on the presence and/or quantity and/or sequence of the fetal nucleic acid.</p>	<p>18. A method of performing a prenatal diagnosis, which method comprises:</p> <p>(i) providing a maternal blood sample;</p> <p>(ii) separating the sample into a cellular and non-cellular fraction;</p> <p>(iii) detecting the presence of a nucleic acid of foetal origin in the non-cellular fraction using the method of [claim 1]; and</p> <p>(iv) providing a diagnosis based on the presence and/or quantity and/or sequence of the foetal nucleic acid.</p>
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2. Australia

Similarly to the US and Europe, “discoveries with no means of putting them into effect,” “mere ideas,” and “scientific theories” *per se* are not patent-eligible in Australia.¹⁹ Rather, the Australian Patent Act dictates

19. IP Australia, *Patent Manual of Practice and Procedure*, § 2.9.2 (Patentable Subject Matter) Manner of Manufacture 2.9.2.5 Discoveries, Ideas, Scientific IP Australia, *Theories, Schemes and Plans*, available at http://www.ipaustralia.gov.au/pdfs/patentsmanual/WebHelp/Patent_Examiners_Manual.htm.

that patentable subject matter must relate to “a manner of manufacture.”²⁰ The High Court of Australia interpreted this term to mean that an invention is patent-eligible if it provides something industrially useful or an “artificially created state of affairs for economic benefit.” See *National Research Development Corporation v. Commissioner of Patents* (1959) 102 CLR 252.

As in the US, the Australian law of patent eligibility was recently under judicial review. The High Court of Australia considered the eligibility of isolated nucleic acid sequences in *D’Arcy v. Myriad Genetics Inc* [2015] HCA 35,²¹ the Australian counterpart to the US *Myriad* case. While *D’Arcy* held that Myriad’s claims to isolated nucleic acids are not patent-eligible as “manner of manufacture,” Myriad’s method claims were not challenged and were not otherwise found ineligible—maintaining the *status quo* of patent eligibility for diagnostic methods under Australian law. *Id.*

In light of these legal principles, consider Sequenom’s Australian patent. As can be seen from the table below, the Australian and US counterpart claims are similar in scope. In fact, the Australian claims could be considered broader than those in the US (e.g., claim 1 of the Australian patent does not require the “paternal” limitation or the “amplification” step present in the US claims). Australian claim 22, as granted, is substantially identical to US claim

20. Section 18(1)(a) of the Australian Patents Act of 1990, available at http://www.austlii.edu.au/au/legis/cth/consol_act/pa1990109/s18.html.

21. Available at <http://eresources.hcourt.gov.au/downloadPdf/2015/HCA/35>.

21. Despite the broader claim scope, patent eligibility was never at issue in the Australian patent. Consistent with the Australian law and practice, Sequenom's Australian claims are patent-eligible.

Table 2. Comparison of US and Australian Claims

US 6,258,540	AU 727919
<p>1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.</p>	<p>1. A detection method performed on a maternal serum or plasma sample from a pregnant female, which method comprises detecting the presence of a nucleic acid of foetal origin in the sample.</p>

<p>21. A method of performing a prenatal diagnosis, which method comprises the steps of:</p> <p>(i) providing a maternal blood sample;</p> <p>(ii) separating the sample into a cellular and a non-cellular fraction;</p> <p>(iii) detecting the presence of a nucleic acid of foetal origin in the non-cellular fraction according to the method of claim 1;</p> <p>(iv) providing a diagnosis based on the presence and/or quantity and/or sequence of the fetal nucleic acid.</p>	<p>22. A method of performing a prenatal diagnosis, which method comprises the steps of:</p> <p>(i) providing a maternal blood sample;</p> <p>(ii) separating the sample into a cellular and a non-cellular fraction;</p> <p>(iii) detecting the presence of a nucleic acid of foetal origin in the non-cellular fraction according to the method of [claim 1];</p> <p>(iv) providing a diagnosis based on the presence and/or quantity and/or sequence of the foetal nucleic acid.</p>
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3. Canada

Using language nearly identical to 35 U.S.C. § 101 (2012), Section 2 of the Canadian Patent Act defines “invention” as “any new and useful art, process, machine, manufacture or composition of matter, or any new and useful improvement in any art, process, machine, manufacture or composition of matter.”²² Similar to the US, Canada has

22. Canada Patent Act (R.S.C., 1985, c. P-4), section 2, *available at* <http://laws-lois.justice.gc.ca/eng/acts/P-4/FullText.html>.

certain exclusions to patentability, namely, a prohibition on patenting “any mere scientific principle or abstract theorem.”²³ With respect to products and laws of nature, Canada has no direct counterparts to the US Supreme Court’s *Myriad* and *Mayo* decisions, and claims to both isolated biomolecules and diagnostic methods remain patent-eligible. The Canadian Intellectual Property Office (CIPO) recently issued guidance²⁴ clarifying their analytical approach for diagnostic methods as follows:

Where *a physical step of data acquisition is identified as an essential element of the construed claim, the claimed subject-matter will likely be statutory.* (Emphasis added.)²⁵

In view of these legal principles, consider the Canadian counterpart of Sequenom’s US patent. As seen from the table below, the Canadian and US claims are substantially similar (for example, compare Canadian claim 24 to US claim 21). As with Europe and Australia, patent eligibility of the Canadian claims has never presented an issue.

23. *Id.*, at section 27(8).

24. Canadian Intellectual Property Office, *Examination Practice Respecting Medical Diagnostic Methods – PN 2015-02* (Jun. 2015), available at <https://www.epo.org/law-practice/legal-texts/html/epc/2013/e/ar52.html>

25. By contrast, a diagnostic method claim construed as consisting solely of essential elements that are disembodied (e.g., mental process, lacking physicality, no practical application, etc.) will be identified as [ineligible]. This would generally apply to situations where the identified solution is only provided by an element or set of elements associated with the analysis or significance of the acquired data (e.g., the correlation). *Id.*

Accordingly, under the Canadian practice, Sequenom's Canadian claims are patent-eligible.

Table 3. Comparison of US and Canadian Claims

US 6,258,540	CA 2,282,793
<p>1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.</p>	<p>1. A method for screening for a presence of a paternally-inherited foetal nucleic acid in a pregnant female, the method comprising the steps of:</p> <p>(1) obtaining a serum or plasma sample from the pregnant female retaining the foetus;</p> <p>(2) amplifying paternally-inherited nucleic acid from the serum or plasma sample; and</p> <p>(3) detecting the presence of a paternally-inherited foetal nucleic acid in the serum or plasma sample.</p>

<p>21. A method of performing a prenatal diagnosis, which method comprises the steps of:</p> <p>(i) providing a maternal blood sample;</p> <p>(ii) separating the sample into a cellular and a non-cellular fraction;</p> <p>(iii) detecting the presence of a nucleic acid of foetal origin in the non-cellular fraction according to the method of claim 1;</p> <p>(iv) providing a diagnosis based on the presence and/or quantity and/or sequence of the fetal nucleic acid.</p>	<p>24. A method of performing a prenatal diagnosis, which method comprises the steps of:</p> <p>(i) providing a maternal blood sample;</p> <p>(ii) separating the sample into a cellular and a non-cellular fraction;</p> <p>(iii) detecting the presence of a nucleic acid of foetal origin in the non-cellular fraction according to the method of [claim 1];</p> <p>(iv) providing a diagnosis based on at least one of:</p> <p>the presence of the foetal nucleic acid, the quantity of the foetal nucleic acid, and the sequence of the foetal nucleic acid.</p>
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4. Japan

Similarly to the US and other jurisdictions, “a law of nature as such” is not patent-eligible subject matter in Japan.²⁶ The Japanese approach to determining patent

26. Japan Patent Office, *Examination Guidelines for Patent and Utility Model in Japan (Provisional Translation)*, Part

eligibility rests upon finding industrial applicability.²⁷ Japanese law expressly acknowledges the fact that inventions rely on the underlying laws of nature: Article 2(1) of the Japan Patent Act defines “invention” as “a highly advanced creation of technical ideas utilizing the laws of nature.”²⁸ Under the Japanese law and practice, diagnostic methods are patent-eligible.²⁹

As seen from the table below, the US and Japanese claims are also substantively similar.³⁰ As in Europe, Australia, and Canada, patent eligibility never presented an issue in the Japanese claims. Like in Europe, Australia, and Canada, industrial applicability of inventions employing natural phenomena is critical to patent eligibility in Japan. Under the Japanese law and practice, claims like Sequenom’s Japanese claims are clearly patent-eligible.

