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Response to USPTO's Patent Eligibility Jurisprudence Study (Docket No.: PTO–P–2021–0032)

Mateo Aboy, Kathleen Liddell, Cristina Crespo, John Liddicoat, Matthew Jordan

Centre for Law, Medicine and Life Sciences (LML)
Faculty of Law, University of Cambridge, UK

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1 Introduction

On July 9, 2021, the USPTO published a Request for Information notice in the Federal Register seeking comments on the current state of U.S. patent eligibility jurisprudence (Docket No.: PTO–P–2021–0032)). These comments will be used to prepare a study on patent eligibility under 35 U.S.C. § 101, focusing on how the jurisprudence has impacted investment and innovation, particularly in technologies such as quantum computing, artificial intelligence, precision medicine, diagnostic methods, and pharmaceutical treatments.

Our research group at the *Centre for Law, Medicine and Life Sciences (LML), Faculty of Law, University of Cambridge, UK* has been conducting evidence-based (empirical) research to assess the impact of the US Supreme Court decisions in *Myriad, Mayo* and *Alice* on biotech, precision medicine, diagnostics, artificial intelligence, and other computer-related inventions affecting digital health. Our key findings directly address several of the questions raised on the Request for Information and have been published as *Patent Articles* in *Nature Biotechnology* (enclosed with this submission):[1]

1. Myriad's impact on gene patents. **Nature Biotechnology**, 34 (11), 1119-1123, 2016
   Summary (1 sentence): A patent landscape study to analyze the broad impacts of of *Myriad* on gene-related patents.

2. After Myriad, what makes a gene patent claim 'markedly different' from nature? **Nature Biotechnology**, 35 (9), 820-825, 2017
   Summary (1 sentence): Examining the types of claim amendments that have transformed isolated gene claims from patent-ineligible into eligible subject matter provides clarity into the threshold of eligibility for gene-related patents.

3. Was the Myriad decision a 'surgical strike' on isolated gene-related patents? **Nature Biotechnology**, 36, 1146-1149, 2018. Summary (1 sentence): On the fifth year anniversary of Myriad, an empirical study examines the wider impacts of the US Supreme Court decision on subject-matter eligibility and patent prosecution on 'products of nature' beyond isolated DNA.

4. Mayo's impact on patent applications related to biotechnology, diagnostics and personalized medicine. **Nature Biotechnology**, 37 (5), 513-518, 2019
   Summary (1 sentence): On the six year anniversary of Mayo, an empirical study examines the impacts of the US Supreme Court decision on subject-matter eligibility and patent prosecution on personalized medicine and diagnostics patents.

5. One year after Vanda, are diagnostics patents transforming into methods of treatment to overcome Mayo-based rejections? **Nature Biotechnology**, 38 (3), 279-283, 2020

[1] We are submitting the author-generated manuscript versions that can be distributed with citations to the respective *Nature Biotechnology* published articles.

Summary (1 sentence): On the first anniversary of Vanda, 1) to what extent have legal arguments and claim amendments based on Vanda been effective in overcoming 35 USC 101 Mayo-based rejections?; and 2) How are applicants transforming diagnostic patent claims into method of treatment claims to overcome Mayo-based subject matter eligibility rejections?

6. How does emerging patent case law in the US and Europe affect precision medicine? **Nature Biotechnology**, 37 (10), 118-1125, 2019
   Summary (1 sentence): An analysis of how today's patent law will affect tomorrow's innovation in three areas of precision medicine: (1) biomarkers and nature-based products; (2) diagnostics; and (3) algorithms, big data, and AI.

2 Comments to Patent Eligibility Jurisprudence Study

2.1 Selected Subject Matter Eligibility Questions

Since 2015 the LML patent research group (MA, KL, CC, JL, MJ) has been 1) examining the impact of three seminal cases (*Myriad*, *Mayo*, *Alice*, and follow-on case law) by developing evidence-based (empirical) IP studies designed to understand the impact of these decisions, and 2) conducting a comparative legal analysis across the US and Europe on the patentability of information age inventions affecting precision medicine (biotech and computer-related inventions). These evidence-based IP studies include empirical legal methodologies at three levels of analysis: 1) broad-level impact analysis (before & after patent landscape effects), 2) claim-level impact analysis (before & after claims, claim scope, claim strategies, claim formulations), and 3) prosecution-level analysis (before & after prosecution timelines, prosecutions strategies, effects on types of entity).

In this response to the USPTO Request for Information we report a selection of relevant results from our evidence-based studies which analyze the impact and effect of these seminal decisions. We offer empirical evidence to on-going legal debates about the significance of these cases on the changing patent landscape involving precision/personalized medicine inventions, including patents claiming 1) nucleic acids, 2) nature-based products, 3) biomarkers, 4) medical correlations and relationships, and 5) algorithms, AI and big data techniques.

In particular, we comment on 20 research questions where there is controversy and a lack of consensus among leading legal scholars and patent practitioners. These include:

1. Did *Myriad* result in a reduction of gene-related patents in general (i.e., beyond isolated DNA patents)?
2. What were the trends in 'isolated gene patent activity' in the last 20 years?
3. Are there any indications that the patent system was already 'self correcting' prior to *Myriad*?
4. Does the patent data tell us anything about what we might expect if the US Supreme Court had reached the opposite decision in *Myriad*?
5. After *Myriad* what makes a gene patent claim 'markedly different' from nature?
6. Has it been easy for patent attorneys to 'draft around' *Myriad*?
7. What proportion of human gene-related patent applications published during the 3-year period preceding *Myriad* contain an isolated nucleic acid product claim (i.e., a claim similar to the isolated gDNA claim in contention in *Myriad*)?

8. What proportion of these applications (with at least one isolated nucleic acid product claim) matured into a granted patent?

9. How were patents that contained simple isolated nucleic acid claims that received a *Myriad*-based rejection amended before the USPTO?

10. How did the USPTO respond to the *Myriad* ruling?

11. To what extent has the *Myriad* decision affected patent eligibility of subject-matter beyond naturally-occurring DNA?

12. What impact has *Myriad* had on the prosecution of such patents?

13. 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?

14. What is the expected prosecution timeline of patent applications receiving a *Mayo*-based rejection?

15. 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, signaling that legal uncertainty surrounding the *Mayo* decision is declining?

16. To what extent have legal arguments and claim amendments based on *Vanda* been effective in overcoming 35 USC 101 *Mayo*-based rejections?

17. How are applicants transforming diagnostic patent claims into method of treatment claims to overcome *Mayo*-based subject matter eligibility rejections?

18. What is the joint impact of *Myriad*, *Mayo*, *Alice* and the subsequent emerging patent case law in the US and Europe on precision medicine?

19. How do US and European patent law compare on the key tenets of subject-matter eligibility for biomarkers, medical relationships, and algorithms/AI-based information age inventions?

20. Does *Myriad* or *Mayo* create problematic uncertainty for developers of diagnostic tests? And does *Myriad* or *Mayo* create a disadvantage for US-headquartered organisations?

2.2 Answers to Research Questions

1. Did *Myriad* result in a reduction of gene-related patents in general (i.e., beyond isolated DNA patents)?

   No. The results of this study indicate that *Myriad* did not result in a reduction of gene-related patenting activity (See Article 1). Except for isolated gDNA, general gene-related patents continue to be issued in increasing numbers. Gene-related patents including SEQ. IDs in the claims continue to increase post-Myriad.

   Additional Information (Methodology, Results, Figures, References): Myriad's impact on gene patents. **Nature Biotechnology**, 34 (11), 1119-1123

2. What were the trends in 'isolated gene patent activity' in the last 20 years?

   There is a reduction in "isolated gene patent activity", but this reduction trend precedes the *Myriad* decision. The downward slope has been constant since 2010 and peaked back in 2001. Our results indicate a significant continuing drop in gene-related patents 3 years after *Myriad* containing the terms "isolated", "purified", and "natural" in any of the claims. These findings are consistent with a significant impact of *Myriad* with respect to issued patents which include claims directed to isolated gDNA. Given the Court decision on this narrow legal issue, it is clear that patentees are avoiding, amending (or canceling) claims directed to isolated genes. In contracts, it is common to find instances of US patent applications filed before the *Myriad* decision which originally contained isolated gene claims which matured into US granted patents with amended claims directed to methods and non-natural genetic constructs. (i.e., the *Myriad*-type claims are amended or canceled to advance prosecution). This is generally possible as long as the patent specification contains sufficient support for the amended claims to comply with the requirements of 35 USC 112 with respect to written description, enablement, and best mode. Nevertheless, such amendment is more than just a draftsperson's exercise because 1) an isolated gene patent cannot be easily transformed into eligible subject matter by claim drafting techniques[22], and 2) even if the isolated gene were to be included as part of an otherwise subject-matter eligible claim, the step of isolation or purification is not sufficient to satisfy the novelty[23] or non-obviousness[24] requirements. Additionally, the combination and joint-effect of *Myriad*, *Mayo*[25], and *Alice*[26] make it substantially more challenging to transform ineligible claims directed to isolated genes, natural products, laws of nature, or abstract ideas into subject-matter eligible claims.

3. Are there any indications that the patent system was already "self correcting" prior to *Myriad*?

   Yes. There is strong evidence of "self-correction." The legal standards of novelty & especially non-obviousness (inventive step) had already been preventing further isolated gene patents from being issued. Our results show that patent activity peaked years before the *Myriad* decision indicating that the patent system has already addressing the patentability of these inventions on the basis of novelty and non-obviousness (inventiveness). It is also important to note that despite the fact that the law has not changed in Europe and isolated DNA claims continue to be eligible, there is a substantial decrease on the number of isolated DNA patents granted.

   Additional Information (Methodology, Results, Figures, References): Myriad's impact on gene patents. **Nature Biotechnology**, 34 (11), 1119-1123

4. Does the patent data tell us anything about what we may expect if the US Supreme Court had reached the opposite decision in *Myriad*? Are there any side-effects?

   Our results show that even if *Myriad* had reached the opposite decision (and isolated gDNA patents were eligible subject matter), it is likely that very few of such patents would be granted at this time since new patent filings (unless claiming priority back to the early 2000s) would not satisfy the non-obviousness requirement for patentability. This effect is also seen in Article 1 Figs., where the reduction trend in isolated DNA patents precedes the *Myriad* decision. In fact, our results show that the downward slope in gene-related patents containing the keyword "isolated" within 3 words of "DNA" in the patent claims has been roughly constant since 2010 and peaked back in 2001. The results of this research indicate that the legal standard of non-obviousness, as opposed to subject-matter eligibility continues to be the main determinant of patent prosecution strategies. The relative importance of subject matter eligibility versus non-obviousness may be studied by comparing filing, publication, and the corresponding priority dates of the patent applications and issued patents. Since patent applicants need to sacrifice valuable patent term in order to claim the priority benefits, the only sound rationale to keep claiming early priority dates is to satisfy the increasingly high-bar of patentability due to the large amount of prior-art now available.

   Our results of assignees obtaining gene-related patents indicate a significant shift in the ratio of small-entities vs. large entities owning US gene-related patents. The proportion of patents owned by small entities dropped dramatically after *Myriad*. This was unexpected and could be a negative side-effect of the decision. It is potentially highly significant, as small entities are important sources of biotech

innovation[27,28].

Additional Information (Methodology, Results, Figures, References): Myriad's impact on gene patents. **Nature Biotechnology**, 34 (11), 1119-1123

5. After *Myriad* what makes a gene patent claim 'markedly different' from nature?

We created a typology to classify the amendments that, after *Myriad*, successfully transformed a simple isolated nucleic acid product claim into a patent-eligible claim. Aside from cancelling the isolated nucleic acid claims (n=183), the typology reveals that applicants are typically employing one of eight prosecution strategies: 1) amending to cDNA; 2) amending to nucleic acids with non-naturally occurring sequence variations; 3)amending to nucleic acids recombinantly linked with heterologous sequences; 4) amending to labelled nucleic acids; 5) amending to a nucleic acid in a vector; 6) amending to a nucleic acid recombined with a non-specific regulatory sequence; 7) amending with a Type-2 change and a negative-claim clause; and 8) amending to a short nucleic acid (so short that it does not naturally occur). The Supplementary Information provides definitions for each of these strategies and details the amendments made in each of the 21 cases, including some of the arguments made by Applicants and Examiners. This Information also records three applications that received a *Myriad*-based rejection and, as a result, the Applicants cancelled the claims.

The most common way to amend and overcome a *Myriad*-based rejection was to claim cDNA, which occurred in seven of these 21 instances. As described below, although some of these eight strategies may appear obvious in hindsight, the concrete examples provide additional guidance on what degree of difference satisfies the USPTO that an isolated nucleic acid product claim is markedly different from those in nature.

Additional Information (Methodology, Results, Figures, References): After Myriad, what makes a gene patent claim 'markedly different' from nature? **Nature Biotechnology**, 35 (9), 820-825, 2017

6. Has it been easy for patent attorneys to 'draft around' *Myriad*?

Our results indicate that in the years immediately after *Myriad* there has been much less amending activity than some commentators had expected. In over 79.2% of M1a cases the simple isolated nucleic acid product claims were canceled. Claim amendments were attempted and successful in less than 18.6% of the cases. We found only 21 (3.2% of the M1a) instances of successful amendments after receiving

an explicit *Myriad* rejection. Furthermore, in none of these cases involving successful amendments, is the scope (breadth) of the granted claims equivalent to the original scope. In general the amended claims are narrower.

When we commenced this study we expected to see more amending activity to overcome *Myriad* rejections; we did not expect so many cancellation of entire patents nor so many canceled claims which excised a nucleic acid claim without any attempt to amend the claim to closely related subject-matter eligible claims. There were potentially many reasons for the large proportion of discontinued isolated nucleic acid product claims. Undoubtedly one reason was the view that such claims were ineligible and difficult to draft around after *Myriad*. No guidelines were initially issued, and even then detailed information for addressing *Myriad*-based rejections in relation to isolated nucleic acids was unavailable. There were also reasons other than patent eligibility, for example, concerns about novelty, obviousness or unity of invention. Another explanation is that such claims are simply not as valuable as they were once perceived to be and are suffering a 'Darwinian fate'.[26]

It is important to note that canceled *Myriad*-type claims could, in some cases, be resurrected and amended in future, claiming the original priority date; for example as a divisional, continuation or continuation-in-part patent application. So it may be that some applicants that discontinued *Myriad*-type claims are waiting to learn more about successful claim-drafting practices before trying to prosecute or amend contentious *Myriad*-type claims. The typology, information and concrete examples in this study of what works and doesn't work is the sort of information that patent practitioners may find helpful. In particular, the file wrappers disclose important nuances that applicants have only learnt through trial and error.

For example, in one of the 21 applications to receive a *Myriad*-based rejection, the applicant attempted to overcome the rejection by claiming an "isolated polydexoyriboneculeotide that, when transcribed and translated, yields a polypeptide [that exists in nature]". However, the examiner maintained the rejection and suggested that the claim be amended to cDNA instead; the applicant accepted this amendment (Case No.1, Supplementary Information). In another application that received a *Myriad*-based rejection, the applicant amended a *Myriad*-type claim to 'synthetic DNA'; however, the examiner maintained the rejection because the claim still included a sequence that existed in nature despite being made in a synthetic, unnatural way (Case No.7, Supplementary Information). In yet another example, an examiner rejected a claim limited to 'designer' nucleic acids because it was not clear how the nucleic acids differed from those in nature. The examiner in this case even said that it is common for experts in the field to "describe natural processes of evolution as

examples of engineering or design". The applicant eventually overcame the rejection by claiming specific, non-naturally occurring sequences (Case No.11, Supplementary Information).

Based on these results, we can conclude that, to date, applicants have not found techniques to draft-around *Myriad* to obtain claims of equal breadth to isolated nucleic acid claims. However, some applicants have been able to amend ineligible isolated nucleic acid claims so that the resulting subject-mater eligible claims lie close to the boundary stated in *Myriad* between ineligible and eligible subject matter. Also we cannot go so far as to say that drafting around *Myriad* to achieve equal breadth is impossible: successful strategies might be found in claims that were, for example, amended for reasons unrelated to subject matter, or that occurred before examination on the merits.

In the immediate aftermath of the *Myriad* ruling, it may turn out that applicants have avoided trying to draft around *Myriad* (preferring instead to cancel the claims) because there is not enough of a business case to warrant this effort. Or it may turn out that applicants have delayed doing so due to current legal uncertainty. This will be clearer in a few years when we can see if a significant number of the canceled *Myriad*-type claims are resurrected as continuations or divisionals, and successfully amended at that point in time.

Additional Information (Methodology, Results, Figures, References): After Myriad, what makes a gene patent claim 'markedly different' from nature? **Nature Biotechnology**, 35 (9), 820-825, 2017

7. What proportion of human gene-related patent applications published during the 3-year period preceding *Myriad* contain an isolated nucleic acid product claim (i.e., a claim similar to the isolated gDNA claim in contention in *Myriad*)?;

   We found 653 applications with at least one simple isolated genomic nucleic acid product claim. This constitutes approximately 50% of the 1292 human gene-related applications found by our S1 search algorithm (See Article Table 1).

   Additional Information (Methodology, Results, Figures, References): After Myriad, what makes a gene patent claim 'markedly different' from nature? **Nature Biotechnology**, 35 (9), 820-825, 2017

8. What proportion of these applications (with at least one isolated nucleic acid product claim) matured into a granted patent?

This question was directed to finding out the proportion of the 653 gene patent applications that were eventually granted. In other words how many of these patent applications 'made it' notwithstanding *Myriad*? Our results show that 313 (47.9%) applications were eventually granted (M1aG), 311 (47.6%) were wholly rejected/abandoned (M1aR) (meaning all claims discontinued), and 29 (4.4%) were, ats of January 2017, pending (M1aP).

Additional Information (Methodology, Results, Figures, References): After Myriad, what makes a gene patent claim 'markedly different' from nature? **Nature Biotechnology**, 35 (9), 820-825, 2017

9. How were patents that contained simple isolated nucleic acid claims that received a *Myriad*-based rejection amended before the USPTO?

   We examine the M1aG subset (n=313) above. The objective was to see how these patents had managed to survive the *Myriad* ruling. Of these, 183 applications (58.5%) advanced prosecution to allowance by surrendering (i.e., canceling) all simple isolated nucleic acid products claims (M1aGC). These patents, when finally granted, no longer contained any of the isolated nucleic acid claims which had been published prior to the *Myriad* decision. The M1aGC cohort, taken together with the M1aR applications (where the simple isolated nucleic acid claims were abandoned or rejected along with every other claim), reveal that a very large proportion of *Myriad*-type claims filed in the three years before *Myriad* were not taken forward by applicants (79.2% of the 653 in the M1a subset). We found only 14 (4.5%) applications were granted without substantive amendments to the originally published isolated nucleic acid claims (M1aGU). Significantly, all but one of these were examined on the merits before the *Myriad* decision. Some of these claims are now at risk of invalidation in light of *Myriad*, but some of these claims may still be valid if they are limited to nucleic acids that do not exist in nature. In any event, the M1aGU subset is small, constituting approximately 1% of the 1292 applications identified in our S1 search algorithm.

   Additional Information (Methodology, Results, Figures, References): After Myriad, what makes a gene patent claim 'markedly different' from nature? **Nature Biotechnology**, 35 (9), 820-825, 2017

10. How did the USPTO respond to the *Myriad* ruling?

    Our results show that the USPTO implemented the *Myriad* ruling swiftly. We found examples where patent applications had received Notices of Allowance in the three

months preceding the *Myriad* ruling (i.e., examination on the merits had concluded) but were stopped from issuance and prosecution reopened with a *Myriad*-based rejection (e.g., Cases No.7 and No.24, Supplementary Information). In general, our results also indicate the USPTO Examiners are interpreting *Myriad* and USPTO Examination Guidance literally and narrowly; though it is still debatable whether they are giving effect to the Supreme Court's statement that differences should be 'marked.' For example, does limiting the claim to a single "molecule that includes a nucleic acid and a fluorescent label" really constitute a 'marked difference' from Nature?

We also found that Examiners are conservative in their use of discretion and do not tend to grant allowances based on claim language that deviates from the specific examples provided in the Examination Guidance. The strict attitude is reinforced by the USPTO's current practice of not granting patents on isolated naturally-occurring polypeptides (Case No.12 Supplementary Information). Although the position against eligibility is conservative overall, there seems to be inter-examiner variability. For example, an oligonucleotide that did not differ to sequences in nature was granted (Case No.21, Supplementary Information), yet a claim to a pair of primers was rejected (Case No.23, Supplementary Information).

The conservative approach of USPTO Examiners probably results in longer prosecution-times and in some cases patent applicants may be surrendering more patent protection scope than needed in order to satisfy the Examiners with regards to 35 USC 101 requirements (depending on one's view of the requirement for a 'marked difference' rather than a mere 'difference' from naturally occurring nucleic acid). If so, a potential positive side effect is that granted patents are more likely to withstand a validity challenge, should one be made via the courts at a future time. On balance it is unclear whether the conservative approach is beneficial. The longer patent prosecution times could disproportionately affect startups and small firms. They may not have the resources for engaging in this type of complex prosecutions involving multiple rounds of examination and RCEs (Requests for Continued Examination), unlike larger firms with more resources. We found some preliminary evidence of such disproportionate effect in our previous empirical study[14]. Strong, reliable patents are typically important for businesses which need 1) to attract investment in a risky R&D environment, and 2) firm growth during the term of the patent (ie., 20 years from the filing date). Thus, strong, reliable patents are particularly important for SMEs. These firms are important providers of disruptive innovation (e.g., new ventures; substitute and new entrant products), which often require a period of market protection to challenge incumbents. In contrast, larger firms tend to dominate continuous improvement (or sustained-innovation) and can rely

more on existing capital, marketing, brand recognition, R&D budgets, and existing distribution channels for competitive advantage.

Additional Information (Methodology, Results, Figures, References): Was the Myriad decision a 'surgical strike' on isolated gene-related patents? **Nature Biotechnology**, 36, 1146-1149, 2018.

11. To what extent has the *Myriad* decision affected patent eligibility of subject-matter beyond naturally-occurring DNA?

Our results show that a) 85% of the *Myriad*-based rejections in our sample were directed to non-isolated DNA patent claims, and b) upon receiving a *Myriad* rejection directed to these claims, applicants advanced prosecution by either amending (71%), cancelling (27%) or providing legal and scientific/technical argument (2%) for these claims. The subject matter that examiners have rejected beyond isolated gDNA is quite diverse. It includes other types of nucleotide-based inventions, such as RNA (Case 4), DNA arrays (Case 5), DNA-based kits, and DNA created after inbreeding (Case 10). It also goes beyond nucleotide-based inventions., including: peptides (Case 1), proteins (Case 2), antibodies (Case 11), cells (Case 12), pharmaceutical compositions (Case 4) and methods of various types (Case 15). All these illustrative cases are located in Supplementary Data.

From the above results, several interesting points emerge which provide a better understanding of the extent to which *Myriad* is affecting patent applications other than gDNA.

Although the Supreme Court justices made several statements that led prominent commentators to think *Myriad* would have a narrow impact on "genes and the information they encode,"[1] empirical evidence shows that at least 6,785 patent applications have been affected by a *Myriad* rejection in 5 years. Furthermore, our results indicate that 85% of these affected applications pertain to subject matter other than naturally-occuring DNA.

Most *Myriad* citations are Examiner initiated (70%), and it is not the case that Examiners are simply citing *Myriad* as one case amongst a string of cases that have reformulated the law of patent eligibility (eg *Alice, Mayo*, etc). Indeed our results show that in 60% of cases *Myriad* is employed as the central, and often sole, reference to justify the 35 USC 101 rejection. This indicates that the impact of *Myriad* on cases other than DNA is not mundane, as predicted by some commentators.

It is also important to note that our results indicate that a *Myriad* rejection does not sound a "death knell" for a patent application. Excluding pending applications, we found that 48.5% ultimately received a Notice of Allowance.

That said, successful prosecution of a patent which receives a *Myriad* citation often appears to require extra time and money. For instance in approximately 45.6% of cases, patent applicants file a RCE and go through an extra round of patent examination. Furthermore, 13.7% go through at least an extra 2 rounds of patent examination with all the time and costs that entails before a Notice of Allowance is issued. This is a high frequency of patent applications to be going through RCEs, as can be seen from a comparison with the latest USPTO statistics which found 18% of patent applications filed 1 RCE and 5% filed 2 RCEs to prosecute successfully (USPTO 2012 RCE Outreach Statistics; RCE by Technology: Chemical/Biological). The results also show that it takes additional time and money for applicants to decide to abandon a patent which has received a *Myriad* citation, meaning greater sunk costs.

The results also indicate that often claims are being narrowed as a result of *Myriad*. To overcome *Myriad* rejections, applicants typically amend claims (71%); arguments alone from the applicant are sufficient only in 2% of cases. Another strategy is to cancel the specific claims affected (27%).

Considering the controversy following *Myriad* about the breadth of its impact ('surgical strike' v. sweeping impact), these empirical results are noteworthy. To summarize: (i) 85% of rejections including a *Myriad* citations concern products other than isolated DNA); (ii) 48.5% of patent applications receiving a *Myriad* rejection are nevertheless ultimately allowed-it's not necessarily "game over"; (iii) but only 2% are allowed solely on the basis of argument (for the rest the affected claims are amended or cancelled to advance prosecution).

It is interesting to consider how and why the *Myriad* case is having this effect on prosecution. To understand this, it is important to look closely at the final USPTO Examination Guidance (MPEP 2106, January 2018) on subject-matter eligibility.

The latest guidance attempts to reconcile case law (including *Myriad*, *Mayo* and *Alice*) into a generally applicable two-step framework for determining subject matter eligibility. This has been a contentious exercise. First (Step 1), the claimed invention must belong to one of the four statutory categories defined in 35 USC 101 (process, machine, manufacture, or composition of matter). Second (Step 2A), the claims

should not be 'directed to' one of the judicially recognised exceptions (abstract ideas, laws of nature, or natural phenomena, including 'products of nature'), unless (Step 2B) they include additional limitations such that the claim as a whole amounts to 'significantly more' than the exception.

Looking more closely at the details of Step 2A in MPEP 2018 one sees that it casts a broader net than one might originally suspect. This helps explain why *Myriad* is being raised more often than 'surgical strike' commentators predicted. First, contrary to what the name might suggest, Step 2A does not restrict the 'product of nature' category to naturally-occurring products. Rather, it extends it to 'nature-based' products, which may be non-naturally occurring products. The test applied at Step 2A is whether the 'nature-based' product has 'markedly different characteristics' from any naturally occurring counterpart. Although the term 'nature-based product' is not explicitly defined, the examples in the guidance span a broad array of substances found in or derived from nature, as well as combinations and compositions comprising such substances (e.g., chemical compounds, foods, proteins, genetically modified organisms, nucleic acids, antibodies). Second, the markedly different test is not limited to DNA or nucleotide-based materials; it is abundantly clear that Examiners have been instructed to apply it to the wider natural world. Third, Examiners are instructed to apply Step 2A if a claim recites (i.e., sets forth or 'includes') a nature-based element, whether alone or in combination. This is enough for a claim to be considered 'directed to' a product of nature for the purposes of Step 2A unless the nature-based product is 'markedly different' from any naturally occurring counterpart.

Looking more closely at Step 2B, one realizes that it offers an additional way to make a claim patentable. It helps explain why, notwithstanding the broadly cast net in step 2A, nature-based claims that are not markedly different are sometimes allowed with amendments. Even if a claim is found to be 'directed to' a 'product of nature' exception in Step 2A, it may still be found patent eligible under Step 2B if it passes the "significantly more" threshold. Reaching either threshold is enough for the claim to be eligible subject matter. Characteristics that have been found by the Courts to render a nature-based claim markedly different from nature include differences in: (1) biological or pharmacological functions or activities, (2) chemical and physical properties, (3) phenotypic characteristics (functional and structural), and (4) function and form, including chemical, genetic, or physical function and form (MPEP 2106).

In the case of *Myriad*, for example, isolated gDNA was found to be a 'product of nature', and thus ineligible for patent protection, because the mere isolation does not

rise to the level of a markedly different characteristic. In contrast, the absence of the introns in cDNA was deemed a marked structural difference with respect to naturally occurring DNA, making it eligible for patent protection.

Immediately following the *Myriad* decision it was unclear whether the ruling was a 'narrowly crafted' decision that delivered a 'surgical strike' on isolated DNA patents while leaving the patent eligibility of all other claim products intact. Over the years that followed, patent attorneys and other readers of the MPEP guidance could see that the USPTO's view was that *Myriad* had broader impact for the purposes of patent examination, at least when interpreted alongside other Supreme Court decisions. Nevertheless, five years on, and prior to this empirical study, the magnitude of *Myriad´*s impact on claims beyond isolated DNA was still unclear. There was also a lot of uncertainty about how the USPTO was applying MPEP guidance in actual examination practice. Our study helps shed light on these issues, in particular it shows: how many times *Myriad* has been cited by examiners; what happens to patents that receive *Myriad* rejections; what proportion of these applications cover subject matter beyond naturally-occurring DNA; what sorts of nature-based products are affected by these rejections; how many advance prosecution without the need for amendment; and the number of rounds of RCEs that take place before the applications are allowed or abandoned.

Overall, the finding that (in our sample) *Myriad* was used to justify 35 USC 101 rejections of non-DNA products in 85% of the cases may seem surprising. It is surprising in light of the Supreme Court's (apparent) attempts to contain its own decision, and also given the line of thinking from some leading legal scholars that *Myriad* was a 'narrowly crafted' decision. It also stands in stark contrast to the equivalent case in Australia, D'Arcy v *Myriad*[20]. However, the high percentage does make sense when considered in light of the last USPTO Examination Guidance (as implemented as part of the MPEP 2106) for nature-based products.

Under the new guidelines, the key to determining whether a nature-based product constitutes an ineligible 'product of nature' lies not in whether or not the product is naturally or non-naturally occurring, but rather in whether it possesses markedly different characteristics from its closest naturally occurring counterpart; or failing which, whether the product claim covers 'something significantly more'. Thus, even synthetically created products (and combinations of these) may be classified as ineligible 'products of nature' if they are neither markedly different nor offer 'significantly more' than the judicial exception.

Additional Information (Methodology, Results, Figures, References): Was the

Myriad decision a 'surgical strike' on isolated gene-related patents? **Nature Biotechnology**, 36, 1146-1149, 2018.

12. What impact has *Myriad* had on the prosecution of such isolated gene-related patents?

    Our analysis of the USPTO file wrappers and prosecution histories for the patent application sample (n=6,875) (Box 1-Step 4) shows that Applicants who finally overcame the rejections of record and ultimately obtained a Notice of Allowance resulting in a granted patent typically received one or more final rejections. Notably, in 45.7% of the cases, applicants were required to engage in a second round of prosecution by filing a Request for Continued Examination (RCE). In 13.5% of the cases two or more RCEs were needed. For rejected applications that were ultimately abandoned the statistics are similar, 43.7% required at least one RCE, and 11.9% with 2 or more RCEs.

    Additional Information: Was the Myriad decision a 'surgical strike' on isolated gene-related patents? **Nature Biotechnology**, 36, 1146-1149, 2018.

13. 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?

    In our study we identified 72,990 USPTO correspondence documents which contained a *Mayo* citation (Article 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 (Article Box 1-Step 2). 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 5.1a).

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 5.1b).

In summary, as of the 6th anniversary of Mayo, study results show that (a), 49.3% of the patent applications were rejected or abandoned, 27.6% were granted after overcoming a 35 USC §101 Mayo-based rejection and 23.1% are still in active examination or 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 or prosecution and the need to file one or more RCEs in 45.8% of the cases (30.3% required two 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).

Additional Information (Methodology, Results, Figures, References): Mayo's impact on patent applications related to biotechnology, diagnostics and personalized medicine. **Nature Biotechnology**, 37 (5), 513-518, 2019.

14. What is the expected prosecution timeline of patent applications receiving a *Mayo*-based 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. This motivated the USPTO to pilot several programs post-2012 to reduce RCE rates (USPTO 2012 RCE Outreach Statistics; RCE by Technology: Chemical/Biological).

Additional Information (Methodology, Results, Figures, References): Mayo's impact on patent applications related to biotechnology, diagnostics and personalized medicine. **Nature Biotechnology**, 37 (5), 513-518, 2019.

15. 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?

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) 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].

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.

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 *apriori* (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.

16. To what extent have legal arguments and claim amendments based on *Vanda* been effective in overcoming 35 USC 101 *Mayo*-based rejections?

At the one year anniversary of the *Vanda* decision, there were 19 patent applications for which there was a final disposition: 16 applications were allowed and issued as granted patents, and 3 were abandoned.

This represents an allowance rate of 84.2% for patent applications with a rejection citing *Mayo* where the applicant responded to the office action with arguments and amendments based on *Vanda*, and for which there is a final disposition. This figure is

substantially higher than the allowance rate previously estimated for applications with a 35 USC 101 rejection citing *Mayo* (35.9%).[2] Additionally, in one of the three abandoned cases, the *Vanda* argument was successful in overcoming the *Mayo* rejection without the claim being amended.

Accordingly, this strategy has been effective in overcoming the 35 USC 101 rejection in 89.5% of the cases for which there is a final disposition (granted patent issued or final abandonment). This sample was then manually reviewed to determine the nature of the legal arguments and claim amendments.

Additional Information (Methodology, Results, Figures, References): Mayo's impact on patent applications related to biotechnology, diagnostics and personalized medicine. **Nature Biotechnology**, 37 (5), 513-518, 2019

17. How are applicants transforming diagnostic patent claims into method of treatment claims to overcome *Mayo*-based subject matter eligibility rejections?

