Comments of Coalition for 21st Century Medicine

on USPTO's December 2014 Interim Eligibility Guidance

March 16, 2015

1. Introduction

The Coalition for 21st Medicine ("**C21**") is pleased at the opportunity to provide the following comments ("**March 2015 Comments**") to the United States Patent and Trademark Office (the "**Office**") on the 2014 Interim Guidance on Patent Subject Matter Eligibility issued December 16, 2014 ("**December 2014 Guidance**"). These March 2015 Comments will address specific points in the Guidance as well as the analytical examples provided so far and examples expected to be released soon. These March 2015 Comments will also reiterate and build upon the comments submitted by C21 ("**August 2014 Comments**") following the last iteration of the March 2014 Guidance.

C21 represents some of the world's most innovative diagnostic technology companies, clinical laboratories, researchers, physicians, venture capitalists and patient advocacy groups – all linked by a common mission: to develop and commercialize state-of-the-art diagnostics that improve patient health. Diagnostics are increasing in importance as the health care system looks to deliver more and more personalized medicine. The recent Precision Medicine Initiative announced by the Administration further underscores the importance and value of diagnostics. The White House Precision Medicine Initiative is intended to accelerate advances in disease treatment and cures by proposing $200 million in new funding for the NIH, including $70 million to the NCI. The initiative specifically proposes DNA sequencing of up to a million Americans with the intention of yielding information that could rapidly advance groundbreaking discoveries and ultimately, clinical outcomes for patients. This basic research is extremely important, however, C21 member companies are also contributing large amounts of time, scientific knowledge and financial resources in an effort to bring novel diagnostics to the market. Patents play a key role in the ability of innovative companies to successfully discover and commercialize new precision medicine diagnostics.

C21 applauds the Office for its openness in taking feedback received following the March 2014 Guidance and incorporating that feedback into the clearly improved December 2014 Guidance. These March 2015 Comments will roughly follow the ordering of the December 2014 Guidance, noting specific places where improvements were made and other areas where C21 believes there is still room for improvement. These March 2015 Comments will therefore point to specific aspects of the December 2014 Guidance that can be made better and to specific suggested ways of doing so.

A central theme shared by these March 2015 Comments and by C21's earlier August 2014 Comments is that of balance. Eligibility for patenting is dictated by (1) the statute itself and (2) court decisions. Understanding and applying the proper balance between these two is critical to good guidance for examiners and ultimately to increasing patent quality. The statute itself sets forth a very broad, inclusive paradigm of eligibility.[1] This broad eligibility is the default, from which court decisions have created limited exceptions that are to be interpreted faithfully yet narrowly based on a close reading of the decisions themselves. In this vein, C21 applauds the extended case law section of the December 2014 Guidance and provides its own insight on select cases.

Another core theme of these March 2015 Comments is that an invention should be eligible so long as it recites any elements beyond a judicial exception and the claim as a whole amounts to "significantly more" than a judicial exception. Unfortunately, as articulated below, portions of the December 2014 Guidance instruct just the opposite: so long as a judicial exception is found anywhere in the claimed invention, examiners are to find the claimed invention to be patent ineligible

2. Comments on Analytical Framework

(a) General comments on flowchart/overall framework

§ 101 subject matter eligibility is an area of patent law that has suffered for years under the ambiguity, arbitrariness and inconsistency predicted by Judge Frankfurter in 1948:

> *It only confuses the issue, however, to introduce such terms as "the work of nature" and the "laws of nature." For these are vague and malleable terms infected with too much ambiguity and equivocation. Everything that happens may be deemed "the work of nature," and any patentable composite exemplifies in its properties "the laws of nature." Arguments drawn from such terms for ascertaining patentability could fairly be employed to challenge almost every patent.*[2]

C21 is encouraged by the Office's efforts to bring objectivity, predictability and analytical rigor to examination of patents under § 101. For example, the flowchart and overall structure of the analytical framework embodied in the December 2014 Guidance recognizes (a) the proper order of § 101 eligibility analysis and (b) that something can be facially directed to a judicial exception ("yes" to Step 2A) but still be eligible for patenting ("yes" to Step 2B).

(b) Comments on Step 1

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[1] See, e.g., Diamond v. Chakrabarty, 447 U.S. 303, 308-309 (1980) ("*In choosing such expansive terms as 'manufacture' and 'composition of matter,' modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope. The relevant legislative history also supports a broad construction. The Patent Act of 1793, authored by Thomas Jefferson, defined statutory subject matter as 'any new and useful art, machine, manufacture, or composition of matter, or any new or useful improvement [thereof].' The Act embodied Jefferson's philosophy that "ingenuity should receive a liberal encouragement." […] The Committee Reports accompanying the 1952 Act inform us that Congress intended statutory subject matter to 'include anything under the sun that is made by man.'*") (internal citations omitted)).

[2] Funk Bros. Seed Co. v. Kalo Seed Inoculant Co., 333 U.S. 127, 134-135 (1948).

The December 2014 Guidance sets forth in its flowchart a "Step 1," which asks "*Is the claim to a process, machine, manufacture or composition of matter?*" The flowchart indicates that if the answer is "no," then the claim is ineligible under § 101. This Step 1, however, is not clarified in the rest of the December 2014 Guidance. More importantly, there are no examples of where the answer to Step 1 is "no." Indeed we struggle to conceive of any situation where the answer to Step 1 could be "no."[3] Given this, and in view of the overall themes of balance and construing eligibility as broadly as governing case law allows, C21 submits that it may be better to remove this from the analysis and instruct examiners to proceed directly to what are now designated Steps 2A and 2B. Alternatively, examples of detailed analysis under Step 1 and claims that fail such analysis would be very helpful.

(c) Comments on Step 2A

(i) "Determine What the Claim Is 'Directed to'"

(A) "Directed to" v. "Involving"; "Encompassing" v. "Comprising"

As a first matter, C21 notes what appears to be a positive step in tone represented by the use of "directed to" in the December 2014 Guidance in favor of "involving" in the March 2014 Guidance. For example, the December 2014 Guidance correctly notes that "[c]ourts tread carefully in scrutinizing such claims because at some level all inventions embody, use, reflect, rest upon, or apply a law of nature, natural phenomenon, or abstract idea."[4] This is an important showing of good faith by the Office, demonstrating that feedback following the March 2014 Guidance was considered.

Moving beyond tone and process improvements to actual impact on prosecution, however, a close reading of the December 2014 Guidance raises questions as to whether there will be any real difference between "directed to" and "involving" in practice. As discussed in later parts of these March 2015 Comments,[5] the December 2014 Guidance suggests that where a non-natural product is combined with a natural product, the combination may nevertheless be "directed to" a natural product and thus be ineligible for patenting. An example of this is the following statement from the December 2014 Guidance: "A claim that recites a nature-based product limitation that does not exhibit markedly different characteristics from its naturally

[3] See, e.g., Classen Immunotherapies, Inc. v. Biogen Idec, 659 F.3d 1057, 1074 (Fed. Cir. 2011) ("*[I]t is difficult to 'invent' any category of subject matter that does not fit within the four classes acknowledged by Title 35: process, machine, [article of] manufacture, or composition of matter.*"). The closest example we can think of is the electromagnetic signal at issue in In re Nuijten. 500 F.3d 1346 (Fed. Cir. 2007); cf. In re Petrus A.C.M. Nuijten, 515 F.3d 1361 (Fed. Cir. 2008) (Linn, J., dissenting from denial of motion for en banc rehearing) ("*[O]ur decision […] conflicts with our own precedent because our predecessor court's decision in In re Breslow forecloses the majority's conclusion that something "transient" or "fleeting" cannot constitute a "manufacture" under 35 U.S.C. § 101. And it conflicts with Supreme Court precedent because it ignores the Supreme Court's analysis of how, in general terms, § 101 is to be construed. As the Court discussed in Diamond v. Chakrabarty, patentable subject matter includes "anything under the sun that is made by man" except for certain enumerated exceptions[…]. The majority's narrow construction of "manufacture" ignores this framework.*") (Internal citations omitted.).

[4] December 2014 Guidance, 79 Fed. Reg. 74618, 74622, left column (Dec. 16, 2014).

[5] See, e.g., Section 2(c)(iii)(A), infra; Section 2(c)(iii)(B)(5), infra; Section 2(d)(iii), infra.

occurring counterpart in its natural state is directed to a 'product of nature' exception."[6] This sounds a lot like the claim is ineligible because it merely "involves" a natural product as one claim limitation despite the claim as a whole likely being "directed to" a non-natural product (i.e., the combination).

In this vein, C21 reiterates a point from our August 2014 Comments,[7] calling for explicit recognition of and guidance to examiners on the critical difference between (a) a claim encompassing a judicial exception as a distinct embodiment of the claim as a whole and (b) the claim as a whole "comprising" a judicial exception, e.g., as one component of a combination or process. As noted in the December 2014 Guidance, all inventions will comprise a judicial exception as at least one element of the overall invention. A combination comprising two or more natural components is prima facie eligible when the combination as claimed does not occur in nature. Eligibility is even clearer when the act of combining confers on the combined unit a new property, utility or activity over that of each natural component in isolation, though such a new feature is by no means required if the structure is sufficiently different from what exists in nature.

On the other hand, a claim is ineligible whenever its scope encompasses a natural product, law of nature or abstract idea per se as one of the distinct embodiments of the claim properly read as a whole. There are at least two important points to understand here. First, this is true regardless of how many eligible embodiments the claim may encompass. Second, when a claim has been invalidated by a court, this only means that at least one embodiment of the claim encompassed a natural product, law of nature or abstract idea per se. When applying § 101 case law, the Office should be careful not to over-interpret cases to hold that all embodiments of a claim were found ineligible.[8]

(B) Careful, Unencumbered Construction of the Claim as a Whole Is the First Step

The Office has improved on the March 2014 Guidance by emphasizing in the December 2014 Guidance a closer analysis and clear articulation by the examiner of what is actually being claimed. C21 urges the Office to go even further, however, because this critical portion of the December 2014 Guidance is (a) still light on details and, thus, relative emphasis and (b) framed too much in terms of actively searching for a possible exception. Put differently, the a priori purpose of a careful reading of the claim language is incorrectly framed by the December 2014 Guidance as finding a judicial exception in the claims. Experience shows that when examiners are instructed to look for a judicial exception they tend to find one.

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[6] December 2014 Guidance, 79 Fed. Reg. at 74623.

[7] See, e.g., August 2014 Comments, p.3 (Section entitled "*'Encompassing' versus 'comprising'*"); id. at p.7 (Section entitled "*'Comprising' language in a substructure claim*").

[8] For example, claim 1 of the '282 patent in Ass'n for Molecular Pathology v. Myriad Genetics Inc., 133 S. Ct. 2107 (2013), encompassed numerous eligible, non-natural embodiments but the claim as a whole was ineligible because it encompassed at least one distinct embodiment (i.e., the full-length gene) that was deemed by the Court to be a natural product.

Instead, the Office should emphasize that the first step is an unencumbered analysis of what is claimed without regard to whether that might be a judicial exception. The examiner must first and foremost determine the meets and bounds of the claim as whole by

(1) analyzing each component to understand exactly what it is (e.g., its structural features and the chemical and/or physical properties inherent in such structure);

(2) analyzing the interplay of all components of the claimed composition or method, including how interaction between components may affect each component's higher level function/utility; and

(3) analyzing the function/utility of the overall composition/method based on the preceding, noting that utility may not and need not be recited explicitly in the claim language (e.g., may be taught in the specification).

Once this has been properly done, examination can proceed to deciding whether it appears that a judicial exception is claimed per se. If it appears so, then further scrutiny as set forth in the December 2014 Guidance (as modified in these March 2015 Comments) is appropriate.

(ii) "Identify the Judicial Exception Recited in the Claim"

The previous section mostly captures C21's comments in this regard, but a few additional points are warranted. For example, the December 2014 Guidance improves on the March 2014 Guidance by urging examiners to clearly define the judicial exception against which the claimed subject matter is to be compared. However, the Office should emphasize this point even more and give more specific guidance to examiners.

While case-based examples found in this section of the December 2014 Guidance are helpful, more helpful would be detail on what specific characteristics of the judicial exception should be clearly articulated in the office action. Important characteristics include, but are not limited to: chemical or other structure, inherent chemical or physical properties, apparent biological activity within a natural product's natural environment, a concise statement of the cause-and-effect involved in a supposed law of nature, etc. While it is true that there can be no bright line rules or inclusion/exclusion criteria, we urge the Office to provide examiners specific guidance on useful red flags or other triggers that invite eligibility analysis (e.g., those identified in our August 2014 Comments,[9] such as "wherein" clauses).

(iii) "Nature-based Products"

(A) "Determine Whether the Markedly Different Characteristics Analysis Is Needed To Evaluate a Nature-Based Product Limitation Recited in a Claim"

The first two paragraphs of this section of the December 2014 Guidance are well-intentioned, but may not be very helpful for the intended purpose (i.e., to help examiners quickly move on from § 101 analysis for inventions that clearly do not require close scrutiny). In fact, the only true guidance on expediting examination boils down to the following: "For claims that recite a nature-based product limitation […] but are directed to inventions that clearly do

[9] August 2014 Comments, pp.9-10.

not seek to tie up any judicial exception, see Section I.B.3. regarding a streamlined eligibility analysis."[10] In a vague and unhelpful way, this equates threshold § 101 analysis to preemption, which as explained in our August 2014 Comments is improper.[11]

The third paragraph of this section of the December 2014 Guidance correctly makes clear that combinations of natural products can be eligible for patenting. The Guidance properly emphasizes that the relevant thing to be analyzed is the combination as a whole (including each interaction between components and the sum thereof) rather than the components. The Guidance would benefit from an explicit recognition that non-natural combinations of natural products will in most instances be eligible. This will prevent much of the element-by-element analysis suggested by other parts of the Guidance.[12]

The fourth paragraph of this section of the December 2014 Guidance, though in broad brushes potentially consistent with the general theme of In re Roslin,[13] should urge examiners to be careful in differentiating between a product claim and a process claim. The Office should also interpret Roslin narrowly to the extent Roslin is seen ruling a clearly unnatural product to be ineligible as directed to a product of nature.

(B) "Markedly Different Characteristics Analysis: Structure, Function and/or Other Properties"

(1) Structure, Function and Other Properties

This section of the December 2014 Guidance is greatly improved over the March 2014 Guidance, primarily for the reason noted in the December 2014 Guidance itself at footnote 27—i.e., addition of functional and "other" characteristics as relevant in deciding whether the claimed subject matter has "markedly different" characteristics from a judicial exception. Particularly encouraging is the recognition in the December 2014 Guidance that "even a small change can result in markedly different characteristics from the product's naturally occurring counterpart."[14]

(2) Context Is Critical

Also improved is the instruction to examiners in this first paragraph of this Section of the December 2014 Guidance to compare the claimed invention to its naturally occurring counterpart in its natural state.[15] Context is critical in understanding the properties, utilities and activities of a particular composition and each of its components within that composition.

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[10] December 2014 Guidance, 79 Fed. Reg. at 74623, left column.

