After six years, what has been *Mayo's* impact on patent applications related to biotech, diagnostics, and personalized medicine?

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On the sixth anniversary of *Mayo,* an empirical study examines the impact of the US Supreme Court decision on patent subject-matter eligibility and patent prosecution of biotech related patent applications before the USPTO.

On March 20, 2012, nine judges of the US Supreme Court held unanimously that "Prometheus' patents set forth *laws of nature*-namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm"[1].

The Court recognized that it takes human action to trigger the metabolite/dosage relationship in a particular person, but held that "if a law of nature is not patentable, then neither is a process reciting a law of nature, *unless that process has additional features* that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself"[1]. To transform an unpatentable law of nature into a patent-eligible application, a patent must do more than simply state the law of nature while adding the words "apply it." It must limit its reach to a particular, inventive application of the law. The Court concluded that Prometheus' claims had insufficient additional features: "[w]hile it takes human action (the administration of a thiopurine drug) to trigger a manifestation of this relation in a particular person, *the relation itself exists in principle apart from any human action.* The relation is a consequence of the ways in which thiopurine compounds are metabolized by the body-entirely natural processes. And so *a patent that simply describes that relation sets forth a natural law*"[1]. The Court's opinion was that Prometheus' patent claim did not go beyond "well-understood, routine, conventional activity, previously engaged in by those in the field"[1] because clinicians had previously adjusted dosages of thiopurine drugs. In essence, the patent was a routine and conventional application of the natural law.

The Court's decision in *Mayo* provided a two-step test of patent eligibility that the Supreme Court confirmed in *Alice v CLS Bank*[2]: (A) first determine if the claims at issue are directed to a patent ineligible concept (e.g. law of nature); (B) if the answer is yes, then consider the elements of the claim to determine whether additional elements transform it into a patent-eligible application – i.e. consider if there is an element or combination of elements that ensure that the patent in practice amounts to significantly more than a patent directed to the ineligible concept itself. (**Supplementary Data**). Despite the two-step test, the *Mayo* decision did not indicate precisely where the line between patent-ineligible laws of nature and patent-eligible medical scientific applications should be drawn. The two step test employs flexible principles rather than precise rules, and Justice Breyer left much uncertainty when he drew a parallel between generally applicable natural laws of science, such as Newton's law of gravity, with the (man-made) drug-specific development of an optimal treatment regime based on individual drug-blood-metabolite relationships. As a consequence, it was evident that much would be left to be clarified by the USPTO and the courts.

The Supreme Court's decision was highly controversial. It has been seen as a substantial threat to the future patentability of diagnostic and personalized medicine. In 2012 Haanes and Cànaves described it as a "game changer" with potentially profound implications for the biotech industry[3]. Nature Biotechnology spoke to patent attorneys who wholeheartedly agreed, calling it "the worst patent decision in the history of the Supreme Court" and "almost impossible to apply"[4]. Litigating parties argued that it would "radically limit" patent protection and "fatally undermine the biomedical field"[5]. Eisenberg opined that diagnostic technology was no longer patent eligible[6]. Minssen and Nilsson were one of the few voices in 2012 suggesting that Mayo would be highly significant but not necessarily devastating[7].

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Voices of doom deepened following the Supreme Court's refusal to hear an appeal after Sequenom's patent (for diagnosing fetal illnesses and disabilities based on detecting and analysing free fetal DNA in a mother's blood) was held ineligible based on the *Mayo* ruling[8]. Holman stated in 2016 that *Mayo* "threatens the availability of patent protection for some of the most innovative and meritorious applications"[9]. As recently as 2017, it has been said that *Mayo* "resulted in whole swaths of healthcare inventions being unpatentable and existing patents being poured out of the courts as invalid"[10]. In April 2018, the USPTO issued a memo (citing the Supreme Court's *Mayo* and *Alice* rulings, and the Federal Circuit decision in *Berkheimer*) reminding examiners that careful consideration is required lest patent ineligibility rules "swallow all of patent law"[11].

Is there any empirical evidence that *Mayo* has already swallowed or eviscerated patent law for precision medicine and diagnostics? Has its impact been as profound as predicted? Or is the speculative worry unsubstantiated? These are important questions for Federal Circuit judges, the USPTO, the Supreme Court, and legislators. All these bodies have been implored to refine, re-interpret and/or change patent eligibility rules that the Supreme Court has developed with determination since 2012.