In order to answer this research question, a manual and expert review of the relevant USPTO file wrappers was conducted. In particular, the prosecution history for each of the granted patent applications was downloaded using the USPTO PAIR (Patent Application Information Retrieval) System. Each application was then analyzed and classified with reference to the first claim receiving the 35 USC 101 rejection citing *Mayo* as either: A) a method of diagnosis (and other related claims that are not methods of treatment) or B) a method of treatment. Paper Fig. 1 shows the results of the classification of the original patent applications (Fig.61.a) and the issued patents. (Fig..1.b). We found that 80% of the claims in the patent application sample were A-type (i.e., methods of diagnosis or related).

Next we used the prosecution histories to follow the fate of the central claim that sorted groups A and B. The majority of the claims in group A (diagnostic-related methods receiving a *Mayo*-based rejection) subsequently transformed into method of treatment claims in the final issued patent. In fact, in 81.3% of the granted/issued patents the claims were directed to methods of treatment (Fig.1). The original claims in the patent applications, the corresponding claims in the granted patents, and our classification and prosecution notes are included in the Supplementary Information.

Notably, in all 16 cases, modifying claim language and citing the *Vanda* decision resulted in a reversal of the existing 35 USC 101 rejection (including a *Mayo* citation), with a Notice of Allowance in the following communication. Furthermore, in several of these cases, as shown in the prosecution notes (Supplementary Information),

the applicants had already tried several times to persuade the examiner, but were unsuccessful until *Vanda* was cited in support of legal arguments and proposed claim amendments. With rather simple amendments that mirrored claim language in *Vanda*, the applicants finally found a way to effectively overcome the 35 USC 101 subject-matter eligibility rejection, where previously they had been unsuccessful.

Reviewing the applicants' arguments and claim language in the patent file wrappers, we observed three types of successful claim transformations. These included: (1) transforming non-method of treatment claims (e.g., diagnostics claims) to method of treatment claims, (2) altering non-method of treatment claims to claims analogous to methods of treatment, and (3) modifying original method of treatment claims using *Vanda* to guide the claim drafting.

The first type of transformation (i.e., diagnostic-related claims transforming into method of treatment claims) was the most common, comprising 11 of the 16 analyzed granted patents.

For example, one applicant transformed the claimed invention from a "method for determining, in a patient presenting with hematuria, the level of risk for having urothelial cancer" to a "method for treating a patient for urothelial carcinonma" (case 4, Supplementary Information). In this case, while the examiner initially rejected the claimed invention based on *Mayo/Alice*, the simple amendment from a method of determining cancer risk to a method of treatment made the claim allowable based on *Vanda*.

In another example the applicant changed the claim language from a "method for diagnosing Systemic Lupus Erythematosus (SLE)" to a "method of treating Systemic Lupus Erythematosus (SLE) in a human subject identified as negative for SLE" (case 7, Supplementary Information). The initial *Mayo*-based rejection (i.e. that identifying SLE disease risk based on various antibody levels is merely a naturally occurring correlation) was overcome by transforming the diagnosis claim into a treatment one, in accordance with the USPTO *Vanda* guidance. Notably, previous arguments and amendments were unsuccessful in several previous responses to office actions.

Finally, while some granted applications did not explicitly mention a "method of treatment," they included an "administration step" following the *Vanda* memo, which passed Step A of the two-step eligibility test. For example, an applicant changed a three-step method of diagnosing a subject with a certain disorder to a six-step method of determining prognosis in a subject diagnosed with the disorder, in which the

fifth step comprised "administering to the subject with an indication of unfavorable prognosis a treatment" (case 11, Supplementary Information). The examiner was persuaded that this active administration of treatment step appropriately applied a law of nature/natural phenomenon, and was therefore patent eligible under *Vanda* (despite being recited at a high level of generality).

There were three examples of the second type of transformation (i.e., altering non-method of treatment claims to claims analogous to methods of treatment). These demonstrated that some examiners were open to claims that were analogous to method of treatment claims. For instance, an applicant modified a "method of identifying a soybean plant that comprises a genotype associated with an stem canker resistance phenotype" to a "method of producing a population of soybean plants that comprises a genotype associated with a stem canker resistance phenotype" through the crossing of selected soybean plants (case 12, Supplementary Information). The examiner found the analogy between the "crossing step" and a *Vanda*-type "administration step" persuasive, and allowed the patent on these grounds.

In another case, an applicant altered a method for diagnosing propensity to CCLR in a dog to a method for breeding a dog, in which the "breeding step" to reduce injury propensity was found to mirror the administration of treatment step in *Vanda* (case 14, Supplementary Information).

The third type of transformation (i.e., modifying original method of treatment claims using *Vanda* to guide the claim drafting) was illustrated by two granted patents. In these prosecution files, the original claims referred to methods of treatment, but the applications were not allowed until after the *Vanda* ruling. An applicant in one example repeatedly modified a method of treating Dengue Hemorrhagic Fever to further increase specificity (narrowing the scope of the claim), but the patent was only allowed after the applicant supplied arguments written after the *Vanda* decision (case 15, Supplementary Information). In these examples, it is possible that the claims in their original form would have been found eligible if the claims and related legal arguments had been made after the *Vanda* guidance.

In summary, in the cohort of 16 patents that we manually reviewed (patent applications with a rejection citing *Mayo* where the applicant responded to the office action with arguments and amendments based on *Vanda*, and for which there is a final disposition), there was clear evidence that most applicants had actively changed their claim type and language in response to *Vanda* to make their patents allowable. It was also evident that examiners had not been ready to accept these arguments prior to *Vanda*, but clearly became receptive to them after the USPTO *Vanda* Examination

Memo.

This research confirms our earlier hypothesis. Following the Federal Circuit's decision in *Vanda*, as interpreted by the USPTO, patent applicants with rejected methods of diagnosis have sought to transform these into patent eligible claims via claim amendments – without having to satisfy Step B in the *Mayo/Alice* test (showing that the claim amounts to significantly more than a natural law). Averaging more than one per month in the year since *Vanda*, rather than claim a method of diagnosis, patent drafters are amending to method of treatment (or analogous) claims to avoid or overcome *Mayo*-based rejections. This mercurial change, particularly its strikingly positive and immediate impact on patent examiners, has an aura of legal 'magic' about it.

This has provoked considerable controversy and debates about whether *Vanda* was a good decision. Parties on both sides of the debate claim that the Vanda decision stands to affect "untold numbers of future patents"[10], hinting at the idea that large numbers of patentees could be affected with major socio-economic ramifications. Our research identified 16 patents in 12 months that were issued pursuant to *Vanda* but which otherwise might have been rejected pursuant to *Mayo* (and 35 additional allowed applications). If *Vanda* is overruled, these sorts of claims (method of diagnosis and method of treatment claims) would be unenforceable unless the claim includes 'significantly more' (Step B *Mayo/Alice*). At this point, we do not think this is a large number of patentees. Nevertheless, there are important policy issues at stake.

Additional Information (Methodology, Results, Figures, References): One year after Vanda, are diagnostics patents transforming into methods of treatment to overcome Mayo-based rejections? **Nature Biotechnology**, 38 (3), 279-283, 2020.

18. What is the Impact of *Alice* and the subsequent emerging patent case law in the US and Europe on precision medicine?

While *Alice* is often considered a decision that affects primarily the patentability of business methods and generic abstract ideas, the decision also affects computer-implemented inventions in general, and therefore precision medicine inventions based on algorithms and AI.

It is possible to distinguish three types of precision medicine inventions in this category, namely, those that have been explicitly excluded from patent protection, those which are not categorically excluded but affected by legal developments, and those whose eligibility has been established by recent case law or specific examination

guidance (Article 6 Fig. 1 category C).

Within the ineligible category (Figure 1 type C.1), one finds inventions directed to mathematical algorithms and mathematical concepts. It is also likely that precision medicine inventions directed to methods of patient engagement (participative care) may be ineligible, on the basis that they are methods of organizing human activity or concepts related to managing human behavior (MPEP 2106). Similarly, expert medical systems applying specialist domain knowledge to diagnose like a human doctor may be deemed ineligible as 'concepts relating to organizing or analyzing information in a way that can be performed mentally or is analogous to 'human mental work' (MPEP 2106). This exclusion also applies to precision medicine inventions claimed at a high level of generality, such as the method for diagnosing an abnormal condition by performing clinical tests and analyzing the results in *In re Grams*.[28]

A significant proportion of precision medicine inventions affected by *Alice* (Figure 1 type C.2) are based on algorithms that analyze patient data (including physiological signals) in order to develop biomarkers which can be used to diagnose or guide individualized treatment. Such algorithms can be deterministic, statistical, or based on artificial intelligence techniques. While all these algorithms are fundamentally different from a technical standpoint, most of them make use of mathematical equations, mathematical algorithms, and digital signal processing in some form. Accordingly, it is often the case that examiners conservatively issue §101 *Alice*-based rejections on the basis that the claimed invention 'recites' mathematics and algorithms. Furthermore, the inventive concept often lies in the algorithm itself and not the hardware (e.g., a new algorithm that can be implemented in any computing device such as a smartphone and processes physiologic signals acquired using standard sensors).

The key to eligibility for these inventions lies in whether the claims satisfy the *Mayo/Alice* test. Recognizing the level of legal uncertainty surrounding this framework, in its most recent update, the USPTO amended the test to help identify ineligible claims more accurately and consistently (USPTO Eligibility Guidance, Jan 2019 Update). Step 2A, which consists of identifying whether a claim is 'directed to' an abstract idea, now takes a two-prong approach, first asking whether the claim 'recites' an abstract idea (e.g., mathematical concept, method of organising human activity, or mental process), and if so, whether the claim as a whole incorporates the abstract idea into a 'practical application.' Contrary to previous guidance and practice, examiners are now instructed to give weight to all elements of the claim when assessing practical application, whether or not they are conventional. The

'significantly more' inquiry of Step 2B is where the additional elements of the claim are examined to identify an inventive concept beyond well understood, routine, or conventional activity. According to the USPTO this approach should yield the same eligibility outcome as the original method, albeit maybe at different steps in the *Mayo/Alice* test.

Similar to the effect of *Vanda* on methods of treatment, the new USPTO guidelines open a window for precision medicine inventions involving algorithms implemented in standard hardware to satisfy the *Mayo/Alice* test at Step 2A, circumventing the 'significantly more' inquiry, by integrating the algorithm into a practical application. The courts have indicated that some elements do not confer practical application, including mere computer implementation of an otherwise ineligible abstract idea (*Benson*);[29] addition of insignificant extra-solution activity such as gathering input data or outputting results, when these are merely a nominal or tangential addition to the claim (*Flook*);[30] nor generally linking the abstract idea to a particular technological environment (*Bilski*).[14]

Conversely, examples of elements that have been considered valid 'practical applications' include: (1) improvement to a technology or technical field, (2) application of the algorithm to effect a particular treatment or prophylaxis for a disease or medical condition, and (3) use of a particular machine or manufacture that is integral to the claim, or (4) transformation of a particular article to a different state or thing. The recent cases of *McRO*,[31] *Enfish* [32] and *FairWarning IP, LLC v. Iatric Systems, Inc.*[33] illustrate these concepts.

In *FairWarning IP, LLC v Iatric Systems, Inc.*,[33] the Federal Circuit found a method and system of detecting improper access of a patient's protected health information in a computer environment ineligible as being directed to an abstract idea. The Federal Circuit explained that the claimed invention did no more than collect information regarding user access to health records, analyzing this log data based on a set of rules, and providing notification if improper access is detected.

The Court likened these claims to those in *Alice*, where the claimed invention essentially amounts to using a computer to automate a process previously being performed by humans. The idea that this produced an improvement in a technology field by increasing speed was rejected, as the improved efficiency arises "from the capabilities of a general-purpose computer, rather than the claimed method." The Court reasoned that in this case, as in *Alice*, "it is [the] incorporation of a computer, not the claimed rule, that purportedly improves the existing technological process."

In the *FairWarning* decision, the Federal Circuit stressed the difference between the claims at hand and those in the previously decided cases of *McRO*[31] and *Enfish*[32]. The *McRO* patent claimed a computer automated method for animating lip synchronization and facial expression of 3D characters. Although, like in *FairWarning*, the method involved the use of specific rules to automate a task previously performed by humans, the Court emphasized that in the case of *McRO* the claimed invention transformed a process traditionally based on subjective rules performed by human animators into a set of specific mathematical rules that allowed implementation in a computer. Therefore, "it [was] the incorporation of the claimed rules, not the use of the computer, that improved [the] existing technological process," and thus constituted an improvement in the technology field of computer animation.

The claims in *Enfish* were directed to a self-referential table for a computer database. Despite being defined in terms of logical structures with no physical components, the Federal Circuit found the *Enfish* claims to be "directed to a specific implementation of a solution to a problem in the software arts", and thus not directed to an abstract idea, but rather an improvement in computer technology. The Federal Circuit pointed to the difference between the focus of the claims being "on an improvement in computers as tools" (*Enfish*) as opposed to "an abstract idea using computers as tools" (*FairWarning*).

Accordingly, in situations where a precision medicine invention can be implemented using standard hardware (standard processors, standard sensors, standard patient monitors, etc) and the inventive concept lies primarily with the novel algorithm or the specific application of AI techniques to solve a particular problem, the claim drafting and prosecution strategies most likely to be successful are those which satisfy the *Alice* eligibility test at Step 2A (i.e., that the claim is not 'directed to' an abstract idea) by ensuring that: a) the claim does not preempt the use of the fundamental techniques in other application domains, b) the invention as claimed is not 'directed to mathematical techniques but instead to the solution of a technical problem, and c) the claimed invention results in a technological improvement in the field of precision medicine (improved detection, diagnosis, monitoring, therapy optimization, etc). A claim-drafting strategy that focusses on Step 2B (the claim as a whole amounts to significantly more than the abstract idea) faces challenges if the invention uses generic hardware (e.g., computer, smartphone, wearables, standard physiologic sensors).

The full extent of *Alice*'s impact remains to be studied using the type of empirical methodologies previously employed to analyze *Myriad*[18,19,20] and *Mayo*.[21] For example, how many applications advance to an issued patent notwithstanding an initial rejection? What sorts of claim amendments assist? How long does patent

prosecution take when *Alice* rejections are raised by examiners?

Even without this evidence, it is clear that the *Alice* decision affects a wide variety of algorithmic developments in precision medicine, but not all will be ultimately ineligible for patent protection. With thoughtful claim drafting and prosecution, it is possible to obtain patent protection for computer-implemented precision medicine inventions provided that they are not claimed at a high level of generality[28] and the focus of the claim is on the improvement of a technology or technical field rather than being either on the algorithm *per se*, or the automation of a mental process for which the computer is merely invoked as a tool.

Additional Information (Methodology, Results, Figures, References): How does emerging patent case law in the US and Europe affect precision medicine? **Nature Biotechnology**, 37 (10), 118-1125, 2019

19. How do the US and European patent law compare on the key tenets of subject-matter eligibility for biomarkers, medical relationships, and algorithms/AI-based information age inventions?
A divergence between US and European laws pertains to the patent subject-matter eligibility of nature-based biomarkers. In Europe, biomarkers are patent-eligible even if merely isolated from their natural environment; whereas in the US biomarkers must be markedly different from naturally-occurring products or the claims must include significantly more (which tends to narrow the claim).

    Although patent eligible, the European system does not necessarily provide biomarkers with significantly greater patent protection than the US. For instance, a DNA sequence can lack novelty (an issue for *Myriad*'s European BRCA patents) and will often be 'obvious' (e.g. where standard techniques of identification and isolation are used). Furthermore some EU member states have added national legislative rules which state that DNA sequence patents are limited to the uses disclosed in the patent (so-called purpose-limited protection).[42] This differs from the usual rule that a product patent covers all uses of the product provided at least one application is disclosed.

    Intriguingly, despite multiple relevant legislative exclusions (e.g. for computer programs *as such*), European doctrine on patent eligibility of algorithms and machine learning is generous compared with the US because, generally, claim-drafting strategies can be deployed to avoid exclusion under EPC Art 52(2).[49]

    Demonstrating inventive step, relative to the prior art, is the more restrictive issue for European patent protection of algorithm-based precision medicine inventions. In

Europe, it is strategic to restrict an algorithm-based claim to a specific technical application or adapt it for specific technical implementation. Then the algorithm has 'technical character' and can be considered as part of the inventive step inquiry to support non-obviousness.[50] Notably this tip concords with the guidance above for drafting algorithm-based claims that meet US patent eligibility rules post-*Alice* in light of *McRO*, *Enflish*, and *FairWarning*. Thus, we seem to be entering a period of increasing convergence with respect to patentability of applied algorithms, mathematical methods (including AI), computer programs, methods of treatment based on biomarkers and diagnosis (provided one considers the combined effect of eligibility and non-obviousness inquiries). This convergence is particularly noticeable following *McRO*,[31] *Enfish*,[32] and *Vanda*,[25] as well as recent EPO and USPTO Examination Guidelines.

For methods of detection, diagnosis and treatment, there are still some cross jurisdictional differences, but convergence is also afoot. In Europe, methods of detection and in vitro diagnosis are generally patent eligible; a competent draftsperson can find language that achieves technical character. In the US, these methods are still affected by the two step *Mayo/Alice* test, particularly methods of diagnosis. In response, and post-*Vanda*, methods of medical treatment are likely to become the claims *de jour* for medical correlations and relationships. Whereas in Europe, methods of medical treatment cannot be claimed per se but with appropriate claim-drafting could be protected as applications of a new method of diagnosis, or in the form of a medical kit or device for detection, diagnosis or treatment.

Additional Information (Methodology, Results, Figures, References): How does emerging patent case law in the US and Europe affect precision medicine? **Nature Biotechnology**, 37 (10), 118-1125, 2019

20. Does *Myriad* or *Mayo* create problematic uncertainty for developers of diagnostics tests? And does *Myriad* or *Mayo* create a disadvantage for US-headquartered organisations?

Our interview-based study has three main findings for these questions. First, Myriad and Mayo have negatively affected the development of tests in several ways. Notably, several organizations deliberately chose to forgo developing tests, and many have found the legal uncertainty following the cases problematic. Second, small patent-precarious organizations (those that rely heavily on patents for competitive advantage) have been more affected by the decisions than other organizations. Third, US-headquartered organizations have been more affected by the cases than European

organizations, even though both types of organizations file US patents under the same eligibility law—a result that the majority of interviewees did not expect. The basis for this disadvantage is that European organizations do not, as a general rule, rely on US patents as significantly as US organizations do.

These results show that *Myriad* and *Mayo* have adversely affected the development of some molecular tests and that the cases may create disadvantages for US-headquartered organizations. However, it is not clear on the basis of these finding alone tha the US law should be altered. The interview-based study was designed to assess only the negative effects of *Myriad* and *Mayo*, not the positive ones. The most obvious potential positive effect is the one argued by the Supreme Court: that the decisions would unshackle "basic tools of scientific and technological work." Until the positive effects are understood, reform is premature.

Additional Information (Methodology, Results, Figures, References): The Effects of Myriad and Mayo on Molecular-Test Development in the United States and Europe: Interviews from the Frontline, VAND. J. ENT. & TECH. L., Vol, 22:4:785

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Myriad's impact on gene patents

Mateo Aboy*, Kathy Liddell, Johnathon Liddicoat, Cristina Crespo, Centre of Law, Medicine, and Life Sciences (LML), Faculty of Law, University of Cambridge, UK, Email: ma608@cam.ac.uk, mateo.aboy@oit.edu

Three years later, the landmark Myriad decision on gene patents has led to some striking and unforeseen implications.

"The lawless science of the law, that codeless myriad of precedent, that wilderness of single instances…" (Lord A. Tennyson 1809– 1892).

In the three years since the US Supreme Court's decision in *AMP v Myriad,*[1] there has been much debate and speculation about the impact of the *Myriad* case on the biotech industry, particularly on the status of gene patents. Was it a significant decision or, as Lord Tennyson might have argued, just another decision in a myriad of single instances that make up a confused and confusing law of patents?

Clearly the case was significant for emphatically rejecting the decades-long view, widely touted by scholars, patent attorneys and the patent offices, that isolated genes are patentable subject matter. That said, the nuance of the decision left open many questions and was "far from illuminating."[2] Put simply, the US Supreme Court, in a unanimous opinion, held that isolated naturally-occurring gDNA sequences coding for the BRCA1 and BRCA2 genes were unpatentable; but cDNA (perhaps long cDNA sequences only) is patent eligible because it is not naturally-occurring. Extrapolating the reasoning, whether or not other product claims involving DNA sequences are patent eligible depends on whether they are "markedly different" from nature. The Federal Circuit applied this reasoning in a subsequent case in 2014[3], concluding that Myriad's patents over single-stranded DNA primers for detecting mutations in the BRCA genes were also unpatentable.

Commentators offered a wide variety of opinions on the significance of the BRCA decisions. Sherkow and Greely said "In the United States…it now seems clear that gene patents are 'not only dead, but…really most sincerely dead'."[4] In contrast, Guerrini *et. al.* cautioned, "it would be a mistake to assume that these decisions spell the end of patents in the [genetic] industry."[5] These comments reflect the dogged legal debates that go on even after the *Myriad* decision.

Meanwhile, there have been few empirical studies testing the validity of these assertions. Indeed there have been relatively few evidence-based studies *at any time* on the filing and grant of patents in the life sciences and biotech field, notwithstanding extensive debate. **Supplementary Table 1** summarizes the leading empirical studies on gene patents currently available.

One of the most important and illuminating studies remains that by Graff *et al.*[6] Published one month prior to the Supreme Court's decision in *Myriad*, the authors tried to identify how many patents were at risk of invalidation by the impending Supreme Court judgement. They were also interested in the characteristics of the organizations that had been assigned those patents (private vs public; large vs small; human, plant, animal or microbe focussed firms). They based their views on data available up to and including 2010 (three years prior to the publication of their article and the *Myriad* decision).

Significantly, Graff *et al.* predicted that if the Supreme Court were to rule that isolated naturally-occurring nucleic acid molecules were unpatentable (which was indeed the outcome), the decision "would likely only accelerate trends that are already very much evident in the data,"[7] and that the outcome was "likely to be less profound than either abolitionists or advocates seem to expect."[8]

This prediction was based on their empirical findings that only 8,703 US patents were at risk of invalidation (of which only 3,535 were related to human medicine)[9]. Claims to isolated nucleotide sequences were, in the authors' analysis, already a strongly diminishing category of patent application; since 2005, it was typical for the USPTO to grant only 500-600 each year. Meanwhile patents for "non-natural" genetic constructs had already begun to surge ahead. By 2010, these isolated synthetic DNA patents represented more than 40% of isolated nucleotide patents, and this trend was likely to continue. Graff *et al.* also pointed out that the ratio between private and public sector assignees was approximately 65%:24% (2% individual inventor assignees and 9% joint public-private entities), and that this had remained relatively stable up to and including 2010; implying that this would likely continue[10].

Despite the number of publications debating the status of gene patents and the potential impact o*f Myriad,* an empirical study analyzing patent publications *after* the *Myriad* decision is still lacking. Consequently, there is a clear need to evaluate the various predictions advanced by practitioners and scholars at the time of *Myriad* against the actual patent data three years after the decision[11, 12, 13, 14, 15, 16].

In this study, our aim is to analyze the impact and effect of the Supreme Court decision in *Myriad* and offer empirical evidence for on-going debates about the significance of this case on the changing

landscape of patents claiming nucleic acids.

There are many ways the changing landscape of patents claiming nucleic acids might be measured – as shown by the variety of foci in the studies published (**Supplementary Table S1)**. Those studies differ in whether they focus on human or non-human patents. They also differ with respect to the search strategy and databases which are used, whether they focus on filed, granted, and/or maintained patents; and whether they constrain the word search to patent titles, specifications, or claims). It is also noteworthy that not all studies rely on a patent search. Some investigators have conducted surveys or case studies to assess the effect (beyond the patent register) for key stakeholders, such as researchers, or genetic labs. One of the overall limitations in this corpus of literature is that the methodologies are often not easily reproducible by other researchers. This diminishes the possibility of evidence-based comparative analysis between the studies, as well as generating study updates and extensions once additional data is available.

Search Strategy & Landscaping

We designed the search strategy following the recommendations of Bubela *et al.* on patent landscaping for life sciences innovation[17]. Specifically, we aimed at maximizing the transparency of the search results by creating a simple *and* reproducible search strategy.

While complex methodologies for conducting searches involving gene patents are available, our approach was to generate the simplest possible search terms that could be easily reproduced by other researchers. **Table 1** shows a simple search strategy adequate for identifying general trends on gene patenting activity. As an example, searching for patents which include claims with the terms "SEQ ID, DNA, deoxyribonucleic acid, nucleic acid or gene" (Search ID **S1** in **Table 1**) identifies 89,841 US granted patents in the last 20 years (1996-2016). Evaluation of the total number, publication per year, classes, and assignees reveals that this very simple search strategy generates results consistent with other more complex methodologies which may increase accuracy at the expense of reproducibility (*see* **Supplementary Figs. 1-6 and Supplementary Table 1**). The general **S1** search strategy in **Table 1** is broad but can be further narrowed to increase the sensitivity and specificity for particular applications by adding specific search terms of domain interest using logical *"and"* and word proximity operators, as well as class limitations.

Results and Discussion

Figure 1 shows the results of employing this simple search strategy for identifying general gene-related patents (defined as any patent containing the **S1** search terms in **Table 1**) and plotting them by their issue date. This graph is consistent with previously published patent studies with regards to its general shape, trends, and patents per year (1996-2010) but adds 6 years of additional data[18,19], including data for the 3 years following *Myriad*.

Our search results show that applicants continue to file and successfully prosecute gene-related patents. The number of granted gene patents (broadly defined) continues to increase since the *Myriad* decision in 2013. This is both expected and unexpected. Given the narrow nature of the Supreme Court justices' decision in *Myriad*, it was predicted by some commentators that the case would have limited effect on gene-related patents other than isolated gDNA product patents. However,

Table 1 Gene Patent Search Strategy & 3 Year Before/After Myriad Analysis

Search Date	12-Jul-16	
Database	US Patents	
Date Range	June 13, 1996-June 13-2016 (20 years)	
Search ID	**Search Strategy**	**No. Patents**
S1	(ACLM:("SEQ ID" OR DNA OR "Deoxyribonucleic acid" OR "nucleic acid" OR gene))	89841
S2	S1 and ACLM:isolated	32279
S3	S1 and ACLM:isolated (expired patents removed)	20652
S4	S1 and ACLM:purified	6860
S5	S1 and ACLM:purified (expired patents removed)	3925
S6	S1 and ACLM:natural	4390
S6	S1 and ACLM:natural (expired patent removed)	3025
S2b	S1 and ACLM:isolated [Filing Date:2010-06-13 and 2013-06-13)	4162
S2a	S1 and ACLM:isolated [Filing Date:2013-06-13 and 2016-06-13)	829
S4b	S1 and ACLM:purified [Filing Date:2010-06-13 and 2013-06-13)	708
S4a	S1 and ACLM:purified [Filing Date:2013-06-13 and 2016-06-13)	150
S6b	S1 and ACLM:natural [Filing Date:2010-06-13 and 2013-06-13)	677
S6a	S1 and ACLM:natural [Filing Date:2013-06-13 and 2016-06-13)	170

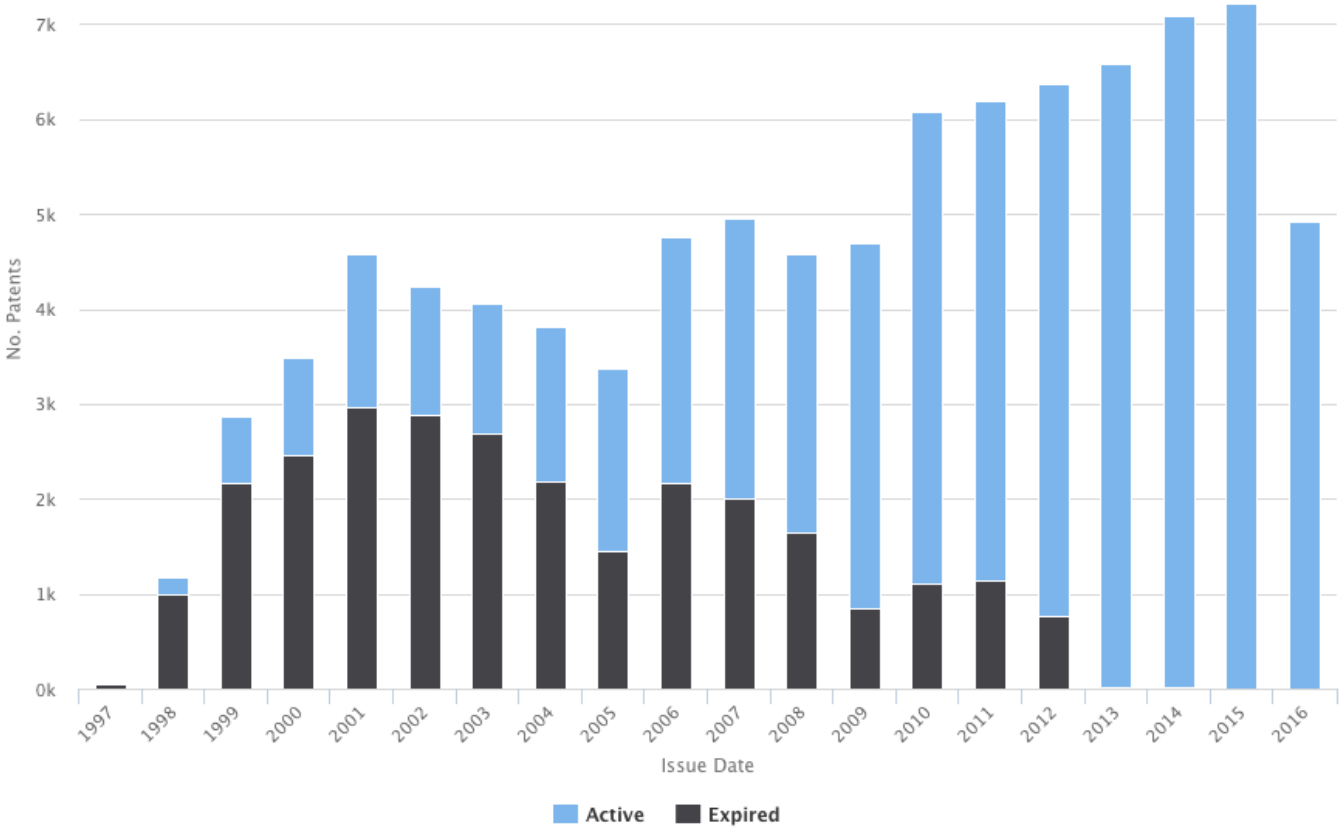

Figure 1 Published granted active and expired patents (1996-2016) with gene-related claims (including the general gene-related search terms identified in search S1 from Table 1). The general shape and total number of gene related patents is consistent with previous studies employing different search methodologies in the 1996-2010 timeframe.

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several authors have previously predicted a tailing off of gene-related patents post-2005[20]. Our results indicate that this has not occurred even after the *Myriad* decision. In this respect, the effects of the *Myriad* ruling on the biotech industry have been less profound than some practitioners, scholars, and patent holders have previously anticipated.

While the general search (**S1** in Table 1) may be adequate to evaluate general patenting trends, this search strategy identifies a broader range of patents than those with claims invalidated by the *Myriad* decision. Since this decision was directed, in essence, to the specific and important narrow legal question of whether *isolated genes* were patentable from a subject-matter eligibility standpoint (35 USC 101), it is important to further narrow the search strategy to capture such claims. The Court held that "a naturally occurring DNA segment is a product of nature and not patent eligible *merely* because it has been *isolated,* but cDNA is patent eligible because it is not naturally occurring." Furthermore, "separating a gene from its surrounding genetic material is not an act of invention" since the identification of the BRCA1 and BRCA2 sequences did not alter the gene itself. Consequently, a potential proxy for the impact of *Myriad* can be obtained by narrowing the general **S1** search in **Table 1** with a requirement that the claims include the word *isolated, natural,* or *purified*. This corresponds to search strategies **S2-S6** respectively. Additionally, proximity operators (e.g, claims with the word "isolated" within 3 words of "DNA") can be employed to increase the specificity of the search (**Fig. 2** and **Fig. 3**).

Our results indicate that there are 32,242 issued gene-related patents containing at least one claim with the word *isolated* (20,652 active). Similarly, we found 6,860 containing the word *purified* (3,925 active) and 4,390 (3,025 active) with the term *natural* (and stem-derivatives). Despite its simplicity, this search strategy yields consistent results when compared to previously published studies employing more complex search algorithms and methodologies[21].

The search strategies **S2**, **S4**, and **S6** in **Table 1** directed to gene-patents including the terms *isolated, purified,* and *natural* (and their stem-derivatives) in any of their claims may be used as first-order general proxies to evaluate the potential impact of *Myriad* in patents containing such claims. This is conducted by analyzing the patent activity after (**S2a**, **S4a**, **S6a**) the *Myriad* decision (3 year period between 2013-06-13 and 2016-06-13) and comparing it with the three years immediately preceding the *Myriad* ruling (**S2b**, **S4b**, **S6b**).