[11] August 2014 Comments, p.13 (Section entitled "*BRIEF NOTE ON PREEMPTION*"); see also, Section 2(d)(iv), infra; see also, Section 3(b)(ii), infra.

[12] See, e.g., Section 2(c)(i)(A), supra; Section 2(c)(iii)(B)(5), infra; Section 2(d)(iii), infra.

[13] In re Roslin Inst., 750 F.3d 1333 (Fed. Cir. 2014).

[14] December 2014 Guidance, 79 Fed. Reg. at 74623, right column.

[15] August 2014 Comments, p.4 ("*Just as the claimed composition must be analyzed as a whole, the supposed natural counterpart must be analyzed as a whole and in its natural context. Structural and functional context are equally important in the analysis.*") (Emphasis added.).

And putting a natural product in a specific, non-natural context that results in a composition with markedly different characteristics from the natural product as found in nature is a patent eligible invention. Thus, the December 2014 Guidance implicitly recognizes an important limitation on the AMP decision when it states that "a product that is purified or isolated, for example, will be eligible when there is a resultant change in characteristics sufficient to show a marked difference from the product's naturally occurring counterpart."[16]

(3) "Closest Naturally Occurring Counterpart"

C21 is intrigued by the related instruction to, if there is no naturally occurring counterpart, compare the claimed invention to "the closest naturally occurring counterpart."[17] This analysis makes sense, and is consistent with our previously suggested analysis.[18] C21 urges the Office to expand this discussion, however, to give examiners more direction on how to perform this analysis. Some examiners may wonder how far they should go in searching for "the closest naturally occurring counterpart." The Office should also make the following observation, which may seem obvious or implicit but is important to make explicit: The farther one goes away from the claimed invention to find a natural counterpart for comparison, the more likely it is that the claimed invention is eligible. If an examiner finds herself struggling to find a natural counterpart against which to compare the claimed invention, this in and of itself is strong evidence the claimed invention is not directed to any natural product.

In this connection, C21 reiterates and recommends to the Office the suggested analytical framework for defining a "discrete biological unit" in our previous comments.[19] We feel this framework lends specificity and objectivity to the process of clearly defining which natural product will be used for eligibility analysis.

(4) Properties versus Functions

This section of the December 2014 Guidance now implicitly recognizes a difference between inherent properties (e.g., "Chemical and physical properties") and higher level functions/utilities/activities (e.g., "Biological or pharmacological functions or activities").[20] However, C21 submits that the discussion on this point in the December 2014 Guidance is vague and ambiguous in that it lists all of these characteristics together as things courts have looked at in determining eligibility. Instead, this discussion should be clarified and expanded to help examiners understand the importance of differentiating between the two and only treating inherent properties as incapable of lending eligibility. That is, the inherent properties of a natural chemical compound (e.g., electronegativity) cannot form the sole basis of eligibility,

[16] December 2014 Guidance, 79 Fed. Reg. at 74623, right column.

[17] December 2014 Guidance, 79 Fed. Reg. at 74623, middle column.

[18] See, e.g., August 2014 Comments, p.29 ("*There is no clear natural product against which to compare the claimed DNA molecule. The closest candidate is the smallest exon of the ALZ1 gene.*"); id. at pp.9-10 ("*Although this will not be possible in all cases, one helpful way to assess whether a natural principle is being claimed is to find the closest prior art process and compare it side-by side to the claimed process.*").

[19] See, e.g., August 2014 Comments, p.4-5 (setting forth a basic "discrete natural unit" framework).

[20] December 2014 Guidance, 79 Fed. Reg. at 74623, right column.

but any new or improved utility, activity, or higher level function (e.g., enabling a non-natural chemical reaction or interaction, killing cancer cells) is sufficient to support eligibility.[21]

In this same vein, the Office should make clear that new/improved characteristics, like utility or activity, need not be explicitly recited in the claim language. In contrast, they need only be taught in the specification or in a declaration.

(5) Combination of an Eligible Thing with an Ineligible Thing is, as a Whole, Eligible

This section of the December 2014 Guidance further adds to the ambiguity throughout the document on how to treat combinations. This is perhaps best seen in the following excerpt:

> If the claim includes a nature-based product that has markedly different characteristics, the claim does not recite a 'product of nature' exception and is eligible (Step 2A: NO) unless the claim recites another exception. […] For claims that are to a single nature-based product, once a markedly different characteristic in that product is shown, no further analysis would be necessary for eligibility because no ''product of nature'' exception is recited (i.e., Step 2B is not necessary because the answer to Step 2A is NO). […] Thus, a claim can be found eligible based solely on a showing that the nature-based product in the claim has markedly different characteristics and thus is not a ''product of nature'' exception, when no other exception is recited in the claim.[22]

This suggests that a clearly eligible thing can somehow become ineligible by the addition of a judicial exception. C21 requests clarification because, if this is what the Office has asserted here, this is wrong under the law and internally inconsistent with the December 2014 Guidance's instruction to consider the claim as a whole.[23] In fact, it appears to potentially be based on the above-mentioned misunderstanding of the difference between a claim encompassing a judicial exception as a distinct embodiment (ineligible) and a claim comprising a judicial exception as one of its elements (eligible).[24]

The urgency of this point cannot be overstated. Since the release of the December 2014 Guidance, examiners have rejected claims to inventions developed by C21 members despite these claims exhibiting clear, life-saving technological advances. A common element in many of these office actions is rejection of the claims base on the simple presence of a judicial exception, regardless of other elements integrating the supposed exception into the claimed method or combining with the exception such that the claim as a whole adds "significantly more" than the exception.

(6) The Name of the Game Is the Claim

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[21] See, e.g., August 2014 Comments, p.5-6 (section entitled "*Properties versus functions*").

[22] December 2014 Guidance, 79 Fed. Reg. at 74624, left column (emphasis added).

[23] December 2014 Guidance, 79 Fed. Reg. at 74622, left column ("*Courts tread carefully in scrutinizing such claims because at some level all inventions embody, use, reflect, rest upon, or apply a law of nature, natural phenomenon, or abstract idea.*"); id. at 74625, left and middle columns (Section I.B.3 "Streamlined Eligibility Analysis").

[24] See, e.g., Section 2(c)(i)(A), supra.

Finally, C21 is very encouraged by the last paragraph in this section of the December 2014 Guidance. Here the Office does a good job of emphasizing that the examiner must point to specific claim language when identifying the allegedly claimed judicial exception ("If a rejection under 35 U.S.C. 101 is ultimately made, the rejection should identify the exception as it is recited (i.e., set forth or described) in the claim…" (emphasis added).).[25] C21 suggests that the Office could make this same point—i.e., always tying § 101 analysis back to the claim language—at more places throughout the Guidance.

(d) Comments on Step 2B

(i) General Comments on Step 2B

This section of the December 2014 Guidance is fairly general, with the real substance lying in the case analysis and examples discussed below. Thus, C21 has only general comments on this part of the analytical framework.

Returning to the central theme noted at the outset of these March 2015 Comments, C21 urges the Office to integrate all governing law in this area. In public meetings discussing § 101 eligibility guidance, the Office has repeatedly reminded stakeholders that it must follow binding case law. This is true, and C21 is mindful of the limits on the Office's discretion.[26] C21 urges the Office to remember, however, that it must follow (a) all relevant case law that has not been clearly overturned and (b) also the statute. We have provided our detailed analysis of the case law section of the December 2014 Guidance below, and thus will not repeat it here.

As to the statute, wherever case law can be respected, but the statute mandates a narrow reading of that case law,[27] the Office must embrace this narrow reading. Indeed, because eligibility under § 101 is not and has never been cast as a question of Constitutionality,[28] the statute is supreme and both the Office and the courts (including the Supreme Court) must act in such a way as to be consistent with the statute.[29] All relevant cases must be read in light of the statute, including its language and its history.

One part of the December 2014 Guidance where this is particularly important is where the Office likens Alice's "significantly more" to "a search for an 'inventive concept.'"[30] When

[25] December 2014 Guidance, 79 Fed. Reg. at 74624, left column.

[26] See, e.g., Section 2(c)(iii)(A), supra (discussing In re Roslin).

[27] See, e.g., Section 1, supra, n.1.

[28] In re Bergy, 596 F.2d 952, 959 n.2 (C.C.P.A. 1979) ("*The only restraints placed on Congress pertained to the means by which it could promote useful arts, namely, through the device of securing 'exclusive rights' which were required to be limited in time, a device known to governments for centuries. The conditions to be imposed on the granting of such rights, which have varied through the years, were left to Congress to devise.*" (Emphasis in original.))

[29] Graham v. John Deere Co. of Kan. City, 383 U.S. 1, 6 (1966) ("*Within the scope established by the Constitution, Congress may set out conditions and tests for patentability. It is the duty of the Commissioner of Patents and of the courts in the administration of the patent system to give effect to the constitutional standard by appropriate application, in each case, of the statutory scheme of the Congress.*" (Emphasis added.)).

[30] December 2014 Guidance, 79 Fed. Reg. at 74624, left column (citing Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 573 U.S. __, 134 S. Ct. 2347, 2357 (2014)).

interpreting the Alice decision, however, the Office must be careful not to revive what Congress expressly and intentionally exterminated. In the 1952 Patent Act, Congress took the prior vague concept of "invention" created by the courts[31] and explicitly overruled and replaced it with distinct components of patentability (eligibility and utility under § 101, novelty under § 102, non-obviousness under § 103, and description under § 112).[32]

Giles Rich, principal author of the 1952 Act, clearly rejected attempts to "import[] into the discussion of compliance with § 101 a requirement for 'invention' in a patentability sense. But there has not been a requirement for 'invention' in the patentability sense in the laws since 1952 -- the requirement was replaced by the § 103 requirement for nonobviousness."[33] He further explained the proper interpretation of the statutory structure he primarily created by analogy to three doors, one each for § 101, § 102 and § 103:

> *The first door which must be opened on the difficult path to patentability is § 101 […]. The person approaching that door is an inventor, whether his invention is patentable or not. […] Thus, section 101 begins with the words "Whoever invents or discovers," and since 1790 the patent statutes have always said substantially that. Being an inventor or having an invention, however, is no guarantee of opening even the first door. What kind of an invention or discovery is it? In dealing with the question of kind, as distinguished from the qualitative conditions which make the invention patentable, § 101 is broad and general; its language is: "any * * * process, machine, manufacture, or composition of matter, or any * * * improvement thereof." […] If the invention, as the inventor defines it in his claims […], falls into any one of the named categories, he is allowed to pass through to the second door, which is § 102; "novelty and loss of right to patent" is the sign on it.*[34]

This is not to say any "process" under § 100(b) is eligible for patenting. Court decisions have created specific and limited categories of subject matter that, until Congress says otherwise, are excluded from the otherwise broad scope of § 101. The point is that examination must start with the presumption that what is claimed is eligible ("any […] process, machine, manufacture, or composition of matter") and exclude from eligibility only those things that are clearly analogous to the specific subject matter held ineligible in a specific case.

(ii) "Significantly More"

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[31] See, e.g., Funk Bros., 333 U.S. at 134-135.

[32] See generally, In re Bergy, 596 F.2d 952 (C.C.P.A. 1979); See also, Giles S. Rich, The Vague Concept of "Invention" as Replaced by § 103 of the 1952 Patent Act, 46 J. PAT. OFF. SOC'Y 855, 859 (1964), reprinted in 14 FED. CIR. B.J. 147, 158 (2004) ("*As I sometimes remind attorneys arguing cases, 'There is always an invention. What we are considering is its patentability.'*" (Emphasis in original.)).

[33] In re Bergy, 596 F.2d at 962; see also, Graham, 383 U.S. at 14 ("*In the title itself the Congress used the phrase 'Conditions for patentability; non-obvious subject matter' (italics added), thus focusing upon 'non-obviousness' rather than 'invention.'*").

[34] In re Bergy, 596 F.2d at 960 (emphasis in original).

This idea that eligible subject matter must represent "significantly more" than something that is ineligible for patenting is a relatively new one and has the potential to be quite vague. Indeed, the Supreme Court has on at least one occasion failed to even try to articulate what would represent sufficiently more to support patenting.[35] The Guidance process is an opportunity for the Office to bring more clarity and predictability to this area of the law. For example, C21 applauds the Office on an important observation in this regard: "It is important to consider the claim as whole. Individual elements viewed on their own may not appear to add significantly more to the claim, but when combined may amount to significantly more than the exception."[36] As with other points in the December 2014 Guidance noted in these Comments, this is worth expanded discussion and clear examples of examination analysis that properly considers the claim as a whole as well as examples of analysis that fails to do so. Indeed, expanding the Guidance to include examples of what not to do, rather than solely correct analysis, would be very helpful to examiners.

This section of the December 2014 Guidance is structured well to comport with the idea that subject matter is presumed eligible unless it is too analogous to something the courts have clearly indicated is ineligible. Specifically, the December 2014 Guidance lists examples from specific cases of the kinds of things that have been upheld and rejected under § 101. This section can be further improved by

(a) making the above presumption of eligibility explicit;

(b) directing examiners not to look for broad categories of things that are ineligible (e.g., "adding insignificant extra-solution activity to the judicial exception"); and instead

(c) requiring examiners to articulate a clear analogy to specific subject matter held ineligible for patenting in a binding court case when rejecting a claim under § 101.

An example of the last point is given in C21's August 2014 Comments (e.g., using a chart that compares, under Mayo, what was routine in the art and what is claimed in the application).[37]

(A) "Improvements to another technology or technical field"

A brief comment on this point is warranted. An important part of the Alice decision was its differentiation between (a) ineligible subject matter that is simply the mapping of a fundamentally non-technical activity (e.g., intermediated transactions) over to a technical environment (e.g., a computer or the Internet) and (b) eligible subject matter that represents an advance in a fundamentally technical field (e.g., curing rubber, molecular medicine, etc.).[38]

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[35] Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. ___, 132 S. Ct. 1289, 1299 (2012) ("*These other steps apparently added to the formula something that in terms of patent law's objectives had significance-they transformed the process into an inventive application of the formula.*") (Emphasis added.).

[36] December 2014 Guidance, 79 Fed. Reg. at 74624, sentence bridging left and middle columns.

[37] August 2014 Comments, p.11.