Previous Empirical Studies

Relatively few empirical studies of *Mayo's* impact have been published in peer-reviewed journals. The publications that do exist have tended to support concerns about *Mayo* having a "colossal" impact[10].

Shortly after the *Mayo* ruling was issued, Haanes and Cànaves conducted a retrospective empirical study to quantify the number of granted patents which *Mayo* was likely to invalidate[3]. They focused on the areas of diagnostic, biomarker and personalized medicine. They reported in Nature Biotechnology that many patents would be vulnerable. Specifically, in the sample they generated, they found only 15 out of 1,180 granted claims were likely to survive the *Mayo* ruling. The patents in this study were drafted without the benefit of knowing the Supreme Court's two step test, so the results did not predict the on-going impact of *Mayo*.

In 2016, Chao and Mapes studied *Mayo's* impact on patent applications in Art Unit 1634 (molecular biology, microbiology and organic compounds) *filed after* the Court's ruling[12]. Citing this "early work" by Chao and Mapes, Heidi Ledford, for Nature, reported that after *Mayo*, the USPTO was nearly four times more likely to deem personalized medicine patents *prima facie* unpatentable, and applicants were less than half as likely to overcome those §101 rejections[13]. This study focused narrowly on Art Unit 1634 and the increase in §101 rejections was due to the joint impact of *Mayo, Myriad,* and *Alice*. A *Mayo*-based rejection in an office action is not necessarily the final outcome. Applicants can provide arguments and amend the claims in order to overcome these rejections. Accordingly, despite the high proportion of 35 USC 101 *Mayo*-based rejections, it is important to study the fate of these applications in order to determine what proportion are eventually allowed (i.e., what is the allowance rate?) and how (i.e., what is the prosecution timeline?).

Research Questions

In this paper we examine *Mayo's* impact on patent applications related to biotech, diagnostics, and personalized medicine in the US. Specifically, we address the following research questions:

1) how many applications have received *Mayo*-based rejections over the last 6 years, and what has been the fate of these applications —were they eventually allowed, allowed with amendments, abandoned or still pending?;

2) what is the expected prosecution timeline of patent applications receiving a *Mayo*-based rejection?; and

3) how has the prevalence of 35 USC 101 subject-matter eligibility rejections changed over the six years since *Mayo*—for example, has the prevalence of USPTO *Mayo*-based rejections reduced with the passage of time signalling that legal uncertainty surrounding the *Mayo* decision is declining?

These are significant questions for current legal practice and future law reform, which have not been fully addressed by previous research. Their answers shed light on the practical impact of *Mayo* for applicants attempting to obtain patent rights for inventions related to diagnostics, personalized medicine, and biotech in general. Equally, they will provide an evidence basis for any discussions on law reform.

Empirical Results

To answer these three research questions we developed an empirical methodology (**Box 1 Methods**). The methodology was designed to elucidate *Mayo's* impact on patent applications across a full technology center – TC 1600 – which relates to Biotechnology & Organic Chemistry, as well as the narrower Art Unit 1634.

Our search algorithm identified 72,990 USPTO correspondence documents which contained a *Mayo* citation (**Box 1-Step 1**) over the last 6 years (March 20, 2012 to March 20, 2018). Of these, 33,878 were identified in Examiner Office Actions, 34,417 in Applicant Responses to Office Actions, and 4,695 in other correspondence such as Appeals (**Box 1-Step 2**).

How many applications received Mayo-*based rejections over the last 6 years, and what has been the fate of these applications?*

The 72,990 correspondence documents we identified correspond to 21,977 patent applications containing a citation to *Mayo* in a 35 USC 101 subject-matter eligibility rejection.

Next (**Box 1-Step 3)** we analyzed the patent applications which were listed as falling within TC 1600. Our search algorithm identified 9,435 patent applications in TC 1600. Given that the search algorithm optimized specificity (instead of sensitivity), we expect that this is a conservative estimate of the number of applications that received rejections citing *Mayo*.