Figure 2 shows published granted patents with gene-related claims containing sequence IDs. This includes the gene-related search terms identified in search **S1** (general) and **S2** (isolated) from **Table 1**, as well as the keyword "isolated" within three words of "DNA". While new grants of gene-related patents in general continue to increase, there is an overall decrease in isolated gene patents regardless of whether the search is conducted by issue (**Fig. 2**) or filing dates (**Table 1**). It

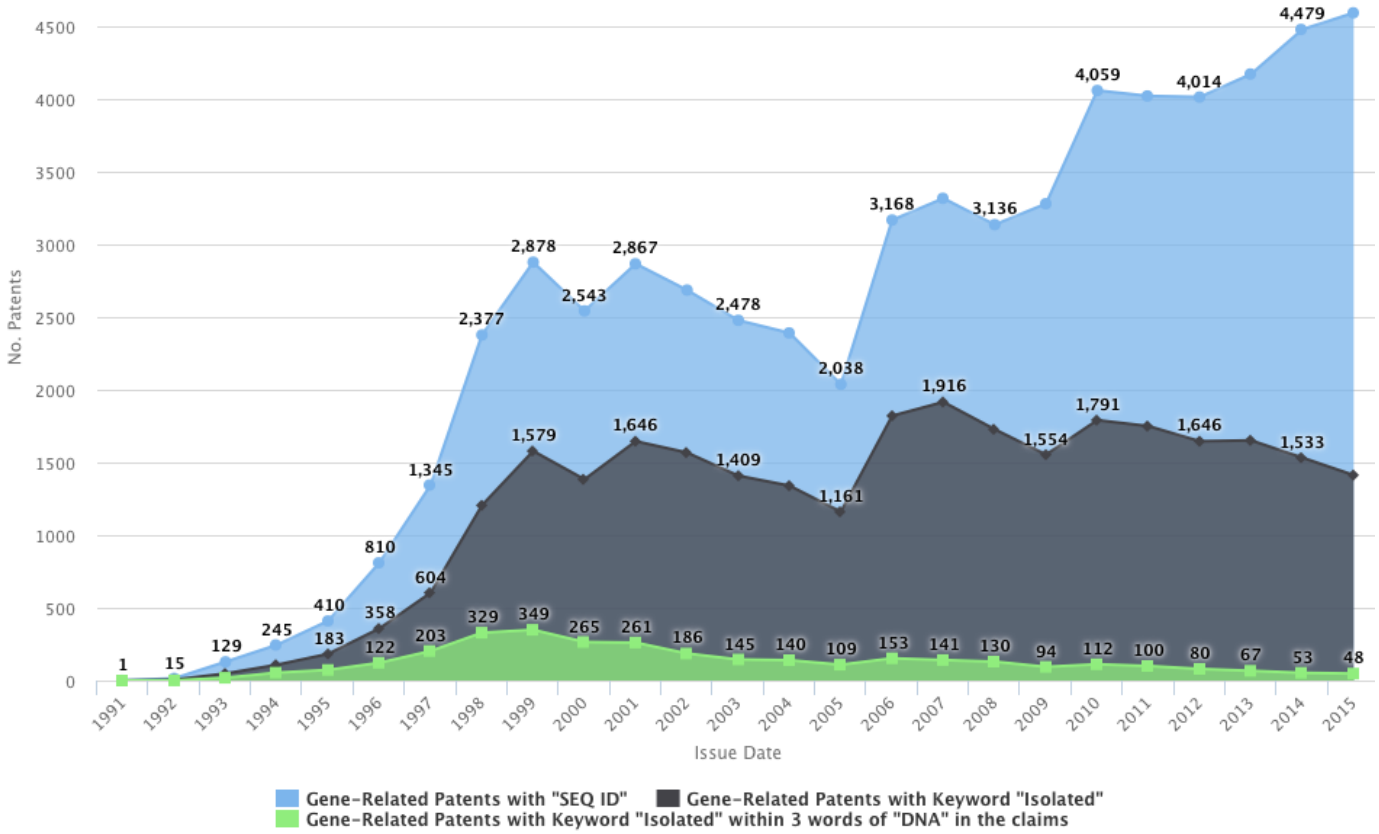

Figure 2 Granted patents with gene-related claims. While issues of gene-related patents in general continue to increase, there is a decrease in isolated gene-related patents regardless of whether the search is conducted by issue (**Fig. 2**) or filing dates (**Table 1**)

is important to note that the before-after results in **Table 1** are provisional, since many patent applications filed after the *Myriad* decision are still under prosecution. The results in **Figure 2** show a reduction of issued patents containing the keyword: 1) "isolated"; and 2) "isolated" near 3 words of "DNA") independently of the filing or priority date.

Supplementary Figs. 3-5 show assignee, survivorship, and class patent landscape results which help compare and verify the search strategy against other methodologies. **Supplementary Fig. 6** shows a combined forward and backward citation analysis documenting the entities with the highest number of patent citations, as well as the number of citations included in their patent portfolio.

Our first-order-*proxy* results indicate a significant drop in gene-related patents 3 years after *Myriad* containing the terms *isolated*, *purified*, and *natural* in any of the claims. These findings are consistent with a significant impact of *Myriad* with respect to issued patents which include claims directed to *isolated* gDNA. Given the crisp and decisive Court decision on this narrow legal issue, it is clear that patentees are avoiding, amending (or canceling) claims directed to *isolated genes*. It is common to find instances of US patent applications filed before the *Myriad* decision which originally contained *isolated gene claims* which matured into US granted patents with amended claims directed to methods and *non-natural* genetic constructs. (i.e., the *Myriad-type* claims are amended or canceled to advance prosecution). This is generally possible as long as the patent specification contains sufficient support for the amended claims to comply with the requirements of 35 USC 112 with respect to written description, enablement, and best mode. Nevertheless, such amendment is more than just a draftsperson's exercise because 1) an isolated gene patent cannot be transformed into eligible subject matter by claim drafting techniques[22] , and 2) even if the isolated gene were to be included as part of an otherwise subject-matter eligible claim, the step of isolation or purification is not sufficient to satisfy the novelty[23] or non-obviousness[24] requirements. Additionally, the combination and joint-effect of *Myriad, Mayo*[25], and *Alice*[26] make it substantially more challenging to transform ineligible claims directed to isolated genes, natural products, laws of nature, or abstract ideas into subject-matter eligible claims.

Our results of assignees obtaining gene-related patents (**Fig. 3** and **Fig. 4**) indicate a significant shift in the ratio of small-entities vs. large entities owning US gene-related patents. The proportion of patents owned by small entities dropped dramatically after *Myriad*. This was unexpected and could be a negative side-effect of the decision. It is potentially highly significant, as

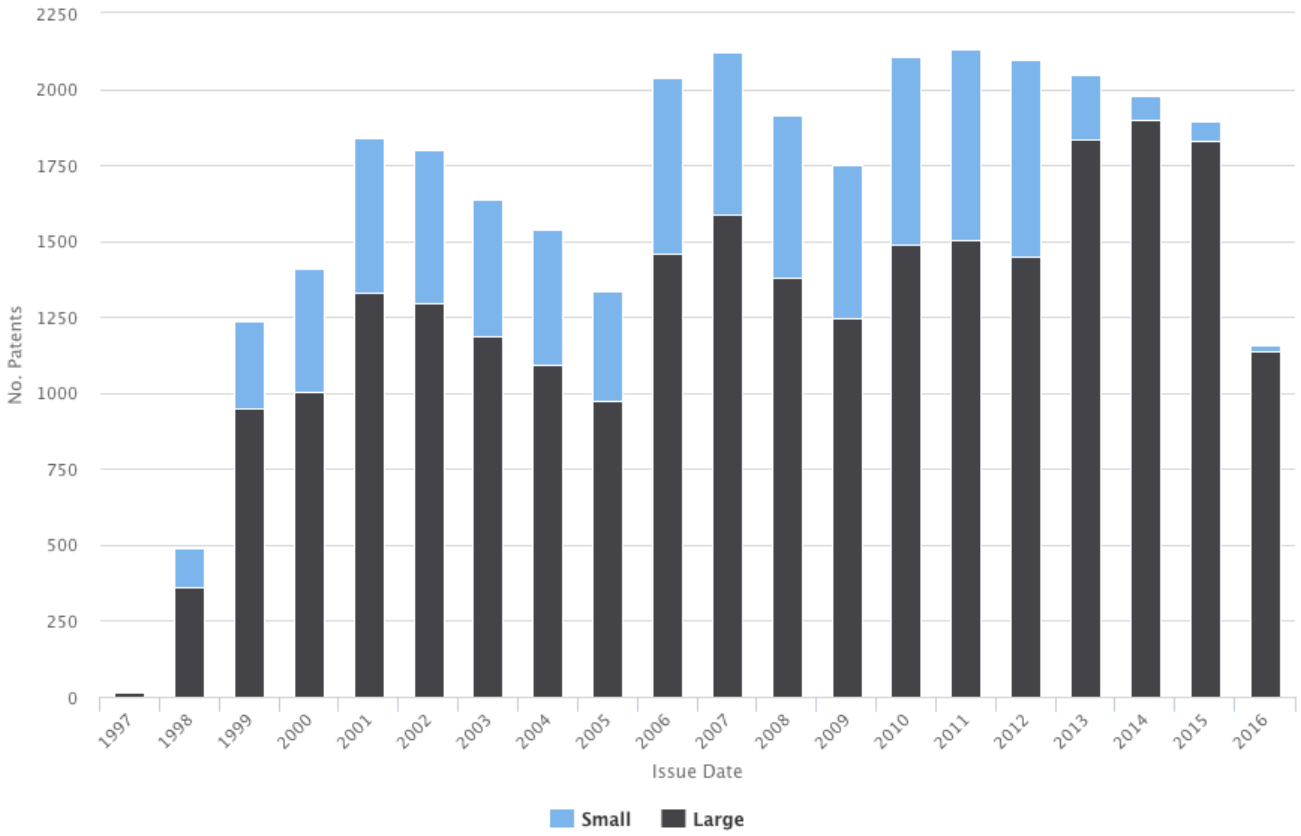

Figure 3 - Granted gene-related patents by small-entities vs large entities (37 CFR definition) based on Search ID S3 in **Table 1** (isolated)

small entities are important sources of biotech innovation[27,28].

Conclusions and Further Research

Our results indicate that the effects of the *Myriad* ruling on gene patenting have been less profound than many of the predictions submitted to the Supreme Court by amicus briefs[29]. Our results instead confirm some of the more modest predictions made by Graff *et al.* prior to the decision. However, our results show the case may be having *unexpected* and *unintended* effects on competitiveness within the biotech industry. Firms seem to be adapting to *Myriad* in various ways and with various degrees of success. Further empirical research is important.

While simple and explicit keyword-based search strategies like the one employed in this article have the advantages of being 1) reproducible, 2) clear, 3) swift, 4) cost-effective, 5) easily updated and compared with subsequent studies, and 6) able to capture the overall general trends, there are limitations to this approach. Notably, automated searching does not take into account nuances in patent claims. Accordingly, automated searching is not as accurate as human expert interpretation of claims or a combination of automatic searching with human review of the results. Consequently, future work includes conducting a human expert review of *Myriad*-type claims in issued patents after *Myriad* in order to document the type of amendments and prosecution strategies resulting in post-*Myriad* gene-patents.

A human review will also enable closer inspection of the shifts in ownership/assignment, including whether public sector ownership of gene-related patents (relative to private sector) is falling alongside small-entity ownership.

We hypothesize that the decrease in small-entity patentees may be due, in part, to the increased challenges to prosecute successfully US patent applications after *Myriad, Mayo* and *Alice,* and the associated increased time of prosecution needed to deal with the 35 USC 101 rejections, resulting in material cost increases. This may explain the reduction of the proportion of small entities with respect to large entities obtaining gene-related patents (**Fig. 3-4**). In order to ascertain whether the demands of the patent pending phase have increased due to US Supreme Court case law, we recommend an empirical prosecution study analyzing the Examiner Office Actions, Applicant Responses, and Appeals before the USPTO.

The continued growth in the overall number of gene-related patents also requires further investigation. Is this evidence of high levels of innovation? And/or an indication of a further 20 or so more years of patent tie-up? Not necessarily. We recommend a patent landscape analysis comparing patent filing and issuance dates, with the corresponding priority dates of the issued patents. We hypothesized that the legal standard of non-obviousness, as

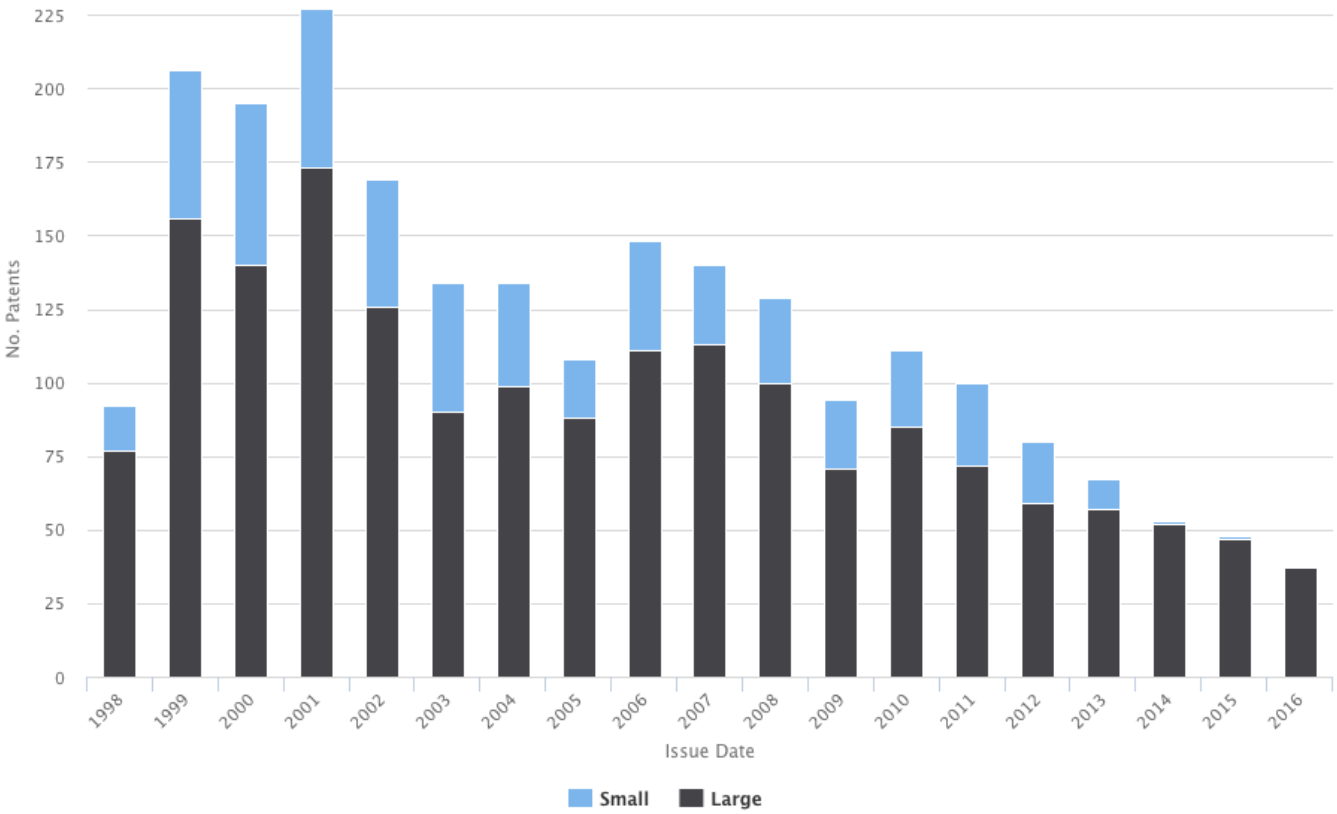

Figure 4 - Granted isolated-gene rated patents by small-entities vs large entities (37 CFR definition) containing "isolated" within 3 words of DNA in the claims.

opposed to subject-matter eligibility continues to be the main determinant of patent prosecution strategies. The relative importance of subject matter eligibility versus non-obviousness may be studied by comparing filing, publication, and the corresponding priority dates of the patent applications and issued patents. Since patent applicants need to sacrifice valuable patent term in order to claim the priority benefits, the only sound rationale to keep claiming early priority dates is to satisfy the increasingly high-bar of patentability due to the large amount of prior-art now available. We expect the results of such subsequent empirical study to reveal that even if *Myriad* had reached the opposite decision (and *isolated gDNA* patents were eligible subject matter), it is likely that very few of such patents would be granted at this time since new patent filings (unless claiming priority back to the early 2000s) would not satisfy the non-obviousness requirement for patentability. This effect is also partially seen in **Fig. 4**, where the reduction trend in isolated DNA patents precedes the *Myriad* decision. In fact, **Fig. 4** shows that the downward slope in gene-related patents containing the keyword *isolated* within 3 words of DNA in the patent claims has been roughly constant since 2010 and peaked back in 2001.

The fact that US law does not allow isolated gene patents, whereas European countries do (pursuant to the European Biotech Directive 98/44/EC and the European Patent Convention 2000) has led some commentators to caution that this fundamental asymmetry of subject-matter eligibility involving isolated gene patents could place the US at a competitive disadvantage.[30] A further study is required to analyze the potential side effects of *Myriad* in isolated gene patenting activity in Europe.

Additional studies, including interviews and surveys, are needed to analyze the ultimate 'coal-face' effect of legal developments from the Supreme Court on the biotech research community, genetic labs, and industry. This cannot be summarized from patent data alone.

In summary, in the third-year anniversary of the ruling, we are inclined to conclude that *Myriad* reinforces the poet's view of the law as a codeless, unfathomable wilderness of judicial decisions. But it is nevertheless a significant decision for the future of biotech, and expert empirical research can offer a lens where the poet sees only chaos.

[1] *Association for Molecular Pathology v. Myriad Genetics, Inc.,* 133 S. Ct. 2107 (2013).

[2] Burk, D., *J. Law Biosci.* **2**, 606-626 (2015).

[3] *In re BRCA1- & BRCA2- Based Hereditary Cancer Test Patent Litig v Ambry Genetics Corp.*, 774 F.3d 755 (Fed. Cir. 2014).

[4] Sherkow and Greely, 'The History of Patenting Genetic Material' (2015) Annual Review Genetics 49:161-182, p175

[5] Guerrini et al, (2016) Nature Biotech p 145

[6] Graff, G.D. *et al.*, *Nat. Biotecnhnol.* **31**, 404-410 (2013).

[7] Graff, G.D. *et al.*, *Nat. Biotecnhnol.* **31**, 404-410 (2013).

[8] *Id. at* 409.

[9] *Id.* at407.

[10] *Id.* at407

[11] Gordon, J., *Cold Spring Harb. Perspect. Med.* **5** (2014).

[12] Cook-Deegan, R. & Niehaus, A., *Curr. Genet. Med. Rep.* **2**, 223-241 (2014).

[13] Woessner, W.D. & Chadwick, R.A., *Pharm. Pat. Anal.* **2**, 165-167 (2013).

[14] Ratner, M.,' *Nat Biotechnol.* **31**, 663-665 (2013).

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[16] Offit, K., *et al.*, *J. Clin. Oncol.* **31**, 2743-2748 (2013).

[17] Bubela, T., *et al.*, `*Nat. Biotechnol.* **31**, 202-203 (2013).

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[19] Cook-Deegan, R. & Heaney, C., *Annu Rev. Genomics Hum Genet.* **11**, 383-425 (2010).

[20] Hopkins, M.M *et al. Nat Biotechnol.* **25**, 185-187 (2007).

[21] Graff, G.D. *et al.*, *Nat. Biotechnol.* **31**, 404-410 (2013).

[22] 35 USC § 101.

[23] 35 USC § 102.

[24] 35 USC § 103.

[25] *Mayo Collaborative Services v. Prometheus Laboratories, Inc.,* 132 S. Ct. 1289 (2012).

[26] *Alice Corporation v. CLS Bank International,* 132 S. Ct. 2347 (2014).

[27] Arora, A., Fosfuri, A. & Gambardella, A., *Markets for Technology* (The MIT Press, 2001).

[28]Sichelman, T. & Graham, S.J., *Mich. Telecomm. & Tech. L. Rev.* **17**, 111-180.

[29] http://www.scotusblog.com/case-files/cases/association-for-molecular-pathology-v-myriad-genetics-inc/

[30] Royzman, I., *Nat. Biotechnol.* **33**, 925-926 (2015).

After *Myriad*, what types of claim amendments change a patent ineligible isolated gene claim into an eligible patent claim that is 'markedly different' from Nature?

Mateo Aboy, Johnathon Liddicoat, Kathleen Liddell, Matthew Jordan & Cristina Crespo

A new empirical study examines the types of claim amendments that have successfully transformed isolated gene (nucleic acid) claims from *ineligible subject matter* into patent *eligible* inventions to the satisfaction of USPTO patent examiners. It provides further clarity into the threshold of subject-matter eligibility for gene-related patents and answers outstanding questions related to claim drafting practice after *Myriad*.

While nearly four years have passed since the US Supreme Court's decision in *AMP v Myriad*, its impact is still not fully understood. The Supreme Court held that "A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring"[1]. The decision left open many questions and was "far from illuminating"[2]. The United States Patent & Trademark Office (USPTO) subsequently published updated Examination Guidance on patent eligible subject matter every year since 2014 (refs. 3, 4, 5). This Guidance comments upon and gives examples of eligible and ineligible claims after *Myriad*[1], *Mayo*[6] and *Alice*[7], but the Guidance has not settled debates[8]. Some believe that the *Myriad* decision will have a profound effect on the genomics industry and biotech innovation[9]. At the opposite end of the spectrum, some commentators believe that the *Myriad* decision is of little practical importance because "patent attorneys are developing strategies to 'draft around' *Myriad* and related cases to ensure their client patents will withstand scrutiny going forward"[10].

Mateo Aboy, Johnathon Liddicoat, Kathleen Liddell, Matthew Jordan & Cristina Crespo, Centre for Law, Medicine, and Life Sciences (LML), Faculty of Law, University of Cambridge, Cambridge, UK. E-mail: ma608@cam.ac.uk

Still others argue that the impact of *Myriad* remains uncertain[11] because, even considering USPTO Guidelines and the Supreme Court decision, there is considerable on-going legal debate about the criteria for eligible gene patents and what makes a claim 'markedly different' from ineligible natural products[12,13,8].

In a recently published empirical study[14], we addressed questions about *Myriad's* impact on *gene-related* patents (including but not limited to isolated gene-related patents). That study employed an automated search algorithm designed to analyze, in a broad way, *Myriad's* impact by looking at granted gene-related patents using consistent search terms before and after the *Myriad* decision.

The empirical results in our previous study indicated that the *Myriad* ruling on subject-matter eligibility had indeed affected gene-related patenting, but in a less profound way than had been predicted by some authors prior to the Supreme Court decision. Instead, the results empirically confirmed more moderate predictions of impact such as those made by Graff *et al*[15]. However, despite being able to analyze the large scale impact by looking at general patenting trends, automated patent search methodologies have intrinsic limitations that prevented us from providing conclusive answers to important questions about how gene-related patent claims are changing after *Myriad*. In particular, methodologies based on automated search algorithms are typically not suitable to answer detailed *claim-related* questions such as what types of claims, claim amendments, and legal arguments in originally published *isolated nucleic acid* patent applications are resulting in allowable subject-matter after examination proceedings by the USPTO. Consequently, manual claim analysis is needed to address currently unanswered questions of significant practical and legal importance. These include: is it *really* possible to draft around *Myriad* and obtain claims with equal (or very similar) scope?[10,13,16]; or has the decision driven patent applicants towards narrower claims?[17]; what types of claim amendments have been successfully applied to transform ineligible *isolated* nucleic acid claims into patent eligible claims in examination proceedings before the USPTO?; and, relatedly, has *Myriad* failed to provide a workable legal test of subject matter eligibility?[18]. The answers to these questions are also important in debates addressing whether *Myriad* has caused a problem such that 35 USC 101 should be amended[19, 20].

Our research also highlights the operation of the USPTO Manual of Patent Examination Procedure (MPEP) and Examination Guidelines,[5] and raises questions about the quasi-legal influence of the USPTO *qua* administrative agency on the innovation ecosystem[21]. How is the USPTO applying its own Examination Guidelines in this area? This in turn casts light on whether future litigation in the courts will confirm or reject the

USPTO's interpretation of *Myriad,* potentially invalidating newly issued patents several years from now.

In an effort to help resolve legal and business uncertainty, we have devised a method (inspired by other claim level empirical studies[22]) that identifies and systematises concrete *post-Myriad* examples of recently granted gene patents which were applied for with at least one isolated nucleic acid claim. These concrete empirical examples highlight what the USPTO considers to make a claim 'markedly different' from naturally-occurring genomic DNA (gDNA).

In the instant study we focussed on answering the following three empirically-based research questions: 1) what proportion of human gene-related patent applications published during the 3-year period preceding *Myriad* contain an *isolated nucleic acid* product claim (i.e., a claim similar to the isolated gDNA claim in contention in *Myriad*)?; 2) what proportion of these applications (with at least one isolated nucleic acid product claim) matured into a granted patent; and 3) how were simple isolated nucleic acid claims that received a *Myriad*-based rejection amended to become patent eligible subject matter before the USPTO?

Methods

A. Search Strategy & Inclusion Criteria

Our study is based on patent applications that were published by the USPTO in the three-year period preceding the *Myriad* ruling (i.e., US patent applications published from 2010-06-13 to 2013-06-13). Furthermore, we restricted our study to applications with biological claims directed to "Homo sapiens." A search algorithm (**S1, Supplementary Information**) was applied in the online, publicly available Lens patent resource[23,24] This search algorithm (**Figure 1** Step 1) is designed to identify patent applications with at least one claim containing a SEQ ID and the keyword *isolated* within 5 words of *nucleic acid* (and synonyms of nucleic acid). The algorithm was intended as a pre-processing step prior to manual expert claim review, and consequently it was designed to optimize its *sensitivity* to isolated nucleic acid patents as opposed to its *specificity,* since specificity is subsequently achieved through expert manual claim review[25].

The effect of this inclusion criteria was that we identified a cohort of applications with relevant claims that were published before the *Myriad* ruling. We were then able to identify a subset of these applications that were examined after *Myriad*, at which point the applicant and USPTO would need to consider carefully the legal arguments and amendments required for the isolated nucleic acid claims to meet patent eligibility after *Myriad*.

B. Patent Application Classification

The output of the automated search algorithm (**S1**) was used as the input for the first step in the expert claim review and manual classification (**Figure 1 Steps 2-4**). These steps involved manually analyzing the claims in each of the applications retrieved and classifying them as containing either: 1) at least one *simple isolated genomic nucleic acid product claim* (i.e., claims akin to those litigated in *Myriad*) (**M1a**)*;* 2) no M1a-satisfying claims but at least one claim to more *complex isolated nucleic acids* (e.g., isolated nucleic acids in vectors, or sequences coding for monoclonal antibodies) (**M1b**); or 3) neither M1-satisfying nor M1b-satisfying claims but *broad gene-related claims* (e.g., polypeptides encoded by specific nucleic acid sequences (**M1c)**. Our definition of simple isolated genomic nucleic acid product claims is similar to that adopted in *Graff et al.*[15]*,* except our definition does not include claims that are limited only to cDNA or recombinant nucleic acids. Applications with only complex isolated nucleic acid claims (**M1b**) and broad gene-related claims (**M1c**) were excluded from this study. The remainder of our study looked at what happened to the **M1a** applications; these are the applications that one would expect to be most directly affected by the reasoning in *Myriad.*

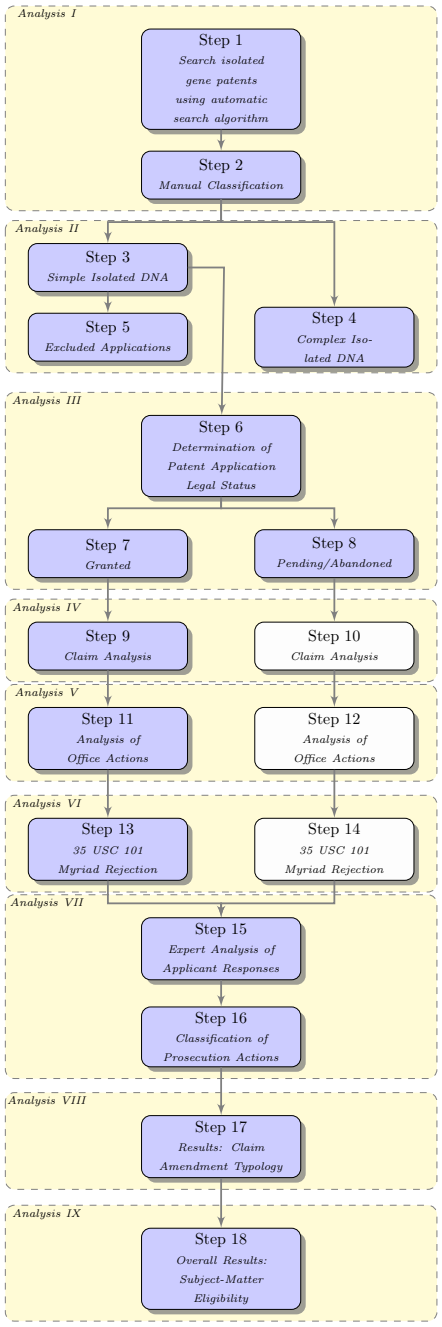

Figure 1 Methodological overview including the automated search, manual classification, and expert prosecution history review steps.

C. Patent Application Prosecution History Review

The prosecution histories of the applications (commonly known as 'file wrappers') with simple isolated genomic nucleic acid claims were obtained from the USPTO Patent Application Information Retrieval System (PAIR) in January 2017. At that time, we determined the legal status of the patent applications and sub-classified them into either 1) Granted (**M1aG**); 2) Rejected/abandoned (**M1aR**), or 3) Pending (**M1aP**) (**Figure 1 Steps 6-8)**. The remaining steps in our method looked closely at the **M1aG** patents to see what happened during their prosecution that enabled them to be granted notwithstanding that when initially published they included at least one simple isolated genomic nucleic acid product claim, and the fact that many of these claims issued after the *Myriad* ruling held such claims to be patent ineligible.

The patent file wrappers were further examined in order to determine if the originally submitted claims had been amended prior to examination on the merits (**Figure 1 Step 9**). This involved expert review of the prosecution history to identify any preliminary amendments where the applicant canceled the isolated nucleic acid claims prior to examination on the merits or where the isolated gene claims were withdrawn from consideration in response to a USPTO Restriction Requirement where the applicant elected the non-isolated gene claims (e.g., method claims, systems claims, etc) for examination on the merits. Amendments were classified as occurring either: (i) prior to examination on the merits, meaning the amendment was applicant-initiated prior to the Patent Examiner issuing an Office Action addressing the patentability of the claimed invention (**M1aGA1**); (ii) in response to a USPTO Restriction Requirement (**M1aGA2**); or (iii) in response to an Office Action during examination on the merits (**M1aGA3**). The patent applications classified as **M1aGA3** were of most interest in this study because the file wrappers record the Examiner's specific rejections and objections, including *Myriad*-based (35 USC 101 subject matter eligibility) rejections, and the arguments and specific claim amendments the Applicant made in response to the Office Actions in order to overcome the rejections of record.

We also studied the timing for discontinuation of the simple isolated nucleic acid product claims in **M1aGR** (**Figure 1 Step 11**). For example, some but not all of the isolated nucleic acid product claims in **M1aGR** were discontinued in response to examination on the merits (**M1aGRC3**). Indeed, some were discontinued by the applicant prior to examination on the merits (**M1aGRC1**), and sometimes discontinuation (claim withdrawal) was in response to a USPTO Restriction Requirement (**M1aGRC2**) meaning that the examiner took the view that the application involved more than one invention to be searched, and only one invention could be taken forward for examination with the patent application. Many applicants of M1aG patent applications elected to take forward non-isolated nucleic acid claims (e.g., method claims, systems claims, etc) for examination on the merits after a Restriction Requirement.

The next step in the analysis involved conducting an expert review of the USPTO Office Actions (Non-Final Rejections, Final Rejections), Examiner Interview Summaries, and Advisory Actions (**Figure 1 Steps 11,13,15**). Each patent application was coded to indicate whether it received a 35 USC 101 (subject matter eligibility) *Myriad*-based rejection (**Figure 1 Step 13**). Each Applicant's Response to a Non-Final Office Action, Final Office Action, Advisory Action, Examiner Interview Summaries, and Appeal Briefs was also reviewed (**Figure 1 Step 15**). This enabled us to observe how many applications received *Myriad*-based rejections, and to analyze claim amendments and legal arguments that overcame them (**Figure 1 Step 16)**. The **Supplementary Information** provides further details about the methodology and coding notation used in this study.

D. Claim Amendment Typology

The results of the Analysis I-VII in **Figure 1** were used to establish a typology of claim amendments which overcame *Myriad*-based rejections (**Figure 1 Step 17).** This typology thus shows the sorts of claim amendments that transformed *ineligible* simple isolated nucleic acid claims into patent eligible inventions after the *Myriad* ruling to the satisfaction of USPTO Examiners.

Results & Discussion

A. Answers to Research Questions

Table 1 shows the primary results from this study. The goal of this study was to help answer three particular questions related to *Myriad's* impact at the claim level. With regards to the first question, we found 653 applications with at least one simple isolated genomic nucleic acid product claim. This constitutes approximately 50% of the 1292 human gene-related applications found by our S1 search algorithm.

The second question was directed to finding out the proportion of the 653 applications that were eventually granted. In other words how many of these patent applications 'made it' notwithstanding *Myriad?* Our results show that 313 (47.9%) applications were eventually granted (**M1aG**), 311 (47.6%) were wholly rejected/abandoned (**M1aR**) (meaning all claims discontinued), and 29 (4.4%) were, ats of January 2017, pending (**M1aP**).