[38] See, e.g., Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 134 S. Ct. 2347, 2358 ("*The claim employed a 'well-known' mathematical equation, but it used that equation in a process designed to solve a technological problem in 'conventional industry practice.'*") (Emphasis added.); id. ("*In other words, the claims in Diehr were patent eligible because they improved an existing technological process, not because they were implemented on a computer.*") (Emphasis added.); id. at 2359 ("*The method claims do not, for example, purport to improve the functioning of the*

C21 is encouraged to see this noted in the December 2014 Guidance, as it accords with U.S. case law and tends towards harmonizing U.S. patent law with foreign patent law (something which is sorely lacking in this area).[39]

Diamond v. Diehr[40] is a good illustration of this principle. In Diehr, the Court found a process for curing rubber patent eligible despite the process involving as a central feature an abstract mathematical algorithm. Curing rubber was routine in the art and in general the steps and elements of the process were known. The inventor's contribution was not an entirely new process for curing rubber, but instead an application of the mathematical algorithm to devise an improved process. And the abstract algorithm directly related to (indeed was integral to) the overall process. While an abstract algorithm was central to the claimed process, the Court emphasized that the process represented an advance in a technological field.[41] This Diehr-articulated and Alice-endorsed inquiry into whether the claim relates to a technical field was recently affirmed by the Federal Circuit, which summarized the test as asking whether a claimed idea "crossed the eligibility threshold by virtue of being in the technological realm, the historical arena for patented inventions."[42]

Though typical patent claims in molecular diagnostics often involve what is arguably an abstract idea or natural law, molecular diagnostic testing (the field of endeavor of C21's member companies) is clearly a technical field rather than, as in Bilski and Alice, an arena of arranging human activities. For example, many molecular diagnostic claims involve the use of algorithms to combine measured biomarker values into a diagnostic score. If the claim recited a bare equation or algorithm to convert a group of numbers into another number, this would likely be an example of an abstract idea.[43] But the numbers in molecular diagnostics relate to tangible, real-world molecules and medical actions (e.g., diagnosing) and, more importantly, the typical claim is not to the algorithm itself. Instead a diagnostic method claim integrates the algorithm into the technical process of gathering specific biomarker information (i.e., the information that is relevant to the specific algorithm), applying the algorithm to that

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computer itself. Nor do they effect an improvement in any other technology or technical field.") (Internal citations omitted; emphasis added.).

[39] This is analogous to the requirement of "technical effect" in Europe. Huys et al., Gene and genetic diagnostic method patent claims: a comparison under current European and US patent law, EUR. J. HUM. GENET. (2011) 19:1104-1107 ("*[T]he implementing regulations to the EPC do specify that the invention must have technical features (Rule 43(1)), which is related to a technical field (Rule 42(1)(a)) and concerned with a technical problem (Rule 42(1)(c)). It is clear from these rules that 'technicality' is a key precondition for qualification as a patentable invention in Europe.*").

[40] 450 U.S. 175 (1981).

[41] Id. at 184 ("*Industrial processes such as this are the types which have historically been eligible to receive the protection of our patent laws.*").

[42] DDR Holdings v. Hotels.com, __ F.3d __, 2014 WL 6845152, slip op. 9 (Fed. Cir. Dec. 5, 2014); id. at slip op. 10 (Holding the claims patent-eligible because, although they addressed a business challenge, that challenge was "*particular to the Internet*," and the claims did not "*merely recite the performance of some business practice known from the pre-Internet world along with the requirement to perform it on the Internet.*").

[43] Gottschalk v. Benson, 409 U.S. 63, 64 (1972) ("*[The applicant] claimed a method for converting binary-coded decimal (BCD) numerals into pure binary numerals.*").

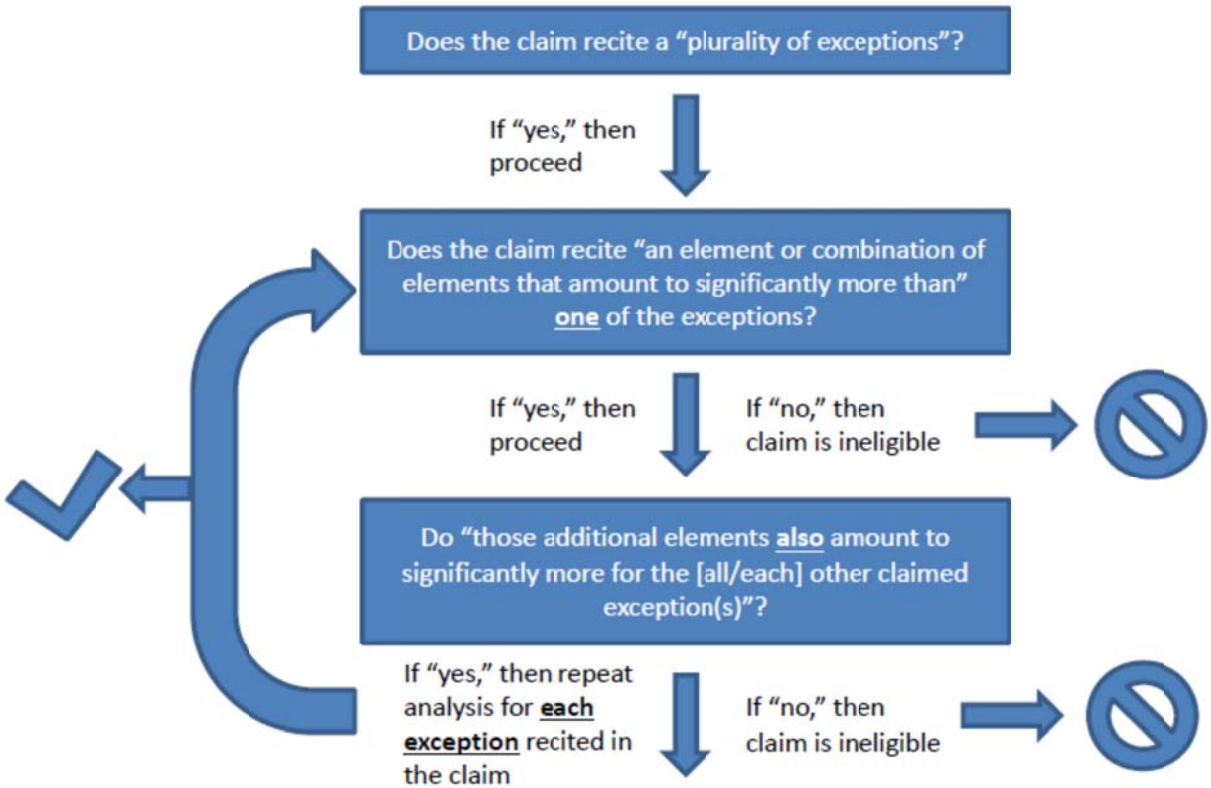
information, and then diagnosing a disease based at least in part on the results of the algorithm. Just as the abstract Arrhenius equation in Diehr was applied to modify and improve the real-world process for curing rubber, the algorithm developed by scientists and doctors is applied to modify and improve the real-world process of diagnosing a specific disease.

(B) "Simply appending well-understood, routine and conventional activities previously known to the industry, specified at a high level of generality, to the judicial exception"

This point also deserves attention. It is important for examiners to articulate what the routine and conventional activities are and to note any variations or adaptions of these activities recited or inherent in the claims. If the method truly recites routine and conventional activity that has not been altered in any way (e.g., to be suitable for use in the method), then this is indeed an indication that ineligible subject matter is claimed. But examiners should not read out of a claim details (whether expressly stated or necessarily implied) that reveal a modification to a well-known technique. The details of that which was truly routine in the art at the time of filing must be compared to the details of the claimed process.[44]

(iii) "A Claim Reciting a Plurality of Exceptions"

This section of the December 2014 Guidance is confusing and potentially quite problematic. This section sets up a separate flow chart roughly as follows:



[44] August 2014 Comments, p.11 (claim charts).

This analysis is difficult to decipher and, depending on how it is read and applied by examiners, an incorrect statement of the law (as well as internally inconsistent). What is meant by a "plurality of exceptions"? How does this differ from a combination of exceptions? Clarification here would be helpful.

There appears to be some unexplained distinction between "pluralities" and "combinations" because the analyses proposed by the Office for combinations and pluralities are different. For example, the December 2014 Guidance elsewhere correctly urges examiners to evaluate the characteristics of a claimed combination as a whole and, if the combination as a whole has markedly different characteristics from the component judicial exceptions, then it is eligible.[45] This section, however, sets forth what appears to be a different analysis, wherein the claim is assessed on a component-by-component basis.

The most troubling aspect of this component-based analysis is that failure to "add significantly more" (Step 2B) than any one exception will apparently render the entire claim ineligible ("[I]f the claim fails under Step 2B for one exception, the claim is ineligible, and no further eligibility analysis is needed.").[46] In other words, failure to "add significantly more" than exception A in a claim apparently makes the claim ineligible even if the claim does "add significantly more" than exceptions B, C and D individually or collectively. Here again the December 2014 Guidance confuses analysis of combinations and what is required for a combination of elements, one of which may be deemed a judicial exception, to be eligible.[47]

(iv) "Streamlined Eligibility Analysis"

As mentioned above, C21 agrees that certain subject matter is clearly not "directed to" a judicial exception and needs no detailed eligibility analysis. We are concerned, however, about the arbitrary nature of what subject matter will or will not qualify for the streamlined analysis noted in Section I.B.3 of the December 2014 Guidance. The "tie up" language appears to refer to (or at least is likely be interpreted by examiners as referring to) preemption and encouraging examiners to engage in some ill-defined inquiry about whether the claims cover all applications of a judicial exception. As demonstrated in our August 2014 Comments, preemption is not a viable or court-endorsed test for patent eligibility.[48] A contrary rule could limit patent eligibility based on what is foreseeable to an examiner or, even worse, what an examiner subjectively considers "commercially viable."[49]

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[45] See, e.g., Section 2(c)(iii)(A), supra.

[46] December 2014 Guidance, 79 Fed. Reg. at 74625, left column (emphasis added).

[47] See, e.g., Section 2(c)(iii)(A), supra; Section 2(c)(iii)(B)(5), supra.

[48] August 2014 Comments, p.13.

[49] Ariosa Diagnostics, Inc. v. Sequenom, Inc., 19 F. Supp. 3d 938, 953 (N.D. Cal 2013) ("*Ariosa argues that even if these articles disclose alternative methods of detecting cffDNA, Sequenom has failed to present any evidence showing that any of these alternative methods are practical and commercially viable. In response, Sequenom argues that it is only relevant that the alternative methods can be practiced, not that they are commercially viable alternatives. The Court disagrees. If the alternative methods are not commercially viable, then the effect of the patent in practice would be to preempt all uses of the natural phenomenon.*") (Internal citations omitted.).

The Office should clearly explain its understanding of the proper role of preemption in eligibility analysis in any subsequent Guidance. C21 reiterates the proposed framework set forth in our August 2014 Comments for filtering out clearly eligible subject matter and using specific, objective criteria (rather than vague, subjective preemption) for deciding what claims need close eligibility scrutiny.[50]

3. Comments on Case Law Analysis

(a) Example 1: Diamond v. Chakrabarty

The analysis of Chakrabarty provided in the December 2014 Guidance is generally quite good. For example, the December 2014 Guidance properly notes the most important fact: "The claimed bacterium has a different functional characteristic from naturally occurring Pseudomonas bacteria, i.e., it is able to degrade at least two different hydrocarbons as compared to naturally occurring Pseudomonas bacteria that can only degrade a single hydrocarbon."[51]

The Chakrabarty case presents the Office with an excellent teaching opportunity, however, to illustrate for examiners the difference between inherent properties on one hand and functions / utilities / activities on the other. The plasmids transferred from source bacteria to the target Pseudomonas bacterium do not gain any new inherent properties in the transfer. They have the same sequence and thus the same inherent properties of their binding specificity (so-called Watson-Crick base-pairing), secondary structure (if any), etc. Each individual transferred plasmid also gains no new functions or activities. They encode the same proteins, whose amino acid sequence is directly dictated by the inherent properties of their nucleotide sequence. And those proteins catalyze the same reactions as in the source bacteria, which catalytic activity is directly dictated by the inherent properties of their amino acid sequence (which is in turn dictated by the nucleotide sequence). Finally, the target Pseudomonas bacterium retains all of its former properties and functions and gains only one new function.

However, the fact the bacterium as a whole has gained at least one new function / activity is sufficient to make it eligible for patenting because this single new function / activity is sufficient to give it "markedly different characteristics" from the natural counterpart (i.e., the target Pseudomonas before the inventor's application of selective breeding).[52] Eligibility is not negated simply because, as will be true in every case, this new function / activity arises naturally and necessarily from the inherent properties of the transferred plasmid noted above.

(b) Example 2: Association for Molecular Pathology v. Myriad Genetics, Inc.[53]

[50] August 2014 Comments, pp.3-4 (Section entitled "*Does the claim appear, on its face, to potentially encompass a product of nature?*"); id. at pp. 9-10 (Section entitled "*Does the claim appear, on its face, to potentially recite a natural principle?*"); see also the example analyses in our August 2014 Comments applying this framework (e.g., id. at p.35).

[51] December 2014 Guidance, 79 Fed. Reg. at 74625, middle column.

[52] Chakrabarty, 447 U.S. at 310 ("*[T]he patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility.*") (Emphasis added.).

[53] 569 U.S. __, 133 S. Ct. 2107 (2013).

The analysis of AMP provided in the December 2014 Guidance is also generally good. It does not overtly expand the narrow ruling of the case and notes most of the important facts. C21 submits a few comments on how this analysis can be improved.

(i) Functional Characteristics

The analysis of claim 1 states "The claimed DNA has no different functional characteristics, i.e., it encodes the same protein as the natural gene."[54] This statement fairly summarizes the Court's reasoning in AMP, but a little more detail is helpful in fully understanding the case. As this statement in the December 2014 Guidance notes, the Court emphasized throughout its decision that the isolated BRCA1 DNA was defined in the claims according to its natural protein-encoding function:

> *Nor are Myriad's claims saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a nonnaturally occurring molecule. Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA. Instead, the claims understandably focus on the genetic information encoded in the BRCA1 and BRCA2 genes.*[55]

Myriad argued that the structural changes in isolated DNA conferred new functions and utilities, but the Court apparently rejected this contention. It is thus important to recognize that, had the record shown the claims recited a molecule with clear functional differences from a natural product, instead of being expressly defined in terms of natural function, the outcome likely would have been different.

(ii) Preemption

The analysis of claim 1 states: "Under the holding of Myriad, this isolated but otherwise unchanged DNA is not eligible because it is not different enough from what exists in nature to avoid improperly tying up the future use and study of the naturally occurring BRCA1 gene."[56] This does not accurately reflect the treatment of preemption in AMP. The word "preemption" is never used in AMP. Nor does the decision base its holding on preemption. Instead, as in all other Supreme Court cases in this area, preemption is cited not as an analytical test for eligibility but instead as the policy concern undergirding the judicial exceptions.[57]

(iii) cDNA

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[54] December 2014 Guidance, 79 Fed. Reg. at 74626, left column.

[55] AMP, 133 S. Ct. at 2118 (emphasis added).

[56] December 2014 Guidance, 79 Fed. Reg. at 74626, left column (emphasis added). Similarly the analysis of claim 2 states: "*Here, the differences in structural characteristics between the claimed DNA and the natural gene are significant, e.g., they are enough to ensure that the claim is not improperly tying up the future use of the BRCA1 gene.*" December 2014 Guidance, 79 Fed. Reg. at 74626, middle column.

[57] AMP, 133 S. Ct. at 2116 ("*As the Court has explained, without this exception, there would be considerable danger that the grant of patents would 'tie up' the use of such tools and thereby 'inhibit future innovation premised upon them.'*").