In order to determine the fate of these patent applications (n=9,435 TC=1600) we classified them according to their patent status: abandoned, patented, or pending (**Box 1-Step 3**). On the sixth anniversary of *Mayo,* 4,650 of these patent applications had been abandoned (49.3%), 2,605 had been granted (27.6%), and 2,180 (23.1%) were still pending (i.e. undergoing active examination/prosecution) (**Figure 1a**). Excluding the pending applications, the overall allowance rate for patent applications in our sample was 35.9%, whereas the percentage of applications which did not reach allowance (for various reasons) after receiving a *Mayo* citation was 64.1% (**Figure 1b**).

What is the expected prosecution timeline for an application receiving a Mayo rejection?

Analysis of the USPTO file wrappers and prosecution histories for patent applications in our sample (**Box 1-Step 4**) revealed that applications which eventually overcame the rejections of record and ultimately obtained a *Notice of Allowance* received several office actions (containing Non-Final and Final Rejections). In 45.8% of the cases, applicants engaged in a second round of prosecution by filing a Request for Continued Examination (RCE). In 30.3% of the cases, two or more RCEs were needed (**Figure 1c**). For rejected applications that were ultimately abandoned the statistics are similar; 45.8% with at least one RCE; and 30.3% with 2 or more RCEs.

This is a high number of RCEs when contrasted to the statistics published by the USPTO in 2012, where 18% of patent applications filing 1 RCE and 5% filing 2 RCEs (in Chemical/Biological technology centers) were considered unacceptably high rates[14]. This motivated the USPTO to pilot several programs post-2012 to reduce RCE rates (USPTO 2012 RCE Outreach Statistics; RCE by Technology: Chemical/Biological).

How has the prevalence of 35 USC 101 rejections changed since Mayo?

Ledford's report in Nature, based on Chao and Mapes' early empirical research emphasized that there had been a significant increase from 15.9% (pre-*Mayo*) to 86.4% (post-*Mayo*) in patent applications receiving subject matter rejections under 35 USC 101 for Art Unit 1634 (ref. 12). In order to compare our results with Chao and Mapes' pre- and post-*Mayo* 35 USC 101 eligibility results, we analyzed the same art unit in further detail. Specifically, we compared a 6 year pre-*Mayo* period (applications filed between 2002-03-20 and 2008-03-20) with those filed post-*Mayo* (between 2012-03-20 and 2018-03-20) and defined pre-*Mayo* applications as those filed before the Supreme Court decision on March 21, 2012. Our selection of the pre-*Mayo* date range was designed to exclude applications filed less than 4 years prior to the decision in order to minimize the number of applications whose examination might still be ongoing after *Mayo* and therefore affected by the ruling.

Our pre-*Mayo* dataset included 5,045 patent applications examined by Art Unit 1634. Of these, we found 10.5% had 35 USC 101 rejections on the first Non-Final Office Action and 8.2% in a Final Office Action. The 6 year post-*Mayo* dataset included 4,931 patent applications examined by the same art unit (Art Unit 1634). Our results confirmed an increase in the prevalence of 35 USC 101 rejections (**Figure 1d**). We found that 55.5% of these post-*Mayo* applications received a 35 USC 101 subject-matter eligibility rejection in the first Non-Final Office Action (Non-Final Rejection)

Box 1 Methods

- **Step 1: Search Strategy**
  - Description: A search of the PAIR system was conducted to identify USPTO correspondence citing *Mayo*
  - Search Terms: "*Mayo" AND "Prometheus"*
  - Classes: All Classes
  - Technology Centers: TC 1600 (Biotechnology)
- **Step 2: Analysis of Office Actions & Responses**
  - Office Actions vs. Response Citations
- **Step 3: Analysis of Patented, Abandoned & Pending**
  - No. of cases resulting in a *Notice of Allowance* (Patented) vs. Abandonment, Pendency Analysis
- **Step 4: Analysis of Prosecution Statistics & Art Units**
  - No. of Office Actions, RCEs, Prosecution Time
- **Step 5: Analysis of *Mayo* Rejections**
  - Selection of Examples: Illustrative examples of claim amendments (changes from application to patent grant)

and 45.5% in a Final Office Action (Final Rejection). While this art unit is primarily affected by *Mayo,* it is important to note that this pre- to post-*Mayo* increase (from 10.5% to 55.5%) in the prevalence of 35 USC 101 rejections may also include the effects of other decisions such as *Myriad*[15] and *Alice*[2].