We then looked more closely at the **M1aG** subset (n=313). We wanted to see how these patents had managed to survive the *Myriad* ruling. Of these, 183 applications (58.5%) advanced prosecution to allowance by surrendering (i.e., canceling) all simple isolated nucleic acid products claims (**M1aGC**). These patents, when finally granted, no longer contained any of the isolated nucleic acid claims which had been published prior to the *Myriad* decision. The **M1aGC** cohort, taken together with the **M1aR** applications

(where the simple isolated nucleic acid claims were abandoned or rejected along with every other claim), reveal that a very large proportion of *Myriad*-type claims filed in the three years before *Myriad* were not taken forward by applicants (79.2% of the 653 in the **M1a** subset). We discuss the significance of this result along with our view that this may be time-dependant and the result of legal uncertainty below.

We found only 14 (4.5%) applications were granted without substantive amendments to the originally published isolated nucleic acid claims (**M1aGU**). Significantly, all but one of these were examined on the merits before the *Myriad* decision. Some of these claims are now at risk of invalidation in light of *Myriad,* but some of these claims may still be valid if they are limited to nucleic acids that do not exist in nature. In any event, the **M1aGU** subset is small, constituting approximately 1% of the 1292 applications identified in our **S1** search algorithm.

Question 3 asked how did the isolated nucleic acid product claims that received a *Myriad*-based rejection change during prosecution in order to become, according to the corresponding USPTO Examiner, patent eligible? We found 116 (37.1% of M1aG) instances where simple isolated nucleic acid product claims were amended (but not canceled) during prosecution (M1aGA). Of these, we found 21 patent applications with simple isolated genomic nucleic acid product claims that were amended in response to an explicit *Myriad*-based rejection (in the other cases Applicants amended their claims prior to receiving an Office Action or the Examination on the Merits occurred before the *Myriad* decision). These patent applications with explicit *Myriad* rejections are of special interest because they record specific communication between the USPTO and Applicants who successfully prosecuted *Myriad*-type claims, including details of the amendments (and legal arguments) that were ultimately successful.

Table 1 Results of isolated DNA Patent Claim Analysis

S1-Results of Automated Patent Search Algorithm	1292	
Manual Classification (M1 Analysis)	N	Pct
M1a-Simple Isolated DNA	653	50.5%
M1b-Complex Isolated DNA	561	43.4%
M1c-Excluded	78	6.0%
Total	**1292**	100%
Patent Status Review of M1a Applications (Isolated DNA)	N	Pct M1a
M1aG-Granted	313	47.9%
M1aR-Rejected/Abandoned	311	47.6%
M1aP-Pending	29	4.4%
M1a Total	**653**	100%
Patent Claim Analysis of M1aG Applications (Granted)	N	Pct M1aG
M1aGC-Isolated Gene Claims Canceled	183	58.5%
M1aGA-Isolated Gene Claims Amended	116	37.1%
M1aGU-Isolated Gene Claims Unchanged	14	4.5%
M1aG Total	**313**	100%
Fate of Isolated-DNA Related Patents (Granted & Abandoned)	N	Pct M1a
Rejected/Abandoned Patent Application (Canceled All Claims)[M1aR]	311	49.8%
Canceled Isolated Gene Claims [M1aGC]	183	29.3%
a) Total Cancelled (Application or Isolated Gene Claims) [M1aR+M1aGC]	**494**	79.2%
b) Amended Isolated Gene Claims	**116**	18.6%
c) Granted as Originally Filed (Unchanged)	**14**	2.2%

We created a typology to classify the amendments that, after *Myriad,* successfully transformed a simple isolated nucleic acid product claim into a patent-eligible claim. Aside from cancelling the isolated nucleic acid claims (n=183), the typology reveals that applicants are typically employing one of eight prosecution strategies: 1) amending to cDNA; 2) amending to nucleic acids with non-naturally occurring sequence variations; 3) amending to nucleic acids recombinantly linked with heterologous sequences; 4) amending to labelled nucleic acids; 5) amending to a nucleic acid in a vector; 6) amending to a nucleic acid recombined with a non-specific regulatory sequence; 7) amending with a Type-2 change and a negative-claim clause; and 8) amending to a short nucleic acid (so short that it does not naturally occur).

The **Supplementary Information** provides definitions for each of these strategies and details the amendments made in each of the 21 cases, including some of the arguments made by Applicants and Examiners. This Information also records three applications that received a *Myriad*-based rejection and, as a result, the Applicants cancelled the claims.

The most common way to amend and overcome a *Myriad*-based rejection was to claim cDNA, which occurred in seven of these 21 instances. As described below, although some of these eight strategies may appear obvious in hindsight, the concrete examples provide additional guidance on what degree of difference satisfies

the USPTO that an isolated nucleic acid product claim is markedly different from those in nature.

B. Is it Easy to Draft Around *Myriad*?

Our results indicate that in the years immediately after *Myriad* there has been much less amending activity than some commentators had expected. In over 79.2% of **M1a** cases the simple isolated nucleic acid product claims were canceled. Claim amendments were attempted and successful in less than 18.6% of the cases. We found only 21 (3.2% of the **M1a**) instances of successful amendments after receiving an explicit *Myriad* rejection. Furthermore, in none of these cases involving successful amendments, is the scope (breadth) of the granted claims equivalent to the original scope.

When we commenced this study we expected to see more amending activity to overcome *Myriad* rejections; we did not expect so many cancellation of entire patents nor so many canceled claims which excised a nucleic acid claim without any attempt to amend the claim to closely related subject-matter eligible claims. There were potentially many reasons for the large proportion of discontinued isolated nucleic acid product claims. Undoubtedly one reason was the view that such claims were ineligible and difficult to draft around after *Myriad*. No guidelines were initially issued, and even then detailed information for addressing *Myriad*-based rejections in relation to isolated nucleic acids was unavailable. There were also reasons other than patent eligibility, for example, concerns about novelty, obviousness or unity of invention. Another explanation is that such claims are simply not as valuable as they were once perceived to be and are suffering a "Darwinian fate"[26].

It is important to note that canceled *Myriad*-type claims could, in some cases, be resurrected and amended in future, claiming the original priority date; for example as a divisional, continuation or continuation-in-part patent application. So it may be that some applicants that discontinued *Myriad*-type claims are waiting to learn more about successful claim-drafting practices before trying to prosecute or amend contentious *Myriad*-type claims. The typology, information and concrete examples in this study of what works and doesn't work is the sort of information that patent practitioners may find helpful. In particular, the file wrappers disclose important nuances that applicants have only learnt through trial and error.

For example, in one of the 21 applications to receive a *Myriad*-based rejection, the applicant attempted to overcome the rejection by claiming an 'isolated polydexoyriboneculeotide that, when transcribed and translated, yields a *polypeptide* [that exists in nature]'. However, the examiner maintained the rejection and suggested that the claim be amended to cDNA instead; the applicant accepted this amendment (Case #1, Supplementary Information). In another application that received a *Myriad*-based rejection, the applicant amended a *Myriad*-type claim to 'synthetic DNA'; however, the examiner maintained the rejection because the claim still included a sequence that existed in nature despite being made in a synthetic, unnatural way (Case #7, Supplementary Information). In yet another example, an examiner rejected a claim limited to 'designer' nucleic acids because it was not clear how the nucleic acids differed from those in nature. The examiner in this case even said that it is common for experts in the field to "describe natural processes of evolution as examples of 'engineering' or 'design'". The applicant eventually overcame the rejection by claiming specific, non-naturally occurring sequences (Case #11, Supplementary Information).

Based on these results, we can conclude that, to date, applicants have not found techniques to draft-around *Myriad* to obtain claims of equal breadth to isolated nucleic acid claims. However, some applicants have been able to amend ineligible isolated nucleic acid claims so that the resulting subject-mater eligible claims lie close to the boundary stated in *Myriad* between ineligible and eligible subject matter. Also we cannot go so far as to say that drafting around *Myriad* to achieve equal breadth is impossible: successful strategies might be found in claims that were, for example, amended for reasons unrelated to subject matter, or that occurred before examination on the merits.

In the immediate aftermath of the *Myriad* ruling, it may turn out that applicants have avoided trying to draft around *Myriad* (preferring instead to cancel the claims) because there is not enough of a business case to warrant this effort. Or it may turn out that applicants have delayed doing so due to current legal uncertainty. This will be clearer in a few years when we can see if a significant number of the canceled *Myriad*-type claims are resurrected as continuations or divisionals, and successfully amended at that point in time.

C. What is 'Markedly Different' from Nature after *Myriad*?

In the *Myriad/Mayo* Examination Guidance published between 2014 and 2016, the USPTO provides just a few concrete examples to demarcate when a claim directed to a nucleic acid has markedly different characteristics from naturally occurring nucleic acids. The primary Guidance published in the Federal Register on Dec 16, 2014 (ref. 3) states that markedly different characteristics may be found in chemical or physical structure, biological or pharmacological function, chemical or physical properties, functional or structural characteristics, or other properties. Alongside this general information, the Federal Register gives one example (ref 3, ibid, p 74625-6): i) a claim to an exons-only cDNA, where the naturally occurring gDNA also includes introns. On the same day (outside the Federal Register), three further examples were issued by the USPTO (ref. 3 Guidance issued on Dec 16, 2014 titled 'Nature-based product examples 9-18') to explain where a claim

directed to a nucleic acid is markedly different: ii) the claimed nucleic acid includes a non-naturally occurring nucleic acid substitution; iii) the claimed nucleic acid includes a non-naturally occurring fluorescent label; iv) the claim is to a non-natural combination of vector and nucleic acid[8].

Our results found seven examples in the **M1a** subset where an applicant successfully amended a claim so that it was directed to cDNA. This type of claim amendment was not surprising in view of it being explicitly mentioned in the Supreme Court opinion and the *Myriad/Mayo* Interim Examination Guidance of 2014. Nevertheless this type of amendment to overcome the *Myriad* product of nature exclusion remains controversial[2]; the apex court in Australia held, in a parallel *Myriad* case, that cDNA is not patent eligible subject matter[27].

Our analysis of the file wrappers also sheds further light on how claims to cDNA must be drafted to comply with *Myriad*. In one instance, an applicant attempted to overcome a *Myriad*-based rejection by claiming a "complementary DNA sequence." The examiner maintained their rejection because a "complementary DNA sequence" could be interpreted as "any DNA sequence that is complementary to some other sequence" (Case #14, Supplementary Information). By contrast, in a different example, a claim to 'complementary nucleic acid (cDNA)' was sufficient to overcome a *Myriad*-based rejection (Case #2, Supplementary Information). The difference between these examples is that the second explicitly includes the term of art "cDNA," as opposed to the more general concept of complementarity.

We found five successful amendments which reached grant by including non-naturally occurring nucleic acid variations. We also found two examples where amending a claim to include a combination of label and nucleic acid successfully transformed a claim that had been challenged pursuant to *Myriad*.

We found one example where the applicant amended the claim so that it was a non-natural combination of vector and nucleic acid.

Some of these amendment types were predictable if one takes into account the non-Federal Register *Myriad/Mayo* Guidance 2014; however, this Guidance was not issued until 18 months after *Myriad*. Moreover, we also observed some important nuances in the arguments raised and accepted by USPTO Examiners about what did and did not amount to 'markedly different characteristics' in cases of amendments directed to sequence variations and labels, even where the Guidance indicated that the characteristics were likely to be considered markedly different. For instance, an isolated nucleic acid that was amended to comprise "at least one modified nucleotide for increased nuclease resistance" was rejected because the claim still included naturally-occurring nucleic acids. Eventually, the applicant amended to claim specific isolated nucleic acids which have moieties that confer nuclease resistance (and do not occur in nature) (Case #10, Supplementary Information). In another example, an amendment that limited a *Myriad*-type claim to instances when the "single stranded nucleic acid is labeled" was rejected because it was not significantly different from that which exists in nature. Ultimately, the applicant overcame the rejection by specifying that "the single stranded nucleic acid is labeled '*with a dye*'" (Case #16, Supplementary Information).

Beyond the Examination Guidance, we found four additional strategies which applicants used to successfully respond to *Myriad*-based rejections. These are described as Types 3, 5, 7, and 8 in the **Supplementary Information**. Amending to claim recombinant nucleic acids (Types 3 and 5) is perhaps an obvious strategy in light of *Myriad;* however, we observed important nuances that must be adhered to here as well. For example: an amendment that merely limited a claim to "recombinant" nucleic acids was rejected because the claim did not encompass nucleic acids that are markedly different from those in nature. A nucleic acid made by recombination does not necessarily differ in structure or function from from a naturally occurring nucleic acid (Case #13, Supplementary Information). An amendment that linked an isolated nucleic acid to a promoter was also rejected because it is "well-known that various promoters and enhancers are present in the human genome …" (Case #24, Supplementary Information).

D. What has been the Response of the USPTO to *Myriad*?

Our results show that the USPTO implemented the *Myriad* ruling swiftly. We found examples where patent applications had received Notices of Allowance in the three months preceding the *Myriad* ruling (i.e., examination on the merits had concluded) but were stopped from issuance and prosecution reopened with a *Myriad*-based rejection (e.g., Cases #7 and #24, Supplementary Information). In general, our results also indicate the USPTO Examiners are interpreting *Myriad* and USPTO Examination Guidance literally and narrowly; though it is still debatable whether they are giving effect to the Supreme Court's statement that differences should be 'marked.' For example, does limiting the claim to a single "molecule that includes a nucleic acid and a fluorescent label" really constitute a "marked difference" from *Nature*?

We also found that Examiners are conservative in their use of discretion and do not tend to grant allowances based on claim language that deviates from the specific examples provided in the Examination Guidance. The strict attitude is reinforced by the USPTO's current practice of not granting patents on isolated naturally-occurring polypeptides (Case #12 Supplementary Information). Although the position against eligibility is conservative overall, there seems to be inter-examiner variability. For example, an

oligonucleotide that did not differ to sequences in nature was granted (Case #21, Supplementary Information), yet a claim to a pair of primers was rejected (Case #23, Supplementary Information).

The conservative approach of USPTO Examiners probably results in longer prosecution-times and in some cases patent applicants may be surrendering *more* patent protection scope than needed in order to satisfy the Examiners with regards to 35 USC 101 requirements (depending on one's view of the requirement for a 'marked difference' rather than a mere 'difference' from naturally occurring nucleic acid). If so, a potential positive side effect is that granted patents are more likely to withstand a validity challenge, should one be made via the courts at a future time. On balance it is unclear whether the conservative approach is beneficial. The longer patent prosecution times could disproportionately affect startups and small firms. They may not have the resources for engaging in this type of complex prosecutions involving multiple rounds of examination and RCEs (Requests for Continued Examination), unlike larger firms with more resources. We found some preliminary evidence of such disproportionate effect in our previous empirical study[14]. Strong, reliable patents are typically important for businesses which need 1) to attract investment in a risky R&D environment, and 2) firm growth during the term of the patent (ie., 20 years from the filing date). But strong, reliable patents are particularly important for SMEs. These firms are important providers of disruptive innovation (e.g., new ventures; substitute and new entrant products), which often require a period of market protection to challenge incumbents. In contrast, larger firms tend to dominate continuous improvement (or sustained-innovation) and can rely more on existing capital, marketing, brand recognition, R&D budgets, and existing distribution channels for competitive advantage.

Assuming the USPTO's interpretation is correct, the information in this paper offers examples of successful claims amendments that could help applicants with their pending patent prosecutions in this technical field. Relatedly, next time a landmark case like *Myriad* is decided, we suggest that the relevant patent office should endeavour to produce updated guidelines quickly and with as much detail as possible.

Conclusions & Further Research

It is important to emphasize that our empirical results involving claim amendments focus on USPTO examination of human gene-related claims in applications receiving a *Myriad* rejection that were examined in the last three years. Based on these results, we conclude that there has been no successful "drafting around" the legal principles in *Myriad* to the point of achieving protection of equal breadth to isolated gDNA claims. There has been some claim drafting to achieve claims that sail close to the boundary between eligible and ineligible subject matter, and there is still some room for debate whether applicants are being issued claims that are different from nucleic acid, but not *markedly* different. In contrast to the limited drafting around activity, many applicants advanced prosecution of their applications containing isolated nucleic acid product claims by cancelling the *Myriad*-type claims during the election process or during examination.

In so far as patent practitioners did engage with claim amendments after a *Myriad*-based rejection from a USPTO Examiner, applicants primarily claimed cDNA; the eligibility of which was explicitly affirmed by the US Supreme Court in *Myriad* and the primary *Myriad/Mayo/Alice* guidance from the USPTO. Other allowable amendments followed other examples in the 2014 USPTO Guidance[5], namely sequence variations, labelling, and nucleic acids inserted into vector. USPTO Examiners were noticeably conservative with what they considered acceptable amendments in these categories. We observed a handful of other amendments - not currently mentioned in USPTO Examination Guidelines - which successfully shifted a simple isolated nucleic product claim from ineligible to eligible subject matter. These are interesting additions to "the patent practitioners' tool box."

In terms of further research, one might conduct manual claims analysis of the **M1b** cohort (patents filed with at least one complex isolated nucleic acid claim) and the **Ma1GA1** and **Ma1GA2** (patents filed with at least one simple isolated nucleic acid claim that were granted after amending the claim during the election process or via preliminary amendment) to see if any additional strategies for drafting around *Myriad* emerge. Another insightful line of enquiry would be to investigate the US family members related to the M1a subset. Such follow-on research could help answer, for instance, whether the *Myriad*-type claims that were cancelled in the uncertain aftermath of *Myriad* are being resurrected and filed as 'children' applications (applications claiming the priority benefit of an earlier application) as the threshold of patent eligibility and business value of nucleic acid patents becomes clearer. In addition to examining the US patent families, another topic ripe for further research is to examine patent family members in other jurisdictions, especially family members filed with the the European Patent Office (EPO). Empirical answers to these questions would help provide further insight into the debate regarding the effects of having divergent patent eligibility requirements in this important technical field across jurisdictions.

Our prediction is that studies like this, further debate, additional USPTO Guidance, future court decisions —in short, the passage of time—will resolve some of the uncertainty that still surrounds the *Myriad* distinction between ineligible claims directed to products of Nature, and eligible claims that have 'markedly different characteristics'[12]. In turn, we think it is

possible that the dominant prosecution and claim amendment strategies in this field may change in the future. For instance, applicants that cancelled *Myriad*-type claims in the aftermath of *Myriad*, may in time decide to amend the claim in a manner which becomes predictably likely to succeed. At that time they can file a divisional, continuation or continuation-in-part application claiming the priority benefit to the older co-pending applications and still obtain some protection for these product claims. However, whether we see this dynamism and time-dependency with claim drafting will also depend upon whether the cancelled, potentially amendable claims are perceived as having economic value. It is also a separate question whether developments in claim-drafting, sailing increasingly closer to the boundary of *Myriad*, are beneficial for scientific research and innovation.

In summary, based on the nuances that we observed in amendments that satisfy current USPTO practice, we would conclude in the immediate aftermath of *Myriad* it has not been necessarily easy for applicants to draft *Myriad*-compliant amendments that obtain the broadest claim scope available, particularly if exclusivity over a cDNA sequence is not a valuable right. However, applicants need not abandon *in toto* their *Myriad*-type claims if one sees good reason for pursuing related amended nucleic acid claims. As shown by this study, there are more than half a dozen tried-and-tested claim drafting strategies that can transform ineligible simple isolated nucleic acid product claims into USPTO eligible claims after *Myriad*. We hope that this study and prosecution examples will help provide further clarity and practical insight into the emerging USPTO threshold for subject-matter eligibility for gene-related patents. One of the key issues that the various stakeholders (e.g., biotech researchers, inventors, entrepreneurs, investors, business, and patent practitioners) agree on is the need for at at least a reasonable degree of legal certainty in order to promote efficiency in genomic research, investment, and innovation, which requires clarity and predictability for the scope of the patent rights in this IP intensive field.

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Supplementary Information

Patent Search Algorithm (S1)

a) Search Strategy: claims:((seq id) AND ("isolated DNA"~5 OR "isolated gene"~5 OR "isolated nucleotide"~5 OR "isolated (deoxyribonucleic acid)"~5 OR "isolated (nucleic acid)"~5))
b) Dates: 2010-06-13 to 2013-06-13
c) Database: Lens.org;
d) Jurisdiction: USA (USPTO);
e) Biologicals: Homo Sapiens

Patent Application Coding Schema

M1a = Simple Isolated DNA
M1aG = Simple Isolated DNA Granted
M1aR = Simple Isolated DNA Rejected/Abandoned
M1aP = Simple Isolated DNA Pending
M1aGA = Simple Isolated DNA Granted Claims Amended
M1aGC = Simple Isolated DNA Granted Claims Cancelled
M1aGU = Simple Isolated DNA Granted Claims Unchanged

Amendment Type
M1aGA1 = Simple Isolated DNA Granted Amended - Preliminary Amendment
M1aGA2 = Simple Isolated DNA Granted Amended - Response to Election/Restriction - Election
M1aGA3 = Simple Isolated DNA Granted Amended - Response to Office Action
M1aGA4 = Simple Isolated DNA Granted Amended - Appeal

Cancelation Type
M1aGC1 = Simple Isolated DNA Cancelled - Preliminary Amendment
M1aGC2 = Simple Isolated DNA Cancelled - Withdrawn in Response to Election/Restriction - Election
M1aGC3 = Simple Isolated DNA Cancelled - Response to Office Action
M1aGC4 = Simple Isolated DNA Cancelled - Appeal

Myriad Rejections
M1aGAxM1 = M1a Granted Claims (any Type) with 35 USC 101 Myriad-Type Rejection
M1aGAxM2 = M1a Granted Claims Amended without 35 USC 101 Myriad-Type Rejection
M1aGAxM2a = M1a Granted Claims Amended without 35 USC 101 Myriad-Type Rejection (after Myriad)
M1aGAxM2b = M1a Granted Claims Amended without 35 USC 101 Myriad-Type Rejection (before Myriad)
M1aGCxM2a = M1a Granted Claims Cancelled without 35 USC 101 Myriad- Rejection (after Myriad)
M1aGCxM2b = M1a Granted Claims Cancelled without 35 USC 101 Myriad-Type Rejection (before Myriad)
M1aGUxM2a = M1a Granted Claims Unchanged without 35 USC 101 Myriad-Type Rejection (after Myriad)
M1aGUxM2b = M1a Granted Claims Unchanged without 35 USC 101 Myriad-Type Rejection (before Myriad)

Pivoting point for granted: date of issuance.

Illustrative Example(s):
Example 1: **M1aGA3M1** indicates a patent application containing at least one product claim directed to **simple** isolated DNA, that was **granted**, and that the isolated DNA claim was **amended** in **response** to an Office Action during **examination of the merits**, and the Office Action **included** a 35 USC 101 **Myriad-**type rejection

Example 2: **M1aGC2M2a** indicates a patent application containing at least one product claim directed to simple isolated DNA, that was granted, and that the isolated DNA claim was cancelled in response to an a Restriction requirement (i.e., the claim was not elected -withdrawn from consideration- and later cancelled) and the Office Actions (at least one provided after the Myriad Supreme Court ruling) did **NOT** a 35 USC 101 Myriad-type rejection (because the claim had already been cancelled.

Amendments due to *Myriad*-based Rejections: Published Application Claims v Granted Claims

Please note:

- Words in the granted claims highlighted in yellow indicate the elements of the claim that were amended to comply with the *Myriad*-based rejection.
- The dates used below refer to the date stamp given to the documents by the USPTO, the dates may not correspond to the dates in which the correspondence was sent or received.
- Where possible, the claim numbers used below correspond to the ones on Lens.com

Summary of Amendments:

Type 1: cDNA – 7
Type 2: Nucleic acid with non-naturally occurring sequence variations – 5
Type 3: Heterologous Recombination - 3
Type 4: Label – 2
Type 5: Recombination with non-specific regulatory nucleic acid – 1
Type 6: Vector – 1
Type 7: Type 2 and a negative-claim clause – 1
Type 8: Short nucleotide – 1
Type 9: Cancelled – 3 (183 total cancelations)

Description of Amendment Classifications:

1. *cDNA* – The amendment meant that only cDNA was claimed.
2. *Nucleic acid with non-naturally occurring sequence variations* – The amendment meant that only nucleic acids with non-naturally sequence variations were claimed.
3. *Heterologous Recombination* – The amendment meant that only nucleic acids linked to sequences from different species were claimed.
4. *Label* – The amendment meant only labelled nucleic acids were claimed.
5. *Recombination with non-specific regulatory nucleic acid* – The amendment meant that only a nucleic acid sequence linked to a non-specific regulatory nucleic acid was claimed.
6. *Vector* – The amendment meant that only a nucleic acid in a vector was claimed.
7. *Type 2 and a negative-claim clause* (*Nucleic acid with non-naturally occurring sequence variations; and a negative-claim clause)* – The amendment meant that only nucleic acids with non-naturally occurring variant(s) were claimed. In addition, the claim specifies that the claimed sequences are no not identical or complementary to all or a portion of other naturally occurring DNA.
8. *Short nucleic acid* – The amendment meant that only a short nucleic acid was claimed.
9. *Cancelled* – The claims were cancelled.

PATENTS

Type 1: cDNA

1. Title: Pregnancy-associated Plasma Protein-a2 (papp-a2) Polynucleotides

Application Publication No: 2013/0095569 A1
Application No: 13/625,088
Relevant Claim:

1. An isolated polynucleotide encoding a polypeptide that
(a) consists of mature PAPP-A2 (amino acid residues 234-1791 of SEQ ID NO:2); or
(b) is at least 95% identical to the polypeptide of (a), and differs from the polypeptide of (a) solely by
(i) deletion of 1-10 amino acid residues from, or addition of 1-10 residues to, the amino terminal, and/or
(ii) deletion of 1-10 residues from, or addition of 1-10 residues to, the carboxy terminal, and/or
(iii) one or more conservative substitutions;
wherein said polypeptide has a proteolytic activity against Insulin Like Growth Factor Binding Protein 5 (IGFBP-5).

Grant Publication No: 9005949 B2
Relevant Grant Claim:

1. A cDNA that encodes a polypeptide that
(a) consists of amino acid residues 234-1791 of SEQ ID NO: 2 (mature pregnancy associated plasma protein A2 (PAPP-A2)); or
(b) is at least 95% sequence identical to the polypeptide of (a), and differs from the polypeptide of (a) solely by
(i) deletion of 1-10 amino acid residues from, or addition of 1-10 residues to, the amino terminal, and/or
(ii) deletion of 1-10 amino acid residues from, or addition of 1-10 residues to, the carboxy terminal, and/or
(iii) one or more conservative substitutions;
wherein said polypeptide has a proteolytic activity against Insulin Like Growth Factor Binding Protein 5 (IGFBP-5).

Amendment type: cDNA

Notes: The applicant initially attempted to make the claim patent eligible by claiming an isolated "polydeoxyribonucleotide" instead of a "polynucleotide", arguing that the claim "no longer read on naturally occurring nucleic acids…". This amendment and argument was, however, rejected (non-final rejection 15 August 2014). The applicant then amended the claim to read "An isolated polydeoxyribonucleotide that, when transcribed and translated yields a polypeptide"… (Response after final action, 13 November 2014). Eventually, after an applicant-initiated interview, the claim was drafted to cDNA (11 December 2014).

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2. Title: Mammalian Alpha-kinase Proteins, Nucleic Acids And Diagnostic And Therapeutic Uses Thereof

Application Publication No: 2013/0011919 A1
Application No: 12/803,001
Relevant Claim:

1. An isolated nucleic acid encoding mammalian melanoma alpha kinase, wherein the nucleic acid is selected from the group consisting of:
a. the DNA sequence of SEQ ID NO: 28;
b. the DNA sequence of SEQ ID NO: 26;
c. DNA sequences that hybridize to the sequence of subparts (a) or (b) under standard hybridization conditions; and
d. DNA sequences capable of encoding the amino acid sequence encoded by the DNA sequences of subparts (a), (b) or (c).

Grant Publication No: US8916379 B2
Relevant Grant Claim:

1. A complementary nucleic acid (cDNA) encoding mammalian melanoma alpha kinase having alpha kinase activity, wherein the nucleic acid is selected from the group consisting of
a. SEQ ID NO: 26; and
b. cDNA sequences capable of encoding the amino acid sequence encoded by SEQ ID NO:27.

Amendment type: cDNA

Notes: The examiner initially raised the *Myriad*-based rejection in an examiner-initiated interview (28 February 2014), which was then repeated in a non-final rejection (28 February 2014).

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3. Title: Use Of Novel Cytokine Receptors As Biomarkers And Therapeutic Targets In Human Cancer

Application Publication No: 2012/0329065 A1
Application No: 13/595,436
Relevant Claim:

1. An isolated nucleic acid selected from the group consisting of a nucleic acid encoding erythropoietin receptor isoform 5 and having the sequence given herein as SEQ ID NO: 12; a nucleic acid that encodes the opposite strand of a nucleic acid of SEQ ID NO: 12.

Grant Publication No: 8617844 B2
Relevant Grant Claim:

1. An isolated nucleic acid selected from the group consisting of a cDNA acid encoding erythropoietin receptor isoform 5 and having the sequence given herein as SEQ ID NO: 12; a cDNA is the full length complement of SEQ ID NO: 12

Amendment type: cDNA

Notes: The *Myriad*-based rejection was raised during an examiner-initiated interview (2 December 2013). This interview actually took place *after* a notice of allowance was issued (6 June 2013). During the interview the applicant authorised the claim amendment above. This amendment, however, didn't make it to the granted patent until a certification of correction was issued (28 October 2014).

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4. Title: Identification And Use Of Genes Encoding Amatoxin And Phallotoxin

Application Publication No: 2010/0267019 A1
Application No: 12/268,22
Relevant Claim:

1. An isolated nucleic acid sequence comprising at least one sequence set forth in SEQ ID NOs:1-4, 55-56, 79-81, 85-86, and 95-96.

Grant Publication No: 9518097 B2
Relevant Grant Claim:

1. A nucleic acid consisting essentially of one of the sequences set forth in SEQ ID NOs: 55, 56, or 79.

Amendment type: cDNA

Notes: These SEQ ID NOs list cDNA sequences (see applicant arguments, 4 June 2014).

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5. Title: Identification Of A Novel Bhd Gene

Application Publication No: 2011/0288031 A1
Application No: 13/179,853
Relevant Claim:

14. An isolated nucleic acid molecule encoding the polypeptide of claim 1, wherein the molecule hybridizes with a nucleic acid probe comprising the sequence shown in SEQ ID NO: 1 under wash conditions of 55° C., 1.0×SSC for 30 minutes.

(Claim 1: A purified folliculin polypeptide: having an amino acid sequence comprising the sequence set forth in SEQ ID NO: 2; having an amino acid sequence comprising a sequence having at least 95% sequence identity to the sequence set forth in SEQ ID NO: 2; encoded by a nucleic acid molecule comprising the sequence set forth in SEQ ID NO: 42; or encoded by a nucleic acid molecule comprising a sequence having at least 90% sequence identity to the sequence set forth in SEQ ID NO: 42.)

Grant Publication No: 8865880 B2
Relevant Grant Claim:

1. An isolated cDNA molecule consisting of a nucleic acid sequence encoding a polypeptide: having an amino acid sequence consisting of the sequence of SEQ ID NO: 2; having an amino acid sequence consisting of a sequence having at least 95% sequence identity to the sequence of SEQ ID NO: 2; wherein the isolated cDNA molecule hybridizes with a nucleic acid probe comprising the sequence shown in SEQ ID NO: 1 under wash conditions of 55° C., 1.0×SSC for 20 minutes.)

Amendment type: cDNA

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6. Title: Mutation Of The Parkin Gene, Compositions, Methods And Uses

Application Publication No: 2012/0064598 A1

Application No: 13/209,495
Relevant Claim:

1. An isolated nucleic acid molecule encoding a human parkin, comprising a DNA sequence of SEQ ID NO:1 with at least one genetic alteration comprising
   a) a deletion of one or more exons, in combination or otherwise,
   b) a multiplication of exons,
   c) a point mutation,
   d) a deletion of 1 or more contiguous base pairs,
   e) an insertion of 1 or more contiguous base pairs or
   f) a combination thereof.

Grant Publication No: 8835618 B2
Relevant Grant Claim:

1. An isolated nucleic acid molecule encoding a human parkin comprising a cDNA sequence of SEQ ID NO:1 with at least one genetic alteration comprising:

a) a deletion of one or more exons selected from the group consisting of: exon 2, exons 2-3, exons 2-4, exons 3-4, exons 3-6, exons 3-9, exon 5, exons 5-6, exon 6, exons 6-7, exons 7-9, and exon 8;
b) a multiplication of exons selected from the group consisting of:
a triplication of exon 2,
a duplication of exon 3,
a duplication of exon 6,
a duplication of exon 7,
and a duplication of exon 11;
c) a point mutation selected from the group consisting of:
a mutation from adenine to thymine at position 584,
a mutation from guanine to adenine at position 601,
a mutation from adenine to thymine at position 734,
a mutation from cytosine to thymine at position 867,
a mutation from thymine to adenine at position 905,
a mutation from cytosine to thymine at position 924,
a mutation from guanine to adenine at position 939,
a mutation from thymine to guanine at position 966,
a mutation from guanine to adenine at position 1084,
a mutation from cytosine to thymine at position 1101,
a mutation from guanine to cytosine at position 1239,
a mutation from guanine to adenine at position 1281,
a mutation from cytosine to adenine at position 1345,
a mutation from guanine to adenine at position 1390, and
a mutation from guanine to adenine at position 1459;
d) a deletion of 1 or more contiguous base pairs selected from the group consisting of:
a deletion of nucleotides adenine and guanine at positions 202-203,
a deletion of adenine at position 255, and
a deletion of nucleotides guanine and adenine at positions 1142-1143; or
e) an insertion of 1 or more contiguous base pairs selected from the group consisting of: an insertion of guanine and thymine at positions 321-322.