The analysis of claim 2 could be improved by a more nuanced discussion of cDNA. For example, the December 2014 Guidance states: "The claimed DNA therefore has different structural characteristics than the naturally occurring BRCA1 gene, e.g., in addition to lacking covalent bonds on its ends, it has a different nucleotide sequence."[58] This is true, but an important issue in the case was the question of what is to be done when nature could foreseeably create something that would be structurally identical to that which was originally created in a lab. What if statistical probability suggests it already has been made and simply never discovered? The Court expressly resolved this issue by stating that, in such a scenario, the lab-created molecule would still be eligible.[59] A discussion of this point would provide a good opportunity for the Office to emphasize to examiners the importance of citing a natural product or law that has been discovered or described in enough detail to allow comparison against what is claimed. Vague allegations of the possible or even likely existence of a natural product or law are insufficient.

The analysis of claim 2 goes on to conclude: "Here, the differences in structural characteristics between the claimed DNA and the natural gene are significant, […] they rise to the level of a marked difference."[60] This conclusory statement is unhelpful in giving real guidance for examination. In what way are the differences between the natural gene and cDNA "significant?"[61] The Court's brief discussion of cDNA's eligibility simply notes that there are differences and never says they are significant. In fact, the Court concedes AMP's argument that the changes are not designed or devised by the inventor and are instead "dictated by nature."[62] In the words of the Court: "That may be so, but the lab technician unquestionably creates something new when cDNA is made."[63] The ultimate take-away from AMP to be conveyed to examiners is thus: what is eligible is what an inventor created, rather than something the "inventor" merely discovered, extracted, and claimed solely according to its natural function / activity.

(c) Example 4: Parker v. Flook[64]

The treatment of Flook provided in the December 2014 Guidance errs in a few important respects, mostly by overstating the holding of the case and inserting unnecessary and unsupported analysis. As an example of overstatement, the analysis states: "Adjusting the alarm limit based on the solution to the mathematical formula is merely post-solution activity

[58] December 2014 Guidance, 79 Fed. Reg. at 74626, middle column.

[59] AMP, 133 S. Ct. at 2119, n.8 ("*The possibility that an unusual and rare phenomenon might randomly create a molecule similar to one created synthetically through human ingenuity does not render a composition of matter nonpatentable.*") (Emphasis in original.).

[60] December 2014 Guidance, 79 Fed. Reg. at 74626, middle column.

[61] The December 2014 Guidance itself notes that "*[t]he claimed DNA has no different functional characteristics, i.e., it encodes the same protein as the natural gene.*" Id.

[62] AMP, 133 S. Ct. at 2119.

[63] Id.

[64] 437 U.S. 584 (1978).

that could be attached to almost any formula."[65] An alarm limit seems fairly specific; it is unclear how adjusting an alarm limit could be attached to almost any formula (e.g., formula for calculating the gravitation pull between two objects). More helpful to examiners would be a discussion of what "post-solution activity" really means, rather than using it as a buzzword without further analysis. The Court even helped in this regard by noting additional limitations that may have rendered the claim eligible.[66]

As an example of unnecessary and unsupported analysis, the December 2014 Guidance states: "Moreover, when considered as an ordered combination, the claim is nothing more than a purely conventional computerized implementation of applicant's formula."[67] This approach appears to be an attempt at applying Alice to the facts of Flook, but nothing like this is found in the Flook opinion itself. This section should make clear that this type of analysis should only be applied in cases whose facts appear to closely resemble Alice—i.e., evidence showing the claim is merely the mapping onto computers of a clearly abstract idea that has no intrinsic tie to computers or any other technical or technological pursuit.

Otherwise, this language could be read to advance the dangerous suggestion that something can become ineligible if it is an obvious implementation of a judicial exception. This approach of treating the judicial exception as if it was in the prior art and then looking to see whether the claim would be novel or obvious in view of that art is precisely what Justice Stewart warned against in his dissent in Flook,[68] what the Supreme Court rejected in Diehr,[69] and what C21 strongly cautioned against in our August 2014 Comments.[70] The Court's analysis of what is "well-understood, routine, conventional" is strictly backward looking.[71]

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[65] December 2014 Guidance, 79 Fed. Reg. at 74627, middle column.

[66] Flook, 437 U.S. at 586 ("*The patent application does not purport to explain how to select the appropriate margin of safety, the weighting factor, or any of the other variables. Nor does it purport to contain any disclosure relating to the chemical processes at work, the monitoring of process variables, or the means of setting off an alarm or adjusting an alarm system.*")

[67] December 2014 Guidance, 79 Fed. Reg. at 74627, middle column.

[68] Flook, 437 U.S. at 599 (Stewart, J., dissenting) ("*The issue here is whether a claimed process loses its status of subject-matter patentability simply because one step in the process would not be patentable subject matter if considered in isolation.*") (emphasis in original); id. at 600 (Stewart, J., dissenting) ("*The Court today […] strikes what seems to me an equally damaging blow at basic principles of patent law by importing into its inquiry under 35 U.S.C. § 101 the criteria of novelty and inventiveness.*").

[69] 450 U.S. at 188-189 ("*In determining the eligibility of respondents' claimed process for patent protection under § 101, their claims must be considered as a whole. It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis. This is particularly true in a process claim because a new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made. The 'novelty' of any element or steps in a process, or even of the process itself, is of no relevance in determining whether the subject matter of a claim falls within the § 101 categories of possibly patentable subject matter.*").

[70] August 2014 Comments, p.12 (Section entitled "*Not an obviousness analysis*").

[71] Mayo Collaborative Serv. v. Prometheus Labs., Inc., 566 U.S. __, 132 S. Ct. 1289, 1298 (2012) ("*Indeed, scientists routinely measured metabolites as part of their investigations into the relationships between metabolite levels and*

(d) Example 5: Mayo Collaborative Serv. v. Prometheus Labs., Inc.

The discussion of Mayo does not contain any obvious analytical errors or misstatements of the law. However, it is somewhat superficial and may not ultimately prove very helpful to examiners. For example, the December 2014 Guidance states "The claims inform a relevant audience about certain laws of nature; any additional steps consist of well understood, routine, conventional activity already engaged in by the scientific community […]."[72] Helpful for examiners would be a discussion of the type of evidence required to prove a prima facie case of ineligibility. This would include evidence of the specific activities engaged in by the scientific community at the time of the applicant's filing and how these activities do not differ in any way from what the claim recites. C21 is hopeful this type of detailed analysis will be given in the forthcoming diagnostic method examples the Office has promised. C21 also reiterates the suggested analytical approach based on Mayo outlined in our August 2014 Comments.[73]

(e) Anticipated Example: BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig. v. Ambry Genetics Corp.[74]

Two days after the Office released the December 2014 Guidance, the Federal Circuit released its decision the Ambry case. As such, the Office has not yet released any analysis of Ambry nor stated how, if at all, the decision might affect the December 2014 Guidance. C21 submits the following observation to help the Office in considering these questions.[75]

Central to the Federal Circuit's holding on the method claims was its finding that "The district court found, and Myriad does not challenge, that the elements of the second paragraphs of claims 7 and 8 'set forth well-understood, routine and conventional activity engaged in by scientists at the time of Myriad's patent applications.'"[76] Viewed from the perspective of the patentee purportedly admitting the claims recited purely well-understood, routine and conventional activity engaged in by scientists at the time of filing, the Ambry holding is a rather unremarkable application of Mayo and should not be interpreted by the Office as breaking any new ground.

4. Suggestions on Planned Diagnostic Examples

INTRODUCTION

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efficacy and toxicity of thiopurine compounds. Thus, this step tells doctors to engage in well understood, routine, conventional activity previously engaged in by scientists who work in the field.") (Emphasis added.).

[72] December 2014 Guidance, 79 Fed. Reg. at 74627, right column.

[73] August 2014 Comments, pp.10-12 (Section entitled "*Side-by-side comparison of claimed process to routine art process*").

[74] 774 F.3d 755, 2014 U.S. App. LEXIS 23692 (Fed Cir 2014).

[75] The Ambry case is discussed in more detail in some claim examples in Section 4, infra.

[76] Ambry, 774 F.3d 755, slip op. 20 (emphasis added).

C21 has provided below examples of how to apply the December 2015 Guidance in view of our comments above.[77] These examples give our interpretation of the law and application of that law to specific hypothetical claims. A brief introduction to the general field of modern molecular diagnostics may be helpful.

Modern diagnostic tests typically comprise the measurement of specific characteristics (e.g., levels) of a collection, or panel, of "markers" (serological, genetic, and even physiological) in a patient suspected of having a particular disease. The results of the individual measurements are analyzed and compared against data from various populations of individuals who are both healthy or who were previously determined to have the particular disease in one form or another. The analyses and comparisons often take the form of a series of statistical comparisons and predictions aided by a computer.

Specifically, the framework of a model claim directed to a method of diagnosing a disease might look like this:

> A method of diagnosing a disease in a patient suspected of having the disease comprising:
>
> > Analyzing a sample obtained from said patient to determine the presence or level or genotype of markers A, B, C, D, and E,
> >
> > Applying a statistical model derived from healthy and diseased patients to the measurements to arrive at an index or likelihood that the patient has the particular disease.

Such a claim may also include specific elements related to the value of the index or likelihood. In any event, such a claim is not abstract, is not directed toward a law of nature, and does not preempt all uses of the markers nor all methods of diagnosing the disease.

In most instances, the levels of the markers or even mutations in these markers are not strictly causative or fully indicative of the disease (i.e., a mutation is not completely penetrant). Rather it is the complex statistical correlation of the invention that produces as an output the likelihood that the individual patient has the disease in question. The levels of the markers in most modern diagnostics are not binary YES/NO indicators of disease or health, as might be seen in some genetic tests for single polymorphisms. Marker levels are often continuous variables and will vary even between individuals who have the particular disease. And, even if the panel contains some measurements of genetic polymorphisms (e.g., mutations), they are typically used in conjunction with other markers to improve the utility of the test.

With that, the use of a panel of markers should not be taken as directed to a one-to-one, cause-and-effect law of nature, although it may arguably involve the nature of pathological states. Further, the use of a specific panel of markers does not preempt all uses of those markers in other combinations or, necessarily, for diagnosis of other diseases.

[77] These examples build on the examples in our August 2014 Comments. We urge the Office to reconsider those earlier examples as well as those provided in these March 2015 Comments.

It has been argued that the use of a panel of markers to diagnose, or prognose the progression of, a disease is little more than abstract manipulation of data. This is hardly the case when one considers that there are real physical samples taken from a real patient, that the samples undergo chemical transformations to measure the levels of the markers in the sample, and that the results of the measurements are used to produce a real diagnosis. This is in stark contrast to the abstract manipulation of data as occurred in Benson.[78]

Finally, the interplay of divided infringement and § 101 eligibility is of particular importance to molecular diagnostic companies. C21 urges the Office to pay special attention to this issue in determining what must be added to a method claim to "add significantly more" than a judicial exception.[79] The Office must avoid requiring activities that are typically (or could easily be) performed by parties not under control of a diagnostic company (e.g., doctors or hospitals) so as to not squeeze diagnostic companies into a divided infringement v. subject matter eligibility dilemma.

We would like to further elaborate on the area of diagnostics by providing examples of how such claims are distinct from claims to a law of nature.

EXAMPLE 1

Background:

Neurofibromatosis type I (neurofibromatosis) is a progressive and fairly well-characterized condition, which can manifest differently even amongst people of the same family. There is no cure for the disorder, which progresses roughly as follows:

(1) Congenital musculoskeletal disorders may or may not be present

(2) Cutaneous conditions may be observed in early infancy

(3) Small tumors may arise in the retina which can eventually lead to blindness

(4) Learning disabilities may arise in preschool children

(5) Neurofibromas may occur and cause many dependent neurological conditions and cutaneous and skeletal disfigurement

(6) Depression and social anxiety may occur as a result of disabilities caused by the condition

(7) Neurofibromas may transition into cancer which can be fatal

Before the inventors' discovery, diagnosis of neurofibromatosis was made based on a patient presenting with one or more of the above clinical features.

The inventors discovered that neurofibromatosis is caused by mutations that inactivate a new gene they named neurofibromin 1 (NF1). They discovered that neurofibromatosis is an autosomal dominant disease, meaning that it is inherited on the non-sex chromosomes and one mutated copy of the gene is sufficient for a patient to have the disorder. They further

[78] See, e.g., n.43, supra, and accompanying text.

[79] See Example 2, "Special Note on Divided Infringement," pp.32-33, infra.

discovered that mutations in NF1 show complete penetrance, meaning every patient with a mutation in NF1 will have the disease.

The specification describes the full structure of the newly discovered NF1 gene. This includes about 350,000 nucleotides of genomic sequence (exons, introns, promoter, etc.) disclosed as SEQ ID NO:2 and 12,381 nucleotides of cDNA disclosed as SEQ ID NO:1. This also includes a 2,818 amino acid protein disclosed as SEQ ID NO:3.

The specification describes actual examples of using the newly discovered reference sequences (SEQ ID NOs 1 & 2) to detect mutations in test patients, using alignment software to compare the patients' test sequences against the reference sequences, detecting mutations in patients, and diagnosing these patients as having neurofibromatosis. The specification defines "diagnosis" to mean conveying to a third party (e.g., patient, physician, etc.) the presence, absence, or character of a particular disease. The specification also describes various treatment options for mitigating symptoms in a diagnosed patient.

The specification describes efforts to deduce NF1's activity and pathways of which it is a member. Homology studies showed that NF1 is 30% similar to proteins in the GTPase Activating Protein (GAP) Family. This homologous sequence was found to be in the central portion of NF1. The specification notes that being similar to the GAP family is recognized in the art as evidence a protein is a negative regulator of the Ras kinase.

Claims:

Claim 1. A method for determining whether a sample harbors a mutation in the NF1 gene, the method comprising:

(1) providing a test nucleotide sequence of the NF1 gene in said sample;

(2) providing a reference nucleotide sequence of the NF1 gene; and

(3) comparing said test sequence to said reference sequence, wherein a difference between said test sequence and said reference sequence indicates the presence of a mutation in the NF1 gene in said sample.

Claim 2. The method of claim 1, wherein said comparing step is performed using a computer.

Claim 3. The method of claim 2, wherein said comparing step is performed using a computer programmed with executable code comprising (a) SEQ ID NO:1 as said reference sequence and (b) an algorithm for aligning said test sequence against said reference sequence and highlighting differences between the two.

Claim 4. The method of claim 1, wherein providing a test nucleotide sequence of the NF1 gene comprises performing a laboratory assay to sequence a plurality of nucleic acid molecules derived from said sample and deducing the test nucleotide sequence of the NF1 gene from the sequences of said plurality of nucleic acid molecules.

Claim 5. The method of either claim 1 or 4, wherein providing a test nucleotide sequence of the NF1 gene comprises the polymerase chain reaction to amplify said plurality of nucleic acids.

Claim 6. The method of claim 5, wherein said assay comprises at least two oligonucleotide primers, each between 20 and about 50 nucleotides in length and each of whose nucleotide sequence comprises at least 20 contiguous nucleotides of SEQ ID NO:1.

Claim 7. The method of claim 6, wherein said at least two oligonucleotide primers comprise (a) at least one forward DNA primer and (b) at least one reverse DNA primer; wherein said forward DNA primer and said reverse DNA primer jointly prime a polymerase chain reaction that synthesizes an amplicon whose nucleotide sequence comprises between about 45 and about 2,000 contiguous nucleotides of SEQ ID NO:1.