III, Chapter 1, Section 2.1.1, *available at* https://www.jpo.go.jp/tetuzuki_e/t_tokkyo_e/files_guidelines_e/all_e.pdf.

27. *Id.* at Part III, Chapter 1.

28. Japan Patent Act (Act No. 121 of 13 April 1959, as last amended in 2006), *available at* http://www.wipo.int/wipolex/en/text.jsp?file_id=188310.

29. Japan Patent Office, *Examination Guidelines for Patent and Utility Model in Japan (Provisional Translation)* Part III, Chapter 1, Section 3.2.1, *available at* https://www.jpo.go.jp/tetuzuki_e/t_tokkyo_e/files_guidelines_e/all_e.pdf.

30. Unlike the European, Australian, and Canadian patents above, JP 04-245666 does not contain a direct counterpart to claim 21 of US 6,258,540.

Table 4. Comparison of US and Japanese Clams

US 6,258,540	JP 04-245666
<p>1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.</p>	<p>1. A method for screening for a presence of a paternally-inherited foetal nucleic acid in a pregnant female, the method comprising the steps of:</p> <p>(1) obtaining a serum or plasma sample from the pregnant female retaining the foetus;</p> <p>(2) amplifying paternally-inherited nucleic acid from the serum or plasma sample; and</p> <p>(3) detecting the presence of a paternally-inherited foetal nucleic acid in the serum or plasma sample.</p>

5. Summary

The opposite outcomes in the application of patent eligibility standards in the US compared to Europe, Australia, Canada, and Japan, while not peculiar to the present case, reflect a fundamental difference in the analytical approaches seemingly designed for the same purpose, to exclude “mere discoveries” from

being patented.³¹ The “significantly more” requirement enunciated in *Mayo*, *Myriad*, and *Alice* has no direct equivalent in the interpretation of patent laws of other industrialized countries and, to be consistently and predictably applied, requires a more refined and definite analytical framework.

The principle of “comity” requires interpretations of 35 U.S.C. § 101 (2012) to work in harmony with related foreign laws. Thus, the interplay of patent eligibility standards in the US and other jurisdictions should be given particular attention in interpreting and applying 35 U.S.C. § 101 (2012).

In particular, procuring a patent comes at the cost of public disclosure of the invention in the patent application publication.³² As a result of publication, trade secret

31. In addition to explicit exclusions to certain things that are not “inventions,” e.g., laws of nature and natural phenomenon *per se*, many jurisdictions have “policy-based” exclusions to patentability. Take, for example, methods of treating or diagnosing the human body, which are not patent-eligible in many jurisdictions, including Europe (EPC Article 53), Canada (*Tennessee Eastman Co v Canada (Commissioner of Patents)*, [1974] S.C.R. 111), and Japan (*Examination Guidelines for Patent and Utility Model in Japan*, Part III, Chapter 1, Section 3.1.1). However, this policy-based exclusion relating to the human body itself comes with clear and consistent provisions for those seeking to protect their otherwise meritorious biomedical inventions. For example, this exclusion does not apply to diagnostic methods practiced on samples *ex vivo*, such as Sequenom’s method discussed above.

32. With respect to the US, *see* 35 U.S.C. § 122(b)(1) (2012). With respect to international applications, *see* Patent Cooperation Treaty (PCT), Article 21 International Publication, *available at* <http://www.wipo.int/pct/en/texts/articles/a21.htm>.

protection is forfeited everywhere in the world. A US-only applicant may file a patent application with a request for non-publication,³³ and if unsuccessful in obtaining a patent, may pursue protection via trade secrets. However, inventors desiring multi-national patent protection do not have that option—patent applications outside the US are generally always published.

Accordingly, if a non-US inventor obtains patents in other countries but is refused a patent in the US, he will have neither patent nor trade secret protection in the US. Likewise, a US inventor, seeking patent protection abroad, will have no choice but to make his invention public, thus forfeiting trade secret protection in the US. Therefore, a practical consequence of the jurisdictional misalignment is the lack of any type of intellectual property protection in the US for those who rely on patents abroad but are forced out of patent protection in the US.

Given the significance of the US market, such an outcome is particularly troubling in the case of meritorious, life-saving inventions. The resulting lack of protection, while directly impacting the US market, is likely to impede investment in the biotechnology industry as a whole.

B. The Federal Circuit’s Interpretation of the *Mayo* Test Frustrates Long-Standing Harmonization Efforts

The newly emerged disparity of patent eligibility standards between the US and the rest of the world frustrates decades-long efforts to harmonize IP laws

33. 35 U.S.C. § 122(a)(2)(B)(i) (2012).

across the world. Such efforts are rooted in international treaties and foundational to the United States' ongoing efforts to promote a modern innovation economy, consistent with the Constitutional directive "[t]o promote the Progress of Science and useful Arts." U.S. Const. art. I, § 8, cl. 8.

The long term, global trend towards patent law harmonization extends back over 130 years to the 1883 Paris Convention for the Protection of Industrial Property. The Paris Convention, which now covers 176 member countries including the US, ensures equal national treatment and priority rights for applicants from all member countries.³⁴

Following the Paris Convention, harmonization continued and expanded, resulting in the numerous treaties and international organizations with essentially universal membership. For example, the WIPO (an agency of the United Nations) was created in 1967 "to encourage creative activity, to promote the protection of intellectual property throughout the world."³⁵ WIPO currently has 188 member states, administers 26 international treaties, including the Paris Convention and the 1970 Patent Cooperation Treaty (PCT), which provides a unified

34. WIPO, *WIPO Summary of the Paris Convention for the Protection of Industrial Property*, available at http://www.wipo.int/treaties/en/ip/paris/summary_paris.html, and *WIPO-Administered Treaties*, available at http://www.wipo.int/treaties/en/ShowResults.jsp?lang=en&treaty_id=2.

35. WIPO, *WIPO Convention Establishing the World Intellectual Property Organization*, available at http://www.wipo.int/treaties/en/text.jsp?file_id=283854.

procedure for protecting inventions in each of its 148 contracting states.³⁶

Similarly, the 1995 Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which is administered by the WTO and covers all 161 WTO member countries, is notable for introducing IP law directly into international trade and for setting down minimum and uniform standards for many forms of intellectual property protection across the industrialized world.³⁷

The Federal Circuit decision in this case also appears to be fundamentally incompatible with recent major legislation in the US. The America Invents Act (AIA), passed in 2011, was conceived as a major step in the harmonization efforts and pre-dates *Mayo* and *Myriad*. The AIA was the most significant and far-reaching IP legislative initiative since the US Patent Act of 1952. Notably, the AIA made no changes to § 101 and preserved the *status quo* on patent eligibility, except adding “a human organism” as an exclusion to patent-eligible subject matter.³⁸

36. WIPO, *WIPO Member States*, available at <http://www.wipo.int/members/en/>; *WIPO-Administered Treaties*, available at <http://www.wipo.int/treaties/en/>; *PCT – The International Patent System*, available at <http://www.wipo.int/pct/en/>; and *Summary of the Patent, Cooperation Treaty (PCT) (1970)*, available at http://www.wipo.int/treaties/en/registration/pct/summary_pct.html.

37. WIPO, *WTO Overview: the TRIPS Agreement*, available at https://www.wto.org/english/tratop_e/trips_e/intel2_e.htm, and *Members and Observers*, available at https://www.wto.org/english/thewto_e/whatis_e/tif_e/org6_e.htm.

38. “LIMITATION ON ISSUANCE OF PATENTS.

As stated by the USPTO, the AIA “pave[d] the way for greater patent harmonization ... to ensure consistency and clarity of rights to the world’s innovators.”³⁹ This is not simply a legislative remit but an economic imperative. In particular, the USPTO emphasized that:

... as innovators seek to tap into global market, it is *imperative* that the international patent system provide consistent, cost effective avenues to obtain *reliable patent rights in multiple jurisdictions*. The passage of the AIA enables the USPTO to lead on a vision of the IP world in which *national and regional patent systems are harmonized in pursuit of creating an optimal environment for technological innovation and diffusion*.⁴⁰

Thus, the continuing erosion of patent-eligible subject matter, as advanced by the Federal Circuit and lower courts, threatens the innovativeness and competitiveness of the US economy, and as such, cannot be what international treaties, Congress, and this Court intended.