Amendment type: cDNA

7. Title: Tryptophanyl-trna Synthetase-derived Polypeptides Useful For The Regulation Of Angiogenesis

Application Publication No: 2012/0238620 A1
Application No:
Relevant Claim:

1. An isolated nucleic acid encoding a polypeptide capable of inhibiting angiogenesis or neovascularization, wherein the nucleic acid comprises a first polynucleotide sequence comprising a coding sequence at least 95 percent identical to a sequence selected from the group consisting of SEQ ID NO:6, a polynucleotide sequence that encodes a polypeptide of SEQ ID NO:12, and a polynucleotide sequence that encodes a fragment of the polypeptide of SEQ ID NO:12; and wherein the nucleic acid does not encode for the amino acid sequence of amino acids 71-93 of SEQ ID NO:1.

Grant Publication No: 8796237 B2
Relevant Grant Claim:

1. An isolated cDNA encoding a polypeptide or a fragment of the polypeptide capable of inhibiting angiogenesis or neovascularization, wherein the isolated cDNA comprises a first polynucleotide sequence comprising a coding sequence at least 95 percent identical to a sequence selected from the group consisting of SEQ ID NO:6, a polynucleotide sequence that encodes a polypeptide of SEQ ID NO:12, and a polynucleotide sequence that encodes a fragment of the polypeptide of SEQ ID NO:12.

Amendment type: cDNA

Note: A notice of allowance was issued on application claim 1 in a slightly modified version to that above (notice of allowance, 3 April 2013). However, this notification was withdrawn due to reconsideration of the patents in light of *Myriad* (notice of withdrawal from issue, 27 November 2013). After a telephone interview with the examiner, the applicant amended the introductory phrase of the claim to "An isolated DNA selected form the group consisting of cDNA, recombinant hybrid DNA and synthetic DNA…" (claims 14 November 2013). This amendment was rejected because no "hybrid DNA" was disclosed and "synthetic DNA" has the same sequence as that which exists in nature (non-final rejection 19 December 2013). Subsequently, the applicant limited the claim to cDNA (applicant arguments, 30 January 2014).

Type 2: Nucleic acid with non-naturally occurring sequence variations

8. Title: Ssx-2 Peptides Presented By Hla Class Ii Molecules

Application Publication No: 2011/0144186 A1
Application No: 12/028,953
Relevant Claim:

1. An isolated nucleic acid molecule encoding an SSX-2 HLA class II-binding peptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7 and SEQ ID NO:8.

Grant Publication No: 920047 B2
Relevant Grant Claim:

1. An isolated nucleic acid molecule encoding an SSX-2 HLA class II-binding peptide comprising an endosomal targeting signal, wherein the SSX2 HLA class II-binding peptide consists of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7 and SEQ ID NO:8.

Amendment type: Nucleic acid with non-naturally occurring sequence variations

Notes: The examiner raised the *Myriad*-based rejections in an examiner-initiated interview (19 March 2015) and then again in a non-final rejection (20 March 2015). The examiner advised that the amendments above would be eligible at the interview and in the non-final rejection because the naturally-occurring version of the protein does not ordinarily have the endosomal targeting signal (non-final rejection 20 March 2015). The applicant adopted these amendment in the next version of the claims (19 June 2015).

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9. Title: Variant Activin Receptor Polypeptides

Application Publication No: 2011/0183897 A1
Application No: 13/080,515
Relevant Claim:

1. An isolated nucleic acid molecule comprising a polynucleotide selected from the group consisting of:
(a) a polynucleotide having sequence set forth in the group consisting of SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 51, 53, 55, 59, 61, 63, 65, 67, 69, 71, 92, 94, and 96 or its complement; and
(b) a polynucleotide encoding a polypeptide having the amino acid sequences set forth in the group consisting of SEQ ID NO: 4, 6, 8, 10, 12, 14, 16, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 52, 54, 56, 60, 62, 64, 66, 68, 70, 72, 87, 88, 91, 93, 95, and 97.

Grant Publication No: 8716459 B2
Relevant Grant Claim:

1. An isolated nucleic acid molecule comprising a polynucleotide selected from the group consisting of:
(a) a polynucleotide having sequence set forth in SEQ ID NO 23;
(b) a polynucleotide encoding a polypeptide having the amino acid sequences set forth in SEQ ID NO: 24;

(c) a polynucleotide encoding a polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence set forth at amino acids 25 through 134 of SEQ ID NO:18, wherein the polypeptide comprises an amino acid substitution at position 28 of SEQ ID NO:18;
(d) a polynucleotide encoding a polypeptide comprising an amino acid sequence at least 98% identical to the amino acid sequence set forth at amino acids 25 through 134 of SEQ ID NO:18, wherein the polypeptide comprises an amino acid substitution at position 28 of SEQ ID NO:18; and
(e) a polynucleotide encoding a polypeptide comprising an amino acid sequence at least 99% identical to the amino acid sequence set forth at amino acids 25 through 134 of SEQ ID NO:18, wherein the polypeptide comprises an amino acid substitution at position 28 of SEQ ID NO:18.

Amendment type: Nucleic acid with non-naturally occurring sequence variations

Notes: Each isolated nucleic acid molecule listed includes non-naturally-occurring modifications). For a discussion on the modifications see, applicant arguments (23 December 2013).

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10. Title: Dna Virus Microrna And Methods For Inhibiting Same

Application Publication No: 2012/0070892 A1
Application No: 13/307,694
Relevant Claim:

1. An isolated nucleic acid Epstein Barr virus (EBV) microRNA molecule having a maximum of 50 nucleotides comprising any one of SEQ ID NOS: 1 and 3-5.

Grant Publication No: 9476048 B2
Relevant Grant Claim:

1. An isolated nucleic acid Epstein Barr virus (EBV) microRNA molecule having a maximum of 50 nucleotides comprising a sequence selected from the group consisting of SEQ ID NOS: 1 and 3-5, wherein at least one ribonucleotide in said sequence is modified to confer nuclease resistance as compared to the unmodified naturally occurring microRNA, and wherein the modification of the ribonucleotide is selected from the group consisting of a C_1 to C_4 alkyl group substituted at the 2′ position, a C_1 to C_4 alkoxy-C_1 to C_4 alkyl group substituted at the 2′ position, and a methylene bridge between the 2′-oxygen atom and the 4′-carbon atom.

Amendment type: Nucleic acid with non-naturally occurring sequence variations

Notes: The applicant attempted to overcome the *Myriad*-based rejection by amending the claim to state that the isolated nucleic acid "molecule comprises at least one modified nucleotide for increased nuclease resistance" (applicant arguments, 10 March 2014). This amendment was, however, rejected for being too broad because it included amendments that were naturally occurring and were already published (final rejection, 2 July 2014). The applicant again tried to overcome the *Myriad*-based rejection by stating that the isolated nucleic acid had been "*chemically* modified" for increased nuclease resistance (applicant arguments, 2 October 2014). This second amendment was rejected because some chemical alterations can result in amendments which are identical to those that exist in nature (non-

final rejection, 30 October 2014). Finally, the applicant amended the claim to read, "wherein the sequence comprises at least one chemical modified ribonucleotide having a moiety which confers nuclease resistance (applicant arguments, 30 January 2015). This amendment was sufficient to overcome the *Myriad*-based rejection, but additional amendments were required for other reasons.

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11. Title: Transcription Activator-like Effectors

Application Publication No: 2012/0270273 A1
Application No: 13/353,662
Relevant Claim:

1. A nucleic acid molecule encoding a designer transcription activator-like effector (dTALE) polypeptide, the nucleic acid molecule comprising a sequence encoding a nucleic acid binding domain and one or more mammalian effector domains, wherein the sequence encoding the nucleic acid binding domain comprises sequences encoding two or more monomer units arranged in a predetermined 5′ to 3′ order, wherein each said monomer unit comprises a variable disresidue that specifically binds a target nucleotide, and wherein the nucleic acid binding domain encoded by the nucleic acid molecule specifically binds a predetermined nucleic acid sequence, and wherein each one or more mammalian effector domains encoded by the nucleic acid molecule mediates an effector function.

Grant Publication No: 9499592 B2
Relevant Grant Claim:

1. A nucleic acid molecule encoding a designer transcription activator-like effector (dTALE) polypeptide fragment, the nucleic acid molecule comprising a sequence encoding a nucleic acid binding domain of the dTALE polypeptide fragment and one or more mammalian effector domains, wherein the sequence encoding the nucleic acid binding domain comprises a sequence encoding two or more monomer units arranged in a predetermined 5′ to 3′ non-endogenous TALE order,
wherein each said monomer unit comprises a variable diresidue that is capable of specifically binding a target nucleotide,
wherein the nucleic acid binding domain encoded by the nucleic acid molecule is capable of specifically binding a predetermined target nucleic acid sequence,
wherein each of the one or more mammalian effector domains encoded by the nucleic acid molecule is capable of mediating an effector function, and
wherein the nucleic acid molecule further comprises an expression vector comprising the sequence of an expression vector of SEQ ID NOs: 192-195.

Amendment type: Nucleic acid with non-naturally occurring sequence variations

Notes: Although the application claim detailed "a designer transcription activator-like effector" the examiner rejected this claim under *Myriad* because the claim "did not set forth specific structural properties of the claimed nucleic acids that make it clear the nucleic acids are non-naturally occurring." (non-final rejection 2 October 2014). The applicant amended the claim to give a little more detail on the invention (2 April 2014), but the examiner maintained that nucleic acids listed could be found in nature. Furthermore, the examiner stated that it is common for people skilled in the art "to make reference to the 'arrangement' of domains in naturally occurring proteins and to describe naturally processes of evolution as examples of 'engineering' or 'design'. (final rejection, 19 May 2015). The applicant

eventually made the claim patent eligible by making the amendment above (applicant arguments 10 November 2015).

The additional clause "wherein the nucleic acid molecule further comprises an expression vector comprising the sequence of an expression vector of SEQ ID NOs: 192-195" was actually added due to a 102 rejection (applicant arguments, 20 June 2016).

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12. Title: Immunogenic Peptides And Methods Of Use

Application Publication No: 2011/0165117 A1
Application No: 13/025,094
Relevant Claim:

> 17. An isolated polynucleotide comprising a nucleic acid sequence encoding the polypeptide of claim 16.
>
> (Claim 16: An isolated polypeptide comprising at most ten consecutive amino acids of the amino acid sequence set forth as (SEQ ID NO: 1)MSARVRSRSRGRGDGX$_1$X$_2$APDVVAFVAPGESQQEEPPTDNQDIEPGQER EGTPPIEERKX$_3$X$_4$GDCQEMDX$_5$EKTRSERGDGSDVKEX$_6$X$_7$PPNPKHX$_8$ KTKE AGDGQP wherein X1 is Q or Y, X2 is E or L, X3 is V or Y, X4 is E or L, X5 is V or L, X6 is K or Y, X7 is T or L, and X8 is A or V and wherein the polypeptide comprises one of
> (a) amino acids 16 to 25 of SEQ ID NO: 1, wherein amino acid X$_1$ is a glutamine and amino acid X$_2$ is a glutamic acid;
> (b) amino acids 59 to 68 of SEQ ID NO: 1, wherein amino acid X$_3$ is a valine and amino acid, X$_4$ is a glutamic acid and X$_5$ is a valine; or
> (c) amino acids 84 to 92 of SEQ ID NO: 1 wherein the amino acid X$_6$ is a leucine, amino acid X$_7$ is a threonine and amino acid X$_8$ is a alanine.)

Grant Publication No: 9175057 B2
Relevant Grant Claim:

> 14. An isolated polynucleotide comprising a nucleic acid sequence encoding the polypeptide of claim 13.
>
> (Claim 13. A polypeptide consisting of amino acids 59 to 68 of SEQ ID NO: 1(X$_3$X$_4$GDCQEMDX$_5$), wherein amino acid X$_3$ is a valine, amino acid X$_4$ is a glutamic acid, and amino acid X$_5$ is a valine.)

Nucleic acid with non-naturally occurring sequence variations

Notes: The examiner rejected amendments to the polypeptide claim because they encompassed naturally occurring sequences of amino acids (see, non-final rejection, 9 January 2015).

Type 3: Heterologous recombination

13. Title: Genes Encoding A Novel Type Of Lysophophatidylcholine Acyltransferases And Their Use To Increase Triacylglycerol Production And/or Modify Fatty Acid Composition

Application Publication No: US2013/0152230 A1
Application No: 13/745,257
Relevant Claim:

1. A nucleic acid molecule, wherein said nucleic molecule is isolated, purified or recombinant, and comprises the sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, or SEQ ID NO:34.

Grant Publication No: 9228175 B2
Relevant Grant Claim:

1. A nucleic acid molecule comprising a first polynucleotide operably linked to a second, heterologous polynucleotide, wherein the first polynucleotide encodes at least one peptide selected from the group consisting of SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, and SEQ ID NO:84.

Amendment type: Heterologous recombination

Notes: The initial *Myriad*-based rejection stated that the recombinant nucleic acid molecules claimed were not eligible subject matter because there was no "indication that the recombinant nucleic acids have any characteristics (structural, functional, or otherwise) that are different from naturally occurring nucleic acids." (non-final rejection 22 May 2015).

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14. Title: Smndelta7 Degron: Novel Compositions And Methods Of Use

Application Publication No: 2012/0322852 A1
Application No: 13/510,149
Relevant Claim:

1. An isolated nucleic acid comprising a nucleic acid sequence encoding a SMNΔ7 degron, wherein said nucleic acid sequence is SEQ ID NO. 3 or SEQ ID NO. 14.

Grant Publication No: 8993741 B2
Relevant Grant Claim

1. An isolated nucleic acid encoding a chimeric polypeptide comprising a degradation signal sequence and a target sequence, wherein the degradation signal sequence consists of SEQ ID NO. 3 or SEQ ID NO. 14.

Amendment type: Heterologous recombination

Notes: The examiner raised the *Myriad*-based rejection in a non-final rejection (4 November 2013). The applicant attempt to make the claim patent eligible by claiming a "complementary

DNA sequence" instead of an "isolated nucleic acid" (applicant's amendments (27 January 2014). This amendment, however, was rejected because, as drafted in the claim, a "complementary DNA sequence" could be interpreted as "any DNA sequence that is complementary to some other sequence", not as a cDNA molecule that was deemed patent eligible in *Myriad* (final rejection, 24 February 2014). The amendment above was made in response to this rejection.

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15. Title: Use Of Regulatory Sequences For Specific, Transient Expression In Neuronal Determined Cells

Application Publication No: 2011/0016547 A1
Application No: 12/894,766
Relevant Claim:

1. A DNA segment comprising a regulatory sequence isolated free of the complete DCX gene protein coding region, wherein the regulatory sequence comprises a regulatory sequence selected from the group consisting of:
(a) regulatory sequences comprising the nucleotide sequence shown in SEQ ID NO: 1, as shown in SEQ ID NO: 2, as shown in SEQ ID NO: 3 or as shown in SEQ ID NO: 4;
(b) regulatory sequences comprising the nucleotide sequence contained in the insertion of clone DSM 15111 and obtainable by amplification using two oligonucleotides having the sequences indicated under SEQ ID NO: 9 and SEQ ID NO: 10;
(c) regulatory sequences comprising at least one nucleotide sequence of SEQ ID NO: 1 from position 1166 to 1746, from position 1166 to 2049, from position 1785 to 1843 or from position 1953 to 2775;
(d) regulatory sequences comprising at least one nucleotide sequence of SEQ ID NO: 2 from position 529 to 1079, from position 529 to 1390, from position 1118 to 1175 or from position 1291 to 2137;
(e) regulatory sequences comprising at least a functional part of a sequence of (a) to (d) and causing specific expression in neuronal determined cells;
(f) regulatory sequences comprising a nucleotide sequence which is at least 75% identical to a sequence as defined in (a) to (d) or which comprises a nucleotide sequence which is at least 78% identical to the nucleotide sequence as shown in SEQ ID NO: 1 from position 1166 to 1746 or from position 1166 to 2049 or to the nucleotide sequence shown in SEQ ID NO: 2 from position 529 to 1079 or from position 529 to 1390, which comprises a nucleotide sequence which is at least 82% identical to the nucleotide sequence as shown in SEQ ID NO: 1 from position 1785 to 1843 or to the nucleotide sequence as shown in SEQ ID NO: 2 from position 1118 to 1175 or which comprises a nucleotide sequence which is at least 75% identical to the nucleotide sequence as shown in SEQ ID NO: 1 from position 1953 to 2775 or to the nucleotide sequence as shown in SEQ ID NO: 2 from position 1291 to 2137; and
(g) regulating sequences comprising a nucleotide sequence which hybridizes with a complementary strand of the regulatory sequence as defined in (a) to (f) for the early, transient expression of a heterologous nucleotide sequence in proliferative neuronal determined cells

Grant Publication No: 8841430 B2
Relevant Grant Claim:

1. A DNA segment comprising a regulatory sequence and a heterologous nucleic acid molecule that is to be expressed and which originates from a different genetic context than said regulatory sequence, the heterologous nucleotide sequence being operatively linked to said regulatory sequence, said regulatory sequence being selected from the group consisting of:
(a) regulatory sequences comprising the nucleotide sequence shown in SEQ ID NO: 1, as shown in SEQ ID NO: 2, as shown in SEQ ID NO: 3 or as shown in SEQ ID NO: 4;
(b) regulatory sequences comprising the nucleotide sequence contained in the insertion of clone DSM 15111 and obtainable by amplification using two oligonucleotides having the sequences indicated under SEQ ID NO: 9 and SEQ ID NO: 10;
(c) regulatory sequences comprising at least one nucleotide sequence of SEQ ID NO: 1 from position 1166 to 1746, from position 1166 to 2049, from position 1785 to 1843 or from position 1953 to 2775;
(d) regulatory sequences comprising at least one nucleotide sequence of SEQ ID NO: 2 from position 529 to 1079, from position 529 to 1390, from position 1118 to 1175 or from position 1291 to 2137;
(e) regulatory sequences comprising a nucleotide sequence which is at least 75% identical to a sequence as defined in (a) to (d) or which comprises a nucleotide sequence which is at least 78% identical to the nucleotide sequence as shown in SEQ ID NO: 1 from position 1166 to 1746 or from position 1166 to 2049 or to the nucleotide sequence shown in SEQ ID NO: 2 from position 529 to 1079 or from position 529 to 1390, which comprises a nucleotide sequence which is at least 82% identical to the nucleotide sequence as shown in SEQ ID NO: 1 from position 1785 to 1843 or to the nucleotide sequence as shown in SEQ ID NO: 2 from position 1118 to 1175 or which comprises a nucleotide sequence which is at least 75% identical to the nucleotide sequence as shown in SEQ ID NO: 1 from position 1953 to 2775 or to the nucleotide sequence as shown in SEQ ID NO: 2 from position 1291 to 2137; and
(f) regulatory sequences comprising a nucleotide sequence which hybridizes under stringent conditions with a complementary strand of the regulatory sequence as defined in (a) to (e) and which provides early, transient expression of a heterologous nucleotide sequence in proliferative neuronal determined cells.

Amendment type: Heterologous recombination

Type 4: Label

16. Title: Forensic Identification

Application Publication No: 2013/0144047 A1
Application No: 13/761,648
Relevant Claim:

1. An isolated single stranded nucleic add consisting of a sequence selected from: SEQ ID NO 1TCTA TCTG TCTA $(TCTG)_4$ $(TCTA)_3$-; SEQ ID NO 2TCTA $(TCTG)_4$ $(TCTA)_7$-; SEQ ID NO 3$(TCTA)_2$ $(TCTG)_4$ $(TCTA)_3$, TCCA $(TCTA)_3$-; SEQ ID NO 4$(TCAT)_4$ CAT $(TCAT)_7$ TCGT TCAT-; SEQ ID NO 7$(TTTC)_3$ TTTT TTCT $(CTTT)_5$ T $(CTTT)_3$ CTCC $(TTCC)_2$-; SEQ ID NO 8$(TTTC)_3$ TTTT TTCT $(CTTT)_{13}$ CCTT $(CTTT)_5$ CTCC $(TTCC)_2$-; SEQ ID NO 9$(TTTC)_3$ TTTT TTCT $(CTTT)_{16}$ CCTT $(CTTT)_5$ CTCC $(TTCC)_2$-; SEQ ID NO 10$(TTTC)_4$ TTTT TT $(CTTT)_{15}$ $(CTTC)_3$ $(CTTT)_3$ CTCC $(TTCC)_4$-; SEQ ID NO 11$(TTTC)_4$ TTTT TT $(CTTT)_{16}$ $(CTTC)_3$ $(CTTT)_3$ CTCC $(TTCC)_4$-; SEQ ID NO 12$(TTTC)_4$ TTTT TT $(CTTT)_{17}$ $(CTTC)_3$ $(CTTT)_3$ CTCC $(TTCC)_4$-; SEQ ID NO 13$(TTTC)_4$ TTTT TT $(CTTT)_8$ $(CTGT)_4$ $(CTTT)_{13}$ $(CTTC)_4$ $(CTTT)_3$ CTCC $(TTCC)_4$-; SEQ ID NO 14$(TTTC)_4$ TTTT TT $(CTTT)_8$ $(CTGT)_5$ $(CTTT)_{13}$ $(CTTC)_4$ $(CTTT)_3$ CTCC $(TTCC)_4$-; SEQ ID NO 15$(TTTC)_4$ TTTT TT $(CTTT)_{11}$ $(CTGT)_3$ $(CTTT)_{14}$ $(CTTC)_3$ $(CTTT)_3$ CTCC $(TTCC)_4$-; SEQ ID NO 16$(TTTC)_4$ TTTT TT $(CTTT)_{10}$ $(CTCT)_5$ $(CTTT)_{13}$ $(CTTC)_4$ $(CTTT)_3$ CTCC $(TTCC)_4$-; SEQ ID NO 17$(TTTC)_4$ TTTT TT $(CTTT)_{12}$ $(CTGT)_5$ $(CTTT)_{14}$ $(CTTC)_3$ $(CTTT)_3$ CTCC $(TTCC)_4$-; SEQ ID NO 18$(TTTC)_2$ TTTT TT $(CTTT)_{14}$ $(CTGT)_3$ $(CTTT)_{14}$ $(CTTC)_4$ $(CTTT)_3$ CTCC $(TTCC)_4$-; SEQ ID NO 19$(TCTA)_4$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA (TCTA)2 TCCATA $(TCTA)_6$ TCGTCT-; SEQ ID NO 20$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_9$ TCGTCT-; SEQ ID NO 21$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_2$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{10}$ TCGTCT-; SEQ ID NO 22$(TCTA)_4$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_8$ TCGTCT-; SEQ ID NO 23$(TCTA)_5$ $(TCTG)_5$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_9$ TCGTCT-; SEQ ID NO 24$(TCTA)_4$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{10}$ TCGTCT-; SEQ ID NO 25$(TCTA)_4$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{11}$ TCGTCT-; SEQ ID NO 26$(TCTA)_6$ $(TCTG)_5$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{11}$ TCGTCT-; SEQ ID NO 27$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{12}$ TCGTCT-; SEQ ID NO 28$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{11}$ TA TCTA TCGTCT-; SEQ ID NO 29$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{12}$ TA TCTA TCGTCT-; SEQ ID NO 30$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{13}$ TA TCTA TCGTCT-; SEQ ID NO 31$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{14}$ TATCTA TCGTCT-; SEQ ID NO 32$(TCTA)_{10}$ $(TCTG)_5$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{12}$ TCGTCT-; SEQ ID NO 33$(TCTA)_{11}$ $(TCTGT)_5$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{12}$ TCGTCT-; SEQ ID NO 34$(TCTA)_{11}$ $(TCTG)_5$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA

$(TCTA)_{13}$ TCGTCT; SEQ ID NO 35$(TCTA)_{13}$ $(TCTG)_5$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{12}$ TCGTCT; and SEQ. ID NO: 36$(AGAA)_8$-.

Grant Publication No: 8940484 B2

Relevant Grant Claim:

1. An isolated single stranded nucleic acid consisting of a sequence selected from: SEQ ID NO 1TCTA TCTG TCTA $(TCTG)_4$ $(TCTA)_3$-; SEQ ID NO 2TCTA $(TCTG)_4$ $(TCTA)_7$-; SEQ ID NO 3$(TCTA)_2$ $(TCTG)_4$ $(TCTA)_3$, TCCA $(TCTA)_3$-; SEQ ID NO 4$(TCAT)_4$ CAT $(TCAT)_7$ TCGT TCAT-; SEQ ID NO 7$(T'TTC)_3$ T'T'T' T'TCT $(CT'T')_5$ T $(CT'T')_3$ CTCC $(T'TCC)_2$-; SEQ ID NO 8$(T'TTC)_3$ T'T'T' T'TCT $(CT'T')_{13}$ CCTT $(CT'T')_5$ CTCC $(T'TCC)_2$-; SEQ ID NO 9$(T'TTC)_3$ T'T'T' T'TCT $(CT'T')_{16}$ CCTT $(CT'T')_5$ CTCC $(T'TCC)_2$-; SEQ ID NO 10$(T'TTC)_4$ T'T'T' TT $(CT'T')_{15}$ $(CT'TC)_3$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 11$(T'TTC)_4$ T'T'T' TT $(CT'T')_{16}$ $(CT'TC)_3$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 12$(T'TTC)_4$ T'T'T' TT $(CT'T')_{17}$ $(CT'TC)_3$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 13$(T'TTC)_4$ T'T'T' TT $(CT'T')_8$ $(CTGT)_4$ $(CT'T')_{13}$ $(CT'TC)_4$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 14$(T'TTC)_4$ T'T'T' TT $(CT'T')_8$ $(CTGT)_5$ $(CT'T')_{13}$ $(CT'TC)_4$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 15$(T'TTC)_4$ T'T'T' TT $(CT'T')_{11}$ $(CTGT)_3$ $(CT'T')_{14}$ $(CT'TC)_3$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 16$(T'TTC)_4$ T'T'T' TT $(CT'T')_{10}$ $(CTCT)_5$ $(CT'T')_{13}$ $(CT'TC)_4$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 17$(T'TTC)_4$ T'T'T' TT $(CT'T')_{12}$ $(CTGT)_5$ $(CT'T')_{14}$ $(CT'TC)_3$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 18$(T'TTC)_2$ T'T'T' TT $(CT'T')_{14}$ $(CTGT)_3$ $(CT'T')_{14}$ $(CT'TC)_4$ $(CT'T')_3$ CTCC $(T'TCC)_4$-; SEQ ID NO 19$(TCTA)_4$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA (TCTA)2 TCCATA $(TCTA)_6$ TCGTCT-; SEQ ID NO 20$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_9$ TCGTCT-; SEQ ID NO 21$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_2$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{10}$ TCGTCT-; SEQ ID NO 22$(TCTA)_4$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_8$ TCGTCT-; SEQ ID NO 23$(TCTA)_5$ $(TCTG)_5$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_9$ TCGTCT-; SEQ ID NO 24$(TCTA)_4$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{10}$ TCGTCT-; SEQ ID NO 25$(TCTA)_4$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{11}$ TCGTCT-; SEQ ID NO 26$(TCTA)_6$ $(TCTG)_5$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{11}$ TCGTCT-; SEQ ID NO 27$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{12}$ TCGTCT-; SEQ ID NO 28$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{11}$ TA TCTA TCGTCT-; SEQ ID NO 29$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{12}$ TA TCTA TCGTCT-; SEQ ID NO 30$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{13}$ TA TCTA TCGTCT-; SEQ ID NO 31$(TCTA)_5$ $(TCTG)_6$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{14}$ TATCTA TCGTCT-; SEQ ID NO 32$(TCTA)_{10}$ $(TCTG)_5$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{12}$ TCGTCT-; SEQ ID NO 33$(TCTA)_{11}$ $(TCTGT)_5$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{12}$ TCGTCT-; SEQ ID NO 34 $(TCTA)_{11}$ $(TCTG)_5$ $(TCTA)_3$ TA $(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{13}$ TCGTCT; SEQ ID NO 35$(TCTA)_{13}$ $(TCTG)_5$ $(TCTA)_3$ TA

$(TCTA)_3$ TCA $(TCTA)_2$ TCCATA $(TCTA)_{12}$ TCGTCT;and SEQ. ID NO: 36$(AGAA)_8$-. wherein the isolated single-stranded nucleic acid is covalently labeled with a dye.

Amendment type: Label

Notes: The *Myriad*-based rejection was initially raised in a non-final rejection (11 September 2013). The addition of the highlighted text was made in response to that rejection, albeit without the term "covalently". Since the next office action (final rejection of 21 February 2014) did not reiterate the *Myriad*-based rejection, this amended appeared to transform the claim into patent eligible subject matter. A non-final office action (3 June 2014), however, raised the issue again against the amended claim. In this non-final office action, the examiner applied new guidelines on subject matter eligibility. The examiner found the label did not make the product 'markedly different' from that in nature and that the addition of a label did not "impose meaningful limit" on the claim's scope. That the label must be "covalently labelled" was an examiner's amendment, made in the notice of allowance (12 September 2014).

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17. Title: Human Immunodeficiency Virus And Uses Thereof

Application Publication No: 2011/0281258 A1
Application No: 13/028,816
Relevant Claim:

1. An isolated complete nucleic acid of the HIV-1 Group P virus wherein the nucleic acid comprises SEQ ID NO: 1.

Grant Publication No: 9150834 B2
Relevant Grant Claim:

1. An isolated nucleic acid of an HIV-1 Group P virus, wherein the nucleic acid consists of SEQ ID NO: 1 and the isolated nucleic acid is labeled with a radioactive compound or with a nonradioactive compound.

Amendment type: Label

Notes: In response to the *Myriad*-based rejection, the applicant initially tried to overcome the rejection by arguing that SEQ ID NO: 1 is isolated proviral DNA (a DNA form of the RNA-based virus that exists when integrated in a host-cell genome). Further, the applicant argued that since the purpose of integration into a cell is to ultimately replicate itself, if the DNA is isolated (as in the claim) then the DNA no longer has this function (see applicant arguments, 24 July 2014). The examiner rejected this argument because the HIV genome is transcribed/reverse transcribed as "both RNA and DNA so it does not appear that amending to a specific nucleic acid will remove the rejection."

Type 5: Vector

18. Title: Method For Predicting And Detecting Tumor Metastasis

Application Publication No: 2011/0152355 A1
Application No: 13/006,603
Relevant Claim:

37. An isolated nucleic acid consisting of a nucleic acid sequence that only encodes the amino acid sequence of SEQ ID NO: 2.

    (The claims in this application were amended many times during prosecution. This claim first appeared in this form 9 October 2012. This is the first-listed isolated-nucleotide claim that received a *Myriad*-based rejection).

Grant Publication No: 8816059 B2
Relevant Grant Claim:

2. A vector comprising a nucleic acid consisting of a nucleic acid sequence that only encodes the amino acid sequence of SEQ ID NO: 2.

Amendment type: Vector

Notes: Claims to cDNA for the same sequence were also made. These cDNA claims, however, were added part way through prosecution.

Type 6: Recombination with non-specific regulatory nucleic acid

19. Title: Polynucleotides Encoding Proteins Involved In Plant Metabolism

Application Publication No: 2013/0007912 A1
Application No:
Relevant Claim:

1. An isolated polynucleotide comprising:
(a) a nucleotide sequence encoding a polypeptide, wherein the amino acid sequence of the polypeptide has at least 90% sequence identity, based on the Clustal alignment method with pairwise alignment default parameters of KTUPLE=1, GAP PENALTY=3, WINDOW=5 and DIAGONALS SAVED=5, with SEQ ID NO:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, or 362; or
(b) a complement of the nucleotide sequence of (a), wherein the complement and the nucleotide sequence consist of the same number of nucleotides and are 100% complementary.

Grant Publication No: 8658858 B2
Relevant Grant Claim:

1. A recombinant DNA construct comprising:
(a) a nucleotide sequence encoding a phosphatidylinositol transfer polypeptide, wherein the amino acid sequence of the polypeptide has at least 90% sequence identity, based on the Clustal alignment method with pairwise alignment default parameters of KTUPLE=1, GAP PENALTY=3, WINDOW=5 and DIAGONALS SAVED=5, with SEQ ID NO:320; or
(b) a complement of the nucleotide sequence of (a), wherein the complement and the nucleotide sequence consist of the same number of nucleotides and are 100% complementary, and wherein the nucleotide sequence is operably linked to at least one regulatory sequence.

Amendment type: Non-specific recombination

Notes: The *Myriad*-based rejection was raised in an examiner-initiated interview (8 August 2013), when the applicant also authorised the examiner-suggested amendment.

Type 7: Nucleic acid with non-naturally occurring sequence variations and a negative-claim clause

20. Title: Methods And Nucleic Acids For Analyses Of Cellular Proliferative Disorders

Application Publication No: 2011/0244458 A1
Application No: 13/096,932
Relevant Claim:

2. A treated nucleic acid derived from genomic SEQ ID NOS:1 to SEQ ID NO:3, SEQ ID NO:24, SEQ ID NO:28, SEQ ID NOS:159 to SEQ ID NO:167, wherein the treatment is suitable to convert at least one unmethylated cytosine base of the genomic DNA sequence to uracil or another base that is detectably dissimilar to cytosine in terms of hybridization.

Grant Publication No: 8900829 B2
Relevant Grant Claim:

1. An isolated nucleic acid molecule selected from the group consisting of SEQ ID NOs: 30, 31, 42, and 43, wherein the nucleic acid molecule is not identical or complementary to all or a portion of SEQ ID NO: 24 or other naturally occurring DNA.