Claim 8. The method of any one of claims 1-7, wherein a mutation in the NF1 gene in said sample indicates a patient from whom said sample was obtained has neurofibromatosis.

Claim 9. The method of any one of claims 2-7, further comprising (4) diagnosing a patient whose sample harbors a mutation in the NF1 gene with neurofibromatosis.

Analysis:

Claim 1: This claim is directed to an abstract idea under Step 2A of the December 2014 Guidance. Specifically, the claim recites no physical element, manipulation or activity. "Providing" is a commonly used generic term for a step in a patent claim, which in this case recites no actual structure or activity. And this specific type of "comparing" step has been found by the Federal Circuit to be susceptible of being performed entirely within a person's mind.[80]

The Federal Circuit went on to hold that a claim very similar to this one, with solely "mental" steps, is directed to an abstract idea.[81] As noted above, C21 urges the Office to emphasize the importance of clearly articulating/describing the precise judicial exception allegedly claimed. Rather than articulating the ineligible subject matter as an abstract idea, the Federal Circuit faulted the claims for reciting an abstract mental process articulated as follows:

> *[O]ne looks at the first position in a first sequence; determines the nucleotide sequence at that first position; looks at the first position in a second sequence; determines the nucleotide sequence at that first position; determines if the nucleotide at the first position in the first sequence and the first position in the*

[80] C21 questions whether any serious sequence comparison can reasonably be performed entirely in a person's mind as a matter of fact. The Federal Circuit has held, however, that this specific activity can be performed entirely within the mind. Ass'n for Molecular Pathology v. United States PTO, 689 F.3d 1303, 1334-1335 (Fed. Cir. 2012) ("*We renew our conclusion that Myriad's claims to 'comparing' or 'analyzing' two gene sequences fall outside the scope of § 101 because they claim […] nothing more than the abstract mental steps necessary to compare two different nucleotide sequences[…]. […] Although the application of a formula or abstract idea in a process may describe patent-eligible subject matter, Myriad's claims do not apply the step of comparing two nucleotide sequences in a process. Rather, the step of comparing two DNA sequences is the entire process that is claimed.*"). C21 urges the Office to follow this ruling only as narrowly as is required, however, and apply the framework for deciding whether something is an "active step" set forth in our August 2014 Comments. See, e.g., August 2014 Comments, p.12 (Section entitled "*What is an 'active' step?*").

[81] Ass'n for Molecular Pathology v. United States PTO, 689 F.3d at 1334-1335.

> *second sequence are the same or different, wherein the latter indicates an alteration; and repeats the process for the next position.*[82]

With this in mind, the claim fails under Step 2B because it recites nothing more than the abstract idea/process. No physical steps, no physical machines or compositions, etc. As stated by the Federal Circuit, "the step of comparing two DNA sequences is the entire process that is claimed."[83]

Claim 2: Under the narrow holding by the Federal Circuit in Ass'n for Molecular Pathology v. United States PTO, claim 2 is not directed to an "abstract mental process" because the claim recites a physical element (i.e., a computer). However, there is still a question under Step 2A in light of Alice. Claim 2 presents a close case, with some elements of the analysis weighing in favor of eligibility and others against. C21 submits that it should ultimately be eligible for patenting if for no other reason than under the "tie goes to eligibility" principle.

A. Merely Mapping to Computer?

A key question under Alice is whether the claim takes something that is abstract (e.g., a fundamental business practice) and simply maps it over to a general purpose computer. Taken in its broadest sense, this analysis may appear to exclude this claim 2. This is particularly true in view of some of the general statements in the Alice decision:

- "We hold that the claims at issue are drawn to the abstract idea of intermediated settlement, and that merely requiring generic computer implementation fails to transform that abstract idea into a patent-eligible invention."[84]
- "We conclude that the method claims, which merely require generic computer implementation, fail to transform that abstract idea into a patent-eligible invention."[85]
- "[S]imply implementing a mathematical principle on a physical machine, namely a computer, [i]s not a patentable application of that principle."[86]
- "[T]he mere recitation of a generic computer cannot transform a patent-ineligible abstract idea into a patent-eligible invention."[87]

However, important in the Alice case and important in § 101 analysis are whether (a) the process was otherwise conducted previously without a computer, (b) the abstract idea is in a technical or non-technical field, and (c) the use of the computer is integral to the method, or nominally improves the ease, speed or efficiency of an otherwise routine process. In this case, the process of claim 2 was not otherwise routine or practiced outside computers and merely

[82] Id. at 1334.

[83] Id. at 1335.

[84] Alice, 573 U.S. __, 134 S. Ct. at 2352.

[85] Id. at 2357.

[86] Id.

[87] Id. at 2358.

mapped over to computers in the claimed "invention." Instead, the underlying method is new irrespective of the computer.

B. Technical v. Non-Technical?

Alice involved a "process[] for organizing human activity"[88] and this was a central reason the claims were found ineligible for patenting.[89] Indeed, this was the primary distinction the Court drew between the claims in Alice and those in Diehr.[90] Claim 2 of this example, in contrast, is in a field that is clearly "technical"—i.e., molecular diagnostics. Following the principle of applying controlling case law faithfully yet narrowly, this weighs heavily in favor of eligibility.

The mere fact of being in a technical field is not sufficient per se to make a claim patent eligible. The claims in Mayo, for example, related to molecular diagnostics. However, being in a technical field is sufficient to rebut the general comments in Alice disapproving of taking a fundamental economic practice and merely implementing it on a general purpose computer.

Moving on to Mayo,[91] claim 2 is distinguishable from the claims in Mayo in at least one way that was central to the reasoning in that decision. Namely, the method in Mayo involved a process that, but for a bare statement of what the Court deemed an underlying natural law, was entirely and exactly disclosed and in fact routine in the art.[92] Claim 2, in contrast, involves active, non-mental steps never before engaged in by researchers in the field. Borrowing from a useful paradigm suggested in our August 2014 Comments, the following table illustrates this point well:

Claim 2 of Example 1	**Closest process routinely engaged in by scientists at the time of filing**
A method for determining whether a sample harbors a mutation in the NF1 gene, the method comprising: (1) providing a test nucleotide sequence of the	A method of determining whether a patient has neurofibromatosis type I, comprising: (1) screening the patient for one or more of the following symptoms:

[88] See, e.g., Bilski v. Kappos, 561 U.S. 593, 617 (2010).

[89] See n.38, supra. See also, Brief for The United States as Amicus Curiae in Alice, 28-29 ("*The ultimate inquiry is whether the claims are directed to an innovation in computing or other technical fields instead of to an abstract method of organizing economic concepts and relationships.*")

[90] Alice, 573 U.S. __, 134 S. Ct. at 2359 ("*The method claims do not, for example, purport to improve the functioning of the computer itself. Nor do they effect an improvement in any other technology or technical field.*") (Internal citations omitted; emphasis added.).

[91] The presence of a "wherein" clause in the claims further raises eligibility concerns. This is especially true where the "wherein" clause does not specify any particular element or structure or detail of the activity carried out in a specific step but instead merely states a fact. See, e.g., August 2014 Comments, pp.9-10. However, a "wherein" clause (even one stating a fact) does not per se make a claim ineligible.

[92] Mayo, 132 S. Ct. at 1294 ("*In particular, the steps in the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field.*") (Emphasis added.); id. at 1298 ("*To put the matter more succinctly, the claims inform a relevant audience about certain laws of nature; any additional steps consist of well understood, routine, conventional activity already engaged in by the scientific community….*") (Emphasis added.).

NF1 gene in said sample; (2) providing a reference nucleotide sequence of the NF1 gene; and (3) comparing said test sequence to said reference sequence, wherein a difference between said test sequence and said reference sequence indicates the presence of a mutation in the NF1 gene in said sample.	(a) Congenital musculoskeletal disorders (b) Cutaneous conditions in early infancy (c) Small tumors in the retina (d) Learning disabilities at preschool age (e) Neurofibromas or associated dependent neurological conditions or cutaneous and skeletal disfigurement (f) Multiple cancers; and (2) diagnosing neurofibromatosis type I based on the number, type, severity, and combination of the above symptoms.

It is clear that the claimed process is entirely new. This is not like Mayo, where the entire process was routine and conventional except for a statement of fact about the underlying pharmacokinetics of the process.

C. Computer Integral to Method?

In Alice, the involvement of the computer in the methods was tangential and incidental.[93] Important in the Court's analysis was the fact the process of intermediated settlement had been practiced without the use of computers for years.[94] The use of a computer at most led to a nominal improvement in the ease, speed or efficiency of a process that could otherwise be and had been conducted without the computer.

Claim 2 is different in that the computer is integral to the sequence comparison.[95] The Federal Circuit held that basic sequence comparison can be done mentally. As a first note, the court's portrayal vastly oversimplifies the actual process of sequence analysis:

> *[O]ne looks at the first position in a first sequence; determines the nucleotide sequence at that first position; looks at the first position in a second sequence; determines the nucleotide sequence at that first position; determines if the nucleotide at the first position in the first sequence and the first position in the second sequence are the same or different, wherein the latter indicates an alteration; and repeats the process for the next position.*[96]

[93] See, e.g., Brief for The United States as Amicus Curiae in Alice, 29 ("*This Court's decisions in Bilski and Mayo establish that 'the prohibition against patenting abstract ideas cannot be circumvented' by incorporating a computer in an ancillary or conventional role.*") (Emphasis added.).

[94] Alice, 134 S. Ct. at 2350 ("*Like the risk hedging in Bilski, the concept of intermediated settlement is 'a fundamental economic practice long prevalent in our system of commerce,' and the use of a third-party intermediary (or 'clearing house') is a building block of the modern economy.*") (Internal citations omitted.).

[95] Alice should not be read broadly to limit eligibility to inventions that improve the overall or general functioning of the computer itself. 134 S. Ct. at 2359 ("*The method claims do not, for example, purport to improve the functioning of the computer itself.*").

[96] Ass'n for Molecular Pathology v. United States PTO, 689 F.3d at 1334.

This type of analysis can indeed be performed mentally, but it is not useful in most molecular diagnostic applications. For example, using the court's analysis, the following two sequences look quite different (similarities are shown with vertical lines).

```
ttttttccagaaacagcatttaaatttaaagccctaaagaaggttgcgcagttagcagttataaatagcctggaaaaggtaagttaca
      |     ||     |       |  | |     |     |       |    | |  ||     || ||
aaacagcatttaaatttaaagccctaaagaaggttgcgcagttagcagttataaatagcctggaaaag
```

In fact, starting at the left end of each sequence and proceeding base-by-base as suggested by the court would show a "difference" at the first six positions and one would likely declare these sequences unrelated.

But computerized sequence analysis, for example, can reveal that there is no genetic difference between the sequences. The lower sequence (exon 6 of the NF1 gene) is identical to a portion of the upper sequence (genomic reference sequence), as shown below:

```
ttttttccagAAACAGCATTTAAATTTAAAGCCCTAAAGAAGGTTGCGCAGTTAGCAGTTATAAATAGCCTGGAAAAGgtaagttaca
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
          AAACAGCATTTAAATTTAAAGCCCTAAAGAAGGTTGCGCAGTTAGCAGTTATAAATAGCCTGGAAAAG
```

Computerized alignment programs are central to practical sequence analysis in modern molecular diagnostics. These programs allow researchers to analyze very long sequences that may initially appear to be quite different, but which are in reality subsets of each other or otherwise the "same" in a genetic sense. Thus, even the addition of a "generic" computer to claim 2 weighs in favor of eligibility because the computer is integral to the practice of the claimed method.[97]

Thus, on balance, claim 2 is likely eligible. Though it appears to run afoul of general statements in controlling cases, it is factually distinguishable from each of those cases in important ways.

Claim 3: This claim is very similar to claim 2, except that details of the computer from claim 2 are recited in claim 3. These additional details only solidify eligibility. In fact, if the close call on claim 2 had gone the other way (i.e., claim 2 was ineligible), then claim 3 would still be eligible.

If claim 2 was found ineligible, it would need to be based on Alice's comments disfavoring "the mere recitation of a generic computer." But claim 3's recitation of "executable code" programmed on the computer, SEQ ID NO:1 as a reference sequence, and an algorithm for aligning the test and reference sequences and highlighting any differences is clearly "something more" than what Alice termed "merely requiring generic computer implementation." It is not a generic computer, but now a computer programmed in a very specific way to enable a specific analysis central to the claimed technical method.

[97] This case is distinguishable from Benson, where the Court noted that "The mathematical formula involved here has no substantial practical application except in connection with a digital computer…." 409 U.S. at 72. There is an important difference between computers being integral to the practice of a method as claimed (weighs in favor of eligibility) and reciting a computer in a method whose only conceivable relevance is in a computer (meaningless limitation that cannot confer eligibility).

Claim 4: Claim 4 is also a close call on eligibility, but only due to the recent Federal Circuit decision in Ambry. The analysis of this claim is different from but analogous to that of claim 2. Mainly, claim 4 (much like claim 2) cures a specific deficiency the Federal Circuit found in claims analogous to claim 1. Instead of being directed to an entirely mental process (like claim 1), claim 4 recites a physical laboratory assay. Thus claim 4 passes muster under Ass'n for Molecular Pathology v. United States PTO.

But the claim must still be eligible under Mayo, where the claims also recited what the court deemed to be physical assay steps ("determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder"). Claim 4 passes this test because the combination of steps in the process, both physical and otherwise, was not routine and conventional at the time of filing. Researchers generally sequenced nucleic acids, but they never derived a sequence of the NF1 gene for any patient.[98] As noted previously, Mayo stands for the limited proposition that a claim to an entirely routine process is not made patent-eligible by the addition of a statement of a natural law underlying that process.

Claim 5: This claim stands or falls with the claims from which it depends. Claim 5 recites additional detail about the assay to be used in sequencing the patient's NF1 gene. But this detail is, upon closer inspection, quite general. While PCR is most commonly used to amplify specific sequences using primers specific for the desired region, other variations on the PCR process exist that do not use "gene-specific" primers. And claim 4 does not recite that the primers or the PCR to be performed are in any way adapted to use with NF1 (e.g., having a sequence associated with NF1, special reaction conditions optimized for NF1, etc.). Thus, claim 5 is eligible only if claim 1 and claim 4 are each eligible.

The Federal Circuit recently held a claim analogous to this claim 5 (as dependent from claim 4)[99] ineligible in Ambry. As noted elsewhere in these March 2015 Comments, this holding explicitly rested on the court's determination that the patentee admitted the claim involved routine and conventional techniques.[100] And the above analysis factually comports with this holding. Claim 5 recites PCR in its truly general sense such that the claim reaches a polymerase chain reaction not at all modified to specifically amplify NF1 (i.e., that which was exactly disclosed in and routine in the art at the time of filing).

