



## COMMENTS ON PTO AMP-MAYO MARCH 2014 GUIDANCE

### FROM THE COALITION FOR 21ST CENTURY MEDICINE

#### Introduction

The Coalition for 21<sup>st</sup> Century Medicine (the “Coalition”)<sup>1</sup> respectfully submits the following comments on the “2014 Procedure For Subject Matter Eligibility Analysis Of Claims Reciting Or Involving Laws Of Nature/Natural Principles, Natural Phenomena, And/Or Natural Products” promulgated by the U.S. Patent and Trademark Office on March 4, 2014 (the “March 2014 Guidance”). Following these brief introductory comments is a proposed practical framework and several detailed examples for examining patent applications for subject matter eligibility under 35 U.S.C. § 101 (the “Proposed Guidance”). The framework and the analysis of each example in the Proposed Guidance are supported by binding case law precedent from the Supreme Court and the Federal Circuit.

The Coalition recognizes the Office’s challenge in creating a practical framework for everyday examination that harmonizes decades of court decisions under changing statutory provisions, especially when such court decisions appear to have intentionally avoided any clear-cut analytical rules.<sup>2</sup> The Coalition submits that, in reviewing and reissuing the March 2014 Guidance, the Office can follow a few general signposts that will ensure proper deference to binding precedent without overextending such precedent to remove large swaths of previously eligible subject matter from the invaluable incentives of the patents system.

The Courts have made clear that the default under § 101 is eligibility. Only if subject matter clearly fits within a category of excluded matter is it ineligible for patenting. And those categories should be interpreted faithfully but narrowly to exclude only that which is clearly a product, law or phenomenon of nature or an abstract idea.<sup>3</sup>

Key court decisions that provide important guidance are discussed and interpreted in detail below. For example, Funk Brothers Seed Co., v. Kalo Inoculant Co. stands not for the broad exclusion of any simple mixture of natural products, but instead the rejection of claims to natural products defined solely according to their natural properties. This fairly uncontroversial principle, rather than an exclusion of any product isolated or even derived from a natural source, in turn dictates the invalidation of claims to isolated natural genes encoding a natural protein in Ass’n for Molecular Pathology v. Myriad Genetics Inc. Diamond v. Chakrabarty makes clear that the overarching question for eligibility for compositions is simply whether what is claimed was made by humans or made by nature. And Mayo Collaborative Services v. Prometheus Laboratories Inc. teaches that a method claim must include something different from what was routine beyond the simple recitation of a law of nature. The scientific details of these cases, as elucidated below, help to understand that each decision was written to exclude

relatively little from the “broad and deliberately expanded statutory grant” of subject matter eligibility under § 101.

The importance of the Office correctly instructing its examiners on how to analyze subject matter eligibility cannot be overstated. The United States is currently a global leader in biotechnology, emerging technologies, and medicine. Restricting the scope of patent-eligibility in the U.S. beyond that required by binding case law may cause a slowing of the growth of human capital, investment, and even academic advancement in those areas, especially as compared to other markets such as China, Europe, Australia, Japan, Russia, and South Korea that continue to offer a superior degree of protection for inventions in these industries.<sup>4</sup> The March 2014 Guidance threatens to erode protection for patents in the U.S., the lifeblood of biotech, and consequently threatens the value of biotech companies by encouraging litigation and potentially chilling venture investment.<sup>5</sup> In an industry where the predictability of strong patent protection was critical to the establishment of America’s leadership position, the March 2014 Guidance injects troubling uncertainty by endangering broad swaths of previously patentable subject matter such as vaccines, antibody compositions, and drugs with active ingredients from plants.<sup>6</sup> From 1981 to 2010 alone, of 1,355 approved new drugs, 47% could be categorized as biologicals, natural products, or derivatives of natural products and vaccines -- 636 of those drugs, therefore, would have faced review and risked exclusion from patent eligibility if subjected to the new Guidelines at the time.<sup>7</sup> Bob Stoll, the former USPTO Commissioner of Patents, urged the Office to heed user community feedback as well as practitioner commentary and warned that “limiting patent eligibility beyond what is required by the law” would harm both the economy and job creation.<sup>8</sup>

The Coalition submits the following to help the Office in revising the March 2014 Guidance to better comport with case law and better drive incentives through a strong, predictable patent system.

## **PROPOSED PROCESS FOR ANALYZING COMPOSITION CLAIMS:**

### **Introduction**

The overarching question that should guide examination for subject matter eligibility under 35 U.S.C. § 101 is “Who/what produced the composition as claimed?” “Congress thus recognized that the relevant distinction was [...] between products of nature[...] and human-made inventions.” Chakrabarty, 447 U.S. at 313. That which is made by nature unaided by the hand of man is “part of the storehouse of knowledge of all men” and ineligible for patenting. “Anything under the sun that is made by man” is eligible for patenting. The following points should be addressed in examining composition claims for subject matter eligibility:

1. *Does the claim appear, on its face, to potentially encompass a product of nature?*
2. *What is the product of nature potentially encompassed by the claim?*
3. *Is the claimed composition structurally identical to a natural product, including any discrete natural unit?*
4. *Does the claimed composition possess a new or enhanced function or utility as compared to the natural product?*

#### **1. Does the claim appear, on its face, to potentially encompass a product of nature?**

This is a threshold question of whether the claim clearly may encompass a product of nature. § 101 is a broad threshold gate through which most compositions should pass. Thus only those claims that appear on their face to implicate the product of nature exception should be subjected to closer subject matter eligibility scrutiny.

##### **a. “Encompassing” versus “comprising”**

Examination must recognize the critical distinction between “encompassing” and “comprising.” A claim “comprising” a product of nature could well be eligible since everything at its core “comprises” a product of nature. For example, a non-natural protein that is a fusion of two naturally-occurring proteins “comprises” a product of nature but is clearly eligible.

A claim is ineligible only if it “encompasses,” as one of its distinct embodiments, a product of nature. For example, claim 1 of the ‘282 patent in AMP 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 a natural product

##### **b. Look for a potential natural counterpart in the specification and the common knowledge in the art.**

If the specification describes extraction of the claimed composition from natural sources or describes a natural product that appears on a facial review to be structurally identical or highly similar to the claimed composition, then close inspection under § 101 is appropriate. “Structure” in this sense and as used throughout this document encompasses a composition and the chemical and conformational structure of each component.

Likewise, if the examiner is aware based on pre- or post-filing art that the claimed composition is available from natural sources or the art describes a natural product that is

structurally identical or highly similar to the claimed composition, then close inspection under § 101 is appropriate.

For example, a claim to virtually any organism (e.g., bacteria, multicellular organisms) facially raises the question of whether a product of nature is being claimed because organisms are predominantly produced by and found in nature. A claim to most proteins or polynucleotides facially raises the question of whether a product of nature is being claimed if the specification or general knowledge in the art teaches that a protein or polynucleotide of similar structure exists in nature. Proteins and especially polynucleotides present special questions of substructure, derivatives, and properties versus functions that will be addressed below. More evidence (the specification or art clearly teaches a small molecule of highly similar structure in nature) will be necessary to justify close scrutiny for “small” molecules since these have been routinely wholly synthesized by humans for centuries.

**c. A claim to anything whose chemical structure as a whole is facially not found or not reasonably suspected of being in nature does not raise the question of subject matter eligibility.**

“Reasonably suspected” should require some specific reason to believe there is a natural analogue, not some generalized notion that compositions of the same type or class exist in nature. For example, a claim to a novel chemotherapy agent does not necessarily present a facial question under § 101 simply because many such agents have been derived from natural compounds. Without some teaching in the specification or art of a naturally-occurring compound structurally similar to the claimed compound, no facial § 101 issue is raised. Notice that the available art for making this facial determination does not stop at the time of filing. Any teaching in the art should be assessed in deciding whether there is a potential natural counterpart to the claimed composition.

**2. What is the product of nature potentially encompassed by the claim?**

This is arguably the most important part of the analysis. A careful and correct identification and definition of what the product of nature is (and is not) will generally determine the outcome.

The examiner must identify a specific organism, organ, tissue, cell, subcellular structure, macromolecule, or small organic or inorganic molecule or freestanding element existing in and produce by nature against which to compare the claimed composition. 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.

**a. Discrete natural unit**

One useful analytical tool for properly defining the natural product is to look for a “discrete natural unit.” The easiest case will be entire molecules found as such in a natural source. Examples include entire individual proteins (e.g., erythropoietin), entire nucleic acids (e.g., mRNAs, chromosomes, Okazaki fragments), or small compounds (e.g., penicillin). These are clearly discrete natural units since they do not form any part of a larger structure (at least not through any covalent attachment) and exert a clear, independent biological function.

More difficult will be substructures or portions of a larger molecule. In this case, the question of “discrete natural unit” focuses on whether the putative unit has reasonably well-defined, natural structural boundaries and a clear natural function. Examples of discrete natural units falling into this category include genes (or other functional sub-chromosomal regions), protein domains (e.g., DNA binding domain of a transcription factor), organs (e.g., kidneys, livers), a leaf plucked from a tree, etc.

Biologically random fragments of larger compositions that, from the perspective of nature, have no clear, independent biological function or significance will not qualify as a “discrete natural unit”. While these molecules may have important functionality to humans, they are random and meaningless from a natural perspective (no apparent biological function or activity). Common examples may include:

1. Most moieties derived from a small organic molecule (e.g., amdoxovir or gusperimus, discussed in Example B below) will not be a “discrete natural unit” as there will be no clear natural boundary between moieties and no clear function (as opposed to artificial functions and boundaries imputed by chemists).

2. Strings of nucleotides (polynucleotides) can present a closer case, depending on important details. At one end of the spectrum, a gene has reasonably clear natural boundaries (e.g., from promoter to poly-adenylation signal) and very clear natural functions (e.g., encoding a protein) and thus is a readily identifiable “discrete natural unit” against which the claimed composition can be compared. An exon within a gene has very clear boundaries, but may not have any clear independent function, and will thus present a close case at the next step of the examination process (i.e., analyzing the structural and functional differences between the claimed composition and the discrete natural unit identified in this step). At the other end of the spectrum, an oligonucleotide with a sequence that has significance only in a laboratory setting has neither natural boundaries nor natural function and is not a “discrete natural unit” against which the claimed composition can be properly compared.

#### **b. Properties versus functions**

One of the most critical tools in correctly determining what the natural product is, and whether something is eligible or not for patenting, is an understanding of the difference between natural properties and natural functions.

All chemical compounds (genes, proteins, vitamins, oligonucleotides, polypeptides) have certain chemical and physical properties. Some may be more electronegative, some may be electrically charged, some may be hydrophobic or hydrophilic, etc. These properties are determined by various physical laws.

A molecule can also have one or more specific biological functions, i.e., its role in the cell/body in maintaining homeostasis. A gene may encode a specific protein. That protein may catalyze a specific reaction. The small molecule product of that reaction may initiate a signaling cascade that ultimately activates another gene, and so on.

A biomolecule’s function is determined by both its own properties and the properties of the other compounds that surround it in a particular composition. For example, the specific chemical structure of an enzyme gives it certain chemical properties, including the ability to bind to particular compounds that themselves have very specific structure and properties.

When the enzyme with these properties is found in a specific composition (e.g., where particular reactants and cofactors are present and certain inhibitors are absent), it can perform its biological function (e.g., bringing the reactants into close proximity so they can form specific reaction end products).

Understanding this distinction is critical for examination. Though all functions are ultimately dictated by natural properties inherent in a molecule's structure, some functions may be natural (e.g., encoding a particular protein) while others can be non-natural (e.g., priming a polymerase chain reaction). A claim does not encompass a natural product simply because the claimed composition shares some or many properties with a natural product. If those properties are put to new, different, or enhanced function or use in the particular composition of the claim, then the claim is to a patent eligible human invention.

**3. Is the claimed composition structurally identical to a natural product, including any discrete natural unit?**

If care has been taken in correctly identifying a natural product against which to compare the claim composition, then structural identity should be fairly straightforward to assess. It is critical to remember at each stage of the analysis, however, that a claimed composition is not structurally identical to a natural product merely because it can be found within a discrete natural unit.

**a. Relatively few or minor structural differences can confer eligibility**

This analysis does not focus on the number of structural differences or even the apparent simplicity or complexity in the changes. Not just any change will be sufficient to make a composition patent eligible. For example, the Court in AMP recognized that the claimed isolated DNA was structurally different from native DNA ("broken covalent bonds") but nevertheless determined the claimed compositions were ineligible for patenting. This was because the claims were not defined in terms of any structural change that yielded an identified functional change and were, instead, defined expressly according to the natural properties and functions of the genes (see fuller discussion under Examples A and C, below).