Amendment type: Modification with negative claim

Notes: The applicant supported this amendment by pointing out that SEQ ID NOs: 30, 31, 42 and 43 were created through bisulfite treatment of genomic DNA consisting of SEQ ID NO 24. Bisulfite treatment converts unmethylated cytosines to uracil, creating nucleic acid molecules that do not exist in nature (see applicant arguments, 18 April 2014).

Type 8: Short nucleotide

21. Title: Spanx-b Polypeptides And Their Use

Application Publication No: 2011/0318374 A1 (note: this link does not contain a pdf of the application, instead, see Google patents: 2011/0318374 A1).
Application No: 13/203,042
Relevant Claim:

> 17. An isolated polynucleotide comprising a nucleic acid sequence encoding the polypeptide of claim 13.
>
> (Claim 13: An isolated polypeptide comprising: the amino acid sequence set forth as (a) SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 1, SEQ ID NO: 26, SEQ ID NO: 27, or SEQ ID NO: 28; or
> (b) at least nine consecutive amino acids of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 14, SEQ ID NO: 15, or SEQ ID NO: 5;
> wherein the polypeptide is nine to twelve amino acids in length.)

Grant Publication No: 8664183 B2
Relevant Grant Claim:

> 8. An isolated polynucleotide comprising a nucleic acid sequence encoding the polypeptide of claim 6.
>
> (Claim 6: An isolated polypeptide comprising the amino acid sequence set forth as SEQ ID NO: 2, wherein the polypeptide is nine to twelve amino acids in length.)

Type: Short nucleic acid

Notes: During an applicant-initiated interview the parties discussed the applicability of *Myriad* to application claim 17 (10 July 2013). The examiner indicated that the claim would not receive a *Myriad*-based objection because "the polynucleotides would not naturally encode a 9-12-mer as recited in [application] claim 13."

Application claim 13 was amended during prosecution due to a restriction requirement (see applicant arguments (30 October 2012) and requirement for restriction/election (1 October 2012).

Cancelled

22. Title: Tumor Antigens Bfa4 And Bcy1 For Prevention And / Or Treatment Of Cancer

Application Publication No: US2011/0117640A1 A1
Application No: 12/888,975
Relevant Claim:

1. An isolated nucleic acid molecule comprising SEQ ID NO.: 3.

Grant Publication No: 8946174 B2
Relevant Grant Claim: N/A

Amendment type: Cancelled.

Notes: The granted patent claims vectors in various forms, including a claim to a 'vector comprising the nucleic acid consisting of SEQ ID NO.:3.' It also claims pharmaceutical compositions with a vector as part of the composition.

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23. Title: Method For The Detection And Diagnosis Of Cancer Involving Primers And Probes For The Specific Detection Of The Mage-a3-marker

Application Publication No: 2012/0040341 A1
Application No: 12/305,742
Relevant Claim:

1. A set of primers consisting of the pair of primers SEQ ID NO:11 and SEQ ID NO:12.

Grant Publication No: 8936919 B2
Relevant Grant Claim: N/A

Amendment type: Cancelled.

Note: Initially the applicant attempted to overcome the *Myriad*-based objection by arguing that the claim was to a *particular set of two* isolated nucleic acid molecules (applicant arguments, 7 May 2014). The examiner rejected this argument because primers, even as a set, are not structurally different from their natural counterparts (final rejection, 6 August 2014).

Although this claim was cancelled, the granted patent included claims to probes (with fluorescent dye), methods of diagnoses and kits (with primers and probes) were granted.

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24. Title: Nucleic Acids Encoding Biologically Active Polypeptides Derived From A Novel Early Stage Pregnancy Factor Designated Maternin (ma)

Application Publication No: 2012/0083587 A1
Application No: 13/159,285
Relevant Claim:

1. An isolated nucleic acid encoding a therapeutic polypeptide selected from the group consisting of:
(a) a polypeptide selected from the group consisting of:

(SEQ ID NO: 2)(i)MA peptide; (SEQ ID NO: 3)(ii)pMA peptide; (b) a polypeptide comprising one or more amino acid sequences selected from the group consisting of:

(i) the amino acid sequence of MA (SEQ ID NO: 2);
(ii) the amino acid sequence of pMA (SEQ ID NO: 3);
(iii) the amino acid sequence of MA_{S1} (SEQ ID NO: 4);
(iv) the amino acid sequence of MA_{S2} (SEQ ID NO: 5);
(v) the amino acid sequence of MA_{S3} (SEQ ID NO: 6);
(vi) the amino acid sequence of MA_{S5} (SEQ ID NO: 7);
(vii) the amino acid sequence of MA_{S9} (SEQ ID NO: 8);
(viii) the amino acid sequence of MA_{S10} (SEQ ID NO: 9);
(ix) the amino acid sequence of MA_{S11} (SEQ ID NO: 10);
(x) the amino acid sequence of β-hCG 55-88 (SEQ ID NO: 11);
(xi) the amino acid sequence of β-hCG 55-90 (SEQ ID NO: 12);
(xii) the amino acid sequence of β-hCG 55-91 (SEQ ID NO: 13);
(xiii) the amino acid sequence of β-hCG 55-74 (SEQ ID NO: 14);
(xiv) the amino acid sequence of β-hCG 6-37 (SEQ ID NO: 15);
(xv) the amino acid sequence of β-hCG 6-38 (SEQ ID NO: 16);
(xvi) the amino acid sequence of β-hCG 6-39 (SEQ ID NO: 17);
(xvii) the amino acid sequence of β-hCG 6-40 (SEQ ID NO: 18); and

(c) functional equivalents of the polypeptides of 1(a) and (b);
With the proviso that 1(b), and 1(c) exclude the full length sequence of (SEQ ID NO: 1).

Grant Publication No: 9175077 B2
Relevant Grant Claim: N/A

Amendment type: Cancelled.

Notes: The non-final rejection that included the *Myriad*-based rejection (19 December 2013) was made *after* a notice of allowance (13 June 2013) had been issued.

The applicant attempted to overcome the rejection by amending the claim to state the isolated nucleic acid is "operationally linked to a promoter" (applicant arguments, 18 June 2014); this amendment was modelled on an examiner-suggested amendment, "operably linked to a heterologous promoter" (non-final rejection, 19 December 2013). The applicant's amendment, however, was rejected because it is "well-known that various promoters and enhancers are present in the human genome and facilitate the expression of various gene products" (final rejection, 9 October 2014). The examiner reiterated that if the nucleic acid were linked to a *heterologous* promoter that this would be patent eligible (final rejection, 9 October 2014). The applicant did not adopt this amendment, instead, cancelling the claim.

Although this claim was cancelled, the granted patent claimed a vector including a nucleic acid sequence that that encoded a polypeptide of SEQ ID No 2. Claims were also granted to cells comprising this vector.

Was the *Myriad* decision a 'surgical strike' on isolated DNA patents, or does it have wider impacts?

Mateo Aboy, Cristina Crespo, Kathleen Liddell, Johnathon Liddicoat, Matthew Jordan

On the fifth anniversary of *Myriad,* this empirical study examines the wider impacts of the US Supreme Court decision on subject-matter eligibility and patent prosecution for nature-based products beyond isolated DNA. Contrary to some of the early predictions that the decision would be a narrow 'surgical strike' carving out isolated gDNA from patent eligibility, our study finds that 85% of the *Myriad*-based rejections have been directed to non-isolated DNA patent claims.

On June 13, 2013, the US Supreme Court held in *AMP v Myriad Genetics* (*Myriad*) that "[a] naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring"[1].

A question immediately called to mind was whether the courts and USPTO would expand the reach of the *Myriad* decision beyond DNA to other naturally-occurring or nature-based products. And if the reach of *Myriad* went beyond isolated gDNA, what would be the impact for patent prosecution in the biotech industry?

In the months immediately surrounding the decision, several academics heralded *Myriad* as a "*narrowly crafted*"[2] decision "that delivered a *surgical strike* against patents that block development in genetics-based diagnostics while preserving protection for therapeutics, personalized medicine, and other fields of biotechnology"[3]. Was this optimism sound? It was based on the distinction drawn in the case between isolated gDNA and cDNA. It was also bolstered by statements in the Supreme Court's opinion about DNA molecules being exceptional molecules as information carriers and the final line in the Supreme Court's decision: "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"[1].

Other commentators, typically aligned with industry, were much less complimentary and warned that the decision would have broad, sweeping implications and chill investment in a wide variety of isolated molecules other than DNA including RNA, antibiotics, antibodies, enzymes, and therapeutic proteins[4]. Was this too pessimistic?

Between these polarised views were commentators who viewed the fate of naturally-occurring products after *Myriad* as uncertain[5]. There was also a line of commentary that whatever impact *Myriad* had on non-DNA patent claims it would be relatively mundane compared with the other Supreme Court subject matter eligibility decisions such as *Mayo v Prometheus*[6].

In time, the USPTO delivered its view. Starting in 2014, the USPTO issued a number of documents providing updated guidance and examples on subject matter eligibility, in an attempt to reconcile cases like *Myriad*, *Chakrabarty*[7], *Funk Brothers*[8], *Mayo*[9], and *Alice*[10]. These developments have been compiled into the latest revision of the Manual of Patent Examining Procedure (MPEP 2106).

Based on the latest examination guidance on subject-matter eligibility (MPEP 2106), the USPTO considers *Myriad* to affect more than isolated gDNA. Courts have also taken this view, for example, finding claims to sheep clones patent ineligible[11].

Nevertheless, despite these developments, the precise breadth of the *Myriad*-exclusion for non-DNA products remains highly elusive[12]. Some have held tight to the view (or is it hope?) that *Myriad* might be limited to the specific scientific facts of the case (DNA)[13,14]. Others maintain the view that *Myriad* is having a highly chilling effect on isolated natural products other than DNA[15,16]. A third view is that the USPTO is applying *Myriad* beyond DNA but in a relatively narrow way, and readily allowing nature-based products so long as the applicant identifies a functional difference between the patented product and the nearest naturally-occurring counterpart[12,17].

Without empirical evidence, all of the above-mentioned views are adrift in uncertainty. It is also unclear what sort of practical impact the MPEP interpretation of *Myriad*

Mateo Aboy, Cristina Crespo, Kathleen Liddell, Johnathon Liddicoat & Matthew Jordan, Centre for Law, Medicine, and Life Sciences (LML), Faculty of Law, University of Cambridge, Cambridge, UK. Corresponding Author E-mail: ma608@cam.ac.uk

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is having on patent prosecution (how many applications and what type of products are affected?, what happens to these applications?). While two previous empirical studies investigated *Myriad's* broad impact on gene-related patents[18] and the types of amendments that transform ineligible isolated DNA claims into patent eligible subject matter[19], these studies did not address the wider impacts of *Myriad* beyond isolated DNA.

The aim of this paper is to examine empirical evidence of *Myriad's* impact on nature-based products other than gDNA. Specifically, we address two overall research questions: 1) to what *extent* has the *Myriad* decision affected patent eligibility of subject-matter beyond naturally-occurring DNA? and 2) in practice, what impact has *Myriad* had on the prosecution of such patents?

Box 1 Methods

- **Step 1: Search Strategy**
  - Description: A search of the PAIR system was conducted to identify USPTO correspondence citing *Myriad*
  - Search Terms: "*Myriad*" *AND* "*Association for Molecular Pathology*"
  - Classes: All Classes; TC 1600
- **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 Myriad Rejections (Classification, Impact, Prosecution)**
  - 5.1 Classification: A) Isolated DNA vs B) Other Nature-Based Products (Non Isolated DNA)
  - 5.2 Myriad Impact Analysis: 1) Central; 2) In Combination (Mayo, Alice); 3) Development of the Law
  - 5.3 Prosecution Strategy Analysis: 1) Cancel Claims, 2) Amend Claims, 3) Argument (unchanged claims)
  - 5.4 Selection of Examples: Illustrative examples of claim amendments (changes from application to patent grant)

Empirical Results & Patent Examination Examples

In order to answer these questions, we developed a methodology designed to provide empirical evidence about the degree and type of *Myriad's* impact during the patent examination process in the US **(Box 1 Methods)**.

First, we searched the USPTO PAIR (Patent Application Information Retrieval) system with the objective of identifying instances where *Myriad* was cited when a 35 USC 101 subject-matter eligibility rejection was issued. The search period included correspondence dated between June 13, 2013 and June 13, 2018. In order to prevent patent applications from being abandoned, applicants must respond to the examiner's office action containing claim rejections. Accordingly, the dataset collects situations (DNA and non-DNA claims) where the applicant had to deal with a *Myriad* rejection in order to advance prosecution, for example, through argument, amendment, or canceling the affected claims. This resulting dataset enabled us to: 1) study how *Myriad* is being applied by patent examiners in actual cases; and 2) analyze the wider impacts of *Myriad* in light of the latest examination guidance on subject matter eligibility (MPEP 2106).

We identified 14,380 USPTO correspondence documents containing a *Myriad* citation (**Box 1-Step 1**). Of these, 10,052 were identified in Examiner Office Actions (containing the claim rejections), 3,795 in Applicant Responses to Office Actions, and 533 in Appeal Correspondence (**Box 1-Step 2**). In all instances, *Myriad* was raised by examiners to justify a 35 USC 101 rejection. This dataset was then used to analyze questions related to i) the overall number of *Myriad* citations, ii) the allowance rate for applications with *Myriad* citations, iii) prosecution statistics, and iv) whether and to what extent (in actual US patent examination practice) *Myriad* has affected subject-matter eligibility beyond naturally occurring DNA.

How many USPTO patent applications have received a Myriad*-based rejection and what has been the fate of these applications?*

Based on our search algorithm, we identified 6,875 patent applications which contained the 14,380 USPTO correspondence documents noted above (correspondence involving a *Myriad* citation). These applications formed the overarching 'patent application sample' for our empirical study. They were further analyzed and classified according to their patent status: abandoned, patented, or pending (**Box 1 Step 3**).

On the fifth anniversary of *Myriad,* 2,449 (35.6%) of these patent applications had been abandoned, 2,590 (37.6%) had been granted, and 1,846 (26.8%) were still in active prosecution (pending). Thus, excluding pending applications, the overall allowance rate for patent applications in our sample (applications which received a citation to *Myriad* based on our search criteria) is 48.5%.

What is the expected prosecution timeline of an application receiving a Myriad *rejection?*

Our analysis of the USPTO file wrappers and prosecution histories for the patent application sample (n=6,875) (**Box 1-Step 4**) shows that Applicants who finally overcame the rejections of record and ultimately obtained a *Notice of Allowance*

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resulting in a granted patent typically received one or more final rejections. Notably, in 45.7% of the cases, applicants were required to engage in a second round of prosecution by filing a Request for Continued Examination (RCE). In 13.5% of the cases two or more RCEs were needed. For rejected applications that were ultimately abandoned the statistics are similar, 43.7% required at least one RCE, and 11.9% with 2 or more RCEs.

What proportion of Myriad*-based rejections apply to subject matter beyond isolated DNA?*

We generated 2 samples of 100 patent applications (n=200) each for detailed expert review (**Box 1-Step 5**). The first sample contained the last 100 granted patents in our dataset where *Myriad* was cited (without restrictions on whether *Myriad* was cited alone or in combination with *Mayo* or *Alice*). The second sample contained the last 100 granted patents where *Myriad* was raised in a 35 USC 101 rejection without reference to *Mayo* or *Alice* (**Supplementary Data**). This review (**Box 1-Step 5.1**) enabled us to estimate the proportion of applications for subject matter other than isolated DNA that received a rejection (**Supplementary Data**). Our results (**Figure 1**) indicate that in 84% of the combined sample (n=200), *Myriad* was used to issue a 35 USC 101 subject-matter eligibility rejection of claims beyond isolated gDNA. The results were concordant in both samples, 83% and 85%, respectively.

What sorts of subject-matter has been affected?

The subject matter that examiners have rejected beyond isolated gDNA is quite diverse. It includes other types of nucleotide-based inventions, such as RNA (Case 4), DNA arrays (Case 5), DNA-based kits, and DNA created after inbreeding (Case 10). It also goes beyond nucleotide-based inventions., including: peptides (Case 1), proteins (Case 2), antibodies (Case 11), cells (Case 12), pharmaceutical compositions (Case 4) and methods of various types (Case 15). All these illustrative cases are located in **Supplementary Data**.

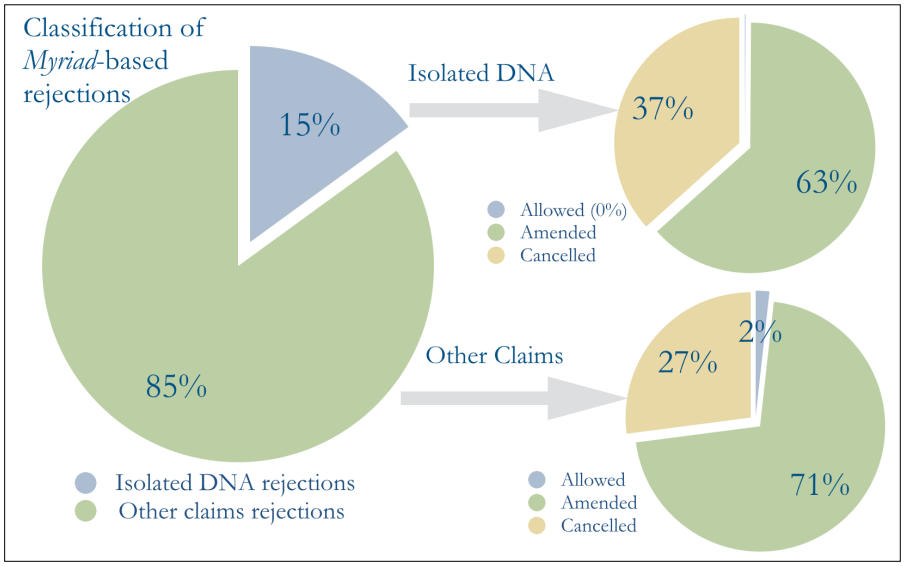

Figure 1 Study results showing that a) 85% of the *Myriad*-based rejections in our sample were directed to non-isolated DNA patent claims, and b) upon receiving a *Myriad* rejection directed to these claims, applicants advanced prosecution by either amending (71%), cancelling (27%) or providing legal and scientific/technical argument (2%) for these claims.

Was Myriad *used as a central reference or in combination to justify the 35 USC 101 rejection?*

In the first sample of patent applications that we reviewed (**Box 1-Step 5.2)** without restrictions on whether *Myriad* was cited alone or in combination with *Mayo* or *Alice*, *Myriad* was employed as the central reference to justify the 35 USC 101 rejection 60% of the time. In approximately 18% of the applications, it was applied in combination with other decisions (eg. *Mayo*), and in 22% of applications, *Myriad* was cited as part of a general line of cases which have developed §101 jurisprudence.

How have applicants overcome the 35 USC 101 Myriad*-based rejections?*

As noted, 85% of 200 patent applications which we sampled received a *Myriad* rejection to claims beyond isolated DNA. We analysed this sub-sample (**Box 1-Step 5.3).** Within this 85%, applicants advanced prosecution by amending the claims in 71% of the cases (**Figure 1**). The affected claims were cancelled in 27% of cases. Only in 2% of the cases was the rejection overcome by the applicant's arguments without the need for claim amendments. The remaining 15% of 200 patent applications which we sub-sampled concerned isolated DNA. To advance prosecution in this set, applicants either canceled (37%) or amended the claims (63%).

We looked more closely at the nuanced claim amendments (and associated arguments) in a subset of patent applications that received a *Myriad*-based rejection but were

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ultimately allowed (**Box 1-Step 5.4)**. This is useful to understand better the threshold of subject matter eligibility for nature-based products beyond isolated DNA **(**see illustrative examples in **Supplementary Data)**. For example, in Case 1 the applicant overcame a *Myriad*-based rejection on a peptide by claiming a method of treatment that included the peptide. In another example, an applicant overcame a rejection to polysaccharides by arguing that the concentration specified in the claim elicited an immune response. This concentration was not found in nature and, therefore, the invention was patent eligible (Case 8). It should be noted, however, that claim amendments are often introduced in response to multiple rejections (35 USC 101, 102, 103, 112). Accordingly, the examples and the statistics may include claim amendments that were crafted to overcome other rejections of record in addition to 35 USC 101.

Discussion

From the above results, several interesting points emerge which provide a better understanding of the extent to which *Myriad* is affecting patent applications other than gDNA.

Although the Supreme Court justices made several statements that led prominent commentators to think *Myriad* would have a narrow impact on "genes and the information they encode"[1], empirical evidence shows that at least 6,785 patent applications have been affected by a *Myriad* rejection in 5 years. Furthermore, our results indicate that 85% of these affected applications pertain to subject matter other than naturally-occuring DNA.

Most *Myriad* citations are Examiner initiated (70%), and it is not the case that Examiners are simply citing *Myriad* as one case amongst a string of cases that have reformulated the law of patent eligibility (eg *Alice*, *Mayo,* etc). Indeed our results show that in 60% of cases *Myriad* is employed as the central, and often sole, reference to justify the 35 USC 101 rejection. This indicates that the impact of *Myriad* on cases other than DNA is not mundane, as predicted by some commentators.

It is also important to note that our results indicate that a *Myriad* rejection does not sound a 'death knell' for a patent application. Excluding pending applications, we found that 48.5% ultimately received a Notice of Allowance.

That said, successful prosecution of a patent which receives a *Myriad* citation often appears to require extra time and money. For instance in approximately 45.6% of cases, patent applicants file a RCE and go through an extra round of patent examination. Furthermore, 13.7% go through at least an extra 2 rounds of patent examination with all the time and costs that entails before a *Notice of Allowance* is issued. This is a high frequency of patent applications to be going through RCEs, as can be seen from a comparison with the latest USPTO statistics which found 18% of patent applications filed 1 RCE and 5% filed 2 RCEs to prosecute successfully (USPTO 2012 RCE Outreach Statistics; RCE by Technology: Chemical/Biological). The results also show that it takes additional time and money for applicants to decide to abandon a patent which has received a *Myriad* citation, meaning greater sunk costs.

The results also indicate that often claims are being narrowed as a result of *Myriad*. To overcome *Myriad* rejections, applicants typically amend claims (71%); arguments from the applicant are sufficient only in 2% of cases. Another strategy is to cancel the specific claims affected (27%).

Considering the controversy following *Myriad* about the breadth of its impact ('surgical strike' v. sweeping impact), these empirical results are noteworthy. To summarise: (i) 85% of rejections including a *Myriad* citations concern products other than isolated DNA); (ii) 48.5% of patent applications receiving a *Myriad* rejection are nevertheless ultimately allowed—it's not necessarily 'game over'; (iii) but only 2% are allowed solely on the basis of argument (for the rest the affected claims are amended or cancelled to advance prosecution). It is interesting to consider how and why the *Myriad* case is having this effect on prosecution. To understand this, it is important to look closely at the final USPTO Examination Guidance (MPEP 2106, January 2018) on subject-matter eligibility.

The latest guidance attempts to reconcile case law (including *Myriad*, *Mayo* and *Alice*) into a generally applicable two-step framework for determining subject matter eligibility. This has been a contentious exercise. First (Step 1), the claimed invention must belong to one of the four statutory categories defined in 35 USC 101 (process, machine, manufacture, or composition of matter). Second (Step 2A), the claims should not be 'directed to' one of the judicially recognised exceptions (abstract ideas, laws of nature, or natural phenomena, including 'products of nature'), unless (Step 2B) they include additional limitations such that the claim as a whole amounts to 'significantly more' than the exception.

Looking more closely at the details of Step 2A in MPEP 2018 one sees that it casts a broader net than one might originally suspect. This helps explain why *Myriad* is being raised more often than 'surgical strike' commentators predicted. *First*,

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contrary to what the name might suggest, Step 2A does not restrict the 'product of nature' category to naturally-occurring products. Rather, it extends it to 'nature-based' products, which may be non-naturally occurring products. The test applied at Step 2A is whether the 'nature-based' product has 'markedly different characteristics' from any naturally occurring counterpart. Although the term 'nature-based product' is not explicitly defined, the examples in the guidance span a broad array of substances found in or derived from nature, as well as combinations and compositions comprising such substances (e.g., chemical compounds, foods, proteins, genetically modified organisms, nucleic acids, antibodies). *Second*, the markedly different test is not limited to DNA or nucleotide-based materials; it is abundantly clear that Examiners have been instructed to apply it to the wider natural world. *Third*, Examiners are instructed to apply Step 2A if a claim recites (i.e., sets forth or 'includes') a nature-based element, whether alone or in combination. This is enough for a claim to be considered directed to a product of nature for the purposes of Step 2A unless the nature-based product is 'markedly different' from any naturally occurring counterpart.

Looking more closely at Step 2B, one realizes that it offers an additional way to make a claim patentable. It helps explain why, notwithstanding the broadly cast net in step 2A, nature-based claims that are not markedly different are sometimes allowed with amendments. Even if a claim is found to be 'directed to' a 'product of nature' exception in Step 2A, it may still be found patent eligible under Step 2B if it passes the 'significantly more' threshold. Reaching either threshold is enough for the claim to be eligible subject matter.

Characteristics that have been found by the Courts to render a nature-based claim markedly different from nature include differences in: (1) biological or pharmacological functions or activities, (2) chemical and physical properties, (3) phenotypic characteristics (functional and structural), and (4) function and form, including chemical, genetic, or physical function and form (MPEP 2106).

In the case of *Myriad,* for example, isolated gDNA was found to be a 'product of nature', and thus ineligible for patent protection, because the mere isolation does not rise to the level of a markedly different characteristic. In contrast, the absence of the introns in cDNA was deemed a marked structural difference with respect to naturally occurring DNA, making it eligible for patent protection.

Case 14 also exemplifies several of these nuances in the MPEP guidance. The applicant originally applied for a pharmaceutical composition, a type of invention that the examiner said 'on its face' was patentable. However, the examiner rejected the claim because on it broadest reasonable interpretation it covered a fragment of a naturally-occurring protein and did not pass the significantly more threshold. The applicant tried a variety of legal arguments and claim amendments to overcome the rejection. Eventually, the applicant overcame the rejection by claiming a polypeptide consisting of a signal peptide linked to the protein fragment of interest. In addition, the granted claim states that the polypeptide both has a specific domain as well as *not* having another domain so it does not cover naturally-occurring polypeptides. These amendments allowed it to pass the markedly different test.

Conclusions

Immediately following the *Myriad* decision it was unclear whether the ruling was a 'narrowly crafted' decision that delivered a 'surgical strike' on isolated DNA patents while leaving the patent eligibility of all other claim products intact. Over the years that followed, patent attorneys and other readers of the MPEP guidance could see that the USPTO's view was that *Myriad* had broader impact for the purposes of patent examination, at least when interpreted alongside other Supreme Court decisions. Nevertheless, five years on, and prior to this empirical study, the *magnitude* of *Myriad's* impact on claims beyond isolated DNA was still unclear. There was also a lot of uncertainty about how the USPTO was applying MPEP guidance in actual examination practice. Our study helps shed light on these issues, in particular it shows: how many times *Myriad* has been cited by examiners; what happens to patents that receive *Myriad* rejections; what proportion of these applications cover subject matter beyond naturally-occurring DNA; what sorts of nature-based products are affected by these rejections; how many advance prosecution without the need for amendment; and the number of rounds of RCEs that take place before the applications are allowed or abandoned.

Overall, the finding that (in our sample) *Myriad* was used to justify 35 USC 101 rejections of non-DNA products in 85% of the cases may seem surprising. It is surprising in light of the Supreme Court's (apparent) attempts to contain its own decision, and also given the line of thinking from some leading legal scholars that *Myriad* was a 'narrowly crafted' decision. It also stands in stark contrast to the equivalent case in Australia, *D'Arcy v Myriad*[20]. However, the high percentage does make sense when considered in light of the last USPTO Examination

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Guidance (as implemented as part of the MPEP 2106) for nature-based products.

Under the new guidelines, the key to determining whether a nature-based product constitutes an ineligible 'product of nature' lies not in whether or not the product is naturally or non-naturally occurring, but rather in whether it possesses markedly different characteristics from its closest naturally occurring counterpart; or failing which, whether the product claim covers 'something significantly more'. Thus, even synthetically created products (and combinations of these) may be classified as ineligible 'products of nature' if they are neither markedly different nor offer 'significantly more' than the judicial exception.

Our results do not answer the question whether US subject matter eligibility laws need congressional reform. However they do show that *Myriad* is having a substantial impact beyond DNA and that innovators with nature-based claims need to be *prepared* because they are likely to encounter *Myriad* type rejections which will take additional time, resources and expertise to address. It will often be possible to deal with *Myriad* rejections, and to assist there are now workable, albeit highly complex and nuanced, protocols under the MPEP 2106. Further guidance on effective claim drafting is also emerging from academic work[19].

Congressional action might simplify the law, but care will need to be taken. Our results are a reminder of how an ostensibly crisp legal decision can have unexpected impacts well beyond what was in mind when the change was implemented.

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

Mateo Aboy, Cristina Crespo, Kathleen Liddell, Timo Minssen, Johnathon Liddicoat

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].

Mateo Aboy, Cristina Crespo, Kathleen Liddell, Johnathon Liddicoat are with Centre for Law, Medicine, and Life Sciences (LML), Faculty of Law, University of Cambridge, Cambridge, UK. Timo Minssen is with the Center for Advanced Studies in Biomedical Innovation Law (CeBIL), University of Copenhagen. Corresponding Author E-mail: ma608@cam.ac.uk

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.

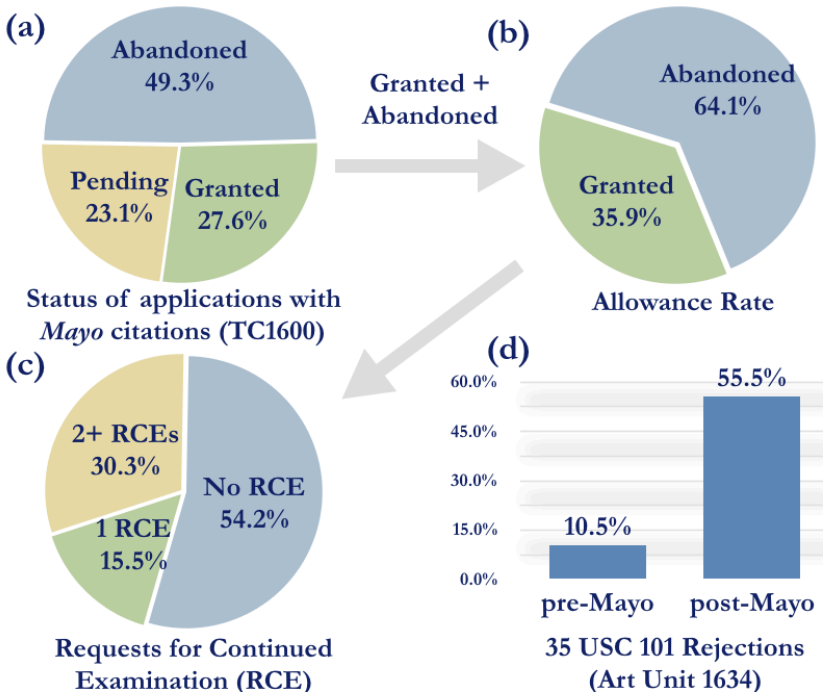

Figure 1 Study results showing that as of the 6th anniversary of *Mayo* (a) 49.3% of the patent applications were rejected/abandoned, 27.6% were granted after overcoming a 35 USC 101 *Mayo*-based rejection and 23.1% are still in active examination/prosecution; (b) the allowance rate for applications 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 amended. 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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One year after *Vanda,* are diagnostics patents transforming into methods of treatment to overcome *Mayo*-based rejections?

Mateo Aboy, Cristina Crespo, Kathleen Liddell, Neil Davey, John Liddicoat, Timo Minssen

On the first anniversary of Vanda, 1) to what extent have legal arguments and claim amendments based on Vanda been effective in overcoming 35 USC 101 Mayo-based rejections?; and 2) How are applicants transforming diagnostic patent claims into method of treatment claims to overcome Mayo-based subject matter eligibility rejections?