What sort of subject-matter has been affected by Mayo?

To illustrate the types of claims receiving *Mayo*-based rejections, we looked more closely at the six most recently granted patents in our sample **(Box 1-Step 5)**. Five of the first six patents directly concerned molecular testing technology, and we describe three of these to illustrate how some applicants have overcome *Mayo*-based rejections. All illustrative cases are located in the **Supplementary Data.**

The first case (Case 1) originally claimed a method for detecting the presence or absence of a gene related to cancer. This claim received a *Mayo*-based rejection because it applied a natural correlation at a high level of generality and only used well-known biological methods. After several office actions, the applicant overcame the rejection by adding a novel treatment step (e.g. using siRNA).

Another application (Case 3) originally claimed a method for determining the presence of inflammatory bowel disease by measuring between one and five biomarkers and comparing concentrations of the biomarkers against control samples. The claim was rejected because it applied natural correlations using routine techniques. The applicant effectively drafted a new claim to overcome the rejection, claiming a method of detecting inflammatory bowel disease by detecting all five biomarkers in a gut sample. This was a much shorter claim that did not mention concentrations, correlations or reference samples but did specify measurement of all five biomarkers. The examiner accepted the amended claim, emphasizing that it is unconventional to detect the five biomarkers in the gut.

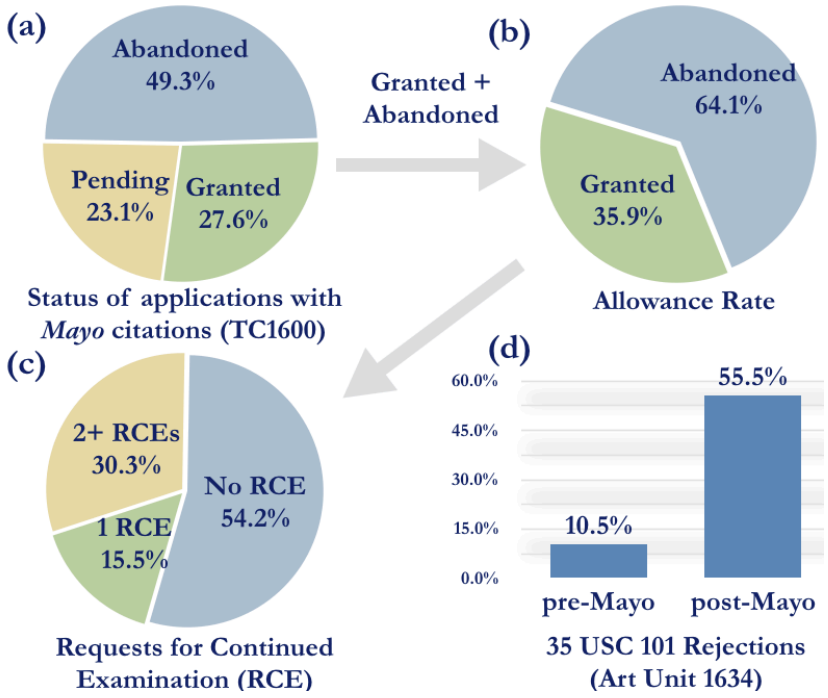

Figure 1 Study results showing that as of the 6th anniversary of *Mayo* (a) 49.3% of the patent applications were rejected/abandoned, 27.6% were granted after overcoming a 35 USC 101 *Mayo*-based rejection and 23.1% are still in active examination/prosecution; (b) the allowance rate for applications with *Mayo* rejections is 35.9%; (c) overcoming the rejections of record in the granted applications required more than one round of examination/prosecution and the need to file one or more RCEs in 45.8% of the cases (30.3% required 2 or more); and (d) prevalence of 35 USC 101 rejections in key art units increased from 10.5% (pre-Mayo) to 55.5% (post-*Mayo*).