On the other hand, any structural change may potentially confer eligibility, no matter how relatively minor, if it imparts some functional change. In Chakrabarty, the structural differences between the claimed bacterium and the natural bacteria were comparatively minor. These changes represented a relatively small insertion of genetic material that produced a relatively miniscule additional complement of proteins. But the important thing for the Court was the impact these small changes had on the function of the bacterium. "Here, by contrast, the patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility." Chakrabarty, 447 U.S. at 310 (emphasis added). The real question under this point is: Has the patentee created something (rather than merely finding something in nature) and has the patentee's activity (the "hand of man") given that something new utilities?

**b. Natural product is an independent molecule**

If the natural product identified in step 2 above is an independent molecule or natural structure (i.e., not a substructure in a larger molecule or structure), simply compare the structure of the claimed composition as a whole to that of the natural product as a whole.

Pay special attention to any compositional differences. The key component compound of the composition may be structurally identical to an individual natural compound or a discrete natural unit. But the specifics of the composition as claimed (e.g., specific levels of purity, absence of a specific inhibitor, presence of a specific enhancer not naturally associated with the key component, etc.) may be an important structural difference between the composition and the natural product. This may yield functional differences, which in turn will generally confer patent eligibility.

**c. Natural product is a substructure.**

If the natural product is a substructure, but is still a “discrete natural unit” under 2.a, then compare the chemical structure of the claimed composition as a whole to that of this substructure and proceed as above.

**d. Three possible scenarios**

1. If the claimed composition as a whole is structurally identical to a natural product as a whole according to the above analysis (i.e., no structural difference between the natural product and the claimed composition), then the claim should be rejected under 35 U.S.C. § 101 for being directed to a natural product.

2. If the claimed composition as a whole is not structurally identical to and does not share substantial structural similarity with a natural product as a whole according to the above analysis, then the composition is patent eligible and examination should proceed to utility under § 101 (indeed, examination probably should not have even reached this point under point 2.d above). If the specification sets forth at least one specific, substantial, credible utility for the composition, then examination should proceed to the substantive requirements of patentability (§§ 102, 103, 112).

3. If the claimed composition as a whole is not structurally identical to, but shares substantial structural similarity with, a natural product as a whole according to the above analysis, then examination should proceed to the next phase of § 101 subject matter eligibility analysis (i.e., function and utility).

**e. “Comprising” language in a substructure claim**

Using open-ended “comprising” language in a claim to a composition that is a substructure of a discrete natural unit could, under the broadest reasonable interpretation, encompass the discrete natural unit itself. Applicants should be required to limit the claim in some way that clearly excludes the natural product from the claim. Note that this merely solves the structural problem; other supporting facts or even claim limitations may be necessary to direct the claim to something with a new or enhanced function/utility under step 4 below.

**4. Does the claimed composition possess a new or enhance function or utility as compared to the natural product?**

Examination should focus on determining whether the claimed composition possesses at least one new or enhanced function or utility, either recited in the specification or in the claim language itself, which is not found in the natural product. The new or enhanced function

or utility must be sufficient under traditional § 101 utility analysis (i.e., specific, substantial, credible).

If the composition is structurally differentiated from a natural product in only a general, negative way (e.g., merely “isolated”) and is claimed according to its natural function, then the composition is patent ineligible. If on the other hand the composition is distinguished from the natural product in a positive, specific way (e.g., a specific structural feature) and is claimed according to that function, then the composition is eligible.

As discussed above, it is critical to carefully differentiate between properties (i.e., chemical or physical properties of a structure) and functions (i.e., what the structure does). Properties are inherent in a structure. Applicants cannot differentiate the claimed composition based solely on inherent chemical properties shared by the natural product. On the other hand, applicants can properly differentiate the claimed composition based on how these properties combine and interact to yield new functions or utilities.

One helpful clue in this analysis is to ask whether the specification teaches that the structural differences introduced by the applicant confer this new or enhanced function or utility. Though not always be required for patent eligibility, this kind of teaching helps to clearly tie the structural differences to any functional differences and solidify a claim to invention.

**5. Special problem: Composition that is a combination of two or more discrete natural units**

**a. Covalent or other “permanent” combinations**

Does the composition comprise as a component anything that includes within its chemical structure a discrete natural unit covalently bonded to anything else (including any other discrete natural unit that is not found naturally bound to the first unit)? Is there some other non-transient connection or combination of natural products (e.g., physical structures interlocked in a non-natural way such that separation does not readily occur without some force)? If so, then the composition is patent eligible.

**b. Transient or “simple” combinations**

Does the claimed composition instead recite at least one natural product in a non-covalent or other “transient” combination with one or more other natural product components (e.g., liquids combined in solution, powders physically mixed, etc.)? The composition can be patent eligible if (a) the combination is recited at some level of specificity to exclude reasonably foreseeable natural combinations and (b) the combination as claimed possesses at least one function not found in any of the natural components alone or any natural combination of the natural components.

**PROPOSED PROCESS FOR ANALYZING METHOD CLAIMS:**

**Introduction**

The case law urges a fairly simple threshold question: “Has the applicant claimed a law of nature per se?” While claims to laws of nature per se are ineligible, claims to applications of laws of nature are eligible. This is embodied by the rough two-step “framework” the Supreme Court outlined in Mayo:



In Mayo Collaborative Services v. Prometheus Laboratories, Inc. we set forth a framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts. First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts. If so, we then ask, “[w]hat else is there in the claims before us?”

Alice Corp. v. CLS Bank Int’l, slip op. 7 (internal citations omitted).<sup>9</sup> This Proposed Guidance fleshes out the Mayo framework to address practical scenarios that are likely to be presented in examination.

Because applicants are unlikely to explicitly claim a bare law of nature, precedent urges patent reviewers to look a little closer at method claims to make sure the applicant hasn’t in effect claimed the law of nature by, e.g., merely including a token reference to “applying” the law of nature.

This caution from the courts should not be over read, however, to mean that broad applications are categorically ineligible or that method claims must recite specifics of the process at arbitrarily high levels of detail. Any application will suffice to pass through the broad door of patent eligibility; the courts merely warn against allowing a clever draftsman to comply with the letter of the law by simply taking a law of nature (which he cannot claim) and then saying “apply it” (since applications are eligible).

The following points should be addressed in examining composition claims for subject matter eligibility:

1. *Does the claim appear, on its face, to recite a natural principle?*
2. *What is the natural principle potentially claimed and how is it recited in the claim?*
3. *Does the claim recite a process that is different in any way from that which is well-understood, routine and conventional in the art?*

**1. Does the claim appear, on its face, to potentially recite a natural principle?**

Notice that to be ineligible, the claim must recite a law of nature per se. This must be distinguished from merely “involving” or operating by a law of nature. Alice Corp. v. CLS Bank Int’l, slip op. 6 (“Thus, an invention is not rendered ineligible for patent simply because it involves an abstract concept.”).

The primary cases in this area are Benson, Flook, Diehr, Mayo, and Alice. These cases tend to give not an actual analytical framework but instead examples from which general principles of analysis can be gleaned. For example, Benson, Flook and Diehr together teach that a claim reciting a mathematical algorithm facially raises the question of whether an abstract idea is being claimed. This is not to say that all claims involving such an algorithm are improperly directed to an abstract idea, as made clear by Diehr. Instead, these cases teach that the presence of the algorithm facially raises the issue and warrants further analysis consistent with this Proposed Guidance.

Mayo similarly teaches that “wherein” clauses in a method claim will often facially raise the question of whether an abstract idea or natural principle is being claimed. Again, this is not because “wherein” clauses are always problematic. Such clauses can often recite important

structure or steps in a process that meaningfully limit a claim to an application of a natural principle. But Mayo illustrates well that in many cases such clauses are used to recite bare statements of a natural principle.

Another facial clue that a natural principle is potentially being claimed includes cause-and-effect elements in a claimed process. For example, a claim that recites performing an action and then recites as a step the natural consequence of that action may raise the question of claiming natural principle. Ultimately, whether a natural principle is actually being claimed may turn on whether the action occurs naturally, but the presence of the “cause-and-effect” element at least raises the facial question.

Another clue can be the recitation of a process that, according to the specification or art, appears to occur in nature. For example, a claim that recites the conversion of one natural compound into another natural compound by the process through which the second compound is naturally produced raises a facial question of whether a natural principle is being claimed.

## **2. What is the natural principle potentially claimed and how is it recited in the claim?**

This may be the most important part of the analysis. A careful and correct identification and definition of what the law of nature is (and is not) will generally determine the outcome.

It is critical to understand the difference between a law of nature and a statistical correlation. A natural principle will include some clear mechanistic connection between two phenomena. A statistical correlation on the other hand is a human-made connection between two phenomena.

For example, gravity is a law of nature. One massive body exerts an attractive force on another massive body according to a predictable equation. The relationship between a numerical gene expression score and the presence of brain cancer is a statistical correlation. There cannot be any single, direct mechanistic connection between a human-created numerical score (i.e., a number) and the presence of the disease. As discussed above, the critical question is whether humans truly made the process or not. No human made gravity; we simply discovered it and the natural laws by which it operates. A human created the numerical expression score and likewise “created” the correlation through statistics (a human-created mathematical endeavor).

Even still, a claim to a statistical correlation may not be patent-eligible as it is arguably an abstract idea. For example, if an applicant has found that obese patients tend to have higher blood lipid levels, the applicant cannot claim “the correlation between obesity and blood lipid levels” or even “a method comprising determining whether a patient is obese, wherein obesity indicates (or correlates to) increased blood lipid levels.” Instead, the applicant must claim an application of the statistical correlation such as a method of using obesity as a prescreen for determining which patients should have their blood lipid levels tested.

## **3. Does the claim recite a process that is different in any way from that which is well-understood, routine and conventional in the art?**

### **a. Side-by-side comparison of claimed process to routine art process**

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. In this way, differences can be assessed to determine whether the only difference is a statement of a natural principle.

The Mayo case provides a prime example of this analysis. In Mayo, the claim recited a process that was routine in the art at the time of filing in every particular and merely appended a bare statement of what the Court deemed a law of nature (i.e., metabolites above a certain level indicate the need to lower the dose and metabolites below a certain level indicate a need to increase the dose). Below is a chart comparing the claimed process to that which was routine and conventional in the art:

Claim 1 of '623 patent in <u>Mayo</u>	Process routinely engaged in by scientists at the time of filing
<p>A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:</p> <p>(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and</p> <p>(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,</p> <p><i>wherein the level of 6-thioguanine less than about 230 pmol per <math>8 \times 10^8</math> red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and</i></p> <p><i>wherein the level of 6-thioguanine greater than about 400 pmol per <math>8 \times 10^8</math> red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.</i></p>	<p>A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:</p> <p>(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and</p> <p>(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder.</p>

The Court found that the only difference between the prior art method and the claimed method was the “wherein” clauses. But these merely describe (or inform an audience about) a pre-existing but newly “discovered” fact about the process; they do not specify any new or even modified step, structure or element of the process. In this way they are not truly a part of the process and do not “meaningfully limit” the claim (or even limit it at all). This simple fact is the central reason the claims in Mayo were patent ineligible:

And so a patent that simply describes that relation sets forth a natural law. The question before us is whether the claims do significantly more than simply describe these natural relations. To put the matter more precisely, do the patent claims add enough to their statements of the correlations to allow the processes they describe to qualify as patent eligible processes that apply natural laws? We believe that the answer to this question is no.

Mayo at 1297 (emphasis added).

The Court in Mayo additionally noted that the claims did not act on or apply the law of nature in any way:

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. In doing so, the court construed the claim's language, "indicates a need to decrease" (or "to increase"), as not limited to instances in which the doctor actually decreases (or increases) the dosage level where the test results suggest that such an adjustment is advisable.

Mayo at 1296. No action or even a diagnostic conclusion was required based on the fact recited in the "wherein" clauses. Instead, the claims in Mayo literally (and fatally) just "inform a relevant audience about certain laws of nature." Id. at 1298 (emphasis added). For this reason the Court deemed the bare statements of the natural principle to be general "apply it" statements that are not enough to confer patent eligibility.

#### **b. Not an obviousness analysis**

It is critical to recognize that, despite the use of terms like "well-understood," "routine," or "conventional," this is not an obviousness analysis. The above analysis (e.g., using a chart to more clearly see the differences between the claimed process and that which was routine and conventional) is much closer to anticipation than it is to obviousness. The claimed process is patent ineligible only if it adds nothing to what was routine and conventional beyond a statement of a natural principle. A claimed process is not ineligible simply because it differs from what was routine and conventional in a way that, in view of the newly discovered natural principle, would have been obvious.