(a) LIMITATION.--Notwithstanding any other provision of law, no patent may issue on a claim directed to or encompassing a human organism.”

Leahy-Smith America Invents Act (AIA) PL112-29, Sept. 16, 2011, 125 Stat. 284, Sec. 33.

39. US Patent and Trademark Office, *Harmonization: The Time is Now*, available at <http://www.uspto.gov/learning-and-resources/ip-policy/harmonization>.

40. *Id.* (emphasis added).

IV. CONCLUSION

The Federal Circuit's application of *Mayo* leads to conflicting outcomes across jurisdictions and frustrates long-standing patent law harmonization efforts.

Accordingly and for the aforementioned reasons, these *amici curiae* respectfully urge the Court to grant certiorari in order to provide a more definite guidance with respect to patent eligibility, pursuant to our common goal of promoting progress in biomedical science.

Respectfully submitted,

Dated: April 19, 2016

KONSTANTIN M. LINNIK
Counsel of Record
LANA A. GLADSTEIN
ISAAC A. HUBNER
NUTTER McCLENNEN & FISH LLP
Seaport West
155 Seaport Boulevard
Boston, MA 02210
(617) 439-2000
linnik@nutter.com
Counsel for Amici Curiae

APPENDIX

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**APPENDIX — JUDGEMENT OF THE
FEDERAL SUPREME COURT**

FEDERAL SUPREME COURT

IN THE NAME OF THE PEOPLE

JUDGEMENT

X ZR 141/13

Handed over on January 19, 2016 Hartmann Judicial
Employee clerk of the court of the Senate Office in the
Nullity action

Reference book: yes

BGHZ: no

BGHR: yes

Receptor Tyrosin Kinase

EPC Art. 52 (2) a) 3), PatG § 1 (3) No. 1, (4), § 1a (1),(2)

“A technical teaching, which teaches the use of a mere discovery to achieve a particular technical object, is patent eligible regardless of whether the teaching comprises an “inventive surplus” that goes beyond the purposeful use of the discovered law of nature or not. This also applies to the provision of a nucleic acid sequence coding for a human protein. It is not necessary to designate the sequence

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as isolated or obtained by a technical process.” BGH, Decision of 19 January 19, 2016 - X ZR 141/13 - Federal Patent Court

The X. Civil Senate of the Federal Court of Justice has decided upon hearing on 19 January 2016, with presiding judge Prof. Dr. Meier-Beck, judges Groening and Dr. Bacher and judges Schuster and Dr. Kober Dehm:

Upon appeal of the parties the decision of the 3rd Senate (Senate invalidity) of the Federal Patent Court announced July 9, 2013 is modified.

European Patent 959 132 is declared invalid with effect for the Federal Republic of Germany in so far as it goes beyond the following claims:

1. A nucleic acid molecule of a tandem duplication mutant encoding FMS-like tyrosine kinase 3 (FLT3), wherein said nucleic acid molecule has a nucleotide sequence corresponding to:

(a) a tandem duplication mutation in the amino acid sequence of juxtamembrane of FLT3, or

(b) a tandem duplication mutation in the nucleotide sequence of exon 11 or exons 11 to 12 of FLT3 which does not shift the reading frame.

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2. A nucleic acid molecule having a nucleotide sequence corresponding to:

(a) a tandem duplication mutation in the amino acid sequence of juxtamembrane of FLT3, or

(b) a tandem duplication mutation in the nucleotide sequence of a region comprising exon 11 or exons 11 to 12 of FLT3 which does not shift the reading frame.

3. [deleted]

4. A polypeptide encoded by the nucleic acid molecule of claim 1, or the nucleic acid molecule of claim 2.

5. A cell expressing the nucleic acid molecule of claim 1, or the nucleic acid molecule of claim 2, or the polypeptide of claim 4.

6. An antibody which is specific for the polypeptide of claim 4.

7. A method for detecting the nucleic acid molecule of claim 1, or the nucleic acid molecule of claim 2, comprising the steps of:

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(a) subjecting a nucleic acid sample from a human to a gene amplification reaction, wherein a nucleic acid fragment comprising exon 11 or exons 11 to 12 of the FMSlike tyrosine kinase 3 (FLT3) gene and having a tandem duplication mutation in the juxtamembrane is amplified, which can be found in FLT3 gene;

(b) detecting the presence of the tandem duplication mutation in the nucleic acid fragment of step (a).

8. The method of claim 7, wherein step (b) is carried out by comparing the amplified nucleic acid fragment obtained in step (a) with a sequence derived from a normal FLT3, thereby detecting the presence of tandem duplication mutation in the juxtamembrane.

9. The method of claim 7 or 8, wherein in step (b), a length mutation is used as an index of the tandem duplication mutation.

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10. The method of any one of claims 7 to 9, wherein the gene amplification reaction in step (a) is carried out with a primer pair selected from the group consisting of: SEQ ID NOs: 26 and 27, SEQ ID NOs: 30 and 31, and SEQ ID NOs: 32 and 33.

11. The method of any one of claims 7 to 10, wherein the tandem duplication mutation is not found in a gene of a normal individual.

12. [deleted]

13. Kit for a method according to any one of claims 7 to 11, wherein said kit comprises primers for amplifying a region in exon 11 or exons 11 to 12 of the FLT3 gene, wherein said primers are selected from the group consisting of: SEQ ID NOs: 26 and 27, SEQ ID NOs: 30 and 31 and SEQ ID NOs: 32 and 33.

14. Use of a hematopoietic stem cell expressing a nucleic acid molecule encoding a tandem duplication mutant polypeptide and a cell expressing the normal FLT3 for screening a drug for examination and treatment of a blood cell disease or a hematopoietic stem

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cell disease, wherein said nucleic acid molecule has a tandem duplication mutation in a nucleotide sequence of a juxtamembrane which does not shift the reading frame.

15. Use of a hematopoietic stem cell expressing the nucleic acid molecule of claim 1, or the nucleic acid molecule of claim 2, or the polypeptide of claim 4 and a cell expressing the normal FLT3 for screening a drug for examination and treatment of a blood cell disease or a hematopoietic stem cell disease.

16. Use of the nucleic acid molecule of claim 1, or the nucleic acid molecule of claim 2 for the preparation of a drug for regulating proliferation, immune response or signal information transmission of a blood cell or a hematopoietic stem cell.

17. A pharmaceutical composition comprising the nucleic acid molecule of claim 1, and/or the nucleic acid molecule of claim 2, and/or the nucleic acid molecule of claim 3, and/or the polypeptide of claim 4, and/or the antibody of claim 6 and, optionally, a pharmaceutically acceptable carrier and/or diluent.

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18. A kit for detection of the polypeptide of claim 4, wherein the kit comprises the antibody of claim 6.

The action is dismissed insofar as it goes beyond. The further appeal by the petitioner is dismissed.

Three quarters of the costs of the proceedings are apportioned to the petitioner and a quarter of the costs of the proceedings are apportioned to the defendant.

Ipsa Jure

Matters of Fact

- 1 The defendant is the owner of European patent 959 132 (the patent) granted with effect for the Federal Republic of Germany which has been filed internationally on 13 October 1997, claiming a Japanese priority of 18 October 1996, and which relates to a nucleic acid encoding a receptor protein kinase. The patent also relates to a polypeptide, a cell, an antibody, kits and medicaments, the use of hematopoietic stem cells and nucleic acid molecules and methods for detecting the claimed nucleic acid. It encompasses 20 claims, with independent claims 1 to 7, 12, 14 and 16 to 20 which are as follows:

“1. A nucleic acid molecule of a tandem duplication mutant encoding FMS-like tyrosine kinase 3 (FLT3), wherein said nucleic acid molecule has a nucleotide sequence corresponding to:

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(a) a tandem duplication mutation in the amino acid sequence of juxtamembrane of FLT3, or

(b) a tandem duplication mutation in the nucleotide sequence of a region comprising exon 11 or exons 11 to 12 of FLT3.

2. A nucleic acid molecule having a nucleotide sequence corresponding to:

(a) a tandem duplication mutation in the amino acid sequence of juxtamembrane of FLT3, or

(b) a tandem duplication mutation in the nucleotide sequence of a region comprising exon 11 or exons 11 to 12 of FLT3.