In 2012, the US Supreme Court issued its much anticipated decision in the case of *Mayo Collaborative Services v. Prometheus Laboratories, Inc* (*Mayo*). The Court concluded that a claim directed to a method of optimizing drug dosage for treatment of a disorder was patent-ineligible for being directed to a law of nature, namely "the correlations between thiopurine metabolite levels and the toxicity and efficacy of thiopurine drug dosages".[1] This decision had a significant impact on the threshold of patentability for life sciences inventions, in particular those involving methods of detection, diagnosis, and treatment.[2]

Mateo Aboy, Cristina Crespo, Kathleen Liddell, Neil Davey, Johnathon Liddicoat - Centre for Law, Medicine, and Life Sciences (LML), Faculty of Law, University of Cambridge, Cambridge, UK. Timo Minssen - Center for Advanced Studies in Biomedical Innovation Law (CeBIL), University of Copenhagen. Corresponding Author E-mail: ma608@cam.ac.uk

One of the outcomes of the *Mayo* ruling was a vaguely outlined two-step enquiry for determining patent subject matter eligibility. It came to be known as the *Mayo/Alice* test after it was refined in the subsequent US Supreme Court decision *Alice Corp v. CLS Bank (Alice)*. The test assesses eligibility by i) determining whether the claim is "directed to" a law of nature (Step A), and ii) if so, identifying whether there are additional non-routine or non-conventional elements so that the claim amounts to "significantly more" than the natural law (Step B). Far from settling the controversy surrounding patent subject matter eligibility, the application of the *Mayo/Alice* test has remained unclear and its results unpredictable.[2]

In an attempt to promote consistent patent examination practices, the USPTO issued several examination guidance documents, providing instructions on the application of this test[3]. This guidance included a list of subject matter eligibility examples in the life sciences. Example 29 set out the USPTO's interpretation of the *Mayo/Alice* test for methods of detection, diagnosis, and treatment, using a set of illustrative claims directed to the detection, diagnosis, and treatment of a fictitious disease called "Julitis". The guidance then explained how each of the illustrative claims fared against the *Mayo/Alice* test. The claim in Example 29 directed to a *method of detection* of the disease was considered eligible at Step A (not "directed to" a *law of nature*). In contrast, other claims directed to methods of diagnosis and treatment were deemed to be directed to natural laws, and were eligible or ineligible based on whether or not they satisfied Step B, the "significantly more" inquiry.[3]

It was against this background that, on April 13, 2018, the US Court of Appeals for the Federal Circuit decided V*anda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals (Vanda)*[4] The court held the claims at issue were not "directed to" a judicial exception, and therefore were patent eligible under 35 USC 101. The claims recited a method of

treatment of schizophrenia with iloperidone, where the drug dosage is adjusted based on the patient's genotype in order to lower the risk of side effects. Following this decision, on June 7, 2018, the Deputy Commissioner for Patent Examination Policy at the USPTO issued a memo to the Patent Examining Corps updating its guidance on how to evaluate the patent eligibility of method of treatment claims in light of *Vanda*.[5] The memo emphasized the Federal Circuit's conclusion that "the [*Vanda*] claim was not "directed to" the recited natural relationship between the patient's genotype and the risk of QTc prolongation," but to an application of that relationship. The memo stated that "methods of treatment" such as the one claimed in *Vanda* "apply" natural relationships, and are not "directed to" them. The key difference identified in the memo between the claim at issue in *Mayo* and the one in *Vanda* was that the *Mayo* claim focussed on a diagnostic test and simply involved a dosage adjustment as part of performing the diagnosis, whereas the *Vanda* claim recited the additional "administration step" of adjusted dosage as part of a direction to treat a particular disease. The memo also conceded that in light of the *Vanda* decision, the two-step *Mayo/Alice* test should have been applied differently in Example 29 (Julitis) of the USPTO guidance, but would nonetheless eventually yield the same eligibility results. More specifically, the method of treatment claims should have been considered patent eligible under Step A of the *Mayo/Alice* test.

Taken at face value, such developments could seem just a slight shift. But on closer inspection, the *Vanda* decision had the potential to be a significant development in the evolving domain of patent subject matter eligibility. Not only did it unequivocally clarify that methods of treatment could be patent eligible under 35 USC 101, but it made this determination at Step A of the *Mayo/Alice* test, thus meaning there was no need to conduct a Step B analysis, and, accordingly, no need to show non-routine or non-conventional steps in the treatment.

Seen in this light, the shift opened a new door for life sciences inventions affected by *Mayo*. But what lay across the threshold? We hypothesised in a recent empirical study examining the impact of the *Mayo* decision that, after *Vanda*, patent applicants with a rejection for a claim directed to a method of diagnosis might seek to amend the claim during prosecution into a method of treatment claim.[2] This could be done, for example, by including a drug administration step based on the results gathered from the diagnostic test.

To date, the empirical reality has not yet been investigated. As some have pointed out, such claims might create unattractive enforcement difficulties for diagnostic companies which generally do not administer drugs to patients[6]. There is also persistent legal uncertainty - will the view of the Federal Circuit in *Vanda* be upheld by the Supreme Court?

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 "*Vanda*" and "*West-Ward and Pharmaceuticals*"
  - 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 & *Vanda* Responses**
  - Selection of Examples: Illustrative examples of claim amendments (changes from application to patent grant)

Research Questions

In this paper we examine the effect of *Vanda* on patent prosecution. Specifically, we address the following research questions:

1) One year after *Vanda*, to what extent have legal arguments and claim amendments based on *Vanda* been effective in overcoming 35 USC 101 *Mayo*-based rejections?; and 2) How are applicants transforming diagnostic patent claims into method of treatment claims to overcome *Mayo*-based subject matter eligibility rejections?

These are significant and open questions for practice and law reform efforts. Their answers shed light into the joint impact of *Mayo* and *Vanda* for applicants attempting to obtain patent protection for inventions involving methods of diagnosis and methods of treatment.

The method to answer these questions (**Box 1**) is derived from similar methods used to analyze the impact of *Mayo* and *Myriad*.[2,7,8,9]

Results & Examples

We identified 407 patent cases where applicants cited *Vanda* in their response to a USPTO office action containing a 35 USC 101 rejection citing *Mayo*.

One year after Vanda, to what extent have legal arguments and claim amendments based on Vanda been effective in overcoming 35 USC 101 Mayo-based rejections?

At the one year anniversary of the *Vanda* decision, there were 19 patent applications for which there was a final disposition: 16 applications were allowed and issued as granted patents, and 3 were abandoned.

This represents an allowance rate of 84.2% for patent applications with a rejection citing *Mayo* where the applicant responded to the office action with arguments and amendments based on *Vanda,* and for which there is a final disposition. This figure is substantially higher than the allowance rate previously estimated for applications with a 35 USC 101 rejection citing *Mayo* (35.9%).[2] Additionally, in one of the three abandoned cases, the *Vanda* argument was successful in overcoming the *Mayo* rejection.

Accordingly, this strategy has been effective in overcoming the 35 USC 101 rejection in 89.5% of the cases for which there is a final disposition (granted patent issued or final abandonment). This sample was then manually reviewed to determine the nature of the legal arguments and claim amendments.

How are applicants transforming diagnostic patent claims into method of treatment claims to overcome Mayo-based subject matter eligibility rejections?

In order to answer this research question, a manual and expert review of the relevant USPTO file wrappers was conducted. In particular, the prosecution history for each of the granted patent applications was downloaded using the USPTO PAIR (Patent Application Information Retrieval) System. Each application was then analyzed and classified with

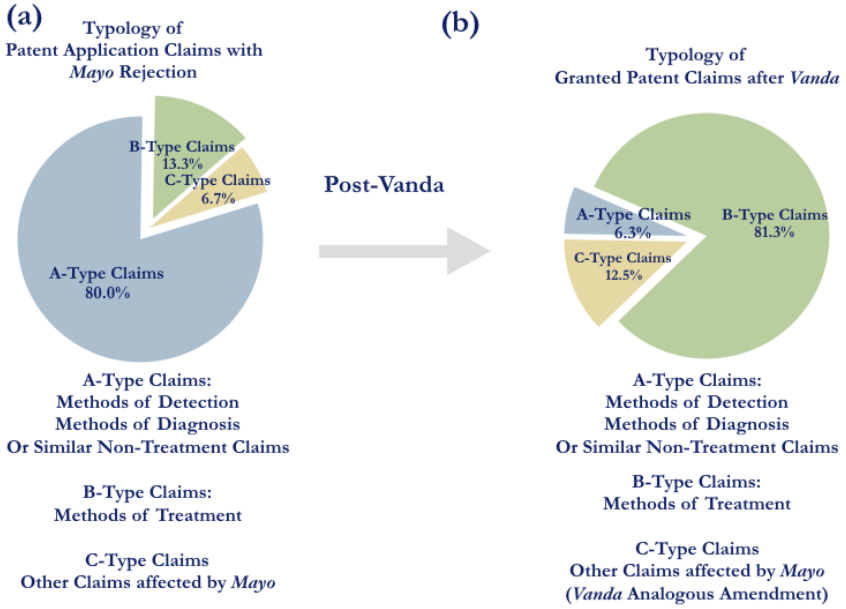

Figure 1 Study results. (**a**) Typology of patent applications claims with *Mayo* rejections. (**b**) Typology of granted patent claims after *Vanda.* The results indicate that a large proportion of diagnostic related claims are being amended to method of treatment claims to overcome *Mayo*-based rejections following the *Vanda* decision and corresponding USPTO examination guidance.

reference to the first claim receiving the 35 USC 101 rejection citing *Mayo* as either: A) a method of diagnosis (and other related claims that are not methods of treatment) or B) a method of treatment. **Fig. 1** shows the results of the classification of the original patent applications (Fig. 1.a) and the issued patents. (Fig.1.b). We found that 80% of the claims in the patent application sample were A-type (i.e., methods of diagnosis or related).

Next we used the prosecution histories to follow the fate of the central claim that sorted groups A and B. The majority of the claims in group A (diagnostic-related methods receiving a *Mayo*-based rejection) subsequently transformed into method of treatment claims in the final issued patent. In fact, in 81.3% of the granted/issued patents the claims were directed to methods of treatment (**Fig. 1**). The original claims in the patent applications, the corresponding claims in the granted patents, and our classification and prosecution notes are included in the **Supplementary Information**.

Notably, in all 16 cases, modifying claim language and citing the *Vanda* decision resulted in a reversal of the existing 35 USC 101 rejection (including a *Mayo* citation), with a *Notice of Allowance* in the following communication. Furthermore, in several of these cases, as shown in the prosecution notes (Supplementary Information), the applicants had already tried several times to persuade the examiner, but were unsuccessful until *Vanda* was cited in support of legal arguments and proposed claim amendments. With rather simple amendments that mirrored claim language in *Vanda*, the applicants finally found a way to effectively overcome the 35 USC 101 subject-matter eligibility rejection, where previously they had been unsuccessful.

Reviewing the applicants' arguments and claim language in the patent file wrappers, we observed three types of successful claim transformations. These included: (1) transforming non-method of treatment claims (e.g., diagnostics claims) to method

of treatment claims, (2) altering non-method of treatment claims to claims analogous to methods of treatment, and (3) modifying original method of treatment claims using *Vanda* to guide the claim drafting.

The first type of transformation (i.e., diagnostic-related claims transforming into method of treatment claims) was the most common, comprising 11 of the 16 analyzed granted patents.

For example, one applicant transformed the claimed invention from a "method for determining, in a patient presenting with hematuria, the level of risk for having urothelial cancer" to a "method for treating a patient for urothelial carcinonma" (case 4, Supplementary Information). In this case, while the examiner initially rejected the claimed invention based on *Mayo/Alice*, the simple amendment from a method of determining cancer risk to a method of treatment made the claim allowable based on *Vanda*.

In another example the applicant changed the claim language from a "method for diagnosing Systemic Lupus Erythematosus (SLE)" to a "method of treating Systemic Lupus Erythematosus (SLE) in a human subject identified as negative for SLE" (case 7, Supplementary Information). The initial *Mayo*-based rejection (i.e. that identifying SLE disease risk based on various antibody levels is merely a naturally occurring correlation) was overcome by transforming the diagnosis claim into a treatment one, in accordance with the USPTO *Vanda* guidance. Notably, previous arguments and amendments were unsuccessful in several previous responses to office actions.

Finally, while some granted applications did not explicitly mention a "method of treatment," they included an "administration step" following the *Vanda* memo, which passed Step A of the two-step eligibility test. For example, an applicant changed a three-step method of diagnosing a subject with a certain disorder to a six-step method of determining prognosis in a subject diagnosed with the disorder, in which the fifth step comprised "administering to the subject with an indication of unfavorable prognosis a treatment" (case 11, Supplementary Information). The examiner was persuaded that this active administration of treatment step appropriately applied a law of nature/natural phenomenon, and was therefore patent eligible under *Vanda* (despite being recited at a high level of generality).

There were three examples of the second type of transformation (i.e., altering non-method of treatment claims to claims analogous to methods of treatment). These demonstrated that some examiners were open to claims that were analogous to method of treatment claims. For instance, an applicant modified a "method of identifying a soybean plant that comprises a genotype associated with an stem canker resistance phenotype" to a "method of producing a population of soybean plants that comprises a genotype associated with a stem canker resistance phenotype" through the crossing of selected soybean plants (case 12, Supplementary Information). The examiner found the analogy between the "crossing step" and a *Vanda*-type "administration step" persuasive, and allowed the patent on these grounds.

In another case, an applicant altered a method for diagnosing propensity to CCLR in a dog to a method for breeding a dog, in which the "breeding step" to reduce injury propensity was found to mirror the administration of treatment step in *Vanda* (case 14, Supplementary Information).

The third type of transformation (i.e., modifying original method of treatment claims using *Vanda* to guide the claim drafting) was illustrated by two granted patents. In these prosecution files, the original claims referred to methods of treatment, but the applications were not allowed until after the *Vanda* ruling. An applicant in one example repeatedly modified a method of treating Dengue Hemorrhagic Fever to further increase specificity (narrowing the scope of the claim), but the patent was only allowed after the applicant supplied arguments written after the *Vanda* decision (case 15, Supplementary Information). In these examples, it is possible that the claims in their original form would have been found eligible if the claims and related legal arguments had been made after the *Vanda* guidance.

In summary, in the cohort of 16 patents that we manually reviewed (patent applications with a rejection citing *Mayo* where the applicant responded to the office action with arguments and amendments based on *Vanda,* and for which there is a final disposition), there was clear evidence that most applicants had actively changed their claim type and language in response to *Vanda* to make their patents allowable. It was also evident that examiners had not been ready to accept these arguments prior to *Vanda,* but clearly became receptive to them after the USPTO *Vanda Examination Memo.*

Pending Applications

From the 407 patent cases we found where applicants cited *Vanda* in their response to a USPTO office action containing a 35 USC 101 *Mayo*-based rejection, we analyzed 19 following inclusion criteria that required the patent application to have been issued or abandoned by the 1 year anniversary of the *Vanda* decision. Accordingly, there is a sizeable number of applications (n=388)

where applicants cited *Vanda* in response to a *Mayo*-rejection that are still patent pending. This is to be expected given standard patent prosecution timelines (e.g., up to 6 months between office actions and applicant responses; additional time for examiner to consider arguments and issue the next communication; and 3-6 months from Notice of Allowance to patent issuance).

Within the pending applications sample, we identified 35 patent applications that had already received a *Notice of Allowance* (NOAs) one year post-*Vanda* (but had not yet issued). Of these, 33 can be classified using the same claim transformation typology as the original sample: 17 transformed to method of treatment claims from diagnostics or other non-treatment types (Type 1 transformation), 13 were originally methods of treatment which were allowed after *Vanda* (Type 3 transformations), and 3 transformed from other types of non-treatment claims to claims analogous to a method of treatment claim based on *Vanda* (Type 2 transformations).

Discussion

Vanda*'s impact on patent prosecution*

This research confirms our earlier hypothesis. Following the Federal Circuit's decision in *Vanda*, as interpreted by the USPTO, patent applicants with rejected methods of diagnosis have sought to transform these into patent eligible claims via claim amendments – without having to satisfy Step B in the *Mayo/Alice* test (showing that the claim amounts to *significantly more* than a natural law). Averaging more than one per month in the year since *Vanda*, rather than claim a method of diagnosis, patent drafters are amending to method of treatment (or analogous) claims to avoid or overcome *Mayo*-based rejections. This mercurial change, particularly its strikingly positive and immediate impact on patent examiners, has an aura of legal 'magic' about it.

This has provoked considerable controversy and debates about whether *Vanda* was a good decision. Parties on both sides of the debate claim that the *Vanda* decision stands to affect "untold numbers of future patents"[10] hinting at the idea that large numbers of patentees could be affected with major socio-economic ramifications. Our research identified 16 patents in 12 months that were issued pursuant to *Vanda* but which otherwise might have been rejected pursuant to *Mayo* (and 35 additional allowed applications). If *Vanda* is overruled, these sorts of claims (method of diagnosis and method of treatment claims) would be unenforceable unless the claim includes 'significantly more' (Step B *Mayo/Alice*). At this point, we do not think this is a large number of patentees. Nevertheless, there are important policy issues at stake.

Diagnostic Companies and Divided Infringement

Holman argued that the *Vanda* solution is inadequate for diagnostic companies facing *Mayo/Alice* rejections, because *Vanda*-type claims (for example drafted as a method of medical treatment claim or including a drug administration step) may be difficult for them to enforce[6] against a defendant diagnostic company that solely provides a diagnostic test and leaves drug administration to other parties[11]. If the method of treatment or administration step cannot be attributed to the defendant diagnostic company, then the company will not have performed all the steps in the patented method and thus is not liable for infringement. This type of scenario is commonly known as divided infringement. Holman argues that challenges remain for diagnostic companies dealing with divided infringement even after the en banc US Federal Circuit reformulated the test of divided infringement law in *Akamai*[12]. We agree that arguably the *Mayo/Alice* precedent, even post-*Vanda*, overly hampers diagnostic companies with business models devoted to diagnostic testing. A substantial number of companies operate in the molecular and tissue testing diagnostics space rather than selling drugs with companion diagnostic tests. But in our view, the legal position is not necessarily as bleak as Holman suggests, and our results in relation to *Vanda* are consistent with this.

Some optimism comes from *Akamai* since the alleged infringer can be liable if a step in a method claim is performed by another actor when the alleged infringer 'conditions … receipt of a benefit upon performance of a step…of a patented method and establishes the manner or timing of that performance.' Potentially a *Vanda*-type claim could be enforced against a defendant diagnostic company (when another actor performs the drug administration step) when the manifest purpose of the diagnostic test is to determine if a drug should be administered. The defendant company arguably creates an *Akamai* scenario where it conditions receipt of a benefit of the test (the effect of the administered drug for the patient) on a third party administering the drug. Arguably, the defendant diagnostic company also establishes the timing of the administration (after receiving the test results), and perhaps even the manner of the administration, if, for instance, dosage is also determined by the test.

Our research is consistent with a degree of optimism. Notwithstanding on-going debates about enforcing *Vanda*-type claims in situations of divided infringement, a significant number of organizations that choose to use the *Vanda* prosecution strategy are

diagnostic companies whose competitors are likely to be other diagnostic companies. It remains an open question what proportion of diagnostic companies do not use *Vanda*, perhaps for the reasons identified by Holman. This is not necessarily highly problematic. They could instead seek to draft claims that meet Step B. In this regard it is important to recall empirical studies that indicate that *Mayo* did not sound the death knell for sustainable business models for diagnostics. Patent prosecution is more drawn out and uncertain in the absence of a *Vanda* "administration step," and tends to result in narrower patents with potential reduced value, but method of diagnosis patents are still issued (when they pass Step B) and diagnostic companies have continued to invest in and develop diagnostic tests.

Legal Uncertainty

An issue for the future is the legal uncertainty surrounding *Vanda*, and indeed the future of the *Mayo/Alice* test. Will these legal tests remain the cornerstone of patent eligiblity? Three sources of unpredictability include the Supreme Court certiorari proceedings currently under way, review of §101 also afoot within the US Congress and Senate, and future refinement of the *Vanda* approach by lower courts or the USPTO. For example, in the recent *INO Therapeutics v. Praxair Distrib. Inc.*, 2018-1019 (Fed. Cir. Aug. 27, 2019) (Nonprecedential), the Majority held that the *INO* claimed method of treatment was ineligible under 35 USC 101. It differentiated the *INO* claims with those in *Vanda* because in this case *iNO* treatment *is withheld* if the patient is identified as subject to the increased risk (i.e., the invention involves the *non-administration* of the treatment). Judge Newman (the most senior judged on the CAFC) dissented.

The US Supreme Court has been asked to overrule the Federal Circuit's approach in *Vanda*. It may decide the matter purely with reference to the meaning it thinks should be ascribed to the words "directed to" within the prevailing *Mayo/Alice* tests. On the other hand, now constituted by justices different from Chief Justice Breyer's court in *Mayo*, it might take a bolder approach and revisit *Mayo*, perhaps recasting it so that the *Mayo/Alice* test is significantly changed, perhaps even abandoned.

There is considerable debate whether - assuming the law is unsatisfactory - the root of the problem is *Mayo/Alice*, or the legal refinements in cases such as *Vanda*. A view put forward in the certiorari proceedings is that the problem rests with *Vanda* because it introduces an unsatisfactory gloss on the *Mayo* exception. According to Counsel for Hikma, and Professor Sarnoff et al (Amici) a method of medical treatment claim is no different from a claim that claims a law of nature with general instructions "to apply it" unless the claim includes non-conventional steps in addition to the newly discovered medical correlation[10].

Responding to the view that *Mayo*, *Alice* and *Myriad* are the source of the problem, a group of senators, headed by Sen. Thom Tillis (R-NC) and Sen. Chris Coons (D-Del.), announced a draft bill in May 2019 which would bypass the judicially created exceptions to subject matter eligibility including the Supreme Court decisions in *Mayo*, *Myriad* and *Alice*. The bill has received mixed reactions ranging from strong support to harsh criticism, as evidenced by the June hearings of the US Senate Judiciary Subcommittee on Intellectual Property. Most recently, at the end of July, a group of law professors, former chief judges of the US Federal Circuit, and former heads of the USPTO sent a letter to the IP Committee in support of the bill. In contrast, the American Civil Liberties Union (ACLU) and other medical, health, and civil rights organizations have expressed vehement opposition.

Comparison with Europe

Vanda focuses legal minds on the meaning of the words "directed to" in the *Mayo/Alice* test. Is a patent claim "directed to" a law of nature (Step A) if it claims an application of the natural law in the format of "a method of medical treatment." Is this a genuinely 'practical application' such that the patent claim is no longer "directed to" a law of nature but actually "directed to" a patent-eligible invention by integrating the laws of nature into an inventive concept? The claim still recites a law of nature, but is it "directed to" that law? What about situations where the claim includes nothing additional apart from well-understood, routine, conventional activity?

This sort of analysis has a sense of hair-splitting. The European approach avoids the semantic meaning of the words "directed to", and might therefore hold some appeal. However, it too has become mired in controversial micro-analysis of words. Under the European Patent Convention claims shall not be granted to "discoveries or scientific theories …as such"[13]. The qualifier 'as such' is open to multiple meanings - just like the qualifier 'directed to'. Not without controversy, EPC case law has taken the route that excludes claims only if they pertain *solely* to a discovery or scientific theory. Claims with a 'technical' element or technical application included in the claim are eligible even when the core leap forward was the scientific discovery or theory.

This can seem more cut-and-dry, less demanding, and helpful for legal certainty. But the European approach has its own controversies

and additional considerations. For example, defining the metes and bounds of technicality, technical effect, technical character and their relation to other patentability criteria remains one of the most disputed issues in European patent law[14]. The current situation is that it is relatively easy for competent draftspersons to draft a token technical element. Some think this is sensible because the key issue then becomes whether the claim is novel and inventive. Others think the European approach fails to protect the proper spirit of the EPC exclusion and allows claims which are, in essence, natural correlations.

According to EPO case law, if the claim includes any kind of technical contribution it is elevated from a claim that claims a discovery or scientific theory as such to a claim that is patent eligible. In other words, the 'as such' element means that if the claim pertains to *no more* than a *discovery* or s*cientific theory* it is patent ineligible. This is less demanding than Step B of the *Mayo/Alice* test, and less semantic than the words 'directed to'. In Europe, the technical element – which shifts the claim from an ineligible discovery to eligible subject matter– can include the process of diagnosis if the process includes collection of physical specimens, kits or platforms. This is quite unlike *Mayo/Alice* and *Vanda*, where the process of diagnosis is considered a mere instruction to apply a natural phenomenon (so the claim is still 'directed to' the natural phenomenon) and insufficient to change a patent ineligible claim to an eligible one. In Europe, the technical element can also be achieved by focusing on a new use of a drug, akin to a method of medical treatment and analogous to *Vanda*. For completeness, it is important to add that in Europe, methods of treatment and diagnostic methods practiced "on" the human body are excluded from European patent protection by a separate provision of patent law, but this provision does not apply to in vitro diagnosis nor products, in particular substances or compositions, for use in any of these methods (EPC Art 53(c)).

Conclusion

These and other issues show there is much to be considered in the future. In the short term, if *Vanda* is upheld, and *certiorari* denied, patent attorneys with pending patent applications receiving *Mayo* rejections would do well to consider whether amendment to a method of medical treatment claim might assist their client. In doing so, our research indicates they are likely to have more and/or swifter success persuading examiners if they link their arguments to the USPTO Examination guidance rather than case law alone. Meanwhile patent law scholars might like to ponder whether *Vanda* is another example of the pre-eminence of draftsmanship notwithstanding repeated calls from the Supreme Court to avoid this.[15]

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How does emerging patent case law in the US and Europe affect precision medicine?

Mateo Aboy, Kathleen Liddell, Cristina Crespo, Glenn Cohen, Johnathon Liddicoat, Sara Gerke & Timo Minssen

An analysis of how today's patent law will affect tomorrow's innovation in three areas of precision medicine: (1) biomarkers and nature-based products; (2) diagnostics; and (3) algorithms, big data, and AI.

No topic in medicine garners more interest today than precision medicine, with its goal of better tailoring treatment to patient needs. It is not only patients who stand to benefit from better diagnosis, prognosis and treatment, but also the organizations investing in its research and development[1]. According to one recent estimate, the global precision medicine market accounted for $43.59 billion in 2016 and is expected to reach $141.70 billion by 2026 with a compound annual growth rate of 11.23% between 2017 and 2026[2].

The commercial viability, and hence development, of precision medicine depends in large part on the intellectual property framework that applies to its various forms. In this paper we examine recent patent law decisions in the U.S. and Europe and their implications for the future of three areas of precision medicine: (1) biomarkers and nature-based products; (2) diagnostics; and (3) algorithms and AI.

Mateo Aboy, Cristina Crespo, Kathleen Liddell, Johnathon Liddicoat - Centre for Law, Medicine, and Life Sciences (LML), Faculty of Law, University of Cambridge, Cambridge, UK. Timo Minssen - Center for Advanced Studies in Biomedical Innovation Law (CeBIL), University of Copenhagen. Glenn Cohen and Sara Gerke - Harvard Law School. Corresponding Author E-mail: ma608@cam.ac.uk

Understanding the three "Precision Medicine" Categories

Before discussing how patent law treats these categories, it is useful to be more specific about each.

A biomarker is "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers" (FDA/NIH BEST)[3]. Examples include a genetic sequence or a hormone level. With suitable knowledge, comparing a biomarker with a baseline measurement enables one to predict or diagnose a disease state, or choose a better treatment or drug dosage. Identifying biomarkers relevant at a population level is the first challenge, but even more difficult is to validate biomarkers that are sufficiently accurate and precise to be clinically useful in individual patients. To date, a large number of potential biomarkers have been identified but very few have been qualified by the FDA for use in clinical trials or entered the clinic as diagnostic tools[4]. Considerable R&D is still required, with associated expense and risk. The *FDA/NIH BEST (Biomarkers, EndpointS, and other Tools) Resource* provides examples for each category of biomarkers, including diagnostic, monitoring, pharmacodynamic/response, predictive, and prognostic biomarkers[3]. As an example, the Oncotype DX is a test based on a biomarker which assists doctors in determining proper cancer treatment[5].

Precision medicine also builds on understandings of relationships and correlations. This requires domain knowledge and judgement of the various inputs, outputs, and their interaction. To develop clinical-grade biomarkers based on relationships and correlations requires significant R&D, as well as scientific validation and regulatory approval or qualification. Natural relationships, correlations and algorithms can be used to develop *digital* biomarkers from quantifiable physiological or behavioral data collected by means of digital devices such as portables, smartphones, wearables, implantables or digestibles to explain, guide or predict health-related outcomes. One example involves measurement of gait and balance using wearable technologies to develop monitoring, prognostic or therapy response biomarkers, which can be used to assess

progression of neurological dysfunction in Parkinson's disease and other movement disorders[6].

Algorithms, big data, and artificial intelligence (AI) in medicine can help examine vast amounts of health data, such as the results of diagnostic tests, physiologic signals, or patient biomarkers, in order to make predictions and recommendations tailored to the characteristics of a patient. Some AI operates using "black box" algorithms, in the sense that some aspects of machine-learning are not explicitly articulated, because AI results can be generated based on implicit correlations within the data, as opposed to following a sequence of specified steps or using fundamental, well-understood correlations based on domain knowledge. In truth it is better to think of this as a spectrum of "opacity" of the "box"[7]. Medical correlations often reflect complex interactions of natural relationships at an individual or group level, rather than universal natural laws such as $E=mc^2$. For instance, the Oncotype DX test is considerably more specific and correlates various biomarkers to create a cancer Recurrence Score[5].

Starting first with the US followed by Europe, we examine how patent law developments in the areas of nature-based products (product biomarkers), correlations, algorithms, and their underlying logic affect each of these areas of precision medicine.

Emerging US Case Law

A. Biomarkers & Correlations

In 2012, the US Supreme Court held in *Mayo Collaborative Services v Prometheus Laboratories (Mayo)* that Prometheus' patents set forth laws of nature and were therefore not patentable[8]. The patent claim at issue involved the relationship between metabolite concentrations in blood and medical predictions whether a dosage of a thiopurine drug will prove ineffective or cause harm. A year later, in 2013, the US Supreme Court held in *AMP v Myriad Genetics* (*Myriad*) that "[a] naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring"[9].

These two US decisions have been controversial, and criticised by many commentators for undermining innovation incentives in precision medicine[10,11]. Some groups have been seeking Congressional action[12]. As of now, the boundaries of patent eligibility remain those set by the Supreme Court, which have been interpreted and applied by the US patent office (USPTO) and lower courts. To understand fully the implications of the Supreme Court cases for precision medicine, one must take account of the nuance in the judges' reasoning.

The Court held in *Mayo* 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"[8]. Thus in order to transform an ineligible 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." The patent must limit its reach to a particular, inventive application of the law. The Court's opinion was that, besides simply describing the natural relationship between concentrations of thiopurine metabolites and optimum dosage, Prometheus' patent claim did not go beyond "well-understood, routine, conventional activity, previously engaged in by those in the field"[8] (because clinicians had previously tailored dosages of thiopurine drugs for individual patients). In essence, the claims were directed to the natural law itself.

B. Algorithms

Turning to the patentability of algorithms and computer-implemented inventions, the US Supreme Court held in *Alice Corp v CLS Bank International* (*Alice*) in 2014 that "merely requiring generic computer implementation fails to transform [an] abstract idea into a patent-eligible invention"[13]. The patent claimed a method for exchanging financial obligations (the process of financial settlement) using a third-party intermediary, and the computer system to carry out the method. The Supreme Court held the patent was ineligible, applying the two-step test developed in *Mayo*. First, determine whether the claims are 'directed to' an abstract idea (Step 2A). If so, consider whether additional claim elements which, individually or as an ordered combination, amount to 'significantly more' than the abstract idea (Step 2B). That is, ascertain the presence of an 'inventive concept' which transforms the abstract idea into a patent-eligible invention. The Court concluded the claims were directed to the abstract idea of using a neutral intermediary to reduce risk during the settlement process, and that merely implementing the idea through a computer did not add anything of substance to the claims that would amount to an 'inventive concept.'

Alice followed several earlier cases, including *Bilski v Kappos*[14] where the abstract idea of risk hedging, a "fundamental economic practice," was ineligible and using a computer to implement the algorithm did not change that.

C. Underlying Concern

In all of these cases the Supreme Court's concern was to exclude patent applications that unduly 'pre-

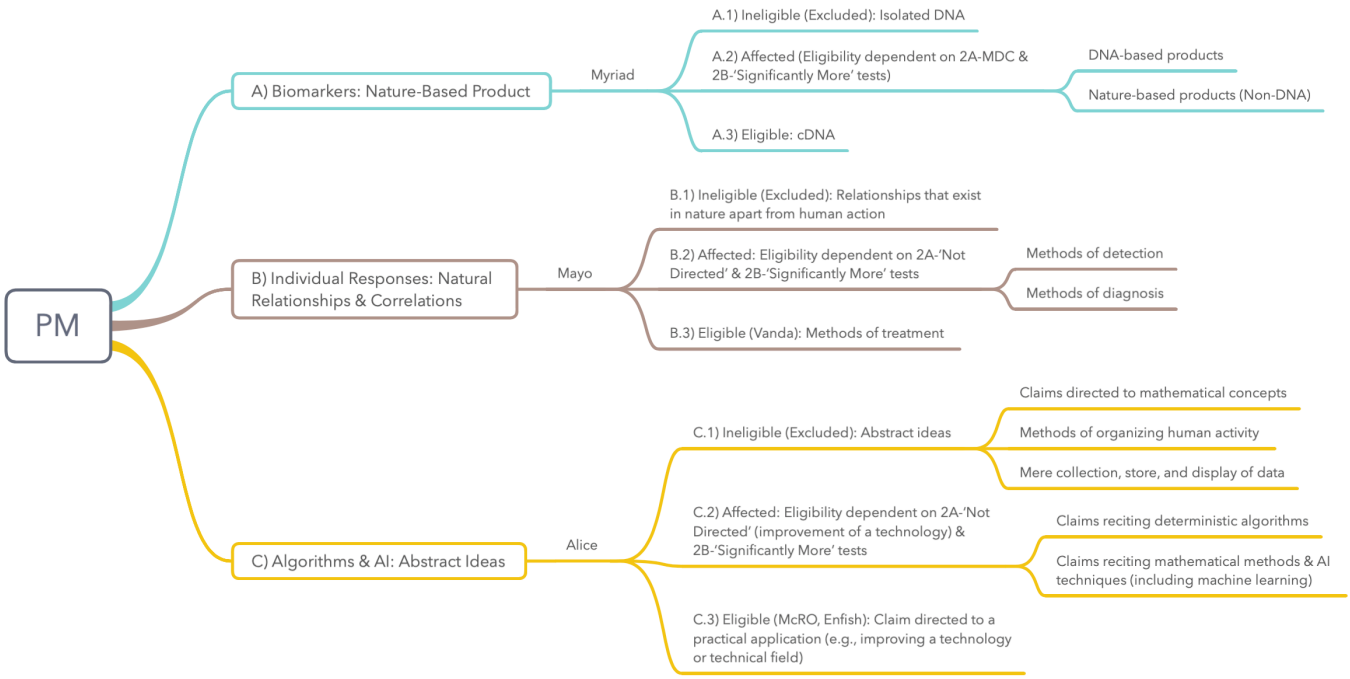

Figure 1 Application and impact of emergent patent case law to different categories of precision medicine, including biomarkers, diagnostics, and algorithms/AI.

empt' future innovation by effectively tying up the underlying 'abstract idea', 'natural law' or 'natural phenomena' (including products of nature), albeit for the limited duration of the patent. But the Court made clear that an invention is not ineligible for patent protection *simply* for involving an abstract concept or a natural law. Applications of an abstract concept (or natural phenomena) "to a new and useful end"[13] or to solve a technological problem, even in "conventional industry practice"[15], are patent eligible.