It is improper to treat the natural principle as "in the prior art" and then evaluate whether the claimed process is obvious in view of it. Instead, the process that was routine in the art at the time of filing is treated as "in the prior art" and the claimed process as a whole is compared to see whether there are any real differences. In this way, a claim to a truly new process is eligible whereas a claim to an old process with a newly discovered natural principle appended to it is not.

#### **c. What is an "active" step?**

Any step recited in a claim is an "active" step that limits the claim and potentially confers patent-eligibility. That a step is carried out by a computer or even could conceivably be performed in the mind does not necessarily mean it is not an "active" step or it can be disregarded in comparing the claimed process to a routine process.

On the other hand, binding precedent states that claims whose only active steps are mental steps are ineligible as directed to an abstract idea. The claim as a whole must be evaluated to determine whether it consists of purely mental steps or whether there are also physical acts that combine to form an eligible process.

Care must be taken when an activity could conceivably be performed in the mind. The proper question is not whether there is any way of imagining the activity being done in someone's mind, but rather whether the broadest reasonable interpretation of the claim encompasses an activity that can reasonably be done in the human mind. Something can reasonably be done in the human mind if one person of average intelligence could foreseeably perform the activity, unaided by any external tool or implement, within an amount of time that is practical under the circumstances.

**BRIEF NOTE ON PREEMPTION:**

Preemption is the idea that patents should not remove from the public the basic tools of science. Preemption is not an analytical test for patent eligibility. The courts have repeatedly stated instead that (1) preemption is the primary policy consideration underlying the exceptions to patent eligibility under § 101 and (2) it serves at most as an after-the-fact confirmation of an already reached conclusion on eligibility. See, e.g., Mayo, 132 S. Ct. at 1302 (“The presence here of the basic underlying concern that these patents tie up too much future use of laws of nature simply reinforces our conclusion that the processes described in the patents are not patent eligible, while eliminating any temptation to depart from case law precedent.”) (emphasis added); Alice Corp. v. CLS Bank Int’l, slip op. at 13 (“This conclusion accords with the preemption concern that undergirds our §101 jurisprudence.”).

This Proposed Guidance cannot ask patent examiners to determine whether a claim effectively covers all applications of a natural law or uses of a natural product. This is an impossible question of fact that no examiner is equipped to answer. Though it has repeatedly discussed preemption as a basis for the eligibility exclusions, the Supreme Court has declined to articulate a preemption test for eligibility despite several invitations to do so. This Proposed Guidance thus declines to sua sponte institute such a test.

**EXAMPLES:**

**A. Composition/Manufacture Claim Reciting A Natural Product**

Claim 1: A stable energy-generating plasmid, which provides a hydrocarbon degradative pathway.

Claim 2: An isolated stable energy-generating plasmid, which provides a hydrocarbon degradative pathway.

Claim 3: A combination of two distinct Pseudomonas bacteria of the sub genus cerus, wherein each bacteria has a separate hydrocarbon degradative pathway and wherein said bacteria do not mutually inhibit each other’s growth.

Claim 4: A bacterium from the genus Pseudomonas containing therein at least two stable energy-generating plasmids, each of said plasmids providing a separate hydrocarbon degradative pathway.

**Background:** Stable energy-generating plasmids exist within certain bacteria in nature. Pseudomonas bacteria are naturally occurring bacteria. Naturally occurring Pseudomonas bacteria containing a stable energy-generating plasmid and capable of degrading a single type of hydrocarbon are known in the art and described in the specification. It is advantageous, e.g., in treating oil spills, to utilize multiple bacteria capable of metabolizing different hydrocarbons.

The specification solves such problems in two ways. First, the specification teaches packaging multiple Pseudomonas species together to provide a broader spectrum of hydrocarbon metabolism. It was previously thought in the art that Pseudomonas bacteria could not be mixed due to their tendency to competitively inhibit each other. Applicant discovered that certain Pseudomonas species, of the sub genus cerus, do not inhibit each other and can be packaged together.

Second, the specification describes crossing multiple strains of Pseudomonas, through conjugation, to yield a single bacterium containing multiple stable energy-generating plasmid and each capable of degrading a single different type of hydrocarbon. The specification defines “isolated” in the context of nucleic acids to mean a nucleic acid removed at least in part from its natural environment, which may include removal of the nucleic acid from a cell and/or removal of surrounding proteins and other biomolecules naturally associated with it.

Analysis of Claim 1:

1. *Does the claim appear, on its face, to potentially encompass a product of nature?*

Claim 1 recites a plasmid, which is a nucleic acid molecule. A claim to virtually any nucleic acid facially raises the question of whether a product of nature is being claimed because nucleic acids are well known biomolecules ubiquitously produced by and found in nature. Further, the specification describes the plasmids ultimately aggregated into the bacterium claimed in claim 3 as originating in a naturally-occurring bacterium.

2. *What is the product of nature potentially encompassed by the claim?*

As to claim 1, the product of nature potentially encompassed by the claim is a stable energy-generating plasmid that, when found in a Pseudomonas bacterium, is capable of degrading a single type of hydrocarbon. Notice that such a plasmid may well not qualify as an independent product of nature since such plasmids are not typically, if ever, found outside the larger structure of a bacterium in nature.

However, even if the plasmid is not an independent product of nature, it is at least a discrete natural unit. Plasmids are nucleic acids that, in the larger context of the bacterium, are structurally and functionally discrete. They are not part of a single larger nucleic acid molecule; they are independent of the bacterial genome. They exert an identifiable function/activity in the bacterial cell, i.e., encoding various proteins required for degrading a specific hydrocarbon. As such, even though the plasmid is arguably a substructure of a larger natural structure (the bacterium), it is a discrete natural unit against which the claimed composition can be compared.

3. *Is the claimed composition structurally identical to a natural product, including any discrete natural unit?*

The claimed composition appears to be structurally identical to the natural product. The claim recites only “A stable energy-generating plasmid, which provides a hydrocarbon degradative pathway.” Such plasmids exist in nature as noted above. The claim does not recite any other structural feature, added or removed, to differentiate the claimed plasmid from those existing in nature. The claim encompasses, as one of its distinct embodiments, a natural plasmid sitting in a natural bacterium.

4. *Does the claimed composition possess a new or enhanced function or utility as compared to the natural product?*

Because the claimed composition is literally structurally identical to a product of nature, it cannot have any new or enhanced function or utility. Further, the claim expressly defines the plasmid in terms of its natural function (hydrocarbon degradation).

**Conclusion:** Because the claimed composition is structurally identical to a product of nature and further is expressly defined according to that natural product's natural function, it encompasses the product of nature and is thus ineligible for patenting.

Analysis of Claim 2:

Same analysis as claim 1 for points 1 and 2.

3. *Is the claimed composition structurally identical to a natural product, including any discrete natural unit?*

The claimed composition, when considered as a whole, is not structurally identical to the natural product. While "A stable energy-generating plasmid, which provides a hydrocarbon degradative pathway" (claim 1) exists in nature, the specification expressly defines an "isolated" nucleic acid as removed from its natural environment. Thus, by definition the claimed composition does not exist in nature.

However, the claim does not recite any positive, specific structural feature that distinguishes the claimed composition from the natural plasmid. Rather, the composition is structurally differentiated from a natural product in only a general, negative way (i.e., lacking at least one undefined thing naturally associated with the plasmid). Thus, absent a clear showing of a new or enhanced function or utility, the composition will be ineligible for patenting.

4. *Does the claimed composition possess a new or enhanced function or utility as compared to the natural product?*

No. In fact, the composition is expressly defined in terms of its natural counterpart's natural function (hydrocarbon degradation). There may arguably be new functions or utilities in an isolated plasmid, but neither the claims nor the specific recite any specific, substantial or credible new or enhanced function or utility.

**Conclusion:** Because the claimed composition is structurally very similar to a product of nature and further is expressly defined according to that natural product's natural function, it encompasses the product of nature and is thus ineligible for patenting.

Analysis of Claim 3:

1. *Does the claim appear, on its face, to potentially encompass a product of nature?*

Yes. A claim to virtually any bacterium facially raises the question of whether a product of nature is being claimed because bacteria are organisms produced by and found in nature.

2. *What is the product of nature potentially encompassed by the claim?*

The product of nature potentially encompassed by claim 3 is a natural mixture of natural Pseudomonas bacterium of the sub genus cerus. Natural Pseudomonas bacteria of this sub genus were shown in the specification to (1) have separate hydrocarbon degradative pathways and (2) not mutually inhibit each other's growth.

3. *Is the claimed composition structurally identical to a natural product, including any discrete natural unit?*

Probably. It is possible that no distinct species within the sub genus cerus have ever been combined naturally. Far more likely, however, is that they have. Regardless, the claim

does not recite any aspect of the composition that appears to be attributable to the applicant. There is no specificity in the ratios of the bacteria that yields some new property, or any such structural change from exactly what exists in nature.

4. *Does the claimed composition possess a new or enhanced function or utility as compared to the natural product?*

No. The claimed bacterial composition has only those functions and utilities found in the natural bacteria. Even assuming the claimed combination does not occur in nature, the composition is claimed purely according to the natural properties of the bacteria (i.e., hydrocarbon degradation and mutual non-inhibition). The applicant has not changed the bacteria in any way or enlarged the scope of their natural function or previous utility.

**Conclusion:** Because the claimed composition is potentially structurally identical to a product of nature, but more importantly because the composition is claimed solely according to the natural and inherent functions and utilities of such product of nature, it claims a product of nature and is thus ineligible for patenting.

Analysis of Claim 4:

1. *Does the claim appear, on its face, to potentially encompass a product of nature?*

Yes. A claim to virtually any bacterium facially raises the question of whether a product of nature is being claimed because bacteria are organisms produced by and found in nature.

2. *What is the product of nature potentially encompassed by the claim?*

As to claim 3, the product of nature potentially encompassed by the claim is a natural Pseudomonas bacterium containing a stable energy-generating plasmid and capable of degrading a single type of hydrocarbon. These types of bacteria are known in the art and described in the specification as one of the source bacteria for the claimed bacterium.

3. *Is the claimed composition structurally identical to a natural product, including any discrete natural unit?*

Probably not. The background states that Pseudomonas bacteria naturally contain plasmids with just a single degradative pathway. A bacterium containing multiple plasmids each with a different degradative is not known to exist in nature. Note, however, that the claimed bacterium was produced by careful manipulation of the natural bacterial breeding process called conjugation.

It is conceivable and perhaps even probable that nature, in the innumerable conjugation interactions amongst untold trillions of bacteria across the eons and across the globe, could have yielded (and perhaps had already yielded) the exact bacterium recited in the claim. However, nothing in the art or the specification gives a specific, credible reason to conclude such a bacterium actually exists. And the applicant clearly did not simply find the bacterium in nature “unaided by man.” The applicant instead produced it through the “hand of man.”

The extent of the structural changes is equivocal. While the plasmid may be several thousands or even hundreds of thousands of nucleotides long, it still pales in comparison to the total nucleic acid content of the natural bacterium (let alone the entire molecular content). From a purely structural perspective, addition of the plasmid is a relatively trivial change.



4. Does the claimed composition possess a new or enhance function or utility as compared to the natural product?

Yes. No known natural *Pseudomonas* bacterium can degrade two different hydrocarbons. The claimed *Pseudomonas* can. Importantly, the claimed bacterium has no truly new function or utility. It received its additional degradative capabilities from a different, natural bacterium. But the additional degradative capabilities are new relative to the single natural product against which the claimed bacterium is being compared, which is sufficient. Aggregation of naturally separate functions into a single non-natural composition (e.g., a bacterium) is an invention that yields a human-made product with “the potential for significant utility.”

**Conclusion:** Because the claimed composition is structurally different from, though very similar to, a product of nature and further possesses new functions and utilities relative to any known product of nature, it claims a human invention and is thus eligible for patenting.

**Case law note:** This example is based on two Supreme Court cases, Funk Brothers Seed Co. v. Kalo Inoculant Co., 333 U.S. 127 (1948), and Diamond v. Chakrabarty, 447 U.S. 303 (1980), and shows the interplay of these two cases with each other and the much more recent case of Ass’n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013). Funk Bros. involved aggregating bacteria into a useful package, but claiming them according to newly discovered properties that were always there. Chakrabarty involved the use of selective breeding to aggregate hydrocarbon degradative capabilities into one bacterium.<sup>10</sup> The composition in Funk Bros. was found ineligible for patenting while that in Chakrabarty was found eligible.