3. A nucleic acid molecule capable of specifically hybridizing under stringent conditions to a nucleic acid molecule corresponding to:

(a) a tandem duplication mutation in the amino acid sequence of juxtamembrane of FLT3, or

(b) a tandem duplication mutation in the nucleotide sequence of a region

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comprising exon 11 or exons 11 to 12 of FLT3 in the nucleic acid of claim 1.

4. A polypeptide encoded by the nucleic acid molecule of claim 1, or the nucleic acid molecule of claim 2.

5. A cell expressing the nucleic acid molecule of claim 1, or the nucleic acid molecule of claim 2, or the polypeptide of claim 4.

6. An antibody which is specific for the polypeptide of claim 4.

7. A method for detecting the nucleic acid molecule of claim 1, or the nucleic acid molecule of claim 2, comprising the steps of:

(a) subjecting a nucleic acid sample from a human to a gene amplification reaction, wherein a nucleic acid fragment comprising exon 11 or exons 11 to 12 of the FMS-like tyrosine kinase 3 (FLT3) gene and having a tandem duplication mutation in the juxtamembrane is amplified, which can be found in FLT3 gene;

(b) detecting the presence of the tandem duplication mutation in the nucleic acid fragment of step (a).

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12. A kit for the method of any one of claims 7 to 11, wherein said kit comprises primers for amplifying a region comprising exon 11 or exons 11 to 12 of the FLT3 gene.

14. Use of a hematopoietic stem cell expressing a nucleic acid molecule encoding a tandem duplication mutant polypeptide and a cell expressing the normal FLT3 for screening a drug for examination and treatment of a blood cell disease or a hematopoietic stem cell disease.

16. Use of a hematopoietic stem cell expressing the nucleic acid molecule of claim 1, or the nucleic acid molecule of claim 2, or the polypeptide of claim 4 and a cell expressing the normal FLT3 for screening a drug for examination and treatment of a blood cell disease or a hematopoietic stem cell disease.

17. Use of the nucleic acid molecule of claim 1, or the nucleic acid molecule of claim 2 for the preparation of a drug for regulating proliferation, immune response or signal information transmission of a blood cell or a hematopoietic stem cell.

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18. Use of the nucleic acid molecule of claim 1, or the nucleic acid molecule of claim 2, or polypeptide of claim 4, for the preparation of material used for pathologic judgment of myelodysplastic syndrome (MDS) or leukemia.

19. A pharmaceutical composition comprising the nucleic acid molecule of claim 1, and/or the of claim 12 and, optionally, a pharmaceutically acceptable nucleic acid molecule of claim 2, and/or the nucleic acid molecule of claim 3, and/or the polypeptide of claim 4, and/or the antibody carrier and/or diluent.

20. A kit for detection of the polypeptide of claim 4, wherein the kit comprises the antibody of claim 6.”

- 2 The petitioner submitted that the subject of claims 1 to 11 were excluded from patentability. The claims 1 to 6 would encompass nonpatentable discoveries, which would relate to parts of the human body excluded from patent eligibility. Claims 7 to 11 would claim a non-patent eligible diagnostic method practised on the human body. Furthermore, the subject matter of the patent were not patentable and went beyond the contents of the application as originally filed. Finally, the subject of claim 7 with respect to the detection

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of tandem duplication mutation was not disclosed in such way as to provide sufficient enablement.

- 3 The defendant has defended the patent on the basis of a main request and three auxiliary requests, which comprised versions modified in relation to the granted version.
- 4 The Patent Court has declared the patent partially invalid by changing the claims in their German language version to a wording which corresponds to claims 7 to 15 of auxiliary request III, as used in the 1st instance defense.
- 5 The appeal of the defendant is directed against this decision. The defendant defends the patent on the basis of a version of the main request according to the Tenor, which differs from the version as defended before the Patent Court amended by removal of claims 3 and 12, changes in claims 1, 2, 13 and 14, as well as a modification of claim 17 due to the removal of claim 3. On an auxiliary basis, the defendant defends the patent with five other amended versions.
- 6 The petitioner objects this request pursues, in his appeal, the first instance request for complete invalidation of the contested patent.

Reasons for the decision

- 7 The admissible appeal by the defendant is justified, the appeal of the petitioner is unfounded.

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- 8 I. The patent relates to a nucleic acid molecule encoding for a receptor protein kinase, namely the FMS-like tyrosine kinase 3 (FLT3), and a method for its detection.
- 9 1. As explained in the specification of the patent, the proliferation and differentiation of cells as well as the responses of cells to various stimuli are controlled by growth factors that act through specific receptors. Receptors containing a tyrosine kinase domain are known as receptor tyrosine kinases (RTK) (desc. para. 2). They include an extracellular region, a transmembrane region and an intracellular region containing a tyrosine kinase domain and a juxtamembrane between the transmembrane region and the tyrosine kinase domain, and are divided into four types divided due to their structural characteristics and their amino acid sequence homology (desc. para 3). The FMS-like tyrosine kinase 3 (FLT3), which is expressed by leukemic cells, is known as receptor of Type III are known (desc. para 8). In receptor tyrosine kinases of this the association of cells to an assembly, for example the doubling, is carried out upon binding of a ligand, for example a growth factor, to the extracellular region, which results in the activation of the kinase (desc. para. 9).
- 10 The patent describes the initial situation at the priority date of the invention as follows: It was suspected that in the case of leukemia, cells proliferate due to an autocrine, i.e., self-emanating , stimulation, because

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the FLT3 ligand is expressed in almost all leukemic cells. It was also reported that FLT3 mRNA is expressed in lymphatic leukemic cells and leukemic myelocytes. However, it was not known how the expression of messenger RNA is connected with the pathology of lymphatic and myeloid leukemia (desc. para. 10). Until the priority date, a human FLT3 cDNA was cloned and the cDNA nucleotide sequence and the amino acid sequence of the FLT3 protein could be determined. However, neither structure nor function of FMS-like tyrosine kinase 3 were well analyzed during the differentiation of hematopoietic stem cells and the malignant transformation of leukemic cells (desc. para. 11).

- 11 2. The Patent Court has derived therefrom correctly that the patent concerns the technical problem to provide a nucleic acid coding for the FLT3 gene that, due to genetic changes, can be used as a marker in the diagnosis of leukemic diseases.
- 12 3. To solve this problem the patent suggests in his latest version a nucleic acid molecule in claims 1 and 2, a polypeptide in claim 4 a cell in claim 5, an antibody in claim 6, a method for detecting the nucleic acids of claims 1 and 2 in claim 7, a kit for the method of claims 7 to 11 in claim 13, the use of haematopoietic stem cells in claims 14 and 15, the use of the nucleic acid of claims 1 and 2 in claim 16, a drug in claim 17, and a kit for the detection of the polypeptide on claim 18.

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- 13 a) The features of the nucleic acid molecule of claim 1 in the version last defended on appeal can be broken down as follows:
1. Nucleic acid molecule of a tandem duplication mutant
 - 1.1 which encodes for FMS-like tyrosine kinase 3 (FLT3) and
 - 1.2 has a nucleotide sequence having
 - 1.2.a either a tandem duplication mutation in the amino acid sequence of juxtamembrane of FLT3, or
 - 1.2.b a tandem duplication mutation in the nucleotide sequence of exon 11 or exons 11 to 12 of FLT3 without shifting of the reading frame.
- 14 b) The features of the nucleic acid molecule of claim 2 in the version last defended on appeal can be broken down as follows:
2. Nucleic acid molecule having a nucleic acid sequence, comprising:
 - 2 a a tandem duplication mutation in the amino acid sequence of juxtamembrane of FLT3, or

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- 2 b a tandem duplication mutation in the nucleotide sequence of exon 11 or exons 11 to 12 of FLT3 without shifting of the reading frame.
- 15 c) Claim 4, which is unamended vis à vis the granted version, relates to a polypeptide encoded by the nucleic acid molecule of claim 1 or claim 2.
- 16 d) Claim 5 in its unamended version relates to a cell which expresses the nucleic acid molecule according to claim 1 or 2 or the polypeptide of claim 4.
- 17 e) Claim 6 in its unamended version relates to an antibody specific for the polypeptide of claim 4.
- 18 f) The features of the method according to claim 7, which the defendant defends in the version as granted, can be broken down as follows:
 - 7.1 The method is used to detect
 - 7.1.1 the nucleic acid molecule of claim 1 or
 - 7.1.2 the nucleic acid molecule of claim 2
 - 7.2 The method comprises the steps of:
 - 7.2 a performing a gene amplification reaction with a nucleic acid sample from a human, wherein a nucleic acid fragment is amplified which
 - 7.2.a.1 can be found in the FLT3 gene

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7.2 a 2 includes exon 11 or exons 11 to 12 of the FMSlike tyrosine kinase-3 (FLT3) gene and

7.2.a.3 has a tandem duplication mutation of juxtamembrane.