Claim 6: This claim, unlike claim 5, is eligible independent of the conclusion reached on claim 4. Claim 6 recites specifics of the PCR to be performed and, in fact, modifies the routine PCR of the art by specifying the sequence of pair of primers used. Claim 5 reaches PCR exactly as performed routine in the art at the time of filing. Claim 6 on the other hand is limited to a new

[98] The analysis of this claim 4 under Ambry is unclear. The holding in Ambry is explicitly based on the court's finding that the patentee admitted in the lower court that the claim involved routine and conventional techniques. While the front end of the techniques recited in claim 4 may reach routine activities (i.e., sequencing whatever nucleic acids are in a sample without prior knowledge of the NF1 gene or its sequence), the back end recites something new. No one had "deduc[ed] the test nucleotide sequence of the NF1 gene from the sequences of" those nucleic acid molecules. This is an active step that was not routine in the art. This claim is likely eligible in view of Ambry, though it is another close call.

[99] If claim 5 were redrafted to depend only from claim 4, it would likely be eligible because claim 4 is likely eligible.

[100] Ambry, 774 F.3d 755, slip op. 20.

version of PCR involving as central components reagents never used before ("at least two oligonucleotide primers[…] whose nucleotide sequence comprises at least 20 contiguous nucleotides of SEQ ID NO:1"). Under both Mayo and Ambry, this claim is eligible.

Claim 7: This claim is similar to claim 6, but is independently eligible because it recites the specific output of the new polymerase chain reaction. This excludes "incidental art" in the form of prior activities using primers that incidentally meet the limitations of claim 6 but were not aimed at NF1 and did not amplify a sequence meeting the limitations of claim 7.

Claim 8: The eligibility of this claim is determined by the underlying claims from which it depends. This is because all it adds beyond those underlying claims is a bare statement of fact ("wherein a mutation in the NF1 gene in said sample indicates a patient from whom said sample was obtained has neurofibromatosis"). This statement of fact cannot be sufficient in and of itself to support eligibility if the underlying claim is ineligible. Nor will it negate eligibility in an otherwise eligible claim.

Ultimately, claim 8 is ineligible because at least one claim from which it depends is ineligible (e.g., claims 1 and 5) and claim 8 adds nothing "significantly more." This illustrates an important point from these March 2015 Comments: a claim is ineligible if at least one of its distinct embodiments is ineligible. It is not the presence of a judicial exception (the statement of fact in the "wherein" clause) or the fact claim 8 "comprises" this judicial exception that makes it ineligible. Claim 8 is ineligible because at least one complete embodiment of the claimed invention (e.g., claim 8 incorporating all elements of claim 1) is directed to a judicial exception.

Claim 9: This claim is a good counterexample to claim 8. The additional limitation of "diagnosing a patient whose sample harbors a mutation in the NF1 gene with neurofibromatosis" is more than a mere statement of fact or natural law. It is instead an active step that, according to the specification, cannot be performed entirely within the mind.

EXAMPLE 2

Background:

Roughly ten years after the discovery that inactivation of the NF1 gene is the cause of neurofibromatosis type I, inventors discovered that constitutive activation of the NF1 gene leads to a previously characterized developmental disorder named Hobbson syndrome. Hobbson syndrome is characterized by short stature and brittle bones. The inventors discovered that mutations that lead to constitutive activation of NF1 are completely penetrant for Hobbson syndrome (i.e., if the gene is constitutively active, then the individual will definitely have the disorder).

The inventors discovered that the most common way the NF1 gene gets activated in Hobbson syndrome is by deletion of very specific region of the gene within exon 6, highlighted below:

AAACAGCATTTAAATTTAAA**G**CCCTAAAGAA**G**GTTGCGCAGTTAGCAGTTATAAATAGCCTGGAAAAG

AAACAGCATTTAAATTTAAA***GG***GTTGCGCAGTTAGCAGTTATAAATAGCCTGGAAAAG

Normally this region accepts a negative regulator of NF1 expression. When this region is deleted, however, the negative regulator cannot lessen NF1 expression and Hobbson syndrome follows. The gene can also be merely over expressed, rather than constitutively active, which the inventors found to be incompletely associated with a milder form of Hobbson syndrome.

The inventors devised two methods of diagnosing Hobbson syndrome based on their discovery: mutation analysis and expression analysis. Mutation analysis was found to be the most definitive test for Hobbson syndrome because it gives a qualitative binary result—i.e., if the regulatory region is deleted, then the individual has the syndrome. Expression analysis was found to be less precise in diagnosing Hobbson syndrome, but capable of giving a quantitative probability estimate of having Hobbson syndrome, including an estimate of the severity of the disorder.

The inventors further investigated whether NF1 expression could be combined with other markers to diagnose disease. The inventors discovered that decreased expression of NF1 along with increased expression of Genes A, B and C was diagnostic of diabetes (a disease not known to have any relationship to neurofibromatosis type I) with a sensitivity of 90% and a specificity of 95%. After deriving this diagnostic panel, the inventors elucidated that Gene B's expression is upregulated in response to numerous complex diabetes-associated biological processes. The other markers' roles in diabetes are not known.

Claims:

Claim 1. A method for diagnosing Hobbson syndrome, the method comprising:

(1) assaying a sample to determine a test nucleotide sequence of the NF1 gene in said sample;

(2) providing a reference nucleotide sequence of the NF1 gene; and

(3) comparing said test sequence to said reference sequence using a computer programmed with executable code comprising (a) SEQ ID NO:1 as said reference sequence and (b) an algorithm for aligning said test sequence against said reference sequence and highlighting and differences between the two;

wherein (i) a difference between said test sequence and said reference sequence indicates the presence of a mutation in the NF1 gene in said sample and (ii) the presence of a mutation that constitutively activates the NF1 gene indicates the patient from whom the sample was obtained has Hobbson syndrome.

Claim 2. The method of claim 1, wherein providing a test nucleotide sequence of the NF1 gene comprises performing a laboratory assay to sequence a plurality of nucleic acid molecules derived from said sample and deducing the test nucleotide sequence of the NF1 gene from the sequences of said plurality of nucleic acid molecules.

Claim 3. The method of either claim 1 or 2, wherein providing a test nucleotide sequence of the NF1 gene comprises the polymerase chain reaction to amplify said plurality of nucleic acids.

Claim 4. The method of claim 3, wherein said assay comprises at least two oligonucleotide primers, each between 20 and about 50 nucleotides in length and each of whose nucleotide sequence comprises at least 20 contiguous nucleotides of SEQ ID NO:1.

Claim 5. The method of claim 4, wherein said at least two oligonucleotide primers comprise (a) at least one forward DNA primer and (b) at least one reverse DNA primer; wherein said forward DNA primer and said reverse DNA primer jointly prime a polymerase chain reaction that synthesizes an amplicon whose nucleotide sequence comprises between about 45 and about 2,000 contiguous nucleotides of SEQ ID NO:1.

Claim 6. The method of claim 1, wherein said mutation is deletion of the following ten nucleotides from exon 6 of the NF1 gene: CCCTAAAGAA.

Claim 7. The method of claim 6, wherein said comparing step comprises contacting a sample with an oligonucleotide probe not more than 100 nucleotides in length and comprising the following sequence AAATTTAAA***GG***GTTGCGCAG, wherein hybridization of said probe indicates the presence of said deletion.

Claim 8. The method of claim 7, wherein said oligonucleotide comprises a detectable label.

Claim 9. A method for diagnosing Hobbson syndrome, the method comprising:

(1) assaying a patient sample to measure the test level of NF1 expression in said sample; and

(2) comparing said test level of NF1 expression to a reference level of NF1 expression; and

(3) diagnosing a patient in whose sample the test level of NF1 expression exceeds said reference level of NF1 expression as having an increased likelihood of Hobbson syndrome.

Claim 10. A method for diagnosing diabetes, the method comprising:

(1) assaying a patient sample to measure the test level of expression of a panel of genes comprising NF1, Gene A, Gene B, and Gene C in said sample; and

(2) comparing said test level of expression for each gene in said panel to a reference level of expression corresponding to each gene in said panel; and

(3) diagnosing a patient in whose sample the test level of NF1 expression is less than a reference level of NF1 expression and the test level of each of Genes A, B and C exceeds a reference level of expression corresponding to each of Genes A, B and C as having diabetes.

Analysis:

Claim 1: This claim is similar to claim 1 in Example 1 above, but it is also different in some important ways. First, this claim expressly recites a physical assay step, which would weigh in favor of eligibility under Ass'n for Molecular Pathology v. United States PTO.[101]

Unlike in Example 1, however, in this example the NF1 gene is now known with its sequence fully characterized. Thus the active steps of the process are now routine and

[101] 689 F.3d at 1334-1335.

conventional in the art. That is, scientists have engaged in sequencing NF1, comparing patient sequences to reference sequences, noting differences as mutations, etc. Even the recitation of specifics of the computer program used to make the comparison does not help in this specific case because this process was described by the inventors in Example 1 (i.e., it was also routine and conventional by the time of the invention in Example 2).

Thus, the only difference between what was routine and conventional in the art and claim 1 is the clause "wherein […] (ii) the presence of a mutation that constitutively activates the NF1 gene indicates the patient from whom the sample was obtained has Hobbson syndrome." But this is, like in Mayo, a bare statement of fact. And because a constitutive activation mutation invariably leads to Hobbson syndrome, it is also a statement of a natural law. Again a table with the differences shown in italics helps illustrate:

Claim 1 of Example 2	**Closest process routinely engaged in by scientists at the time of filing**
A method for diagnosing Hobbson syndrome, the method comprising: (1) assaying a sample to determine a test nucleotide sequence of the NF1 gene in said sample; (2) providing a reference nucleotide sequence of the NF1 gene; and (3) comparing said test sequence to said reference sequence using a computer programmed with executable code comprising (a) SEQ ID NO:1 as said reference sequence and (b) an algorithm for aligning said test sequence against said reference sequence and highlighting and differences between the two; wherein (i) a difference between said test sequence and said reference sequence indicates the presence of a mutation in the NF1 gene in said sample *and (ii) the presence of a mutation that constitutively activates the NF1 gene indicates the patient from whom the sample was obtained has Hobbson syndrome*.	A method for diagnosing Hobbson syndrome, the method comprising: (1) assaying a sample to determine a test nucleotide sequence of the NF1 gene in said sample; (2) providing a reference nucleotide sequence of the NF1 gene; and (3) comparing said test sequence to said reference sequence using a computer programmed with executable code comprising (a) SEQ ID NO:1 as said reference sequence and (b) an algorithm for aligning said test sequence against said reference sequence and highlighting and differences between the two; wherein a difference between said test sequence and said reference sequence indicates the presence of a mutation in the NF1 gene in said sample.

Under a relatively straightforward application of Mayo, this claim is ineligible.

Special Note on Divided Infringement: It is worth noting something of concern to C21 member companies and others throughout the stakeholder community. Many examiners are taking a claim like claim 1 in this Example 2 and requiring a treatment step for eligibility. This practice is problematic for at least two reasons. First, it is apparently based on a misreading of Mayo. The Court in Mayo did in fact note the absence of a treatment step in the claims at issue there.[102]

[102] Mayo, 566 U.S. ___, 132 S. Ct. at 1296 ("*The District Court also accepted Prometheus' view that a doctor using Mayo's test could violate the patent even if he did not actually alter his treatment decision in the light of the test.*"); id. at 1302 ("*They tell a treating doctor to measure metabolite levels and to consider the resulting measurements in*

But this tangential note should not be read as the Court requiring the presence of a treatment step for eligibility. Instead, the Court's example of a step that could confer eligibility provides further support for C21's proffered reading of Mayo to merely require something (anything) new beyond a bare statement of the law of nature underlying a routine process.

More importantly, however, this practice by examiners severely undercuts patent protection in molecular diagnostics by placing applicants in an impossible dilemma. Adding a treatment step to a diagnostic method may be sufficient for eligibility (though C21 again emphasizes it is not necessary). But it also introduces an extraneous actor (e.g., a doctor or hospital) into the overall method and, in so doing, may make such a claim practically unenforceable. The courts are currently grappling with the question of divided infringement, but the current state of the law is that multiple parties performing distinct steps cannot infringe a method claim unless one party controls all others involved. Specifically, the Supreme Court has held that multiple parties' activities cannot be combined for indirect infringement.[103] And the current state of Federal Circuit law is that these parties' actions cannot be combined for direct infringement purposes.[104] Thus, as predicted by amici in the Akamai case,[105] reading § 101 case law too broadly (e.g., requiring a treatment step in a diagnostic method claim) places applicants in the quandary of choosing between an ineligible claim and an unenforceable claim.

Claims 2-5: The added detail in these claims does not confer eligibility in Example 2 despite being helpful in Example 1. This is because these assay details were routine and conventional at the time of Example 2's filing, whereas they were new at the time of Example 1's filing.

Claim 6: Specifying the mutation has an unclear effect on eligibility. The natural law is still arguably the only thing differentiating the claimed method from what was routine in the art. On the other hand, the Federal Circuit in Ambry suggested that specifying a particular mutation

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light of the statistical relationships they describe. In doing so, they tie up the doctor's subsequent treatment decision whether that treatment does, or does not, change in light of the inference he has drawn using the correlations.").

[103] See generally, Limelight Networks, Inc. v. Akamai Techs., Inc., 134 S. Ct. 2111 (2014).

[104] Id. at 2119 ("But the reason Limelight could not have induced infringement under §271(b) is not that no third party is liable for direct infringement; the problem, instead, is that no direct infringement was committed. Muniauction (which, again, we assume to be correct) instructs that a method patent is not directly infringed--and the patentee's interest is thus not violated--unless a single actor can be held responsible for the performance of all steps of the patent") (Emphasis in original.).

[105] Brief for Amici Myriad Genetics, Inc. and Genomic Health, Inc. in Limelight, 28-29 ("*The result is a dilemma for those seeking to protect their risky, expensive and valuable inventions: Either languish at the patent office wrestling with the current law of patent eligibility, or comply with the Patent Office's interpretation of patent eligibility and receive a patent claim that can be readily practiced without fear of liability under an unreasonably restrictive rule for divided infringement. If this Court does not affirm the Federal Circuit's en banc decision in Akamai II, it will in effect result in the 'removal of interactive methods [such as personalized medicine methods] from the purview of the patent system.'*") (Citing McKesson Techs. Inc. v. Epic Sys. Corp., No. 2010-1291, 2011 U.S. App. LEXIS 7531 (Fed. Cir. Apr. 12, 2011), at *20 (Newman, J., dissenting).)

may be an important distinction for eligibility purposes.[106] Given this, C21 submits that on balance claim 6 should be eligible.

Claim 7: This claim is eligible because it recites a new reagent to be used to modify the routine assays of the art. While probe hybridization was generally known and applied to the NF1 gene generally, the claim recites a specific probe not taught in the art and targeted to detect a specific mutation. Even under Ambry, this claim is eligible for patenting.[107]

Claim 8: This claim is eligible independent of any conclusion reached on claim 7 because the probe as a whole (and thus the method as a whole) is directed to something significantly more than a product of nature. The label is not an insignificant post-solution addition; instead it significantly increases the utility and functioning of the probe by making it readily detectable. Nor is it relevant that labels and labeled probes were generally well-known in the art before the inventors' filing. Mayo must be read narrowly to invalidate only subject matter where every element of the method was well-known and routine and the only contribution of the inventor was adding a bare statement of a law of nature.