The distinction between these cases driving the opposite outcomes was not that Funk Bros. claimed a composition having natural properties while Chakrabarty claimed human-made properties. Both compositions aggregated existing, natural, previously separate functions into a single composition and neither composition had any entirely new property or function. Dr. Chakrabarty’s bacterium gained properties and functions already existing in nature that were transferred to it from other naturally occurring bacteria through Dr. Chakrabarty’s manipulation of the natural process of conjugation. The spectrum of oils the new bacterium could “eat” was indeed expanded beyond what it was formerly capable of before Dr. Chakrabarty turned his hand to it, but it included no entirely new or non-natural property because other natural bacteria could “eat” all of those additional oils. The invention was an aggregation of naturally occurring properties and functions from several naturally occurring bacteria into one non-naturally occurring bacterium.

The downfall of the patentee in Funk Bros. was not that he claimed a simple mixture of natural products or even that the claimed mixture shared properties with natural bacteria, but instead that (1) he claimed what he found in nature and (2) he claimed it expressly according to its natural properties.<sup>11</sup> The claim was to any mixture of *Rhizobium* bacteria that were mutually non-inhibitive. The patentee may have been the first to recognize the bacteria could be packaged together without inhibiting each other. He may have been the first to recognize this natural property in the bacteria. But he made the crucial mistake of claiming the bacteria according to their natural non-inhibitive properties rather than any property or function he instilled in them.

This in turn was precisely the downfall of the broadest claims at issue in AMP. The Court expressly noted that Myriad's claims may have survived if they were defined in terms of some property or function given to the compositions by the inventors:

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.

AMP, 133 S. Ct. at 2118 (Emphasis added).<sup>12</sup> The claims failed because in the Court's view, like in Funk Bros., by claiming any "nucleic acid encoding [a BRCA1 protein]" the claims were instead expressly defined in terms of the natural properties and functions of the gene.

### **B. Composition vs. Method Claims, Each Reciting A Small Organic Molecule**

Claim 1. A composition of purified spergualin.

Claim 2. The composition of claim 1 having at least 25% spergualin by weight.

Claim 3. The composition of claim 1 having no more than 1 nM inhibitin.

Claim 4. A composition comprising 5-methyl spergualin.

Claim 5. A composition comprising gusperimus.

Claim 6. A method of killing fungi comprising contacting a culture of fungi with a composition comprising spergualin, wherein said composition kills said fungi.

Claim 7. The method of claim 6, wherein said composition has at least 25% spergualin by weight.

Claim 8. The method of claim 6, wherein the fungus is chosen from the group consisting of Candida and Cryptococcus.

Claim 9. The method of claim 8, wherein the fungus is of the genus Cryptococcus.

Claim 10. A method of treating an inflammatory disease in a human patient, comprising administering a composition comprising gusperimus to said patient.

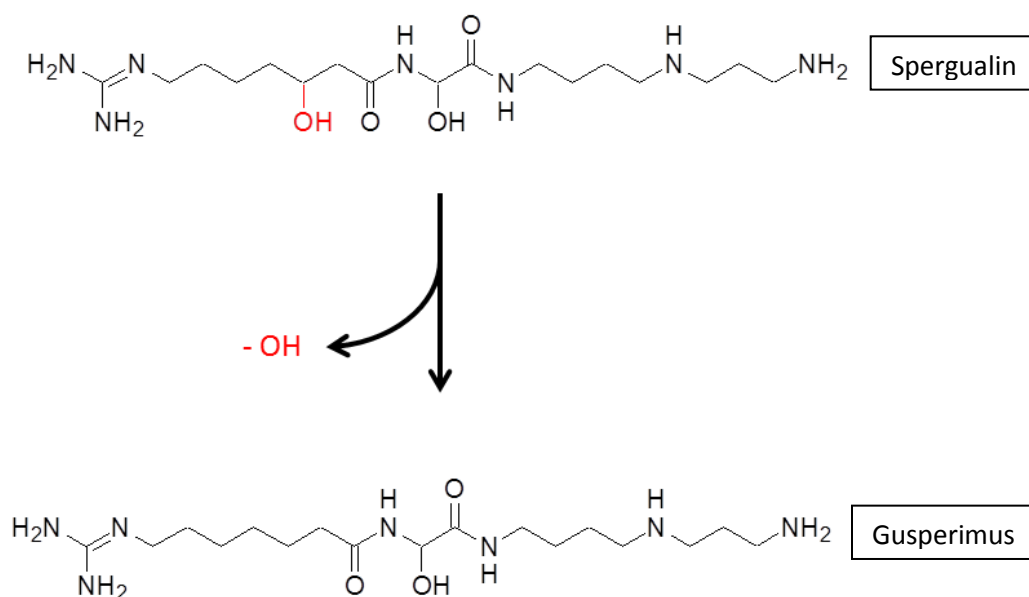
Claim 11. The method of claim 10, wherein said composition is administered in a daily dose of gusperimus to a patient suffering from said inflammatory disease for a period of time from 10 days to 20 days, wherein said daily dose comprises about 0.75 to about 1.25 teaspoons of gusperimus.

**Background:** Applicant was the first to identify spergualin as a distinct compound and purify it from the bacterium Bacillus laterosporus. Spergualin is naturally secreted by the bacterium and naturally protects it from (i.e., kills) fungi of the genus Candida. B. laterosporus has been ingested as a holistic medicine treatment for upset stomach.

Applicant determined that compositions having at least a minimum concentration of spergualin (at least 25% by weight) could be used to kill fungi of the genus Cryptococcus. Applicant also discovered that a natural compound secreted by B. laterosporus, called inhibitin, competitively binds to and inactivates spergualin when concentrations of inhibitin rise due to excessive growth in a B. laterosporus culture. However, reducing the concentration of inhibitin

in a given composition to 1 nM or less was shown to abolish its inhibitory effect. After applicant's filing, studies showed that inhibitin concentrations in natural *B. laterosporus* cultures never drop below 10 nM.

Applicant created numerous derivatives of spergualin, including 5-methyl spergualin and gusperimus. 5-methyl spergualin is spergualin with a methyl group covalently bonded to the number 5 carbon in its primary alkyl chain. Gusperimus is spergualin with one hydroxyl removed from the number 5 carbon, as shown below:



Applicant determined that administering a composition of gusperimus significantly reduces inflammation in humans as shown by a standard carrageenan paw test.

The specification defines "purified" in the context of a chemical compound as any composition having the recited compound substantially separated from at least one compound naturally associated with it.

#### Analysis of Claim 1:

1. *Does the claim appear, on its face, to potentially encompass a product of nature?*

Claim 1 recites spergualin, which is a natural compound the applicant first purified from a natural bacterium. A claim to virtually any chemical compound found naturally as a discrete chemical entity facially raises the question of whether a product of nature is being claimed.

2. *What is the product of nature potentially encompassed by the claim?*

The product of nature potentially encompassed by the claim is spergualin.

3. *Is the claimed composition structurally identical to a natural product, including any discrete natural unit?*

The claimed composition, when considered as a whole, is not structurally identical to the natural product. While spergualin exists in nature, the specification expressly defines "purified" spergualin as substantially separated from at least one compound naturally

associated with it. Thus, by definition the claimed composition as a whole (spergualin with at least one naturally-accompanying compound removed) does not exist in nature.

However, the claim does not recite any positive, specific structural feature that distinguishes the claimed composition from spergualin. Rather, the composition is structurally differentiated from a natural product in only a general, negative way (i.e., lacking at least one undefined thing naturally associated with spergualin). Thus, absent a clear showing of a new or enhanced function or utility, the composition will be ineligible for patenting.

4. *Does the claimed composition possess a new or enhanced function or utility as compared to the natural product?*

No. The specification teaches no new or enhanced function or utility for spergualin with, e.g., just one associated compound separated. To the contrary, the specification teaches that a minimum level of purity must be achieved before certain new functions/utilities are gained (e.g., at least 25% spergualin by weight before *Cryptococcus* fungi are killed). There may arguably be new functions or utilities in spergualin with the trivial amount of “purification” encompassed by that term as defined in the specification, but (a) neither the claims nor the specification recite any such specific, substantial or credible new or enhanced function or utility and (b) there is reason to doubt so nominal a purification would yield any new or enhanced function or utility.

**Conclusion:** Because the claimed composition is structurally very similar to a product of nature and there is no evidence of any new or enhanced function or utility, it in effect claims a product of nature and is thus ineligible for patenting.

#### Analysis of Claim 2:

Same analysis as claim 1 for points 1 and 2.

3. *Is the claimed composition structurally identical to a natural product, including any discrete natural unit?*

No. While spergualin exists in nature, nothing suggests a composition having the specified concentration of spergualin exists in nature. The “25% spergualin by weight” limitation is distinguishable from the “purified” limitation in claim 1 in that it is a positive, specific structural feature that distinguishes the claimed composition from spergualin.

Recall the discussion above of “compositional” differences between what exists in nature and what is recited in a patent claim. It is common to think of a claimed composition as having just one chemical compound in it (e.g., literally only spergualin). In reality, however, “‘composition 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.’” Chakrabarty, 447 U.S. at 308 (citing Shell Development Co. v. Watson, 149 F.Supp. 279, 280 (D.D.C. 1957) (emphasis added).

The composition of claim 2 is a mixture of spergualin and other components, with spergualin representing at least some specific proportion of the mixture. And this non-naturally occurring composition yields new or enhanced functions over the natural composition, which

has its own specific components and proportion of spergualin. Spergualin in the abstract, completely separated from everything else, is not being claimed.

Still, this structural difference may be relatively minor and so the functional effect of this limitation is more important to the ultimate conclusion on eligibility.

4. *Does the claimed composition possess a new or enhanced function or utility as compared to the natural product?*

Yes. The specification teaches that upon reaching at least 25% spergualin by weight, a composition gains the new ability to kill *Cryptococcus* fungi. *B. laterosporus* bacteria are naturally susceptible to, and have no natural defense against, *Cryptococcus* infection. Importantly, this activity is not entirely new. Other compounds are known to kill *Cryptococcus* fungi. But the additional ability to kill *Cryptococcus* is new relative to the natural product against which the claimed composition is being compared, which is sufficient.

**Conclusion:** Because the claimed composition is structurally distinct from a product of nature and this structural difference confers a new function/utility, it claims a human invention and is thus eligible for patenting.

**Case law note:** Here again examination must be guided not by the broadest possible reading of leading cases, but instead the narrowest faithful reading. AMP does not stand for the broad rule that compounds purified from natural sources are categorically excluded from patenting. In fact the opposite is true. AMP was careful to emphasize the narrowness of its holding: “We merely hold that genes and the information they encode are not patent eligible under §101 simply because they have been isolated from the surrounding genetic material.” AMP, 133 S. Ct. at 2120 (emphasis added).

And the Court and parties appeared to agree that concentration and purification to yield a new function or utility was sufficient for patentability. This is captured well by the following exchange during oral argument in AMP, where Justice Alito and AMP’s counsel discussed a hypothetical very similar to this Example B:

JUSTICE ALITO: Suppose there is a substance, a chemical, a molecule in the leaf the leaves of a plant that grows in the Amazon, and it’s discovered that this has tremendous medicinal purposes. Let’s say it treats breast cancer. [...] You make a drug out of that. Your answer is that [...] it’s not eligible for patenting because the chemical composition of the drug is the same as the chemical that exists in the leaves of the plant.

MR. HANSEN: If there is no alteration, if we simply pick the leaf off of the tree and swallow it and it has some additional value, then I think it is not patentable. You might be able to get a method patent on it, you might be able to get a use patent on it, but you can’t get a composition patent.

JUSTICE ALITO: But you keep making the hypotheticals easier than they’re intended to be. It’s not just the case of taking the leaf off the tree and chewing it. Let’s say if you do that, you’d have to eat a whole forest to get the value of this. But it’s extracted and reduced to a concentrated form. That’s not eligible?

MR. HANSEN: No, that may well be eligible because you have now taken what was in nature and you’ve transformed it in two ways. First of all, you’ve made it substantially

more concentrated than it was in nature; and second, you've given it a function. If it doesn't work in the diluted form but does work in a concentrated form, you've given it a new function. And by both changing its nature and by giving it a new function, you may well have patent [...].

AMP Oral Argument Transcript at p.7, l.2 to p.8, l.12 (available at [http://www.supremecourt.gov/oral\\_arguments/argument\\_transcripts/12-398\\_h3dj.pdf](http://www.supremecourt.gov/oral_arguments/argument_transcripts/12-398_h3dj.pdf)).