7.2.b Detection of the presence of the tandem duplication mutation in the nucleic acid fragment of step (a).

19 4. The essence of the invention is formed by provision of the nucleic acid molecule according to claim 1, referred to as the molecule of a tandem duplication mutant, and which is characterized, on one hand, by the FMS-like tyrosine kinase 3 encoded by this molecule, and on the other hand, by a specific nucleotide. The latter is either (a) a tandem duplication mutation in the amino acid sequence of juxtamembrane of FLT3, or (b) a tandem duplication mutation in the nucleotide sequence of exon 11 or exons 11 to 12 of FLT3 which does not shift the reading frame. The presence of a tandem duplication mutation serves as a marker for leukemia. For the determination of the subject matter of the invention, the term “tandem duplication” or “tandem duplication mutation”, which is contained in the latest defended version of the patent, with the exception of claim 1, in claims 2 and 14, and, due to the reference to the claims also in the other patent claims. is therefore of central importance.

20 a) According to the definition in the specification of the patent, the tandem duplication relates to

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an FLT3 nucleotide sequence in which an entire portion or a portion of a nucleic acid that encodes the juxtamembrane of FLT3 gene, is repeated one or more times. in the same orientation. The repeated nucleotide sequences do not necessarily follow one another, but there may be other sequences (optional nucleotide sequences) in between. The patent states, in this context, that mutations may lie between the mating tandem duplications (corresponding tandem duplications) caused by deletion, substitution or addition of one or more bases (see. desc. para. 20). The doubling is therefore referred to as tandem duplication, because the insertion of the repeated sequence occurs either directly after its first occurrence, or in close proximity, and hence occurs as “tandem”.

- 21 The juxtamembrane is located between the transmembrane region and the kinase domain of the receptor protein kinase and forms an intracellular membrane region together with the kinase domain (desc. para. 18 [= 19 T2]). The gene encoding the juxtamembrane region is defined by 18 base pairs on the 3`-side of exon 10 and 117 base pairs on the 5`-side of exon 11, while comprehensive region encompassing 16 base pairs on the 3`-side of exon 11 and exon 12 encodes a section of the tyrosine kinase (desc. para. 28 [= 30 T2]).
- 22 b) The Patent Court has discussed the term “tandem duplication mutation” in connection with the question of a possible inadmissible extension and assumed that

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from the explanations in the patent, in particular paragraphs 18 and 30, it results that “the origin and/or the site of insertion “of the tandem duplication must lie in an area which would be determined by 18 base pairs on the 3`-side of exon 10 and 117 base pairs on the 5`-side of exon 11, because otherwise the participation of the nucleotide sequence encoding the juxtamembrane of FLT3 on the tandem duplication, which was intended by the teaching of the patent is not warranted. In view of this, tandem duplication mutations which satisfy this requirement would also be described in Examples 1 and 2. For example, it was found that five cases examined in example 1 of the patent that the length mutations detected in these samples go back to tandem duplications in nucleotide sequences of the juxtamembrane of FLT3 gene. Because this finding even applies for the case designated as M155, wherein the tandem duplication comprising 46 base pairs on the 3`-side of exon 11 and the first 16 base pairs of exon 12, a part of the 46 base pairs on the 3`- page of exon 11 would have to match with the gene encoding the juxtamembrane of FLT3 region in exon 11 (cf. desc. para. 67 [= 69 T2]). With respect to Example 2 it would also apply that the mutations are located in the juxtamembrane of FLT3 gene, while no mutations were found in the nucleotide sequence coding for the domain of the tyrosine kinase. (cf. desc. para. 70-72 [72-74 = T2]).

- 23 With respect alternative b of claim 1 (feature 1. 2. b) the patent court had to construe the wording of auxiliary requests II and III of the latest main

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request, “in the nucleotide sequence of exon 11 or exons 11 and 12 of FLT3”. The court assumed that such wording also encompassed those nucleic acid molecules in which neither the origin nor the place of insertion of tandem duplication is in the part of exon 11 which encodes juxtamembrane of FLT3. Since exon 11 has sections which, just like exon 12, do not encode for juxtamembrane, alternative b would encompass nucleic acid molecules in which the tandem duplication mutation would lie entirely in a region encoding for the adjacent tyrosine kinase.

- 24 c) The Patent Court has thus correctly determined that according to the patent’s own definition of the tandem duplication mutation, the origin of the tandem duplication has to occur, entirely or partially, in the gene encoding the juxtamembrane region, while the insertion site can be in this area, but does not have to. Although the language used by the Patent Court, namely that “the origin and/or the site of insertion” lies in the gene encoding the juxtamembrane region, encompasses also the variant that in an insertion of duplication in the gene encoding the juxtamembrane region the origin of doubling does not necessarily have to be in this range. The Patent Court has, however, apparently merely used the wrong wording in the phrase “and/or”. This is because in it’s further discussion with respect to the teaching of the invention, it has clearly explained that for this purpose, the origin of the tandem duplication in the region encoding juxtamembrane region is vital and indispensable. The petitioner’s opinion that not only

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the origin of the tandem duplication must stem from the nucleotide sequence encoding juxtamembrane, but that also the site of insertion must lie in the region encoding juxtamembrane, because only in such way the modification of juxtamembrane as demanded by the teaching of the patent could be accomplished, does however not find any support neither in the wording of claim 1 nor in the patent. As stated, the definition in the patent does only specify as essential that the repeated sequence stems completely or at least partially from the region encoding juxtamembrane. The definition does not prescribe that the duplicate sequence has to be inserted, in the region encoding juxtamembrane, between the 18 base pairs on the 3'-side of exon 10 and the 117 base pairs on the 5'-side of exon 11.

Instead, it becomes clear from the example cases of FLT3 nucleic acids disclosed in the patent – to which both the Patent Court and the defendant correctly refer - that there are cases in which the original sequence stems entirely from the juxtamembrane encoding region of exon 11, and that the insertion of the duplicated sequence takes place entirely in this region (M34 and M810). On the other hand, there is also the case that the original sequence lies only in a portion of the juxtamembrane region in exon 11 and in an adjoining part of exon 12. In this case, as the FLT3 nucleic acid M155 shows, the duplicated sequence which needs to follow the original sequence is necessarily inserted into exon 12. This is also confirmed by the description, according to which

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the region which has the tandem duplication in juxtamembrane of FLT3 surrounds a region which encompasses the whole or a section of the region of 18 base pairs on the 3`-side of exon 10 to 117 base pairs on the 5 `side of exon 11, but without being limited to said juxtamembrane coding region, as long as the region comprises an exon 11 site. (desc. para. 40 [= 42 T2]).

- 25 d) Contrary to the Patent Court's opinion the patents' own definition of tandem duplication mutation also determines the subject of the tandem duplication mutation recited in alternatives a and b of claim 1. The Patent Court's assumption that alternative b would include, both in the granted version with reference to a region comprising exon 11 or exons 11 to 12, as well in the version defended in the auxiliary request and in the main request on appeal, also such nucleic acid molecules in which neither the origin nor the location of insertion of the tandem duplication lies in part of exon 11 encoding the juxtamembrane of FLT3, is not necessarily provided by the language of the claim, and is certainly inconsistent with the Patent Court's own and correct definition of the tandem duplication mutation.
- 26 5. Claim 2 defines - unlike claim 1 - the nucleic acid molecule not as the one of a tandem duplication mutant which encodes FMS-like tyrosine kinase 3. Like in claim 1, however, the molecule needs to have a nucleotide sequence having a tandem duplication mutation in (alternative a) or from (alternative b) the

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sequence of the juxtamembrane of FLT3. Therefore, the difference between the objects of claim 1 on the one hand and claim 2 on the other hand lies only in the fact that the molecule according to claim 2 needs to have the specific tandem duplication mutation, but not necessarily all FLT3-coding sequences.