This analysis also clarifies the December 2014 Guidance's discussion of a plurality of exceptions and its ambiguous treatment of combinations comprising an exception. Even assuming the mutation-specific probe is an exception (it is not), combining it with a label is sufficient (though not necessary) for eligibility. The composition as a whole may comprise a supposed exception, but this exception is paired with a non-natural element. Claim 8, independent of claim 7, is not directed to a judicial exception under Step 2A (i.e., no natural law or product is being claimed) and the claim is eligible for patenting.

Claim 9: This claim illustrates the significance of complete penetrance as distinguished from likelihoods based on human-derived statistical models (explored in more detail in Example 3 below). Whereas the deletion mutation in exon 6 is completely penetrant (i.e., all carriers have Hobbson syndrome), increased expression of NF1 is not. Expression in this case is a quantitative (rather than qualitative) variable that, when applied to a non-natural statistical model, yields a likelihood or prediction on whether the patient will ultimately show signs of Hobbson syndrome. As discussed in more detail in Example 3 below, the multiple biological agents may interact in a complex web of physiological pathways to determine how much NF1 ultimately gets expressed, how active this expressed protein is in the broader context of the cell, and how all of this manifests itself (or not) as Hobbson syndrome symptoms.

While this example is quite specific, it illustrates a broader principle that is critical in the molecular diagnostic field. Most statistical correlations established (i.e., created) by biostatisticians are not "natural laws," but are instead imperfect (though clinically acceptable) estimations. They set forth a likelihood a certain clinical fact is true based on a measured biomarker rather than stating an absolute natural law like gravity or relativity. For the reasons stated above claim 9, unlike claim 1, is not directed to a judicial exception under Step 2A (i.e., no natural law is being claimed) and the claim is eligible for patenting.

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[106] Ambry, 774 F.3d 755, slip op. 20 ("[T]he detection in claim 21 is limited to the particular mutations the inventors discovered….").

[107] Id.

Claim 10: This claim introduces the concept of multi-marker diagnostics, which is explored in more detail in Example 3. Because complete penetrance (or analogous ideas in fields other than genetics) is rare, most modern molecular diagnostic tests analyze and combine data from multiple markers to reach a particular diagnostic conclusion. In most cases, the biological role of each marker, if any, in the disease ranges from well-known to incompletely understood to completely uncharacterized. What is known, however, is that data from these markers can be manipulated by human scientists, using human-created statistical models, into a form usable by human clinicians to draw clinical conclusions. This process is not a law of nature and claims to the process of diagnosing patients according to this process are not "directed to" any judicial exception.

Thus, even assuming claim 9 was ineligible (it is not), claim 10 would be eligible. The claim sets forth a panel of markers whose expression can be applied in a statistical model to diagnose diabetes. Unlike a gene with relatively clear-cut natural boundaries (i.e., a discrete natural unit), nothing in nature clearly calls out this set of four markers as important in diabetes. Instead, the human endeavor of statistics has established (i.e., created) a connection amongst these four markers and between the combination of these markers and diabetes.

For three of the four genes, their role in the disease is completely unknown. Increased expression of Gene B was shown to be a consequence of diabetes rather than a driver of the disease. Such downstream (or output) markers are distinguishable from drivers in that no cause-and-effect "law of nature" can even arguably be asserted. These are "markers" in the truest sense of the word: they can be used statistically to flag the existence of the disease without playing any role in its development.

For all of these reasons claim 10, independent of claim 9, is not directed to a judicial exception under Step 2A (i.e., no natural law is being claimed) and the claim is eligible for patenting.

EXAMPLE 3

This Example 3 is adapted from Example D submitted in C21's August 2014 Comments.[108] This version adapts the example to the December 2014 Guidance and our new March 2015 Comments.

Background:

Sepsis is a complex, incompletely understood and often fatal disorder, typically accompanied by pyrexia (or fever). D1 is 15-amino-acid peptide that, among its multiple effects, induces pyrexia. D1 has been shown to be useful as a biomarker in diagnosis of stroke and inflammatory bowel syndrome, as a biomarker of neural transmitter activity in animal health diagnosis, and as a biomarker for identifying a patient susceptible to particular cancer therapies. The specification teaches for the first time that increased plasma concentrations of D1 are associated with sepsis.

The biochemical or physiological role of D1 in sepsis is unknown and there is no indication that D1 plays any role in fighting infection or sepsis, but the specification presents

[108] August 2014 Comments, pp.33-43 (section entitled "*D. Process Claim Involving A Natural Principle*").

evidence suggesting a possible mechanism for how infection may lead to increased D1 levels. Bacterial infection was shown in rats to trigger increased production of C-Reactive Protein (CRP), which is itself a non-specific indicator of inflammation. Pyrexia incident to severe bacterial infection induces production of Enzyme A. CRP reacts with Enzyme A to produce Effector B. Effector B is a small organic molecule similar in structure to testosterone that triggers a signaling cascade that upregulates expression of a number of genes, including the gene encoding the D1 protein. D1 is the most stable (i.e., longest-lasting) protein upregulated by this cascade, lending to its practical value as a blood marker.

The specification teaches the use of D1 levels to determine a septic patient's prognosis according to the established APACHE II scoring system. D1 levels in a test patient exceeding the mean D1 levels in non-diseased individuals are shown to predict sepsis with sensitivity of 85% and specificity of 92%. The specification teaches the development of a multi-biomarker assay, measuring and comparing the relative levels of D1, D2 & D3 to better diagnose sepsis. The specification further refines this multi-biomarker panel by showing that the combination of D1, D2 & D3 level measurements into a single index score yields a test where patients with an index score exceeding a particular reference score are predicted to have sepsis with sensitivity of 95% and specificity of 97%.

D1, D2 & D3 are all well-known proteins in the art. The art teaches numerous techniques for measuring these biomarkers in several specimen types. D1, D2 & D3 levels are routinely measured in emergency room patients as part of a comprehensive panel comprising 22 other markers. This panel screens for several critical conditions common to emergency room patients, including anemia, tachycardia and sepsis. Nothing in the art discloses measuring D1 for the purpose of detecting sepsis. D1 is in the routine emergency room panel as a rough screen for acute anemia associated with blood loss. The art teaches measuring D2 independently as a rough screen for sepsis. The art further teaches measuring D3 as part of a 5-marker panel for hypotension, a dangerous condition in its own right and a common sign of sepsis as well as several other critical conditions.

Claims:

Claim 1. A method for the diagnosis of sepsis, the method comprising: determining the level of D1 in a blood sample from a mammalian patient suspected of having sepsis, wherein elevated levels of D1 relative to a normal control are indicative of sepsis.

Claim 2. A method for detecting sepsis, the method comprising:

(a) determining the level of D1 in a blood sample from a mammalian test patient suspected of having sepsis,

(b) comparing the level of D1 in said blood sample to that in a non-diseased reference patient, and

(c) diagnosing the test patient as having sepsis when the level of D1 in said blood sample exceeds that in said non-diseased reference patient.

Claim 3. The method of claim 2, wherein said determining step comprises assaying said sample using a radioimmunoassay or an ELISA assay.

Claim 4. A method for predicting a septic test patient's APACHE II score, the method comprising:

(a) determining the level of D1 in a blood sample from said test patient,

(b) comparing the level of D1 in said blood sample relative to that in a plurality of reference patients each with a distinct APACHE II score, and

(c) predicting said test patient to have an APACHE II score within 2 points of the APACHE II score of said reference patient with a D1 level closest to the level of D1 determined in said blood sample.

Claim 5. The method of claim 4, further comprising administering drug Y if said test patient's APACHE II score is predicted to exceed 50.

Claim 6. A method for the diagnosis of sepsis, the method comprising:

(a) measuring the concentration of D1 in a blood sample obtained from a test patient;

(b) measuring the concentration of D2 in the blood sample;

(c) measuring the concentration of D3 in the blood sample;

(d) determining a ratio of D1 to D2;

(e) determining a ratio of D1 to D3; and

(f) diagnosing said test patient as having sepsis when the concentration of D1 is greater than 0.5 ng/ml and the ratio of D1/D2 is greater than 0.0001 and the ratio of is D1/D2 greater than 0.3 is indicative of sepsis.

Claim 7. A method for determining the likelihood a test patient has sepsis, the method comprising:

(a) measuring the concentration of D1, D2, and D3 in a blood sample obtained from said test patient;

(b) normalizing the levels of D1, D2, and D3 measured in (1) to obtain normalized protein levels;

(c) calculating a test quantitative score for said test patient, wherein the test quantitative score is calculated as follows: (0.1 x [D1]) + (0.3 x [D2]) - (0.5 x [D3]), wherein [D1] represents the normalized level of D1 protein in the sample, [D2] represents the normalized level of D2 protein in the sample, and [D3] represents the normalized level of D3 protein in the sample; and

(d) comparing said test quantitative score with a reference quantitative score;

(e) predicting the likelihood said test patient has sepsis based on the comparison in (d).

Claim 8. The method of claim 7, further comprising diagnosing said test patient as having sepsis if said test quantitative score exceeds said reference quantitative score.

Claim 9. The method of claim 7, further comprising reporting or recording the results of said comparison.

Claim 10. The method of claim 8, further comprising reporting or recording said diagnosis.

Analysis:

Claim 1: Under Step 2A, the question is whether the claim is "directed to" a judicial exception. In this case, there is no clear cause-and-effect law of nature to which the claim is directed. The specification describes the use of statistics to establish a correlation between D1 levels and sepsis. It is important to understand that correlation does not imply causation. The role of D1 in sepsis is not well-understood except that sepsis contributes to a cascade of events that results in D1 expression. In fact, D1 is at most a downstream marker of sepsis rather than a causative driver of the disease. Thus, this correlation is not a law of nature. However, for the sake of argument and to illustrate the analysis in this instance, we let us assume this is a law of nature.

Under Step 2B, the question is whether the claim adds anything significantly more than the natural law. The answer is "no." This is a very common structure of molecular diagnostic claims, especially before the Supreme Court's decision in Mayo. However, the claim suffers from the same primary defect as the invalid claims in Mayo. Namely, the only difference between the claimed process and that which was routine in the art at the time of filing is a statement of what is considered by the Court to be a natural principle. The process to be compared here is not a process that occurs naturally in the body but instead non-natural processes engaged in routinely in the field before applicant's filing. This is readily seen in the following chart:

Claim 1	**Process routinely engaged in by scientists at the time of filing**
A method *for the diagnosis of sepsis*, the method comprising: determining the level of D1 in a blood sample from a mammalian patient suspected of having sepsis, *wherein elevated levels of D1 relative to a normal control are indicative of sepsis.*	A method comprising: determining the level of D1 in a blood sample from a mammalian patient suspected of having sepsis.

The background states that D1 is routinely tested in emergency room patients as part of a 25-marker screening panel. Sepsis is common in emergency room patients and is one of many diseases screened in the 25-marker panel mentioned in the background section. Hence, patients administered the routine emergency room panel are often "suspected of having sepsis."

Just as in Mayo, the "wherein" clause here adds no limitation, step, structure or element to the claimed process. It is a bare statement of fact that does not limit the claim in any way. The only other difference is the preamble language stating that the method of claim 1 is "for the diagnosis of sepsis." Preamble language can in some cases be a positive limitation on the scope of claims, but in this case it is not. It is merely a statement of intended use—a new purpose for running a process that is routine in the art—rather than a new or modified step in that process. Assuming a law of nature is recited, the claim adds nothing more to make the

claim eligible for patenting. Because no law of nature is recited, the claim is eligible for patenting under § 101. The claim may be anticipated under § 102 if all active steps of the process were known in the art.

Claim 2: This claim provides another opportunity to revisit the question of whether a law of nature is claimed. (a) Sepsis leads to elevated levels of D1. This natural fact described in the background can be extrapolated, using human clinical and statistical ingenuity to derive the following: (b) Elevated levels of D1 relative to a normal control are indicative of sepsis. While the two statements appear to be mirror images, there is an important difference. Statement (a) is truly a description of a natural process/principle. It is a biochemical fact, with a clear biochemical pathway underlying it, that bacterial infection leads to elevated D1 levels. Statement (b), the reverse, diagnostic connection is not a natural process but instead a human-made statistical connection that can be applied in several ways, one of which is to diagnose sepsis as in claim 2.

At each step in the complex physiological progression from bacterial infection to D1 production, a single component may exert numerous effects on interconnected systems and multiple potential diagnostic markers are presented. This is likely the reason D1 is not a perfect, absolute predictor of sepsis (sensitivity of 85% and specificity of 92%). This is distinguishable from classical laws of nature mentioned in numerous court decisions.[109] For example, the law of gravity says that all massive objects necessarily attract each other according to a specific equation. Gravity is a law of nature because there is no sensitivity or specificity (or at least they are both 100%). It is the application of human statistical ingenuity, on the other hand, that works backward to generate a new, useful (though not absolute), diagnostic connection between D1 and sepsis. This is not a natural principle.

Nor is this an abstract idea simply because statistical analyses are performed. Nothing in this method is abstract. The disease is real, the measurements are real, and the outcome of the diagnosis is real and may ultimately be used to apply, guide, or recommend treatment to the patient.

However, as with claim 1 we will assume it is a law of nature in order to illustrate analysis under Step 2B. Unlike claim 1, claim 2 does add something significant to the supposed law of nature. Again the following chart is helpful:

Claim 2	**Process routinely engaged in by scientists at the time of filing**
A method *for detecting sepsis*, the method comprising: (a) determining the level of D1 in a blood sample from a mammalian test patient suspected of having sepsis, (b) comparing the level of D1 in said blood sample to that in a non-diseased reference patient*, and*	A method *for detecting sepsis*, the method comprising: (a) determining the level of D1 in a blood sample from a mammalian test patient suspected of having sepsis, (b) comparing the level of D1 in said blood sample to that in a non-diseased reference patient, and

[109] This is also distinguishable from claim 1 of Example 1 above, where a clear cause-and-effect law of nature is recited.

(c) diagnosing the test patient as having sepsis when the level of D1 in said blood sample exceeds that in said non-diseased reference patient.	(c) diagnosing the test patient as having acute anemia caused by blood loss when the level of D1 in said blood sample exceeds that in said non-diseased reference patient.

The background states that D1 is routinely tested in emergency room patients and used to diagnose acute anemia associated with blood loss. Thus, the routine process and the claimed process are different. One involves a step of diagnosing anemia while the other recites a step of diagnosing sepsis.

The "diagnosing" step is the critical part of each process. It is also an active step that is integrated into the process as a whole, in contradistinction to the "wherein" clause appended to claim 1. Whereas the "wherein" clause in claim 1 adds no limitation, step, structure or element to the claimed process, diagnosis is a non-abstract, active, and integral step in the overall process. And the diagnosis step's presence in the claim limits the process to a specific application of the various natural principles at work. Rather than being merely a statement of intended use—a new purpose for running a process that is routine in the art—diagnosing sepsis based on D1 levels is a new, modified step in that process.