#### Analysis of Claim 3:

Same analysis as claim 1 for points 1 and 2.

3. *Is the claimed composition structurally identical to a natural product, including any discrete natural unit?*

No. The specification teaches that inhibitin concentrations below a certain unknown level lose a certain amount of inhibitory effect such that the *B. laterosporus* culture can resume growth. But after-filing art teaches that inhibitin levels in a natural *B. Laterosporus* culture never drop below 10 nM. Importantly, after-filing art can be taken into account in the specific way illustrated in this example. It cannot be used, however, to make a claim ineligible based solely on the random natural production of a composition first artificially created by an inventor. See, AMP footnote 8.

4. *Does the claimed composition possess a new or enhanced function or utility as compared to the natural product?*

Probably. The specification teaches inhibitin inhibits spergualin's anti-fungal activity. Thus removing at least a specific amount of inhibitin is a specific form of the purification of claim 1. However, it is not clear whether reducing the inhibitin concentration to this level will actually result in anti-Cryptococcal activity. Such activity, in view of the weight of the art and the specification, may be reasonably expected or not. If it is, then this criterion is met. If not, then it is not.

**Conclusion:** If the claimed composition possesses a new function/utility, then it claims a human invention and is thus eligible for patenting.

#### Analysis of Claim 4:

Same analysis as claim 1 for points 1 and 2.

3. *Is the claimed composition structurally identical to a natural product, including any discrete natural unit?*

No. While spergualin exists in nature, nothing suggests the compound 5-methyl spergualin exists in nature. Addition of the methyl at carbon number 5 is a clear, covalent addition to the natural compound which results in a new chemical entity.

4. *Does the claimed composition possess a new or enhanced function or utility as compared to the natural product?*

The specification does not teach any new function or utility for 5-methyl spergualin. However, because it is an entirely new, synthetic chemical entity there is no requirement of new utility under the eligibility prong of s.101. Note, however, that the requirement of a

specific, substantial and credible utility under s.101 remains and must be met for ultimate patentability.

**Conclusion:** Because the claimed composition is clearly structurally distinct from a product of nature, it claims a human invention and is thus eligible for patenting.

Analysis of Claim 5:

Same analysis as claim 1 for points 1 and 2.

3. *Is the claimed composition structurally identical to a natural product, including any discrete natural unit?*

No. While spergualin exists in nature, nothing suggests the compound gusperimus exists in nature. Because gusperimus can be “seen” within the larger structure of natural spergualin, however, examination must consider whether gusperimus is a discrete natural unit.

There is nothing in the specification or art (whether pre- or post-filing) suggesting gusperimus is a discrete functional unit within spergualin. In the nearly infinite events in which spergualin degraded by the removal of certain moieties, it is almost certain that for some transient period gusperimus existed in nature. However, gusperimus does not perform any function in the *B. laterosporus* bacterium. It is not a domain with the larger spergualin molecule responsible for any specific known activity (e.g., binding an enzyme). Thus, gusperimus is neither an independent natural product nor a discrete natural unit.

4. *Does the claimed composition possess a new or enhanced function or utility as compared to the natural product?*

The specification teaches that gusperimus can reduce inflammation and thus be used to treat inflammatory diseases.

**Conclusion:** Because the claimed composition is clearly structurally distinct from a product of nature (or any discrete natural unit thereof) and because it possesses new utility, it claims a human invention and is eligible for patenting.

Analysis of Claim 6:

1. *Does the claim appear, on its face, to recite a natural principle?*

Yes. Claim 1 recites the use of spergualin to kill fungi. The specification teaches that spergualin naturally kills fungi when secreted by *B. laterosporus*.

2. *What is the natural principle potentially claimed and how is it recited in the claim?*

The fact that spergualin kill fungi is recited as a statement of fact (i.e., “wherein said composition kills said fungi”).

3. *Does the claim recite a process that is different in any way from that which is well-understood, routine and conventional in the art?*

No. The claim recites a process that has been occurring in nature for eons. Natural *B. laterosporus* bacteria have secreted spergualin and, in so doing, have contacted fungal cultures with the compound. Furthermore, humans have ingested *B. laterosporus* for millennia. This

ingestion has allowed the *B. laterosporus* (really the spergualin it secretes) to kill overgrown *Candida* fungi in the person's gut.

The only difference between these routine processes and the claimed method is a statement of a natural principle that was unknown but always at work in the old processes (i.e., spergualin kills fungi). As such, the claim is in effect to the natural principle itself.

**Conclusion:** Because the claimed method is directed to a natural principle itself, it is ineligible for patenting.

Analysis of Claim 7:

Same analysis as claim 6 for points 1 and 2.

3. *Does the claim recite a process that is different in any way from that which is well-understood, routine and conventional in the art?*

Yes. The claim recites administering a non-natural composition (spergualin concentrated to a specific degree) that had not been administered before applicant's filing. There is nothing to suggest historical ingestion of ingested *B. laterosporus* resulted in compositions having this concentration. This specific composition is a meaningful limitation on the claims in that it excludes the natural processes.

Furthermore, administration of spergualin concentrated in this way yields at least one important new utility for the method: treating *Cryptococcus* infection. Humans' earlier ingestion achieved its mild therapeutic benefit due to low levels of spergualin killing *Candida*. Administration of higher, non-natural concentrations kills *Cryptococcus*.

Note that this new utility derives from the same chemical properties of the spergualin compound (it likely binds the same enzyme, etc.). So the properties of the composition being administered likely have not changed much if at all. But the function/utility has changed dramatically. This bolsters the conclusion the method is a man-made process rather than a natural principle.

**Conclusion:** Because the claimed method is directed to a man-made process rather than a natural principle itself, it is eligible for patenting.

Analysis of Claim 8:

Same analysis as claim 6 for points 1 and 2.

3. *Does the claim recite a process that is different in any way from that which is well-understood, routine and conventional in the art?*

No. The claim covers two alternative embodiments. One is eligible (see discussion of claim 9 below) while the other is not. Specifically, it was routine in the art of holistic medicine (as well as in nature) to kill *Candida* fungi by administering spergualin. No one knew it was spergualin that killed the bacteria, but the method was nevertheless routine (see discussion of claim 7 above). The specific recitation of *Candida* does not help this claim 8 or distinguish it over claim 7, because the additional limitation is simply another explication of what was naturally occurring.



If a claim covers numerous embodiments, just one of which is ineligible, then the whole claim is ineligible. It is irrelevant that other embodiments may be eligible.

**Conclusion:** Because the claimed method is directed to a natural principle itself, it is ineligible for patenting.

Analysis of Claim 9:

Same analysis as claim 6 for points 1 and 2.

3. *Does the claim recite a process that is different in any way from that which is well-understood, routine and conventional in the art?*

Yes. This claim, as distinguished from claim 8, covers only eligible embodiments. Specifically, it was not routine in the art of holistic medicine (or in nature) to kill *Cryptococcus* fungi by administering spergualin. There is no evidence anyone ever killed *Cryptococcus* using spergualin, whether knowingly or not. The specific recitation of *Cryptococcus* thus helps this claim 9 and distinguishes it over claim 7, because the additional limitation modifies (in a meaningful way) the natural and routine processes.

**Conclusion:** Because the claimed method is directed to a man-made process rather than a natural principle itself, it is eligible for patenting.

Analysis of Claim 10:

1. *Does the claim appear, on its face, to recite a natural principle?*

No. Claim 10 recites the use of gusperimus (a man-made compound as determined under claim 5 above) to treat inflammation in humans. There is nothing in the art or specification suggesting the natural existence of gusperimus and thus any use thereof must be non-natural.

Note that gusperimus's activity in fighting inflammation will undoubtedly be based on some chemical properties shared with spergualin. But recall that shared properties with a natural product are not fatal to a claim as all composition will share numerous properties with natural products. As long as the new composition possesses new or enhanced functions or utilities, it is eligible for patenting.

**Conclusion:** Because the claimed method does not facially recite a natural principle, it is eligible for patenting.

Analysis of Claim 11:

1. *Does the claim appear, on its face, to recite a natural principle?*

Very similar analysis as claim 10. Note that the additional limitations specifying dose and frequency of administration are irrelevant from a subject matter eligibility perspective. Under the analysis for claim 10, claim 11 is eligible with or without these additional limitations.

**Conclusion:** Because the claimed method does not facially recite a natural principle, it is eligible for patenting.

**Factual note:** This example is based on a real-life instance of an anti-inflammation drug (gusperimus; claimed in U.S. patent no. 4,518,532) derived from a natural antimicrobial agent (spergualin) by the “mere” removal of a hydroxyl group.

**C. Composition vs. Method Claims, Each Reciting Two Natural Products**

Claim 1. An isolated DNA encoding a polypeptide with the amino acid sequence of SEQ ID NO:2.

Claim 2. The isolated DNA of claim 1 comprising the nucleotide sequence of SEQ ID NO:1.

Claim 3. A polynucleotide comprising at least 15 consecutive nucleotides of the DNA of claim 1.

Claim 4. The polynucleotide of claim 3 consisting of between 15 and 150 nucleotides.

Claim 5. A pair of DNA primers, each comprising at least 15 consecutive, non-overlapping nucleotides of SEQ ID NO:1.

Claim 6. The pair of DNA primers of claim 5, wherein said pair of primers is capable of amplifying in a polymerase chain reaction a target region comprising at least 50 consecutive nucleotides of SEQ ID NO:1.

Claim 7. The pair of DNA primers of claim 5, the first primer comprises the sequence of SEQ ID NO:3 and the second primer comprises the sequence of SEQ ID NO:4.

Claim 8. A method of amplifying a target DNA sequence, the method comprising:

(a) providing a reaction mixture comprising a double-stranded target DNA, the pair of primers of claim 7 wherein the first primer is complementary to a sequence on the first strand of the target DNA and the second primer is complementary to a sequence on the second strand of the target DNA, Taq polymerase, and a plurality of free nucleotides comprising adenine, thymine, cytosine and guanine; and

(b) performing a polymerase chain reaction to amplify said target sequence.

Claim 9. The method of claim 8, wherein said performing step comprises:

(b1) heating the reaction mixture to a first predetermined temperature for a first predetermined time to separate the strands of the target DNA from each other;

(b2) cooling the reaction mixture to a second predetermined temperature for a second predetermined time under conditions to allow the first and second primers to hybridize with their complementary sequences on the first and second strands of the target DNA, and to allow the Taq polymerase to extend the primers; and

(b3) repeating steps (b1) and (b2) at least 20 times.

Claim 10. The method of claim 8, wherein said target sequence is amplified in a sample from a test individual and said target sequence in reference individuals with general population risk of Alzheimer’s disease comprises at least 100 consecutive nucleotides of SEQ ID NO:5.

Claim 11. The method of claim 10, wherein said target sequence amplified in said sample is compared to said target sequence in reference individuals.

Claim 12. The method of claim 11, further comprising diagnosing said test individual with an increased risk of Alzheimer’s disease if said target sequence amplified in said sample differs

from said target sequence in reference individuals in such a way as to truncate the protein encoded by the ALZ1 gene in said test individual.

**Background:** The specification describes the identification of a new gene, ALZ1, inactivating mutations in which confer up to a 75% risk of Alzheimer's disease. The gene comprises 5 exons spread across 50,000 nucleotides of chromosome 1, with this entire genomic sequence disclosed in the specification (SEQ ID NO:6). The largest exon consists of 500 nucleotides and the smallest consists of 200 nucleotides.

The specification describes isolation of one mRNA transcribed from the ALZ1 gene as well as the generation of a corresponding cDNA having a 1,500 nucleotide coding sequence (SEQ ID NO:1). The ALZ1 gene is predicted to encode a protein consisting of 500 amino acids (SEQ ID NO:2). Five years after applicant's filing, genomic sequencing of HIV patients stumbled upon the existence of a complete, processed ALZ1 pseudogene in one patient comprising SEQ ID NO:1.

The specification describes numerous oligonucleotide probes used to capture out of solution and detect ALZ1-specific nucleic acids. These probes range from 30 to 100 nucleotides in length. The specification further describes numerous pairs of DNA primers and their use in PCR to amplify specific target regions of the ALZ1 gene. These primers range from 20 to 60 nucleotides in length. One specific pair of primers (SEQ ID NO:3 and SEQ ID NO:4) is described as useful for amplifying exon 3 of the ALZ1 gene (consensus wild-type sequence of SEQ ID NO:5), in which a particularly prevalent mutation was discovered to be enriched in Scandinavian patients.