- 27 6. The method protected under claim 7 for detecting the nucleic acid molecule of such a tandem duplication mutation according to claim 1 comprises two steps.
- 28 a) Step a) consists of performing a gene amplification reaction using a human nucleic acid sample, wherein a nucleic acid fragment is amplified, which can be found in the FLT3 gene which encompasses exon 11 or exons 11 to 12 of the FLT3 gene and has a tandem duplication mutation of juxtamembrane. For the definition of the tandem duplication mutation the remarks on claim 1 apply accordingly.
- 29 b) step b consists of the detection of the presence of the tandem duplication mutation in the nucleic acid fragment of step a, wherein it is left to the expert how said detection is accomplished. As the Patent Court has correctly pointed out, said detection is recited, stepwise, in dependent claims 8 and 9.

According to claim 8 it consists of a sequence comparison with a “normal”, i.e., unmutated FMS-like sequence derived from tyrosin kinase 3. According to claim 9 the sequence comparison may take place in that a length mutation as used as an indication of the

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tandem duplication mutation (“index of the tandem duplication mutation”). In other words: A sequence analysis is not required; rather, the presence of the tandem duplication mutation is indicated by the extension of the fragment resulting from the insertion of the duplicated nucleotide sequence.

- 30 c) The appeal of the petitioner against the Patent Court’s conclusion drawn therefrom, namely that the detection of the length mutation would be a sufficient proof of the tandem duplication mutation in the meaning of feature b of patent claim 7 is without success
- 31 aa) The Patent Court has explained this elaborately as follows: The detection of a tandem duplication mutation in step b does not require, contrary to the petitioners opinion, a detection that goes beyond the length detection, e.g., in the form of DNA sequence analysis. For the interpretation of claim 7, claims 9 and 10, which refer thereto (claims 8 and 9i in the version of the main request as defended in the 2nd instance) would be of primary importance. These described process features, which would specify the detection in step b of the method according to claim 7 in more detail. So would claim 9 (in the now defended version claim 8) describe said detection as a sequence comparison, which, due to the reference to claim 7, would be accomplished on the basis of the sequence lengths mentioned therein, while the length of a mutated FLT3 sequence would be compared with a non-mutated sequence.

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Claim 10 (now claim 9) would further determine this comparison in that the comparison would not be done against the wild-type FLT3 sequence, but against a length mutation used as “index” (indicator). In the description of the patent one would find multiple hints that the detection of tandem duplications would be done by comparing the lengths of amplified DNA fragments, preferably by means of agarose gel electrophoresis (para. 24 and 42 [= 26 and 44 T2]). Contrary to the petitioner’s view, the sequence analyses mentioned in the patent would not provide any reason for understanding the patent-specific detection in step b of claim 7 as a combination of length comparison and sequence analysis. One could derive from the patent that sequencing would be only necessary for the initial finding of the patent-specific tandem duplication mutation in the juxtamembrane of the FLT3 gene, while the detection of the tandem duplication could be accomplished, on the basis of this teaching, solely by a length comparison, if - as in the case of claim 7 - the nucleotide sequence encoding for of the juxtamembrane of FLT3 gene were used. Finally, the petitioner cannot rely on the fact that according to the article of Schnittger et al. (K29) about a third of cases with proven length mutation would not concern tandem duplication mutations, but other mutations, which would demonstrated that a mere length comparison was not sufficient for sad detection. This knowledge was published in 2012 and was not known at the priority date.

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- 32 bb) This withstands the attack of the appeal by the petitioner. The Patent Court has correctly determined the patent's unambiguous disclosure under reference to the respective passages in the patent. The appeal fails to identify the basis according to which it would result that feature 7.2. b is to be understood as meaning that the detection of a tandem duplication mutation requires more than a mere length comparison, for example in the form of DNA sequencing.
- 33 II. From the statements with regard to the subject of the patent it is readily apparent that the Patent Court has wrongly assumed an inadmissible extension of claims 1 and 2, and those claims that refer to both or either of these claims. Because the disclosure of the original documents is almost identical to the description of the patent, as the Patent Court has rightly pointed out, claims 1 and 2 thus do not protect different nucleic acid molecules than the ones that were originally disclosed.
- 34 III. The decision of the Patent Court, to the extent that it has decided against the defendant, is not correct for other reasons either. Rather, the patent is also valid in the version of the main request in the 2nd instance, for the same reasons which the Patent Court found applicable for the version it found valid in the contested decision. This entails that the appeal of the petitioner is to fail.
- 35 1. The defense of the patent with the new main request is admissible in accordance with § 116 (2) PatG. It is

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relevant and can be based on facts which the Senate has to use as the basis in the hearing and the decision on the appeal pursuant to § 117 PatG.

- 36 a) Claims 1 to 6 of the new main request correspond essentially to the main request in the first instance. As far as the phrase “nucleotide sequence of a region comprising” has been replaced by “nucleotide sequence of” in claims 1 and 2, and the restriction that no frameshift occurs has been introduced, these changes correspond to the wording used in auxiliary requests II and III filed in the first instance, which wording has been discussed by the Patent Court and has found its way into the claims the Patent court deemed valid.
- 37 b) As regards the remaining claims that are defended, these correspond to the main request filed in the first instance, with the proviso that the missing frame shift has been included in claim 14 too, and the subject matter of claims 12 and 13 of the version as granted has been combined in a new claim 13. The former version is relevant for the reasons discussed at a. There are no objections against the reformulation of claim 13, because independent claim 12, which has been included into claim 13 in unamended form, has already been discussed by the Patent Court.
- 38 c) There are furthermore no objections either against the clarity of the claims submitted for decision.

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- 39 Insofar as the petitioner claims that the characterization of the primers in claims 10 and 13 lacks clarity, this objection is irrelevant, because that patent has been granted with these claims. An examination of already granted claims for clarity is neither provided by the European Patent Convention nor by the German Patent Act. The grant of the patent provided the patentee with a legal position which can be wholly or partially withdrawn only in the cases provided by law, hence in case of the existence of a ground for opposition or invalidity. Both the European Patent Convention and national law restrict the grounds for opposition or invalidity, and lack of clarity does not belong thereto (Art 100, 138 EPC. §§ 21, 22 PatG). It follows that an examination of the clarity is not permitted insofar as the alleged lack of clarity was already comprised in the granted claims (see EPA, decision of 24 March 2015 - G 3/14; BGH, judgement of 27 October 2015 - X ZR 11/13 Rn. 31 juris - Fugenband).
- 40 2. The subject matter of the patent in the version as defended in the main request is also patentable.
- 41 a) The Patent Court has stated with regard to the prior art cited in view of claim 7:
- 42 In the article “Expression of the FMS/KIT-like gene FLT3 in human acute leukemias of the myeloid and lymphoid lineages”, *Blood*, 1992, 2584 (K3), which the petitioner claims to be novelty relevant, the authors, Birg et al., report about the results of a study on

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the expression pattern of the FLT3 gene in acute leukemia of the myeloid and the lymphoid type. Since the FLT3 gene belongs to the family of genes which encode type III receptor tyrosine kinases, as FMS or KIT, which would be expressed in both normal hematopoietic progenitor cells as well as in myeloid leukemic cells, Birg et al. investigated in their study the FLT3 expression in human leukemic cells. They used the Southern or Northern blot analysis, a molecular biology method, in which the DNA or RNA molecules are separated from one another by their length and are then transferred to a membrane, where they are detected by specific probes. A gene amplification reaction as provided in the method according to claims 7 and 8, in which short, well-defined sections of a nucleic acid are multiplied using primers and a specific enzyme, would not have been used in this study and could not be read along in said disclosure. Further, K3 would not disclose a nucleic acid molecule, which, like step a of claim 7, encompasses exon 11 or exons 11 and 12 of the FLT3 gene, and comprises a tandem duplication mutation. K3 would indeed disclose, next to the non-mutated wild-type mRNA of FLT3, also extended mutants of FLT3. However, K3 would neither specify the nature nor the position of the mutation, which led to the extension of the mRNA. Instead, many variations would come into question for the development of the mRNA transcripts of FLT3 observed by Birg et al., namely in the form of sequence insertions (insertions) and/or sequence repeats (duplications) within the gene encoding for the FLT3 gene region.