The third example (Case 5) initially claimed a method of stratifying respiratory disorder in patients by analysing a biomarker. The examiner rejected the claim because it relied on a natural correlation without adding significantly more. On advice from the examiner, the applicant overcame the rejection by merging the claim with a later, dependent claim that used an antibody to detect the biomarker. The examiner accepted the revised claim on the grounds that using the antibody to detect the biomarker was unconventional.

Discussion

Our results indicate that *Mayo* has had a significant impact on patent prosecution in the life sciences. For instance, we found at least 4,650 (49.3% of our sample) patent applications in TC1600 (biotechnology) were abandoned after they received a rejection with a *Mayo* citation. Excluding pending applications, this corresponds to a rejection/abandonment rate of 64.1%.

That said, our results *also* show that the impact of *Mayo* may not be as devastating for biotech, diagnostics and personalized medicine patent applications as many commentators

have stated. In fact, at least 2,605 patent applications in TC1600 overcame 35 USC 101 rejections based on *Mayo*. In most of these cases, the claims were amended. It will require further research to analyze how the claims changed to satisfy the two step *Mayo/Alice* test.

We estimate an overall allowance rate of 35.9% for patent applications that received a *Mayo* rejection. This indicates it is possible to draft claim language that satisfies the post-*Mayo* 35 USC 101 threshold for life sciences inventions. Therefore, one should be careful not to equate a *Mayo*-based rejection in an office action with unpatentability. Some of these rejections can be overcome through legal argument or claim amendments during prosecution.

Our results show that although *Mayo* rejections can be overcome, it has not been easy for applicants to do so. In this respect our results provide evidence that confirms and extends a point suggested by patent attorneys[16], namely that *Mayo* has significantly increased the time and costs for prosecuting biotech, diagnostics and personalized medicine patent applications. Notably, we found that in 45.8% of TC1600 applications where applicants overcame a rejection based on *Mayo* and ultimately obtained a *Notice of Allowance,* the Applicant had to file one or more Requests for Continued Examination (RCEs), meaning additional cost and time. In 30.3% of the cases, two or more RCEs were needed. This is a high rate for RCEs[14].

A fourth point emerging from our results is that post-*Mayo* there has been a marked increase in the prevalence of 35 USC 101 subject-matter eligibility rejections relevant to biotechnology, diagnostics, and personalized medicine. We found an increase from 10.5% (pre-*Mayo*) to 55.5% (post-*Mayo*) in 35 USC 101 rejections for Art Unit 1634. This is consistent with the 'early look' by Chao and Mapes, but the differences warrant closer inspection. In their study, they observed an increase in 35 USC 101 subject matter eligibility rejections from 15.9% (pre-*Mayo*) to 84.6% (post-*Mayo*) for the same art unit (by studying a sample of applications filed after 2006, with office actions issued between August 2007 and March 2016). The higher percentages they obtained can be explained by their sampling methodology. They selected every 10th application and "then determined whether each application was drawn to personalized medicine technology." Their results are therefore based on applications that are more likely affected by *Mayo*, since "[a]pplications directed to the diagnosis or treatment of a specific disease, or to specific markers were included. All other types of applications were excluded"[12]. Accordingly, a higher percentage of 35 USC 101 rejections can be expected. In order to avoid selection bias, our study included all the applications in the art unit for the entire 6 year period following *Mayo*. Notably, even with our broad inclusion criteria, a substantial increase in §101 rejections is observed.

Legal Uncertainty

It is particularly noteworthy that the prevalence of 35 USC 101 rejections and *Mayo* citations has remained high for a full 6 year period (**Supplementary Data**). This indicates that legal uncertainty about *Mayo* has also remained high. If the threshold of eligibility had become clear and predictable with the passage of time, the patent bar would not be submitting so many patent applications that still receive *Mayo*-based rejections. Unlike the requirements of novelty and non-obviousness (which are relative matters based on comparing the claimed invention with a large and dynamic prior art base), patent eligibility is an inherent and substantive legal matter. A claim either meets the test of patent eligibility or it does not. This determination (since it is not affected by related art) can be made *a-priori* (prior to filing an application) with a high degree of accuracy . Our results (for Art unit 1634) indicate that historically, pre-*Mayo*, patent attorneys judged eligibility accurately in approximately 90% of their applications, whereas post-Mayo this has dropped to 44.5%. If the legal test is basically clear and workable, patent practitioners will generally not submit patent claims that do not comply with eligibility rules. Our results indicate that pre-*Mayo* levels of 35 USC 101 rejections were around 10%, whereas in the six year period following *Mayo* 55.5% (of the patent applications filed since *Mayo* in Art Unit 1634) received a 35 USC 101 subject-matter eligibility rejection.