#### Analysis of Claim 1:

1. *Does the claim appear, on its face, to potentially encompass a product of nature?*

Claim 1 recites a composition comprising a DNA molecule. Most claims to DNA compositions facially raise the question of whether a product of nature is being claimed because DNA is a well-known naturally-occurring molecule. In this case, the specification describes the identification of a new gene, which further confirms that facial question of patent-eligibility is raised.

2. *What is the product of nature potentially encompassed by the claim?*

The ALZ1 gene. Note that the ALZ1 gene is not an independent natural product since it is naturally integrated within chromosome 1. However, the ALZ1 gene is a discrete natural unit since it has (1) reasonably clear natural structural boundaries (the beginning and ending sequences described in the specification) and (2) a clear natural function (encoding the ALZ1 protein).

3. *Is the claimed composition structurally identical to a natural product, including any discrete natural unit?*

Essentially yes. The claim encompasses numerous embodiments, many of which are structurally distinct from any discrete natural unit. However, at least one embodiment of the claim, an isolated nucleic acid comprising SEQ ID NO:6, is essentially<sup>13</sup> structurally identical to the natural ALZ1 gene found on chromosome 1.

4. *Does the claimed composition possess a new or enhanced function or utility as compared to the natural product?*

No. The specification teaches no new or enhanced function or utility for a full-length isolated ALZ1 gene. To the contrary, claim defines the composition expressly in terms of the natural gene's natural function (i.e., encoding the ALZ1 protein). There may arguably be new functions or utilities in isolated full-length ALZ1 with the trivial amount of "isolation" encompassed by that term as defined in the specification, but (a) neither the claims nor the specification recite any such specific, substantial or credible new or enhanced function or utility and (b) there is reason to doubt so nominal a purification would yield any new or enhanced function or utility.

**Conclusion:** Because the claimed composition is structurally essentially identical to a discrete natural unit and there is no evidence of any new or enhanced function or utility, it in effect claims a product of nature and is thus ineligible for patenting.

Analysis of Claim 2:

1. *Does the claim appear, on its face, to potentially encompass a product of nature?*

Same analysis as claim 1 above.

2. *What is the product of nature potentially encompassed by the claim?*

The ALZ1 gene or the ALZ1 mRNA transcript. Note that one way of producing a cDNA molecule is to reverse transcribe an mRNA molecule, further suggesting the ALZ1 mRNA as an appropriate natural product against which to compare the composition of claim 2. Note also that the ALZ1 mRNA, unlike the ALZ1 gene, is an independent natural product since it is not integrated into a larger molecular structure.

The ALZ1 pseudogene is not a proper natural product for purposes of subject matter eligibility analysis, even though its sequence is identical to at least one embodiment of claim 2. This is because at the time of filing, there was no known pseudogene and the mere possibility of it later arising (as ultimately happened) or having already arisen (potentially true but as yet undiscovered) does not negate patent-eligibility under AMP. Specifically, footnote 8 of AMP teaches that the possibility of a random natural event producing something structurally identical to the claimed composition does not negate the fact the applicant created it.

3. *Is the claimed composition structurally identical to a natural product, including any discrete natural unit?*

No. The cDNA of claim 2 has exons removed as compared to the natural ALZ1 gene, a fairly significant structural difference. The cDNA of claim 2 is structurally different from the ALZ1 mRNA because each nucleotide unit in an RNA molecule is chemically different from each nucleotide unit in a DNA molecule (DNA lacks a specific hydroxyl group). The sequence of nitrogenous bases is nearly identical, with a difference in that mRNA has a uracil in place of each thymine found in DNA.

4. *Does the claimed composition possess a new or enhanced function or utility as compared to the natural product?*

Potentially, but the result of step 3 above makes such a question irrelevant. The claimed composition is structurally significantly distinct from any natural product and is thus patent-eligible. The fact that it is defined in terms of a natural function (i.e., encoding a natural protein) is thus irrelevant.

**Conclusion:** Because the claimed composition is structurally distinct from a discrete natural unit, the claim does not encompass a product of nature and is thus eligible for patenting.

Analysis of Claim 3:

The analysis of this claim is essentially the same as claim 1. Claim 3 encompasses some embodiments that are patent-eligible (e.g., oligonucleotides as discussed below). But because there is no upper limit on the size of the claimed DNA molecule (“polynucleotide” just means a molecule at least two nucleotides in length with no upper bound), the claim also encompasses as one of its distinct embodiments the full-length isolated ALZ1 gene. Thus this claim is patent-ineligible.

Analysis of Claim 4:

1. *Does the claim appear, on its face, to potentially encompass a product of nature?*

Same analysis as claim 1. Note that, unlike claim 3, claim 4 is limited so as to not encompass the full-length gene.

2. *What is the product of nature potentially encompassed by the claim?*

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. Exons may in some cases be discrete natural units, especially when they encode a specific functional domain of the protein. In this case, there is no such teaching and so using the smallest ALZ1 exon as a discrete natural unit for comparison is likely improper.

3. *Is the claimed composition structurally identical to a natural product, including any discrete natural unit?*

No. The claimed oligonucleotide’s sequence can be “seen” within the larger ALZ1 gene and even within specific regions of the gene such as exons and introns. However, even assuming the smallest ALZ1 exon is a discrete natural unit, the claimed composition is structurally distinct since the claimed DNA must be no more than 150 nucleotides long and the smallest exon is 200 nucleotides long.

There may be random fragments of genomic DNA floating around in a cell that meet the structural description of claim 4, but these are not discrete natural units for reasons analogous to those detailed in the above discussion of pseudogenes and AMP footnote 8. Such fragments are completely random, meaningless and non-functional from a biological perspective. However, because the claimed oligonucleotide is structurally quite similar to a natural product (i.e., its sequence can be “seen” within a larger discrete natural unit), functional analysis is appropriate in reaching a final determination of patent-eligibility.

4. *Does the claimed composition possess a new or enhanced function or utility as compared to the natural product?*

Yes. Smaller oligonucleotides of the size range recited in claim 4 are useful in specific laboratory techniques for which larger polynucleotides such as those encompassed by claims 1 & 3 are unsuited. These techniques include silicon microarrays for detection of specific DNAs in a sample, primers for DNA synthesis reactions, etc.

**Conclusion:** Because the claimed composition is structurally distinct from any putative discrete natural unit and possesses new utilities, the claim does not encompass a product of nature and is thus eligible for patenting.

Analysis of Claims 5, 6, & 7:

1. *Does the claim appear, on its face, to potentially encompass a product of nature?*

The claims recite a composition comprising a DNA molecule. Most claims to DNA compositions facially raise the question of whether a product of nature is being claimed because DNA is a well-known naturally-occurring molecule.

2. *What is the product of nature potentially encompassed by the claim?*

There is no clear natural product against which to compare the claimed pair of primers. Unlike polynucleotide, the term “primer” implies an upper bound for length that is significantly less than the full-length gene or even the smallest exon.

If random genomic fragments are not a discrete natural unit against which to compare single oligonucleotides, then a fortiori they are not proper to be compared to a claimed pair of DNA molecules. It is not hard to imagine a single random genomic fragment incidentally meeting the limitations of claim 4. It is not reasonably foreseeable, however, that two paired oligonucleotides meeting the art-accepted conception of “primers” ever randomly existed in close enough proximity to be considered a “composition.”

Note that the term “pair of DNA primers” implies the two primers are designed as a coordinated pair of molecules capable of catalyzing a polymerase chain reaction. The broadest reasonable interpretation of the claim thus does not encompass just any two random oligonucleotides (which may lack sufficient utility). Claim 6 more explicitly recites this capability and even specifies the size of the amplified target region, though this is not necessary for patent-eligibility. Similarly claim 7 recites specific primer sequences, which is boosts utility to solidify eligibility, but is not necessary.

3. *Is the claimed composition structurally identical to a natural product, including any discrete natural unit?*

No. Same analysis under this point as for claim 4 above.

4. *Does the claimed composition possess a new or enhanced function or utility as compared to the natural product?*

Yes. The term “primer” already implies the primary utility of the composition (priming a DNA polymerase chain reaction). This is a new utility since such reactions do not take place naturally, especially in a human cell. DNA synthesis primed by random RNA primers (called Okazaki fragments) occurs in human cells, but exponential amplification primed by paired DNA primers does not.

This illustrates the importance of clearly defining the natural product and the bounds of its natural functions as opposed to its properties. Random genomic fragments share many properties with each DNA primer (and with the oligonucleotide of claim 4), primary among them being a sequence (i.e., chemical structure and accompanying chemical properties) that allows for specific hybridization to complementary sequences in the ALZ1 gene. But these random fragments do not have the new utilities found in the pair of primers of claims 5, 6 & 7 or even the oligonucleotides of claim 4.

The function of a pair of DNA primers is to work in an interactive, coordinated way to catalyze a non-natural polymerase chain reaction to amplify a specific sequence of interest. No natural DNA molecule (e.g., chromosomes) and no discrete natural unit thereof (e.g., genes) function this way.<sup>14</sup> A pair of DNA primers cannot have the same function inside and outside the body because primers do not exist in the body and thus can have no function in the body.

Opposite to the bacteria aggregated in Funk Bros., which were specifically claimed to be independent of and not interactive with each other, two paired DNA primers are expressly interdependent and interactive. Importantly, this interdependence and interactivity is not random, but a result of the inventor's careful design of the molecules. A scientist designing DNA primers does not simply find a couple small DNA fragments floating around in someone's blood and, by random chance, find that they are capable of amplifying a sequence of interest in a polymerase chain reaction. Instead, the scientist carefully designs what each molecule will look like, including its specific desired chemical properties, and how they will interact with each other and their environment in the ultimate chemical reaction.<sup>15</sup> The structure of the pair of primers and the non-natural environment into which they are ultimately placed (including bacterial enzymes, and rapidly cycling high and low temperatures), as specifically determined by the scientist rather than nature, are responsible for the new, non-natural utility/function.

**Conclusion:** Because the claimed composition is structurally distinct from any putative discrete natural unit and possesses new utilities, the claim does not encompass a product of nature and is thus eligible for patenting.

**Case law note:** These primers are readily distinguishable from the isolated nucleic acids found ineligible for patenting in AMP. They do not exist in nature as a discrete biological unit. Unlike the genes at issue in AMP, primers "encode" no information have no natural function. It is true that DNA primers have nucleotide bases with the same chemical properties as that same stretch of bases found in native DNA, i.e., they "hybridize to their complementary nucleotide sequences." But this is simply a chemical property of a subportion of the larger DNA molecule—i.e., the nitrogenous bases. Focusing on this would ignore the rest of the molecule and its chemical properties and, more importantly, would improperly discount each molecule's function in the sense that term is used in AMP. The Supreme Court faulted the claims in AMP for reciting a natural biological/cellular function (AMP, 133 S. Ct. at 2113 ("Put differently, claim 1 asserts a patent claim on the DNA code that tells a cell to produce the string of BRCA1 amino acids listed in SEQ ID NO:2.")) (Emphasis added.), not for simply having some chemical properties that were similar to the properties of a subportion of a natural molecule.

Indeed, the following exchange between Justice Sotomayor and AMP's counsel shows that the Court and parties agreed that the AMP decision would not affect the eligibility of short, biologically random oligonucleotides (e.g., probes and primers):

JUSTICE SOTOMAYOR: The primers and probes stand.

MR. HANSEN: Would still remain. Even if you were to rule for Petitioners, you would not have to rule concerning the use of DNA as a probe or a primer.

AMP Oral Argument Transcript at p.11, ll.7-12 (available at [http://www.supremecourt.gov/oral\\_arguments/argument\\_transcripts/12-398\\_h3dj.pdf](http://www.supremecourt.gov/oral_arguments/argument_transcripts/12-398_h3dj.pdf)).

Analysis of Claims 8 & 9:

1. *Does the claim appear, on its face, to recite a natural principle?*

Yes. The PCR process is clearly non-natural. On the other hand, its general features were routine and conventional at the time of filing and arguably the only new feature is the sequence of the ALZ1 gene, which is a natural principle. While the ultimate conclusion may well be that the claim is patent-eligible, further analysis is warranted since this is only a threshold question as to whether there is apparent recitation of a natural principle.

2. *What is the natural principle potentially claimed and how is it recited in the claim?*

Portions of the sequence of the ALZ1 gene is recited as the target sequence to be amplified as well as in the sequence of the primers to be used in amplification.

3. *Does the claim recite a process that is different in any way from that which is well-understood, routine and conventional in the art?*

Yes. The general features of PCR were routine and conventional at the time of filing. But the claims do not recite any and all polymerase chain reactions. The claims instead claim a specific reaction using specific primers unknown before applicant's filing. In essence, each polymerase chain reaction is a different chemical reaction where unique primers critically specify the target region to be amplified. Thus the processes of claims 8 & 9 differ from any prior polymerase chain reaction in the primers used and the region amplified, the two central features of any reaction.