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- 43 Rosnet et al., who are the authors of the article “Human FLT3/FLK2 genes: cDNA cloning and expression in hematopoietic cells”, *Blood*, 1993, 1110 (K4), have indeed performed gene amplification reactions for the detection of the expression of FLT3 in human cells and tissues, and have detected the products obtained thereby with gel electrophoresis. However, the authors would not have detected tandem duplication mutations such as in claims 7 and 8. The aim of their study would not have been to look for defects in the FLT3 gene, but to show the distribution of FLT3 in the hematopoietic cells and tissues of the human body. The primers specific for the 5'-end of the coding region of FLT3 and the probes distributed over the entire cDNA had been selected for this purpose, too. According to the disclosure of K4, even the use of the primers used in the gene amplification reactions would not provide any FLT3 mutants with the discussed tandem duplication mutations, because only the mRNA transcript typical of the wild-type mRNA of FLT3 having a length of 3,7 kb, or shorter subsequences, could be amplified therewith.
- 44 The authors Birg et al. of the study submitted as K5 (“The Expression of FMS, KIT and FLT3 in hematopoietic malignancies”, *Leukemia and Lymphoma* 1994, 223) would have indeed looked for genetic mutations in the sections encoding for the type III receptor tyrosine kinases such as FLT3, FMS, but merely found that the human FMS gene would be activated by point mutations in cases of myeloid leukemia. Hence, this study would not disclose the

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detection of nucleic acid molecules with the tandem duplication mutations in the juxtamembrane of FLT3 referred to in patent claims 7 and 8.

- 45 The skilled person would thus receive from K3 the hint that, in samples from patients with acute myeloid leukemia (AML), further mRNA transcripts of FLT3 would exist next to the wildtype mRNA of FLT3, which, with 13 kb, or 3,9 - 4 kb would be greater than the 3,7 kb long wild-type mRNA. K3, beyond mere speculations, would not provide and statements about how the extension could be put into practice in detail, and in which encoding section said extension would occur, because the authors did not yet have the genomic DNA and cDNA of FLT3 required therefore. The aim of the study discussed in K3 was to develop a relatively specific and robust marker for acute leukemia, through the detection of the expression of the FLT3 gene at the mRNA level in leukemic cells. Although the authors of K3 have thus drawn the attention of the expert circles to the relationship between the expression of FLT3 and the occurrence of certain leukemic phenotypes, the skilled person would receive from K3 neither any hint that prolonged mRNA transcripts of FLT3 are associated with certain leukemic phenotypes, nor that tandem duplications in the juxtamembrane of FLT3 under participation of exon 11 and exon 11 to 12 would be responsible for the occurrence of leukemic phenotypes. Reference K4 would teach the expert neither the further information which would be necessary to arrive at the solution according to the invention.

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Although the authors of K4 came to the conclusion that changes in the FLT3 gene should be examined in connection with the development of leukemia, they did not refer to genetic modifications of the FLT3 gene. Reference K5 would provide to the expert at most a suggestion to search for genetic alterations in the FLT3 gene. How these mutations would look like, whether they would play a role in the development of blood diseases and whether they were suitable as a specific pattern for leukemic phenotypes in detection methods would not be disclosed in that reference. Even with a combined consideration of references K3, K4 and K5, the skilled person would have had to add inventive input, because the mere presumption to find FLT3 mutations would not have resulted in the expectation of success to find a type of mutation uniformly occurring in the human body which could serve as a reliable prognostic marker for certain leukemic human diseases. The other references submitted by the petitioner did not lead to a different conclusion. The referenced prior art does hence not provide any clue that the detection of tandem duplication mutations in the juxtamembrane of FLT3 under participation of exon 11 or exons 11 and 12 could be of interest for the assessment of leukemic diseases.

- 46 b) From these considerations, which withstand the review on appeal and have not been attacked substantially by the petitioner, it follows that the subject matter of claims 1 and 2 is not anticipated or has been rendered obvious either.

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- 47 The petitioner argues in that regard that the subject matter of the invention is not new, because K3 would disclose all steps for the detection of nucleic acid molecules with the patent specific tandem duplication by length comparison. If, as the defendant contends, the detection of a length mutation for the detection of a nucleic acid molecule according to claims 1 and 2 were sufficient, K3 would also anticipate the subject matter of this claim. The petitioner yet disregards the fact that claims 1 and 2 require that the tandem duplication has its origin in the section encoding the juxtamembrane region, while in K3 no hints can be found as to what causes the length mutations detected with the method disclosed therein. The petitioner hence fails to show that the nucleic acid molecule of one of the two claims has been described in the prior art or was otherwise available to the skilled person.
- 48 The same applies for the attack on inventive step. As far as the latter is further based on the fact that the alleged problem was not solved, such attack is just as implausible, as is the objection that the Patent Court's position to deny a reasonable expectation of success for investigations that could discover the nucleic acid molecule of the invention, while at the same time to require further experiments with the object of finding activating mutations in the FLT3 gene of leukemic cells, would be based on a mistake. Contrary to the opinion of the petitioner's appeal this position does not comprise a contradiction, because the interest in finding (possible) activating mutations does not say anything about the point whether the skilled person

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was incentivized to such studies, with which it could have arrived at the findings that form the basis of the patent, and whether he would have had a reason to carry such studies with an expectation of success corresponding to the respective effort, that was not described by the petitioner. The Patent Court has not found any respective evidence, nor has the petitioner provided such evidence in the written submissions of the 1st instance to which the appeal refers.

- 49 c) The objection according to which the subject matter of claims 1 and 2 would represent a non-patentable discovery is likewise unfounded.
- 50 aa) Under Art. 52 (2) (A), (3) EPC, a discovery as such is not patent eligible, just like a scientific theory or a mathematical method isn't either. Contrary to the decision of the US Supreme Court (566 US (2012). *Mayo v Prometheus*), however, a technical teaching which teaches the use of a discovery to achieve a certain object, is patent eligible under European - and German - law, regardless of whether the teaching comprises an "inventive surplus" that goes beyond the purposeful use of the discovered law of nature. This is because all technical activities rely on a purposeful use of laws of nature. It is therefore inappropriate, when considering whether the technical teaching relies on an inventive step, to ignore the question whether the finding of the physical, chemical or biological relationship which forms the basis of the teaching of the invention was obvious for the skilled person.

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- 51 bb) The fact that the technical teaching is restricted to the instruction to provide the nucleic acid molecule recited in claims 1 and 2 does therefore not preclude patent eligibility of these claims.

Further, Rule 29 AOEPÜ, which, in accordance with § 1a (1) PatG, determines that the human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions, does not lead to a different finding. The latter only reaffirms the principle resulting already from the general concept of inventions, namely that it is not the discovery of a sequence, but rather the disclosure that, and how, such sequence can be made technically usable by isolation (Rule 29 (2) AOEPÜ, § 1a (2) PatG), which constitutes a teaching that is accessible to patent protection. Contrary to the petitioner's request, the sequence does not have to be "clearly designated" as isolated or produced by a technical process either, because it is an immanent feature to a product claim which identifies the protected technical teaching by designating the subject matter, to provide exactly that matter (by a technical process).

- 52 cc) Nor is the objection relevant – which has not been explained in detail anyway – that the invention was filed in an "unfinished" state, and that for verification of the technical teaching provided a considerable effort would have been necessary. The inventor does not have to have realized why the technical teaching of

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the invention works, nor does he have to provided by a scientific explanation therefore. It is sufficient that he furnishes the expert with the information necessary to carry out the technical teaching of the invention. The Patent Court has correctly explained that this requirement was fulfilled in the case in dispute.