Looking holistically at the results and discussion points already mentioned, it is clear that patent applicants in biotech, diagnostics and personalized medicine need to be prepared. The chance of receiving a rejection based on the *Mayo* two step test is high; and so are the chances of needing to file one or more Requests for Continued Examination in order to contest the rejection (leading to allowance, amendment or abandonment). Applicants will thus need expertise, money and time. Worryingly, smaller businesses are less likely to have these resources, and yet patent protection may be even more important for them than for large and established businesses; making it difficult to get a foothold, obtain investment, or remain competitive in the life sciences sector.

Is Law Reform Needed?

Is the impact of Mayo so unsatisfactory that law reform is required? This is always a difficult

question to answer in a rigorous and evidence-based manner. Certainly there are many calls for law reform; but the examples and evidence backing up these calls have typically been limited. On the other hand, calls not to reform also rely on limited and ad hoc evidence.

Some commentators are calling for the USPTO to revise its interpretation of the law in the Interim Examination Guidance. Others are calling for legislative intervention by Congress. For example David Kappos (Director of the USPTO, 2009-2013) has proposed abolishing §101 altogether[17]. Others, such as Robert Sachs have proposed modifying §101 to loosen the eligibility restrictions[18]. Modifications could also clarify or tighten the restrictions. To date, the calls for reform have not been taken up by Congress.

Our results do *not* provide *conclusive* evidence that §101 should be abolished. Claims are being granted, and further research is needed to appreciate the types of inventions that are receiving patent protection. Perhaps the current law (through the claims it is allowing and disallowing) already achieves an adequate balance between innovators using natural laws and products as a basis for their inventions, and other stakeholders who want unfettered access to natural laws and products? Or perhaps the claims that are disallowed happen to be highly significant for continued innovation in personalized medicine? Further research on the claims being allowed and disallowed, and the implications for R&D, would be required to answer these questions.

However, our results do support the need for greater legal certainty post-*Mayo*. Although there is an ever-present need to strike a balance between legal certainty and legal flexibility, the levels of uncertainty post-*Mayo* are substantial and on-going, as evidenced by our data.

A residual issue is what sort of law reform would best provide greater certainty around the *Mayo* test? Congressional action, Federal circuit case law, or another Supreme Court decision? Federal Circuit case law is the more straightforward option, and there are some significant, recent developments.

Recent Federal Circuit Case Law

A noteworthy development is the decision in *Vanda Pharmaceuticals v West-Ward Pharmaceuticals*[19], and the USPTO examination guidance memo which immediately followed[20]. The full impact of these developments requires further research, but it appears there is now more certainty (and eligibility) for personalized medicine claims in the form of method of medical treatment claims, but not necessarily for diagnostic claims.

The claims in *Vanda* recite a method of treating schizophrenia with iloperidone, a drug known to cause cardiac side effects in patients having a particular genotype associated with poor drug metabolism, wherein the dosage of iloperidone administered is adjusted based on the patient's genotype (12 mg/day or less if the patient has a CYP2D6 poor metabolizer genotype, or a greater dose up to 24 mg/day otherwise).

Prior to the US Court of Appeal for the Federal Circuit's decision in *Vanda*, district courts were reaching different conclusions in light of *Mayo* about the eligibility of medical treatment claims including an administering, diagnostic or patient selection component. Some such claims were held ineligible; a view a dissenting judge in the Court of Appeal for the Federal Circuit in *Vanda* ultimately agreed with.

The District Court in *Vanda* found the claims eligible[21], and the case went on appeal. The claims were again held eligible on appeal, but for different reasons. The reasoning of the higher court will be significant in future cases.

The District Court accepted that the claims were directed to a natural relationship (Step A), but held that the additional step of conducting CYP2D6 genotyping tests to inform the dosage adjustment was not "well-understood, routine or conventional activity"[21], and thus the claim as a whole was "significantly more" than a natural law (Step B).