Notably, the extra detail in claim 9 is unnecessary and irrelevant in determining patent-eligibility. These details are common to many polymerase chain reactions and were routine in the art at the time of filing. Thus they cannot confer eligibility. But the claim is eligible for the same reasons a claim 8 (i.e., the unique primers used and the unique target region amplified).

**Conclusion:** Because the claimed method is directed not to a natural principle itself but instead a non-natural process, it is eligible for patenting.

Analysis of Claims 10, 11 & 12:

Essentially the same analysis as for claims 8 & 9 above. Claims 10-12 recite additional elements that move the process beyond agnostic PCR amplification into a process for determining whether a patient has a mutation in ALZ1 and diagnosing a predisposition to disease based on the presence of a mutation. Because of this, there is an additional potential natural principle implicated in these claims: Mutations in ALZ1 increase risk of Alzheimer's disease.<sup>16</sup>

However, the process as a whole recites significantly more than what was routine and conventional at the time of filing. There were likely many methods of assessing Alzheimer's



disease risk, but none assessed the ALZ1 gene or used the specific polymerase chain reaction recited in the claims. As discussed above, PCR was well-known in its general aspects but this specific polymerase chain reaction was unknown.

**Conclusion:** Because the claimed method is directed not to a natural principle itself but instead a non-natural process, it is eligible for patenting.

#### **D. Process Claim Involving A Natural Principle**

Claim 1. A method of stimulating production of CRP, the method comprising: inoculating a patient with an infectious bacterium, thereby increasing the amount of CRP circulating in the patient's blood.

Claim 2. A method of stimulating production of D1, the method comprising: inoculating a patient with an infectious bacterium, thereby increasing the amount of D1 circulating in the patient's blood.

Claim 3. The method of claim 2, wherein said inoculating step (a) induces production of CRP and induces pyrexia, (b) pyrexia induces production of Enzyme A, (c) CRP and Enzyme A react to produce Effector B, (d) Effector B initiates a signaling cascade that increases expression of D1, and (e) said D1 is secreted by the patient's cells into the patient's blood.

Claim 4. A method of producing Effector B, the method comprising: inoculating a patient with an infectious bacterium and reacting CRP with Enzyme A, thereby producing Effector B.

Claim 5. 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 6. 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 7. The method of claim 6, wherein said determining step comprises assaying said sample using a radioimmunoassay or an ELISA assay.

Claim 8. 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 9. The method of claim 10, further comprising administering drug Y if said test patient's APACHE II score is predicted to exceed 50.

Claim 10. 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 D1/D3 greater than 0.3 is indicative of sepsis.

Claim 11. A method for determining the likelihood a test patient has sepsis, the method comprising:

- (a) measuring the concentration of D1 in a blood sample obtained from said test patient;
- (b) measuring the concentration of D2 in the blood sample;
- (c) measuring the concentration of D3 in the blood sample;
- (d) combining the measured concentrations to derive a numerical index score;
- (e) comparing said index score with a numerical reference score, wherein said comparison indicates the likelihood said patient has sepsis.

Claim 12. The method of claim 11, further comprising diagnosing said test patient as having sepsis if said index score exceeds said reference score.

Claim 13. The method of claim 11, further comprising reporting or recording the results of said comparison.

Claim 14. The method of claim 12, further comprising reporting or recording said diagnosis.

**Background:** The specification teaches that sepsis is a complex, incompletely understood and often fatal disorder, typically accompanied by porphyria. D1 is 15-amino-acid peptide that, among its multiple effects, induces porphyria. 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 is unknown and there is no indication that D1 plays any role in fighting infection or sepsis, but the specification presents 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 (or fever) 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 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 23 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.

Analysis of Claim 1:

1. *Does the claim appear, on its face, to recite a natural principle?*

Yes. The claim describes a natural process—i.e., a bacterial infection increasing the amount of CRP circulating in a patient's blood. Note that the "thereby" clause can be a red flag for patent-eligibility similar to a "wherein" clause discussed above. This is because a "thereby" clause can similarly merely describe what is naturally occurring in a particular process rather than describing a "hand of man" modification to a natural process.

2. *What is the natural principle potentially claimed and how is it recited in the claim?*

Bacterial infection induces production of CRP.

3. *Does the claim recite a process that is different in any way from that which is well-understood, routine and conventional in the art?*

No. The claim merely describes a process that has presumably occurred for millennia—a human gets a bacterial infection and that infection induces increased production and circulation of CRP. Notably, the claim does not require that the process occur outside the human body. This is readily seen in the following chart:

<b>Claim 1</b>	<b>Process routinely engaged in by scientists at the time of filing</b>
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<p>A method of stimulating production of CRP, the method comprising:  inoculating a patient with an infectious bacterium,  thereby increasing the amount of CRP circulating in the patient’s blood.</p>	<p>A method of stimulating production of CRP, the method comprising:  inoculating a patient with an infectious bacterium (i.e., a person getting an infection),  thereby increasing the amount of CRP circulating in the patient’s blood (i.e., that which biochemically follows from such infection).</p>
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**Conclusion:** Because the claimed method recites an entirely natural process, it is ineligible for patenting.

Analysis of Claim 2:

Very similar to the analysis of claim 1. Note that the biochemical connection between bacterial infection and increased D1 levels is far more indirect than the connection between infection and CRP production. Nevertheless, the claim still merely describes/claims an entirely natural process as it occurs within the human body. The applicant no more “invented” this process than the process in claim 1 or any other natural process. Thus, the claim is ineligible for patenting.

Analysis of Claims 3 & 4:

Very similar to the analysis of claims 1 & 2. Claim 4 recites more than one intermediate step in the natural process. Claim 3 recites in detail all steps in the process leading to increased D1 levels. Just as in claims 1 & 2, however, the claims still merely describe/claim an entirely natural process as it occurs within the human body. Claiming a physiological process itself amounts to claiming one of the basic tools of science. Claims 3 & 4 are therefore ineligible for patenting.

Analysis of Claim 5:

1. *Does the claim appear, on its face, to recite a natural principle?*

Yes. The claim includes a “wherein” clause that appears to be framed as a statement of fact.

2. *What is the natural principle potentially claimed and how is it recited in the claim?*

Sepsis leads to elevated levels of D1.

3. *Does the claim recite a process that is different in any way from that which is well-understood, routine and conventional in the art?*

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. Unlike claims 1 to 4, 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:

<p><b>Claim 5</b></p>	<p><b>Process routinely engaged in by scientists at the</b></p>
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	time of filing
A method <i>for the diagnosis of sepsis</i> , the method comprising: determining the level of D1 in a blood sample from a mammalian patient suspected of having sepsis, <i>wherein elevated levels of D1 relative to a normal control are indicative of sepsis.</i>	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.

**Conclusion:** Because the claimed method recites a routine process and merely appends a statement of a natural principle, it is directed to the natural principle itself and is therefore ineligible for patenting.

#### Analysis of Claim 6:

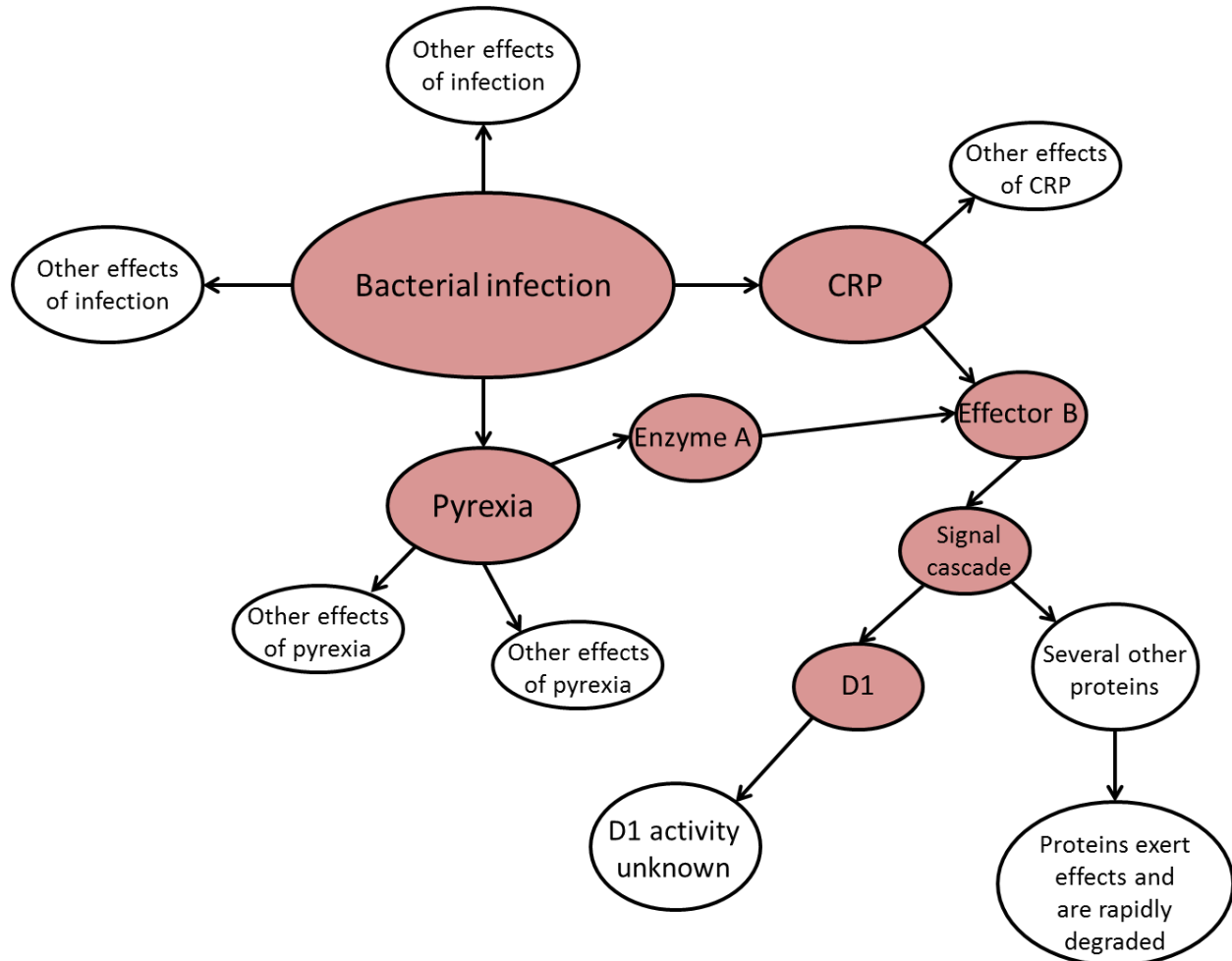
1. *Does the claim appear, on its face, to recite a natural principle?*

Yes. Diagnosis of disease is clearly a non-natural process. On the other hand, the claim at least appears to recite a connection between a biomarker and a disease, which may be a natural principle. While the ultimate conclusion may well be that the claim is patent-eligible, further analysis is warranted since this is only a threshold question as to whether there is apparent recitation of a natural principle. Notably, this is something more than merely “involving” a natural principle; it is a potential recitation of the principle.

2. *What is the natural principle potentially claimed and how is it recited in the claim?*

(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. 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.

Bacterial infection leads to increased CRP as well as numerous other physiological effects. One of those is pyrexia, which in turn leads to numerous effects including production of Enzyme A. CRP and Enzyme A react to produce Effector B. Effector B initiates a signaling cascade that leads to production of several proteins including D1, each of which has a specific activity. And ultimately D1's activity is unknown. This complexity is summarized below, with the specific connection between bacterial infection and D1 levels highlighted in yellow:



At each step in this 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. For example, the law of gravity says that all massive objects necessarily attract each other according to a specific equation. This 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<sup>1</sup> to generate a new, useful (though not absolute), diagnostic connection between D1 and sepsis. This is not a natural principle.

<sup>1</sup> In many cases the putative mechanism is worked out after the marker is identified.

3. Does the claim recite a process that is different in any way from that which is well-understood, routine and conventional in the art?