- 53 d) Due to the reference, the subject matter of claims 4, 5 and 6 is for the same reasons patentable as the subject matter of claims 1 and 2, and nothing else applies to the method according to claim 7 and claims 8 to 11, which refer thereto, and the kit according to claim 13 for a method according to any one of claims 7 to 11. Finally, nothing else applies to the subject matter of claims 14 (in the version of the main request), 16 and 17 (15 and 16 in the numbering of the main request) and 19 and 20 (17 and 18 in the numbering of the main request), each of which are supported by the patentability of the nucleic acid molecule or the polypeptide encoded thereby, which are used or expressed in these claims.
- 54 3. The further grounds for invalidity raised by the petitioner do not apply either.
- 55 a) The Patent Court has rightly denied an inadmissible extension for the claims it deemed valid.
- 56 aa) It held as follows:
- 57 Claims 7 and 8 would not be rendered inadmissibly extended by the fact that the term “nucleotide

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sequence of a region comprising exon 11 or exons 11 to 12 of FLT3” disclosed in the patent and the originally filed documents was replaced by the words “nucleotide of exon 11 or exons 11 to 12 of FLT3 “ This would restrict the nucleotide sequence necessary for the detection method according to the invention to the exact sequence of exon 11 or exons 11 to 12, because the inclusion of other nucleotide sequences on the 3`- and 5`-side of exon 11 and 12 would be excluded. Such a restriction would be disclosed by both the patent and the originally filed documents, which both assumed that the tandem duplication mutation lies in the nucleotide sequence of exon 11 or exons 11 to 12.

- 58 Nor would claims 7 and 8 be inadmissibly extended because, unlike claim 15 of the originally filed documents, they would no longer comprise the feature of producing a human nucleic acid sample. According to the method of the patent, the sample production would be done with a routine method known to the skilled person. Given that according to the teaching disclosed in the patent and the originally filed documents, the tandem duplication mutation would lie within the nucleotide sequence of exon 11 or exons 11 and 12, and, that the juxtamembrane of FLT3 would encompass a region of 18 base pairs on the 3`-side of exon 10 and 117 base pairs on the 5`- side of exon 11, even the recitation of the primers in claims 11 and 14 of auxiliary request III would not represent an inadmissible extension.

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- 59 Contrary to the petitioner's opinion, claim 8 would not either extend beyond the original application only because it was not limited to encoding nucleic acid molecules. According to the originally filed documents, not only the nucleic acid molecules encoding for the amino acid sequence of juxtamembrane of FLT3 would be of importance, but also the significantly shorter nucleic acid molecules of SEQ ID NOs 6 – 15, which would not have juxtamembrane encoding properties. Moreover, claim 15 of the original application would provide that in method step b not only nucleic acid sequences having a tandem duplication mutation for a receptor protein kinase would be amplified, but also partial sequences thereof, which only would have to come only from the encoding nucleic acid sequence.
- 60 Claim 12 would not comprise an inadmissible extension either. It could have been derived from the entirety of the original application that hematopoietic stem cells expressing the patent specific tandem duplication mutation, would be compared with cells expressing the normal FLT3 gene, which would only be possible if mutant cells would be compared with unmutated cells of a healthy - normal - test person. Likewise would the intended uses recited in claim 16 (15 in the numbering of the main request) – screening for a drug and for examination and treatment of a blood cell disorder – result from the originally filed documents (para 63 of the publication of the application = para 62 of the patent [= para 64 T2]).

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- 61 bb) This assessment stands against attacks by the petitioner's appeal, which are essentially based on the incorrect assumption according to the interpretation of claim 1, namely that the applicable claims would not require a tandem duplication mutation stemming from the amino acid sequence of juxtamembrane. As far as the petitioner means that the originally filed documents would not disclose a mere "length mutation", this is also based on an incorrect understanding of the protected teaching and can hence not justify the assumption of an inadmissible extension.
- 62 The objection repeatedly put forward by the petitioner that the length mutation would not represent a reliable indicator towards a tandem duplication mutation in the amino acid sequence of juxtamembrane of FLT3 is also irrelevant. Apart from the fact that this allegation is not sufficiently substantiated, it is not an argument against the original disclosure of the patented teaching, but an irrelevant objection against the reliability of the method specified in claim 9, in which the length mutation is treated as a (principally sufficient) indicator to the presence of the tandem duplication mutation in the nucleic acid fragment of step a of the method according to claim 7.
- 63 For the same reasons referred to by the Patent Court for claim 8, the fact that claim 2 does not require an FLT3 encoding molecule does not result in an inadmissible extension either. Based on the interpretation of claim 2 described above, the explanations of the Patent Court prove accurate. The same applies to claim 15.

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- 64 b) The Patent Court has also correctly considered the teaching of the invention as sufficiently enabled.
- 65 aa) It held as follows:
- 66 Contrary to the petitioner's opinion, the subject matter of claims 7 and 8 were disclosed clearly and completely, so that the skilled person could carry it out. The patent would not only disclose information about how the human nucleic acid sample used in the detection method according to claims 7 and 8 human nucleic acid sample could be isolated, but also how the nucleic acid fragment comprising a tandem duplication mutation in the juxtamembrane of FLT3 gene were to be amplified. Furthermore, the patent would describe, with agarose gel electrophoresis or hybridization, detection methods already known to the skilled person, for which he would per se not need any further information, which however would be described in more detail in example 1
- 67 The claimed method, therefore, is not to be considered insufficiently disclosed, only because - as the petitioner alleged - the process contains no step with which mutated samples could be detected before the actual detection. According to the wording of claim 7, it is not mandatory that a tandem duplication mutation would have to be found in the juxtamembrane of the FLT3 gene. Therefore, the method according to claims 7 and 8 would also encompass a negative detection.

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68 bb) On that background, the appeal is limited to the already discussed argument, according to which the finding of a length mutation would be insufficient for a (reliable) detection of a tandem duplication mutation in the juxtamembrane of FLT3 gene, for which reason the invention would not be sufficiently disclosed over the whole width of the claimed protection. The petitioner cannot invalidate the correct explanations of the Patent Court on this basis.

69 IV. The apportionment of costs is based on § 121 (2) PatG and § 97 (1), § 92 (1) ZPO.

Meier-Beck	Gröning	Bacher
Schuster	Kober-Dehm	

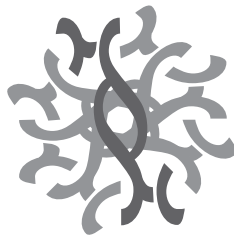
1st Instance:

Federal Patent Court, decision of July 9, 2013 – 3 Ni 37/11 (EP)

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Appendix

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P A T E N T A N W Ä L T E

Nutter McClennen & Fish LLP T
Konstantin M. Linnik, Ph.D. T
Seaport West T
155 Seaport Boulevard T
Boston, MA 02210 T
USA T

T
T
T

Your Ref. T
T
T

Our Ref. T
0003 / ST T

Düsseldorf, T
18 April 2016 T

**Michalski · Hüttermann & Partner
Patentanwälte mbB**

Düsseldorf · München

Hafenspitze
Speditionstraße 21
40221 Düsseldorf
Germany

Phone +49 211 159 249 0
Fax +49 211 159 249 20

E-Mail mail@mhpattent.de
Web www.mhpattent.de

ERTIFICATE OF TRANSLATION C

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**Decision X ZR 141/13 of the German Federal Supreme Court, pub-C
lished January 19, 2016 C**

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I, Dr. Ulrich Storz, am competent to translate from German into English, T
and certify that the attached translation of Decision X ZR 141/13 of the T
German Federal Supreme Court, published January 19, 2016 is true and T
accurate to the best of my abilities. I declare under penalty of perjury T
under the laws of the United States of America that the foregoing is true T
and correct. T

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[Dr. Ulrich Storz] T T T T Date: T18 April 2016 T

Encl.: Translation T

T
T
T**Patentanwälte**

Dr. Stefan Michalski
Dr. Aloys Hüttermann
Dr. Sonja Althausen
Dr. Ulrich Storz
Dr. Nicole Griebel
Dr. Nicole Giesen
Dipl.-Ing. Andreas Gröschel
Dr. Patrick Liptau
Dr. Dirk Schulz
Dr. Cersten Bethke
Dr. Lars Müller
Dr. Uwe Albersmeyer
Dr. Andreas Hübel
Dipl.-Ing. Guido Quiram
Dipl.-Ing. Harald Bienert
Dr. Torsten Exner
M.Sc. Beiyi Xu
Dipl.-Ing. John-Hans Tsay
Dr. Ralf Malessa

Consultants

Dr. Hans Christoph Wilk
Prof. Dr. Andreas Möbius
Dr. Dariush Hourfar

National-Bank AG
IBAN DE50 3602 0030 0006 0347 72
SWIFT-BIC NBAGDE3E

Stadtsparkasse Düsseldorf
IBAN DE93 3005 0110 1005 8654 54
SWIFT-BIC DUSSDE33XXX

Sitz Düsseldorf, AG Essen, PR 1874
VATIN DE 250 369 233

ST:aj C