While preemption is not the test for patent-eligibility, it is a useful after-the-fact check to see whether examination has come to the right conclusion (i.e., a conclusion that comports with the primary concern underlying the exclusions to subject matter eligibility). In this case, D1's use in sepsis does not preempt all uses of the marker or all of it diagnostic uses. The background describes several additional diagnostic uses for D1 fairly far afield from sepsis (e.g., animal health diagnosis). Assuming a law of nature is recited, the claim is still eligible because it adds something significant.

Claim 3: Same analysis as claim 2. The recitation of specific techniques for assaying D1 in blood indeed limits the claims, but it is irrelevant to the question of whether the applicant is claiming a natural principle or an application thereof. The additional limitations are not required for eligibility and, thus, the claim is eligible for patenting for the same reasons as claim 2.

Claim 4: The analysis under Step 2A is similar to claim 2. (a) Sepsis leads to elevated levels of D1. This natural fact described in the background can be extrapolated, using human clinical and statistical ingenuity to derive the following: (b) the degree of plasma D1 level increase predicts prognosis as independently measured by the APACHE II system. Statement (a) is a natural principle while statement (b) is not. Instead statement (b) is a statistical correlation between a biomarker measurement and a human-created, numerical score that can be applied to determine a patient's prognosis.

We will again assume this is a law of nature in order to illustrate analysis under Step 2B. Claim 4 adds something significant to the supposed law of nature under similar reasoning to claim 2:

Claim 4	Process routinely engaged in by scientists at the time of filing
A method for predicting a septic test patient's APACHE II score, the method comprising: (a) determining the level of D1 in a blood sample from said test patient, (b) comparing the level of D1 in said blood sample relative to that in a plurality of reference patients each with a distinct APACHE II score*, and* *(c) predicting said test patient to have an APACHE II score within 2 points of the APACHE II score of said reference patient with a D1 level closest to the level of D1 determined in said blood sample*.	A method for predicting a septic test patient's APACHE II score, the method comprising: (a) determining the level of D1 in a blood sample from said test patient, (b) comparing the level of D1 in said blood sample relative to that in a plurality of reference patients each with a distinct APACHE II score.

The background states that D1 is routinely tested in emergency room patients and used to diagnose acute anemia associated with blood loss. While emergency room patients are routinely prognosed using the APACHE II system, there is no indication that D1 has been used to predict APACHE II prognosis score. Thus, the routine process and the claimed process are different.

The "predicting" step is a critical part of the claimed process and is missing from the routine art process. It is also an active step that is integrated into the process as a whole, in contradistinction to the "wherein" clause appended to claim 1. Whereas the "wherein" clause in claim 1 adds no limitation, step, structure or element to the claimed process, predicting APACHE II score is an active, integral step in the overall process. And the predicting step's presence in the claim limits the process to a specific application of the various natural principles at work. Rather than being merely a statement of intended use—a new purpose for running a process that is routine in the art—prognosing a septic patient based on D1 levels is a new, modified step in that process. Assuming a law of nature is recited, the claim is still eligible because it adds something significant.

Claim 5: Same analysis as claim 4. The recitation of additional active steps based on the prognosis reached in claim 4 further limits the claims and further applies the natural principle, but such recitation is irrelevant to the question of whether the applicant is claiming a natural principle or an application thereof. The Court noted the absence of such a step in Mayo, but this should not be construed as a requirement of a treatment step for eligibility. Prognosing (and diagnosing) are active, non-abstract applications sufficient to confer eligibility without a treatment step.

Claim 6: The analysis under Step 2A here is similar to claims 2 and 4. Sepsis leads to elevated levels of D1 (same as claim 2). The ratios of D1 to D2 and D1 to D3 as measured in the patient sample are utilized in the claims, but these are not natural laws or phenomenon. First, any connection between these ratios and sepsis is mechanistically unclear and remote. Second, there is no indication whether a particular ratio is causative or a result of sepsis. In other

words, there is no clear mechanistic natural law or phenomenon. Additionally, this is not a claim to an abstract idea simply because there is a mathematical construct in the claim. As stated earlier, the patient, the measurements and the result of the process are real and tangible.

We will again assume this is a law of nature in order to illustrate analysis under Step 2B. Claim 6 adds something significant to the supposed law of nature:

Claim 6	**Process routinely engaged in by scientists at the time of filing**
A method for the diagnosis of sepsis, the method comprising: (a) measuring the concentration of D1 in a blood sample obtained from a test patient; (b) measuring the concentration of D2 in the blood sample; (c) measuring the concentration of D3 in the blood sample*;* *(d) determining a ratio of D1 to D2;* *(e) determining a ratio of D1 to D3; and* *(f) diagnosing said test patient as having sepsis when the concentration of D1 is greater than 0.5 ng/ml and the ratio of D1/D2 is greater than 0.0001 and the ratio of is D1/D2 greater than 0.3 is indicative of sepsis*.	A method for the diagnosis of sepsis, the method comprising: (a) measuring the concentration of D1 in a blood sample obtained from a test patient; (b) measuring the concentration of D2 in the blood sample; (c) measuring the concentration of D3 in the blood sample.

The background states that D1, D2 & D3 are all routinely tested in emergency room patients to diagnose, respectively, acute anemia associated with blood loss, sepsis and hypotension. Thus, the routine process and the claimed process are identical up to and including the point of measuring these three markers. However, the claimed process adds important elements and steps to the routine process which distinguish it from the judicial exceptions by (1) comparing the three markers' concentrations to each other and (2) diagnosing sepsis based on their relative concentrations. The "determining a ratio" steps in claim 6 are just as active as the "measuring" steps and just as integral to the claim process as the "diagnosing" and "predicting" steps in claims 2 and 4, respectively.

The background teaches that it was routine in the art to screen for sepsis using D2. However, the claims do not purport to claim the independent use of D2 to diagnose sepsis and are instead limited to the use of D2 in conjunction with D1 & D3. Similarly, D3 is routinely used in the art in conjunction with four other markers, to diagnose hypotension. Though there is a physiological connection between hypotension and sepsis, hypotension is worth testing for based solely on its own dangers condition and D3 is not used in the art to diagnose sepsis. And, just like D2, the claims do not cover use of D3 alone to diagnose sepsis.

Assuming a law of nature is recited, the claim is still eligible because it adds something significant.

Claim 7: This claim illustrates well that a diagnosis of disease, while not abstract, may not be absolute. In numerous instances, the diagnosis is more often a likelihood that a patient has a particular disease or that the disease they have has a particular likelihood of worsening or retreating. This is often called the prognosis of the disease. Physicians will often form preliminary diagnoses which guide the direction of further tests which are used to narrow or more precisely define the nature of the actual disease in the patient.

The presence of a numerical score does not per se make the claim directed to an abstract idea. The claim is not directed to a number or even a method of calculating a number. Instead the claim recites using the number to predict likelihood of having a specific, real-world disease.

We will again assume this is a law of nature in order to illustrate analysis under Step 2B. The analysis of claim 7 is similar to claim 6:

Claim 7	**Process routinely engaged in by scientists at the time of filing**
A method for determining the likelihood a test patient has sepsis, the method comprising: (a) measuring the concentration of *D1, D2,* and D3 in a blood sample obtained from said test patient; *(b) normalizing the levels of D1, D2, and D3 measured in (1) to obtain normalized protein levels;* *(c) calculating a test quantitative score for said test patient, wherein the test quantitative score is calculated as follows: (0.1 x [D1]) + (0.3 x [D2]) - (0.5 x [D3]), wherein [D1] represents the normalized level of D1 protein in the sample, [D2] represents the normalized level of D2 protein in the sample, and [D3] represents the normalized level of D3 protein in the sample; and* *(d) comparing said test quantitative score with a reference quantitative score;* *(e) predicting the likelihood said test patient has sepsis based on the comparison in (d).*	A method for determining the likelihood a test patient has hypotension, the method comprising: (a) measuring the concentration of D3 and four other markers [not D1 or D2] in a blood sample obtained from said test patient; and (b) combining these 5 markers into a score to predict likelihood of hypotension.

The claimed process adds important elements and steps to the routine process by (1) combining the three markers' concentrations to derive a quantitative score and (2) comparing this quantitative score to a reference score (let alone leading to a prediction of likelihood of sepsis rather than hypotension). The "combining" and "comparing" steps in claim 7 are just as active as the "measuring" steps and just as integral to the claim process as the "diagnosing" and "predicting" steps in claims 2 & 4, respectively. The background teaches that it was routine in the art to combine D3 with other markers to diagnose hypotension. Combining D1, D2 & D3 into a numerical score is new.

Assuming a law of nature is recited, the claim is eligible because it adds something significant.

EXAMPLE 4

Background:

The human adaptive immune system is able to mount an immune response specific to foreign antigens by generating a repertoire of highly polymorphic T-cell and B-cell antigen receptors with sufficient diversity to recognize the vast universe of potential pathogens.

In T cells, most of this T cell receptor diversity is found in the third complementarity-determining region (CDR3) of a T cell receptor's (TCR) α and β chains. The CDR3 regions of the α and β chains are formed by recombination between noncontiguous variable (V), diversity (D), and joining (J) gene segments in each locus. CDR3 sequence diversity is further increased by template-independent addition and deletion of nucleotides at the V-D, D-J, and V-J junctions during the process of TCR gene rearrangement.

Assessing the total diversity of the T cell receptor repertoire can have important applications for understanding, diagnosing and treating cancer and autoimmune diseases, and for monitoring or predicting response to immunotherapy, vaccination, or transplant.

To estimate the diversity of an individual's TCRB repertoire, the inventors developed multiplex PCR primers that are complementary to specific V-segment genes and J-segment genes of the TCRB CDR3 region. The primers enable amplification of substantially all of the diversity of TCRB CDR3 rearranged sequences in a sample. The resulting amplicons can then be sequenced by high throughput sequencing methods to generate sequence reads, which are used to estimate the total diversity of TCR rearranged CDR3 sequences.

The primers each include a first sequence that is complementary to the V-segment or J-segment genes, and a second sequence that is a sequencing adaptor oligonucleotide. The sequencing adaptor oligonucleotide is designed to not be found in the target gene and to not be complementary to the target gene. The sequencing adaptor oligonucleotide is compatible for use in a high throughput sequencing system.

The inventors additionally developed a scoring system capable of using the sequence data derived from the sequencing assays described above to estimate a patient's TCRB diversity. The inventors further developed algorithms applying this scoring system to predict a patient's response to specific vaccines, assess the severity of a patient's autoimmune disease, diagnose a patient with immune-cell cancers such as leukemia, etc.

Claims:

Claim 1. A composition, comprising:

(a) a plurality of V-segment primers, and

(b) a plurality of J-segment primers,

wherein each of said plurality of V-segment primers comprises a first sequence and a second sequence, wherein said first sequence is located 3' to said second sequence on said V-segment primer and is complementary to a portion of a T Cell Receptor (TCR) V-region

gene segment, wherein said second sequence of said V-segment primer is a sequencing oligonucleotide sequence that is not complementary to any TCR V-region gene segment,

wherein each of said J-segment primers comprises a first sequence and a second sequence, wherein said first sequence is located 3' to said second sequence on said J-segment primer and is complementary to a portion of a TCR J-region gene segment, wherein said second sequence is a sequencing oligonucleotide sequence that is not complementary to any TCR J-region gene segment.

Claim 2. A method of estimating a patient's T-cell receptor B (TCRB) diversity comprising:

(1) sequencing a plurality of V-segment genes and J-segment genes of the TCRB CDR3 region in a sample obtained from said patient to obtain a plurality of unique CDR3 sequence reads;

(2) determining a diversity score for the sample by determining a total number of unique CDR3 sequences observed in the sample; and

(3) estimating the total TCRB diversity of the subject by applying an unseen species algorithm to the diversity score of the sample.

Claim 3. A method of predicting a patient's response to an immunotherapy, comprising:

(1) calculating an immune response score based on the total diversity of unique CDR3 sequences in the patient determined in claim 2;

(2) determining a threshold for classifying an immune response score based on a set of immune response scores of patients with known responses to said immunotherapy; and

(3) predicting an immunological response to said immunotherapy for said patient based on a comparison of said immune response score with said threshold.

Analysis:

Claim 1: This claim is directed to a composition of matter in the truest sense of that term.[110] Under Step 2A of the December 2014 Guidelines, the claim is not directed to a "law of nature" or a "product of nature" because each primer constitutes a chimeric sequence. Each primer comprises a naturally occurring sequence, which in isolation may or may not be a judicial exception (i.e., a product of nature). But the primer as a whole has a non-naturally occurring sequence because this natural, target-complementary sequence is attached to a second sequence that is not complementary to the target (i.e., an artificial sequencing adaptor). As a combination of a putative judicial exception and what is clearly not a judicial exception, the claimed composition as a whole is not directed to a judicial exception under Step 2A.[111] Thus, the claim is patent eligible under § 101.

[110] Chakrabarty, 447 U.S. at 308 (citing Shell Development Co. v. Watson, 149 F. Supp. 279, 280 (D.D.C. 1957) (emphasis added) ("'[C]omposition of matter' has been construed consistent with its common usage to include 'all compositions of two or more substances and … all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids.'").

[111] See, e.g., Section 2(c)(i)(A), supra ("*In this vein, C21 reiterates a point from our August 2014 Comments, calling for explicit recognition of and guidance to examiners on the critical difference between (a) a claim encompassing a*

Claim 2: This claim is directed to a method of estimating TCRB diversity. TCRB diversity as recited in the claim and described in the specification is a human-created construct that relates to natural phenomena (i.e., the sequences found in various TCRB genes), but which interprets these phenomena in an artificial way digestible by clinicians. The claimed method is a way of estimating this diversity by further digesting data about the natural phenomena (sequence diversity) into a numerical score.

This is not a law of nature. It is not claiming a phenomenon of nature, but rather a specific way of measuring multiple phenomena of nature (TCRB gene sequences) and combining them into a human-made construct that is clinically meaningful. Nor are the claims directed to an abstract idea. The presence of a numerical score or mathematical algorithm for calculating and/or applying that score does not mean the claim is "directed to" an abstract idea.[112] The score corresponds to and allows clinicians to interpret real-world biological phenomena. Thus, the claim is not directed to a judicial exception and is patent eligible under § 101.

Claim 3: This claim's eligibility largely follows from the eligibility of claim 2. That is, the process of calculating the diversity score is eligible and so a method of applying that score to predict a clinical outcome is likewise eligible. Even assuming the score and the method of calculating it were ineligible (they are not), the correlation between a specific TCRB diversity score and likelihood of response to an immunotherapy is not a judicial exception. This correlation is not a natural law or an abstract idea. It is a statistical construct established (i.e., created) by human endeavor. And a method of applying that correlation to predict clinical response is eligible for patenting. Thus, the claim is not directed to a judicial exception and is patent eligible under § 101.

Again, we appreciate the opportunity to provide these comments.

Sincerely,

/Hathaway P. Russell/

Hathaway Pease Russell

Counsel to The Coalition for 21st Medicine

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judicial exception as a distinct embodiment of the claim as a whole and (b) the claim as a whole "comprising" a judicial exception, e.g., as one component of a combination or process.").

[112] Diehr, 450 U.S. at 185 ("*Our conclusion regarding respondents' claims is not altered by the fact that in several steps of the process a mathematical equation and a programmed digital computer are used.*").