Yes. Again the following chart is helpful:

Claim 6	Process routinely engaged in by scientists at the time of filing
<p>A method <i>for detecting sepsis</i>, the method comprising:</p> <p>(a) determining the level of D1 in a blood sample from a mammalian test patient suspected of having sepsis,</p> <p>(b) comparing the level of D1 in said blood sample to that in a non-diseased reference patient, <i>and</i></p> <p>(c) <i>diagnosing the test patient as having sepsis when the level of D1 in said blood sample exceeds that in said non-diseased reference patient.</i></p>	<p>A method <i>for detecting sepsis</i>, the method comprising:</p> <p>(a) determining the level of D1 in a blood sample from a mammalian test patient suspected of having sepsis,</p> <p>(b) comparing the level of D1 in said blood sample to that in a non-diseased reference patient, and</p> <p>(c) <i>diagnosing the test patient as having acute anemia cause by blood loss when the level of D1 in said blood sample exceeds that in said non-diseased reference patient.</i></p>

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 5. Whereas the “wherein” clause in claim 5 adds no limitation, step, structure or element to the claimed process, diagnosis is an active, 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 its diagnostic uses. The background describes several additional diagnostic uses for D1 fairly far afield from sepsis (e.g., animal health diagnosis).

**Conclusion:** Because the claimed method recites a new rather than routine process that is a specific application of a natural principle, it is not directed to the natural principle itself and is therefore eligible for patenting.

Analysis of Claim 7:

Same analysis as claim 6. 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 6.

Analysis of Claim 8:

1. *Does the claim appear, on its face, to recite a natural principle?*

Yes. Prognosis of disease is clearly a non-natural process. On the other hand, the claim at least appears to recite a connection between a biomarker and severity of that disease, which may be a natural principle. While the ultimate conclusion may well be that the claim is patent-eligible, further analysis is warranted since this is only a threshold question as to whether there is apparent recitation of a natural principle.

2. *What is the natural principle potentially claimed and how is it recited in the claim?*

(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.

3. *Does the claim recite a process that is different in any way from that which is well-understood, routine and conventional in the art?*

Yes, for essentially the same reasons as claim 7:

Claim 8	Process routinely engaged in by scientists at the time of filing
<p>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, <i>and</i>                      (c) <i>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.</i></p>	<p>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.</p>

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 the 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 5. Whereas the “wherein” clause in claim 5 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.

**Conclusion:** Because the claimed method recites a new rather than routine process that is a specific application of a natural principle, it is not directed to the natural principle itself and is therefore eligible for patenting.

Analysis of Claim 9:

Same analysis as claim 8. The recitation of additional active steps based on the prognosis reached in claim 8 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 applications sufficient to confer eligibility without a treatment step.

Analysis of Claim 10:

1. *Does the claim appear, on its face, to recite a natural principle?*

Yes, for the same reasons as claim 6.

2. *What is the natural principle potentially claimed and how is it recited in the claim?*

Sepsis leads to elevated levels of D1 (same as claim 6). The ratios of D1 to D2 and D1 to D3 are utilized in the claims, but these are not natural principles. First, any connection between these ratios and sepsis is mechanistically unclear and remote (see diagram in analysis of claim 6 above). Second, there is no indication whether a particular ratio is causative or a result of sepsis. In other words, there is no other clear mechanistic natural principle.

3. *Does the claim recite a process that is different in any way from that which is well-understood, routine and conventional in the art?*

Yes. Again the following chart is helpful:

Claim 10	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;	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.

<p>(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.</p>	
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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 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 10 are just as active as the "measuring" steps and just as integral to the claim process as the "diagnosing" and "predicting" steps in claims 6 & 8, 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.

**Conclusion:** Because the claimed method recites a new rather than routine process that is a specific application of a natural principle, it is not directed to the natural principle itself and is therefore eligible for patenting.

Analysis of Claim 11:

1. *Does the claim appear, on its face, to recite a natural principle?*

Yes, for the same reasons as claim 6. Additionally, there is a "wherein" clause in claim 11.

2. *What is the natural principle potentially claimed and how is it recited in the claim?*

Same as claim 10. Note that 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, but instead a method of calculating the number. And this is not a case of providing merely a new method for calculating or converting numbers per se as in Gottschalk v. Benson. This number is associated with the real-world, tangible phenomenon of sepsis.

3. *Does the claim recite a process that is different in any way from that which is well-understood, routine and conventional in the art?*

Yes:

<b>Claim 11</b>	<b>Process routinely engaged in by scientists at the</b>
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	<b>time of filing</b>
<p>A method for determining the likelihood a test patient has sepsis, the method comprising:</p> <p>(a) measuring the concentration of D1 in a blood sample obtained from said test patient;</p> <p>(b) measuring the concentration of D2 in the blood sample;</p> <p>(c) measuring the concentration of D3 in the blood sample;</p> <p><i>(d) combining the measured concentrations to derive a numerical index score;</i></p> <p><i>(e) comparing said index score with a numerical reference score, wherein said comparison indicates the likelihood said patient has sepsis.</i></p>	<p>A method for determining the likelihood a test patient has sepsis, the method comprising:</p> <p>(a) measuring the concentration of D1 in a blood sample obtained from said test patient;</p> <p>(b) measuring the concentration of D2 in the blood sample;</p> <p>(c) measuring the concentration of D3 in the blood sample.</p>

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 by (1) combining the three markers' concentrations to derive a numerical index score and (2) comparing this index score to a reference score. The "combining" and "comparing" steps in claim 11 are just as active as the "measuring" steps and just as integral to the claim process as the "diagnosing" and "predicting" steps in claims 6 & 8, 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.

Beware a mechanical reaction to the presence of the "wherein" clause in claim 11. Just as in claim 5, the wherein clause does not further limit the claim and thus cannot confer patent-eligibility. But the claim already recites additional steps that ensure a natural principle is not being claimed so the presence of the "wherein" clause cannot hurt eligibility.

**Conclusion:** Because the claimed method recites a new rather than routine process that is a specific application of a natural principle, it is not directed to the natural principle itself and is therefore eligible for patenting.

Analysis of Claims 12 & 13:

Same analysis as claim 11. The recitation of additional steps based on the comparison performed in claim 11 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.

Note that "recording" and "reporting" are active steps that could independently confer eligibility under the proper circumstances. The Federal Circuit in AMP struck down claims reciting only mental steps. "Recording" and "reporting" by definition cannot be mental. And this is a meaningful limitation since it makes it so that certain claims that would otherwise block someone's use of their own mind cannot reach such internal mental activity, a clear concern in Mayo.

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<sup>1</sup> More information on the Coalition can be found at the following website: <http://www.twentyfirstcenturymedicine.org/about-us/>.

<sup>2</sup> See, e.g., Bilski v. Kappos, 130 S. Ct. 3218, 3231 (2010) (“In disapproving an exclusive machine-or-transformation test, we by no means foreclose the Federal Circuit’s development of other limiting criteria that further the purposes of the Patent Act and are not inconsistent with its text.”).

<sup>3</sup> Ultramercial, Inc. v. Hulu, LLC, 722 F.3d 1335, 1342 (Fed. Cir. 2013) (“[B]ecause eligibility requires assessing judicially recognized exceptions against a broad and deliberately expanded statutory grant, one of the principles that must guide our inquiry is these exceptions should apply narrowly.”).

<sup>4</sup> Sherry Knowles, A de facto expansion of the law, *Managing Intellectual Property*, at 35 (June 2014).

<sup>5</sup> Id.

<sup>6</sup> Michael Loney and Alli Pyrah, Is Myriad spiraling out of control?, *Managing Intellectual Property*, at 31 (June 2014); see Ass’n for Molecular Pathology v. Myriad Genetics Inc., 133 S. Ct. 2107, 2111 (2013).

<sup>7</sup> Newman and Craig, Natural Products as Sources of New Drugs over the 30 Years from 1981 to 2010, *J. Nat. Prod.* 2012 March 23; 75(3): 311-335.

<sup>8</sup> Knowles, supra note 1, at 37.

<sup>9</sup> Alice further suggests a possible “technical effect” factor in determining patent eligibility of method claims. See, e.g., Alice slip op. at 12 (“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. slip op. at 13 (“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. slip op. at 15 (“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). Bilski means that this language cannot be read to categorically exclude business methods from patent eligibility. Bilski, 130 S. Ct. at 3229 (“[T]he Patent Act leaves open the possibility that there are at least some processes that can be fairly described as business methods that are within patentable subject matter under § 101.”). But this language in Alice suggests a clear technical effect (e.g., laboratory methods of medical diagnosis as opposed to improved methods of ordering human affairs) strongly weighs in favor of eligibility. This has clear analogy 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.”).

<sup>10</sup> The bacterium in Chakrabarty was not “genetically engineered” as that term has come to be used and commonly understood. There was no gene splicing or any of the modern genetic manipulation techniques we now associate with genetic engineering. Instead, the patented bacterium was produced by bacterial conjugation, which is a natural process and essentially analogous to sexual reproduction. Dr. Chakrabarty placed multiple strains of bacteria into a carefully designed environment that encouraged conjugation to produce a single bacterium having genetic material from each of the source bacteria. It was selective breeding on a bacterial scale.

Hence Chakrabarty’s extensive discussion of the Plant Patent Act and the principles of patenting plants developed through selective breeding. For example, the Court noted that Congress, by passage of the Plant Patent Act, addressed the general stance that “plants were natural products not subject to patent protection” by “explain[ing] at length its belief that the work of the plant breeder ‘in aid of nature’ was patentable invention.” Chakrabarty, 447 U.S. at 311-321.

This little understood scientific nuance of the Chakrabarty case reinforces footnote 8 from AMP and its emphasis that the fact something made by man could potentially arise through natural processes does nothing to change the fact it was made by man. It is probable that nature, in the innumerable conjugation interactions

amongst untold trillions of bacteria across the eons and across the globe, could have yielded (and perhaps had already yielded) the exact bacterium Dr. Chakrabarty produced in his lab. But this does not change what Dr. Chakrabarty did. He did not merely find his bacterium in nature and claim it as such; he instead conceived and produced a new bacterium and properly claimed it in a patent.

<sup>11</sup> It is a long-standing principle in patent law that one cannot claim the inherent properties of a product of nature. See, e.g., In re Marden, 47 F.2d 958, 960 (CCPA 1931) (“The ductility or malleability of vanadium is, therefore, one of its inherent characteristics and not a characteristic given to it by virtue of a new combination with other materials or which characteristic is brought about by some chemical reaction or agency which changes its inherent characteristics”); In re Marden, 47 F.2d 957, 958 (CCPA 1931) (“[T]he applicant was not entitled to a patent upon a product of nature, or upon one of its qualities[...].”).

<sup>12</sup> See id. at 2113 (“The first claim asserts a patent on ‘[a]n isolated DNA coding for a BRCA1 polypeptide,’ which has ‘the amino acid sequence set forth in SEQ ID NO:2.’ SEQ ID NO:2 sets forth a list of 1,863 amino acids that the typical BRCA1 gene encodes. Put differently, claim 1 asserts a patent claim on the DNA code that tells a cell to produce the string of BRCA1 amino acids listed in SEQ ID NO:2.” (Emphasis added; internal citations omitted.)), id. at 2116 (“It is undisputed that Myriad did not create or alter any of the genetic information encoded in the BRCA1 and BRCA2 genes.” (Emphasis added.)).

<sup>13</sup> As with claim 1 of Example B above, the composition of claim 1 of this Example E is, strictly speaking, structurally different from even the discrete natural unit of the ALZ1 gene in chromosome 1. While the ALZ1 gene exists in nature, the specification expressly defines an “isolated” nucleic acid as substantially separated from at least one compound naturally associated with it. Thus, by definition the claimed composition as a whole (the ALZ1 gene with at least one naturally-accompanying compound removed) does not exist in nature.

However, as with Example B, the composition is structurally differentiated from the natural ALZ1 gene in only a general, negative way (i.e., lacking at least one undefined thing naturally associated with ALZ1). Thus, the claimed composition is essentially identical to natural the ALZ1 gene.

<sup>14</sup> RNA can function in a somewhat similar way. Random short RNAs work as primers in DNA replication (called Okazaki fragments). Importantly, however, they do not work as pairs to catalyze an amplification reaction (e.g., exponential copying of a specific sequence). This is notably similar to cDNA, which has a natural RNA counterpart in mRNA and yet was still found to be eligible for patenting.

<sup>15</sup> This has a clear parallel in Chakrabarty and the fact the bacterium in that case could have arisen and likely did arise randomly somewhere in nature. That fact is irrelevant to the question of whether what is claimed is a product of human ingenuity. That DNA is naturally cleaved into random fragments in the blood and that some of these fragments could have at some point by random chance have had the ability to function as PCR primers is likewise irrelevant. See, e.g., AMP, 133 S. Ct. at 2119, n.8.

<sup>16</sup> See Example D for a fuller discussion of what a natural principle is and is not in the context of medical diagnostics.