In contrast, the majority of the Court of Appeal for the Federal Circuit read the *Mayo* case more tightly. The majority held that, unlike the claims in *Mayo*, "method of treatment claims" are *not* "*directed to*"a natural relationship (the recognized judicial exception) but rather, they are an application of the natural relationship to the treatment of a disease[19]. In other words, method of treatment claims do *not* trigger the threshold requirement in Step A of the *Mayo* two step test; thus further analysis about whether the treatment step is conventional or routine (Step B) is unnecessary.

The Federal Circuit emphasized the difference between method of treatment claims and the claims in *Mayo*, stating "although the representative claim in *Mayo* recited administering a thiopurine drug to a patient, the claim as a whole was not directed to the application of a drug to treat a particular disease." It further explained that "the claim in *Mayo* did not go beyond recognizing (i.e., 'indicates') a need to increase or decrease a dose."[19] The dissenting judge disagreed with this reasoning. Judge Prost held that this particular method of treatment claim, based on a genetic variation that regulates drug metabolism, essentially

monopolized a law of nature in a way that Breyer J disallowed in *Mayo*.

Recent USPTO Examination Guidance

The decision in *Vanda* was immediately reflected in a USPTO examination guidance memo (June 7, 2018)[20]. The memo explains that since method of medical treatment claims pass the "directed to" inquiry of Step A, there is no need to conduct a Step B analysis to search for anything not routine or conventional that amounts to "significantly more." Notably, Examiners are instructed to apply this approach to claims 5 and 6 of the hypothetical Example 29 provided in the Subject Matter Eligibility Guidance issued by the Office in May 2016[22]. In previous guidance, the personalized method of diagnosis and treatment of fictitious disease Julitis involving a newly identified protein marker was originally found to be "directed to" a judicial exception under Step 2A, but eligible under Step 2B after further enquiries determined there were also unconventional and non-routine elements. The memo thus changes the reasoning and increases the ease with which examiners will be able to assess the eligibility of "method of treatment" claims.

If the *Vanda* decision stands, method of treatment claims will be easier, clearer and more predictable to prosecute. A knock-on effect of the *Vanda* decision and subsequent USPTO memo is that claims directed to 'methods of diagnostics' might be claimed (or amended) as 'methods of treatment' through the strategic application of the "draftsman's art." This remains to be studied in the post-*Vanda* period.

Conclusions and Future Research

Even 6 years after the Supreme Court decision in *Mayo*, the dust has not yet settled. There is still much controversy about implications of the case, and its impact on biotech, diagostics and personalized medicine. Arguably the biggest problem to flow from *Mayo* was the extensive degree of legal uncertainty. Commentators have pointed to this, and our empirical results confirm it. Uncertainty means more office actions and RCEs (as confirmed by our research), which in turn means applicants must budget for these and not confuse legal uncertainty with ineligibility. Smaller companies with limited budgets and access to experts are likely to be hardest hit, and also in greatest need of patent protection to get a foothold in the life sciences industry.

It is important that steps are taken to clarify the *Mayo* test. All laws have a degree of uncertainty, but empirical data in this study indicates that the degree of uncertainty is unusually high. Care will need to be taken during the process of clarification lest the USPTO, the Federal Circuit and/or Congress exacerbate rather than reduce the problem of legal uncertainty. Expectations will also need to be managed as there is likely to be a *perception* that the *Mayo* test has been (controversially) tightened or loosened during the process of clarification even if this was not the intention. This is somewhat inevitable when the current threshold is as uncertain as it is.

The *Vanda* development is an interesting and potentially profound clarification for diagnostics and analytics that point towards a definite medical treatment. But it is unlikely to assist predictive diagnostics for which there is no stipulated treatment. It also remains somewhat unclear whether the Supreme Court would agree with the majority or dissent in the Federal Circuit. Perhaps six years on, and with the benefit of further empirical evidence the Supreme Court will accept the Federal Circuit's attempt to confine Justice Breyer's broad and elusive judgment.

Meanwhile, applicants should not confuse legal uncertainty with ineligibility. Our research confirms an allowance rate of approximately 35% for applications which have received *Mayo*-based rejections, and with further research it should be possible to have clearer information about the amendments which make the difference.

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