This nuance can also be seen in an earlier case involving medical device technology, *In re Abele*[16]. The patent concerned the invention of a tomographic scanner. Some claims were found ineligible as they were directed to the algorithm *per se* ("the algorithm is neither explicitly nor implicitly applied to any certain process"[16]), whereas other claims were eligible as they were directed to the technical application of the algorithm, resulting in "an improved CAT-scan process."[16] The improvement resided "in the application of a mathematical formula within the context of a process which encompasses significantly more than the algorithm alone."[16]

The Supreme Court's view is that pre- or post-solution activities included in a claim (i.e., activities incidental, nominal or tangential to the primary process or product) should be scrutinised carefully to assess whether the claims genuinely amount to 'significantly more' than ineligible subject matter. After all, a "competent draftsman could attach some form of post-solution activity to almost any [abstract idea or natural phenomenon]"(MPEP §2016.05(g)). Crafty drafting should not be allowed to mask pre-emptive claims. Otherwise, for instance, extra-solution activity such as data gathering before performing a clinical test, or determining the level of a biomarker in the blood[8], or assessing the meaning of a biological test measurement could mask an unduly pre-emptive claim and allow the patent to tie up a natural relationship.

Impact on Precision Medicine

The cases of *Myriad*, *Mayo*, and *Alice* affect the patent eligibility of all three broad categories of inventions in precision medicine, namely those involving: 1) biomarkers and nature-based products (*Myriad*), 2) relationships and correlations (*Mayo*), and 3) algorithms and AI (*Alice*).

Figure 1 shows a summary of how these US cases apply to the three categories of precision medicine, as well as the patent eligibility status of various types of inventions within each of these groups.

Notably, patent subject-matter eligibility (35 USC §101) is just one of several criteria that the patent application must meet. The invention must also be novel (35

USC §102), non-obvious (35 USC §103) and appropriately disclosed (35 USC §112). While the initial requirement of subject-matter eligibility for precision medicine inventions is the focus of this article, inventions that meet this hurdle can still be rejected based on other criteria, such as not being novel or non-obvious in light of prior art.

In the immediate aftermath of *Myriad, Mayo and Alice* there was a high degree of uncertainty as to their impact on precision medicine. For example, would *Myriad* affect biomarker patents other than isolated DNA? Given that precision medicine can rely on individual responses to particular treatment, would *Mayo*'s exclusion of relationships and correlations that exist "in principle apart from human action" drastically limit patent protection in this field? Would the abstract idea exclusion developed in *Alice* affect the eligibility of algorithms for precision medicine?

Having the benefit of the latest USPTO Examination Guidance (MPEP 2106 and January 2019 Examination Guidance Update[17]), additional decided cases, and empirical studies[18,19,20,21], it is timely to assess the current state of patent eligibility for precision medicine.

A) Biomarkers & Nature-Based Products

In the case of *Myriad*, although the decision was predicted by some legal scholars to be a 'surgical strike', merely excluding isolated genomic DNA from patent eligibility[22] (**Figure 1** Type A.1), the case has had broader impact[20]. In fact, our prior research estimated that when *Myriad* was cited by examiners as grounds for a 35 USC 101 rejection, 85% of the cases concern nature-based product patent claims beyond isolated DNA[20]. The explanation is that, over time, the USPTO and lower courts have interpreted *Myriad* as a general product of nature case and reconciled it with the two-step test adopted in *Mayo/Alice*. Thus the product of nature exclusion presently affects patent claims that 'recite' a nature-based product (Step A), except if the nature-based product is 'markedly different' from a naturally-occurring product or if the claim includes 'significantly more' (Step B). Accordingly, the product of nature exclusion narrows product claims in relation to a wide variety of nature-based biomarkers (e.g., proteins, RNA, hormones)[20].

Our previous research also found that it has not been easy to draft around *Myriad*. In more than 70% of the patent applications examined in the 3 years after *Myriad,* applicants responded by *cancelling* the isolated DNA claims or *abandoning* their applications[19].

However, although a broad variety of precision medicine biomarkers are harder to patent since *Myriad*, it is not impossible. The Supreme Court confirmed that cDNA is patentable (provided it is long enough to be structurally different from naturally occurring gDNA) (**Figure 1** type A.3). Furthermore, our previous research indicates that approximately 48% of patent applications have managed to advance to allowance after receiving a *Myriad*-based rejection[19]. Besides claiming cDNA, there are at least eight types of amendments that have transformed ineligible subject matter into patent eligible claims (passing the 'markedly different characteristics' or 'significantly more' tests (**Figure 1** type A.2)[19].

B) Individual Responses & Methods of Diagnosis: Natural Relationships & Correlations

The trio of Supreme Court cases has had a particularly strong impact on precision medicine inventions that rely on relationships and correlations to diagnose or target treatment to patients. But the proverbial pendulum appears to be swinging back. How far is presently unclear.

To appreciate the impact, it is useful to sub-categorize invention claims as follows: 1) methods directed to the underlying relationships of human response (these are ineligible), 2) methods of detection or methods of diagnosis (affected by the case law; eligibility depends on closer analysis of claims), and 3) methods of treatment (eligible*)* (**Figure 1** category **B)**. These sub-categories concern patent claims directed at methods, but may also involve, *inter alia,* diagnostic, prognostic, and predictive biomarkers.

As mentioned, in *Mayo,* the US Supreme Court rejected the eligibility of a method to optimize the dosage of a thiopurine drug relying on a relationship between measured levels of thiopurine metabolite and patient response. The Court held the relationship exists in principle without human action (**Figure 1** type B.1).

The Court of Appeals for the Federal Circuit reached a similar conclusion in *Sequenom* in 2015[23]. A patent concerning non-invasive pre-natal testing, with potentially significant implications for screening embryos and foetuses for genetic conditions[24], was ineligible for US patent protection. The court concluded the patent set forth a platform for detecting the natural phenomenon of fetal DNA circulating in the mother's blood and did not offer significantly more—only non-inventive applications of circulating fetal DNA in diagnosing well-known genetic disorders such as Down's Syndrome (**Figure 1** type B.1).

A clear sign of a less restrictive interpretation of *Mayo* emerged with the decision of the Court of Appeals for the 2018 Federal Circuit in *Vanda*[25]. The softening in the

Court's decision hinged on the patent claim being interpreted as a method of treatment claim (**Figure 1** type B.3). The Court held that method of treatment claims involve human intervention; accordingly the invention is not directed to a natural relationship itself and consequently is not directed to an ineligible law of nature or natural phenomena.

The reasoning in *Vanda* indicated it will be significantly easier to prosecute a method of treatment claim than methods of detection or diagnosis, even though to some extent all involve natural relationships between the human body and something else. Since a method of treatment claim is *prima facie* held 'not directed to' an ineligible law of nature, the patent applicant does not have to marshal arguments to show that the application involves 'significantly more' than a law of nature. Drafting the claim as a method of medical treatment claim circumvents Step 2 of the *Mayo* test.

In contrast, precision medicine innovations that hinge on a method of detection or diagnosis typically have to contend with step 2 of the *Mayo/Alice* test (**Figure 1** type B.2). Of these, methods of detection generally have better odds of satisfying Steps 2A or 2B of the *Mayo/Alice* test, provided they employ unconventional/non-routine techniques.

Inventions with claims merely directed to methods of diagnosis (i.e., those without further human action in the form of a treatment) are likely the most difficult to patent post-*Mayo*.

While the *Mayo* decision has been highly controversial, with some arguing it would be disastrous for meritorious inventions in the life sciences, biotech and precision medicine[26,27], recent empirical studies show that in approximately 35% of the cases applicants have been able to overcome *Mayo*-based rejections[21]. It should be noted, however, that since *Mayo* there has a been a high degree of uncertainty regarding eligible and ineligible inventions. As a consequence, patent applications in the field of precision medicine are rejected at a relatively high frequency for failing to satisfy the patent eligibility test of 35 USC §101. In previous research we estimated an increase in the numbers of patent applications receiving a §101 rejection rising from 10.5% to 55% in the 6 years following *Mayo* (Art Unit 1634). We also found that there was a significant increase in the time and expense involved in prosecuting a precision medicine patent[21]. After *Vanda*, it is expected that, where possible, patent attorneys may use claim constructions that more closely approximate methods of treatment (**Figure 1** type B.3), and the rejection rate where examiners cite §101 with *Mayo* will subside to some extent.

In summary, it is still possible (provided claims are carefully drafted and/or constructed as method of treatment claims) but currently challenging, to obtain broad US patent protection for precision medicine inventions that rely on relationships and correlations.

C) Algorithms and AI

While *Alice* is often considered a decision that affects primarily the patentability of business methods and generic abstract ideas, the decision also affects computer-implemented inventions in general, and therefore precision medicine inventions based on algorithms and AI.

It is possible to distinguish three types of precision medicine inventions in this category, namely, those that have been explicitly excluded from patent protection, those which are not categorically excluded but affected by legal developments, and those whose eligibility has been established by recent case law or specific examination guidance (**Figure 1** category C).

Within the ineligible category (**Figure 1** type C.1), one finds inventions directed to mathematical algorithms and mathematical concepts. It is also likely that precision medicine inventions directed to methods of patient engagement (participative care) may be ineligible, on the basis that they are methods of organizing human activity or concepts related to managing human behavior (MPEP 2106). Similarly, expert medical systems applying specialist domain knowledge to diagnose like a human doctor may be deemed ineligible as "concepts relating to organizing or analyzing information *in a way that can be performed mentally* or *is analogous to human mental work*" (MPEP 2106). This exclusion also applies to precision medicine inventions claimed at a high level of generality, such as the method for diagnosing an abnormal condition by performing clinical tests and analyzing the results *in In re Grams*[28].

A significant proportion of precision medicine inventions affected by *Alice* (**Figure 1** type C.2) are based on algorithms that analyze patient data (including physiological signals) in order to develop biomarkers which can be used to diagnose or guide individualized treatment. Such algorithms can be deterministic, statistical, or based on artificial intelligence techniques. While all these algorithms are fundamentally different from a technical standpoint, most of them make use of mathematical equations, mathematical algorithms, and digital signal processing in some form. Accordingly, it is often the

case that examiners conservatively issue §101 *Alice*-based rejections on the basis that the claimed invention 'recites' mathematics and algorithms. Furthermore, the inventive concept often lies in the algorithm itself and not the hardware (e.g., a new algorithm that can be implemented in any computing device such as a smartphone and processes physiologic signals acquired using standard sensors).

The key to eligibility for these inventions lies in whether the claims satisfy the *Mayo/Alice* test. Recognizing the level of legal uncertainty surrounding this framework, in its most recent update, the USPTO amended the test to help identify ineligible claims more accurately and consistently *(USPTO Eligibility Guidance, Jan 2019 Update*[17]*)*. Step 2A, which consists of identifying whether a claim is 'directed to' an abstract idea, now takes a two-prong approach, first asking whether the claim 'recites' an abstract idea (e.g., mathematical concept, method of organising human activity, or mental process), and if so, whether the claim as a whole incorporates the abstract idea into a 'practical application.' Contrary to previous guidance and practice, examiners are now instructed to give weight to all elements of the claim when assessing practical application, whether or not they are conventional. The 'significantly more' inquiry of Step 2B is where the additional elements of the claim are examined to identify an inventive concept beyond well understood, routine, or conventional activity. According to the USPTO this approach should yield the same eligibility outcome as the original method, albeit maybe at different steps in the *Mayo/Alice* test.

Similar to the effect of *Vanda* on methods of treatment, the new USPTO guidelines open a window for precision medicine inventions involving algorithms implemented in standard hardware to satisfy the *Mayo/Alice* test at Step 2A, circumventing the 'significantly more' inquiry, by integrating the algorithm into a practical application. The courts have indicated that some elements do not confer practical application, including mere computer implementation of an otherwise ineligible abstract idea (*Benson*[29]); addition of insignificant extra-solution activity such as gathering input data or outputting results, when these are merely a nominal or tangential addition to the claim (*Flook*[30]); nor generally linking the abstract idea to a particular technological environment (*Bilski*[14]). Conversely, examples of elements that have been considered valid 'practical applications' include: (1) improvement to a technology or technical field, (2) application of the algorithm to effect a particular treatment or prophylaxis for a disease or medical condition, and (3) use of a particular machine or manufacture that is integral to the claim, or (4) transformation of a particular article to a different state or thing. The recent cases of *McRO*[31]*, Enfish*[32] and *FairWarning IP, LLC v. Iatric Systems, Inc.*[33] (**Box 1**) provide a good illustration of these concepts.

In situations where a precision medicine invention can be implemented using standard hardware (standard processors, standard sensors, standard patient monitors, etc) and the inventive concept lies primarily with the novel algorithm or the specific application of AI techniques to solve a particular problem, the claim

Box 1 Notable Post-*Alice* Cases
FairWarning, McRO, Enfish

In *FairWarning IP, LLC v Iatric Systems,* Inc.[33], the Federal Circuit found a method and system of detecting improper access of a patient's protected health information in a computer environment ineligible as being directed to an abstract idea. The Federal Circuit explained that the claimed invention did no more than collect information regarding user access to health records, analyzing this log data based on a set of rules, and providing notification if improper access is detected.

The Court likened these claims to those in *Alice*, where the claimed invention essentially amounts to using a computer to automate a process previously being performed by humans. The idea that this produced an improvement in a technology field by increasing speed was rejected, as the improved efficiency arises "from the capabilities of a general-purpose computer, rather than the claimed method." The Court reasoned that in this case, as in *Alice*, "it is [the] incorporation of a computer, not the claimed rule, that purportedly improves the existing technological process."

In the *FairWarning* decision, the Federal Circuit stressed the difference between the claims at hand and those in the previously decided cases of *McRO*[31] and *Enfish*[32]. The *McRO* patent claimed a computer automated method for animating lip synchronization and facial expression of 3D characters. Although, like in *FairWarning*, the method involved the use of specific rules to automate a task previously performed by humans, the Court emphasized that in the case of *McRO* the claimed invention transformed a process traditionally based on subjective rules performed by human animators into a set of specific mathematical rules that allowed implementation in a computer. Therefore, "it [was] the incorporation of the claimed rules, not the use of the computer, that 'improved [the] existing technological process'," and thus constituted an improvement in the technology field of computer animation.

The claims in E*nfish* were directed to a self-referential table for a computer database. Despite being defined in terms of logical structures with no physical components, the Federal Circuit found the *Enfish* claims to be "directed to a specific implementation of a solution to a problem in the software arts, and thus […] not directed to an abstract idea," but rather an improvement in computer technology. The Federal Circuit pointed to the difference between the focus of the claims being "on an improvement in computers as tools" (E*nfish*) as opposed to "an abstract idea using computers as tools" (*FairWarning*).

Table 1 Comparison of US and European patent subject-matter eligibility of precision medicine inventions.

PATENT ELIGIBILITY COMPARISON	CLAIM DIRECTED TO	US	Europe
Precision medicine inventions based on **Nature-Based Products**	Isolated DNA	**NO** (*Myriad*) Natural Phenomena Exclusion	YES (EPC Art. 52(2) & 52(3); R. 26,27,29)
	cDNA	YES (*Myriad*)	YES (EPC Art. 52(2) & 52(3); R. 26,27,29)
	Other natured-based products	Only if 'markedly different' or claim includes 'significantly more'	YES (EPC Art. 52(2) & 52(3); R. 26,27,29)
Precision medicine inventions based on **Individual Responses & Correlations**	Responses & Correlations	**NO** (*Mayo, Ariosa/Sequenom*) Law of Nature Exclusion	YES (*Illumina, Sequenom*) Technical character conferred by technical application in precision medicine
	Methods of Detection	Only if 'not directed' to a law of nature or claim includes 'significantly more'	YES (*Illumina, Sequenom*) Technical character conferred by technical application in precision medicine
	Methods of Treatment	YES (*Vanda*)	Only if claim avoids EPC Art. 53(c) exclusion, either as dosage regimes and/or new medical indications (e.g., for a particular patient
	Method of Diagnosis	Only if 'not directed' to a law of nature or claim includes 'significantly more'	YES (if method of in-vitro diagnosis does not fall under the Art 53(c) exclusion)
Precision medicine inventions based on **Algorithms**	Pure Mathematical Methods or Algorithms (including AI) *as such*	**NO** (*Alice*) Abstract idea exclusion	**NO** EPC Art. 52(2) Exclusion; Devoid of 'technical character'
	Mathematical Methods or Algorithms (including AI) *implemented in a computer or device*	**NO** (*Alice*) Abstract idea exclusion, mere computer implementation is not enough	YES, involving the use of technical means (e.g. a computer) or device confers 'technical character' to satisfy ECP. Art. 52 (but the algorithm still lacks 'technical character' for EPC Art. 56 inventive step inquiry)
	Mathematical Methods or Algorithms (including AI) directed to a *technical application* or *specific technical implementation*	Yes, (*McRO & Enfish*), claim not directed to the abstract idea itself but it to a practical application (e.g. improvement of a technology or technical field)	YES, 'technical application' or specific 'technical implementation' confers 'technical character' to the algorithm for the purposes of EPC Art. 52 & 56

drafting and prosecution strategies most likely to be successful are those which satisfy the *Alice* eligibility test at Step 2A (i.e., that the claim is not 'directed to' an abstract idea) by ensuring that: a) the claim does not preempt the use of the fundamental techniques in other application domains, b) the invention as claimed is not directed to mathematical techniques but instead to the solution of a technical problem, and c) the claimed invention *results in a technological improvement* in the field of precision medicine (improved detection, diagnosis, monitoring, therapy optimization, etc). A claim-drafting strategy that focusses on Step 2B ("the claim as a whole amounts to significantly more than the abstract idea") faces challenges if the invention uses generic hardware (e.g., computer, smartphone, wearables, standard physiologic sensors).

The full extent of *Alice*'s impact remains to be studied using the type of empirical methodologies previously employed to analyze *Myriad*[18,19,20] and *Mayo*[21]. For example, how many applications advance to an issued patent notwithstanding an initial rejection? What sorts of claim amendments assist? How long does patent prosecution take when *Alice* rejections are raised by examiners?

Even without this evidence, it is clear that the *Alice* decision affects a wide variety of algorithmic developments in precision medicine, but not all will be ultimately ineligible for patent protection. With thoughtful claim drafting and prosecution, it is possible to obtain patent protection for computer-implemented precision medicine inventions provided that they are not claimed at a high level of generality[28] and the focus of the claim is on the improvement of a technology or technical field rather than being either on the algorithm *per se*, or the automation of a mental process for which the computer is merely invoked as a tool.

European Perspective

Patent law in Europe is organised differently, and requires some explanation to compare its effects on precision medicine with the US. The European Patent Convention (EPC) is an international treaty, which provides harmonized rules for the grant of a bundle of European patents designated in EU Member States (and a few other countries). Like the US, patent eligibility is a requirement alongside novelty, inventive step, and disclosure. **Table 1** compares the two regimes.

The guiding principle for patent eligibility in Europe is found in the decisions of the European Patent Office and the Enlarged Board of Appeal. The principle is that a patent claim is patentable if, considered as a whole, it has 'technical character'. Technical character is assessed without regard to prior art, it is not a test of technological improvement[34].

This principle has substantially affected the interpretation of the

statutory exclusions that one finds in the provisions of the EPC, namely that patents shall not be granted for: "discoveries, scientific theories, mathematical methods […] methods for performing mental acts […] and programs for computers […] *as such"* (EPC Art 52(2),(3)) or methods of medical treatment and diagnostics methods practised on the human body (EPC Art 53(c)).

A) Biomarkers & Nature-Based Products

Notwithstanding the exclusion of discoveries as such since EPC 1973, and social opposition to isolated DNA sequence patents, the EPO developed an approach supportive of biotechnological patents which was reflected in the EU Directive of 98/44/EC, and formally adopted in the 2002 EPC Implementing Regulations[35]. Unlike the US, biological material including a DNA sequence, which is isolated from its natural environment or otherwise produced by a technical process, is eligible for patent protection[36]. Technical character can be conferred by a technical effect (e.g., the use of the DNA sequence in making a polypeptide or gene therapy)[37] or technical processes used to identify, purify, classify, and produce it outside a living cell[38].

Consistent with these rules, the EPO held that isolated DNA claims in Myriad's European BRCA patents and the Howard Florey Institutes Relaxin European patents were patent eligible in opposition proceedings in the 2000s[39,40].

In 2017, the patentability of isolated DNA was expressly confirmed by the German Federal Court of Justice (Bundesgerichtshof), which is Germany's highest court of *i.a.* patent jurisdiction. This was significant, as national courts and the EPO are part of different legal orders, and the case followed the US Supreme Court decisions. The German Court stated that the mere disclosure of a DNA sequence is not patentable but the disclosure of how to create the sequence through a technical process such as isolation is, even if the process is not specifically mentioned in the claims[41]. The Court also clarified that in Europe and Germany, unlike in the US, there is no need to identify an inventive concept nor 'inventive surplus' to distinguish a patentable invention from an unpatentable discovery.

Comparing the U.S. and European Regimes

Although patent eligible, the European system does not necessarily provide biomarkers with significantly greater patent protection than the US. For instance, a DNA sequence can lack novelty (an issue for Myriad's European BRCA patents) and will often be 'obvious' (e.g. where standard techniques of identification and isolation are used). Furthermore some EU member states have added national legislative rules which state that DNA sequence patents are limited to the uses disclosed in the patent (so-called purpose-limited protection)[42]. This differs from the usual rule that a product patent covers all uses of the product provided at least one application is disclosed.

B) Individual Responses & Methods of Diagnosis: Natural Relationships & Correlations

Despite first appearances, the statutory exclusion in EPC Art 53(c) for methods of diagnosis practised on the human body has limited impact on precision medicine. Since it excludes only 'methods', patents may be obtained for diagnostic instruments or medical devices for use in such methods. Furthermore, the EPO has taken the somewhat surprising view that methods of diagnosis based on blood, saliva, urine, etc. are not excluded, because these methods of diagnosis do not take place *on* the human body, but rather in a laboratory using human tissue without the patient's 'body' being present[43]. The key question is whether the claimed method of *in vitro diagnosis* has technical character. Including a step of gathering, analyzing, or reporting data using an apparatus can suffice. For the subsequent inventive step enquiry, recognizing medical illness or abnormalities seems to count as a technical purpose[44]. Putting it another way, the steps involved in medical diagnosis provide a technical solution to a technical problem.

The EPO held methods of diagnosing breast cancer based on BRACA sequences were patent eligible[45]. More recently, in 2017, the German Bundesgerichtshof, in the receptor tyronkinase case, considered whether a method claim for detecting a specific variant of DNA was patentable. Detection can be used to diagnose leukemia. Since the detection claim included the isolated DNA claims, the Court was satisfied the method claims possess technical character[41].

The European patent for NIPT, the equivalent of the US patent found invalid in *Sequenom*, was litigated in the UK case *Illumina Inc v. Premaitha Health Plc.*[46] The defendants argued that the claims were invalid because they disclosed only the unpatentable discovery that paternally inherited fetal nucleic acid is detectable in pregnant women. In stark contrast to the US case, however, the Court held the claims were valid, finding they included the technical steps of creating samples for analysis and detecting nucleic acids.

Comparing the U.S. and European Regimes

Methods of detection and diagnosis based on correlations and relationships are more straightforwardly eligible in Europe than the US. New methods of treatment in precision medicine are patentable in both jurisdictions, but claim drafting must be approached differently due to the exclusion in EPC Article 53(c) for methods of medical treatment. In Europe, methods of *in vitro* diagnosis or detection which a doctor uses in

medical treatment are eligible. Unlike the US, it is problematic (not helpful) to *direct* the claim to a method of treatment.

C) Algorithms and AI

Although the EPC excludes mathematical methods (including AI methods) and programs for computers *as such* from patent protection (EPC Art 52(2)), many of the next generation applications in precision medicine based on some form of mathematical method, algorithm or machine-learning method are patent eligible. This is because the Art. 52(2) exclusion applies only if a claim is directed to a purely abstract mathematical method (or AI method) *per se* and the claim does not require any technical means (Art 52(3)).

If the claim is directed either to *a method involving the use of technical means* (e.g. a computer) or to *a device*, its subject-matter has 'technical character' as a whole and is thus not excluded from eligibility under Art. 52(2). The EPO considers a patent claim to have the all-important 'technical character' if the claim recites the use of technical means for implementation (e.g., implementing a discovery, mathematical method, mental acts or presentations of information through a general or mini-computer, smartphone, tablet, measuring device, or computer-readable storage mechanism such as a memory stick)[47].

A computer-implemented claim can have 'technical character' by: 1) reciting the use of any other technical means for implementation (e.g., computer), 2) reciting an algorithm that has a technical application (the algorithm produces a technical effect by serving a technical purpose) and/or 3) the claim is directed to *specific technical implementation* of the mathematical method and the mathematical method is *particularly adapted* for that implementation **(Figure 1)**.

All of the following pass the patent eligibility threshold if they are implemented by technical means (e.g., some kind of computer): mathematical relationships, mathematical algorithms, algorithms to collect and store data and for data visualisation, deterministic algorithms and statistical algorithms. In contrast, patent claims are likely to fail the EPC's eligibility criteria if they recite no more than the use of an artificial intelligence model (e.g., a neural network), or a computer program (in the narrow sense of a sequence of instructions to be executed by a computer).

A caveat to the principle that including a general purpose computer suffices to confer technical character arises in the case of *computer programs*, but these are very narrowly defined (as 'a sequence of computer-executable instructions specifying a method'), and distinguished from computer-implemented-methods ('a method being actually performed on a computer')[48]. In the case where the claim cannot be characterized as a computer-implemented method, but instead is a computer program, the caveat for eligibility is that there must be a 'further technical effect' (running a computer program on a computer does not confer technical character and is not sufficient for eligibility, notwithstanding that electrical currents are involved)[48]. A 'further technical effect' is a technical effect going beyond the 'normal' physical interactions between the program (software) and the computer (hardware) on which it is run.

Interaction with Inventive Step

Given that a competent draftsperson can usually present a claim as a computer-implemented method of detection or in vitro diagnosis rather than as a 'computer program' or method of medical treatment, patent eligibility (Art. 52) is not a difficult hurdle for computer-implemented precision medicine inventions in Europe. As already explained, it is relatively straightforward for a mathematical model, algorithm, or machine learning method to be eligible for patent protection; the claim simply needs to recite the use of technical means of implementation. That said, the draftsperson must also consider the *inventive step* inquiry. Passing this hurdle can prove challenging, if 'technical character' in the claim is achieved *solely* by reciting a computer (or any other technical means for its implementation).

To demonstrate an inventive step to satisfy the EPO the claim must involve a non-obvious technical solution to a technical problem[47]. To establish this, all features that contribute to the technical character of the invention are considered. Features that fall within Art 52(2) categories of mathematical methods, presentations of information, and computer programs can contribute to the assessment of non-obviousness[45] *only* if they contribute to the technical character. This limits the manner in which algorithms (and other Art 52(2) features) can be the seat of the non-obvious development.

There are a variety of situations when a new algorithm contributes to the claim's 'technical character.' For example the algorithm could help produce a 'technical effect' that serves a technical purpose, either by 1) its 'application to a field of technology' and/or 2) 'by being adapted to a specific technical implementation.'

If the principles we have articulated are followed, many precision medicine applications will be deemed patent eligible subject matter in Europe (**Box 2**).

Comparing the U.S. and European Regimes

Despite multiple relevant legislative exclusions, European doctrine on patent eligibility of algorithms and machine learning is generous compared with the US because, generally, claim-drafting strategies can be deployed to avoid exclusion under EPC Art 52(2)[49].

Demonstrating inventive step, relative to the prior art, is the more restrictive issue for European patent protection of algorithm-based precision medicine inventions. In Europe, it is strategic to restrict an algorithm-based claim to a specific technical application or adapt it for specific technical implementation. Then the algorithm has 'technical character' and can be considered as part of the inventive step inquiry to support non-obviousness[50]. Notably this tip concords with the guidance above for drafting algorithm-based claims that meet US patent eligibility rules post-*Alice* in light of *McRO, Enflish,* and *FairWarning*.

Conclusions

Patent law can be likened to a pendulum, seeking an equilibrium between competing interests and tensions[51]. Finding a balance in the field of precision medicine is no easy feat where there are many interests: patients, various kinds of healthcare providers and health professionals, plus all manner of organizations involved in research, development and commercialization (e.g., small, large, public, private, public-private). Arriving at balanced principles is particularly difficult when patent law principles must not discriminate against technologies but accommodate also articles of manufacture, machines, and compositions based inventions[52]. So it is not surprising that the law on patent eligibility oscillates, nor that the patenting of precision medicine is complex and uncertain.

The difficulty with a swinging pendulum in law is that, unlike a physical pendulum, there is no set path or timing. In the aftermath of *Mayo*, *Myriad*, and *Alice*, the legal protection for precision medicine inventions faced a high degree of uncertainty, as the evolving doctrine of patent eligibility was reformulated. We are still witnessing the effects of that uncertainty, just as we begin to see signs that a new era is emerging. Post-*Vanda* and with Andrei Iancu taking over from Michelle Lee as the Director of the USPTO, and with patent attorneys learning new claiming-drafting approaches, the restrictive and uncertain patentability of biomarkers, medical correlations and algorithms is easing off. In this era, other patent doctrines will probably come to the fore as key policy levers (e.g., non-obviousness). But how, when, and to what degree these developments will take shape remains uncertain.

In Europe, there has also been some swinging of the proverbial pendulum for precision medicine and patentable subject matter. The swing has not been as wide nor as forceful as in the US, thus the law has felt more stable; but swing it does, nevertheless. Notably the EPC and US are swinging to a different beat. Presently the EPC law on patentable subject matter is relatively generous for precision medicine in biomarkers, correlations, *in vitro* methods of detection and diagnosis, and algorithms[53].

A divergence between US and European laws pertains to the patent subject-matter eligibility of nature-based biomarkers. In Europe, biomarkers are patent-eligible even if merely isolated from their natural environment; whereas in the US biomarkers must be markedly different from naturally-occurring products or the claims must include significantly more (which tends to narrow the claim). In contrast, we seem to be entering a period of increasing convergence with respect to patentability of *applied* algorithms, mathematical methods (including AI), computer programs, methods of treatment based on biomarkers and diagnosis (provided one considers the combined effect of eligibility and non-obviousness inquiries). This convergence is particularly noticeable following *McRO*[31], *Enfish*[32], and *Vanda*[25] as well as recent EPO and USPTO Examination Guidelines.

Box 2 Precision Medicine Examples Meeting European Subject Matter Eligibility Requirements

As discussed in this article, an Art 52(2) type feature can contribute to technical character through 'technical application' if it produces a specific technical effect for a technical purpose. The claim must be functionally limited to the technical purpose, either expressly or implicitly. Some examples related to precision medicine involving mathematical methods and algorithms include (1) providing a genotype estimate based on an analysis of DNA samples together with a confidence interval of reliability, and (2) providing a medical diagnosis by an automated system that processes physiological measurements. Examples in the case of artificial intelligence and machine learning include (3) the use of a neural network in a heart-monitoring apparatus for the purpose of identifying irregular heartbeats, and (4) the use of machine learning in a method to classify types of irregular heartbeats, where generating the training set and training the classifier support a technical purpose (*EPO November 2018 Examination Guidance*). An example in the case of presentations of information is (5) presenting a visual stimulus to a person for the purpose of producing in that person a physiological reaction (e.g. involuntary eye gaze) which can be measured in the context of assessing a medical condition (e.g. brain damage, or vision impairment). Additionally, an Art 52(2) type feature can contribute to technical character through 'technical implementation' if the claim states the Art 52(2) type feature is adapted to a specific technical implementation. For instance, if an algorithm is adapted by technical considerations to the internal functioning of a computer.

For methods of detection, diagnosis and treatment, there are still some cross-jurisdictional differences, but convergence is afoot. In Europe, methods of detection and *in vitro* diagnosis are generally patent eligible; a competent draftsperson can find language that achieves technical character. In the US, these methods are still affected by the two step *Mayo/Alice* test, particularly methods of diagnosis. In response, and post-*Vanda*, methods of medical treatment are likely to become the claims *de jour* for medical correlations and relationships. Whereas in Europe, methods of medical treatment cannot be claimed *per se* but with appropriate claim-drafting could be protected as applications of a new method of diagnosis, or in the form of a medical kit or device.

As an IP intensive field, a reasonable degree of legal certainty is needed in order to promote research, technology-transfer, investment, and innovation. These legal principles, with their cross-Atlantic similarities and differences, and swinging natures, have considerable significance for the future of precision medicine.

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The Effects of *Myriad* and *Mayo* on Molecular-Test Development in the United States and Europe: Interviews from the Frontline

Johnathon Liddicoat[*]*, Kathleen Liddell*[**] *& Mateo Aboy*[***]

ABSTRACT

US Supreme Court decisions in Mayo Collaborative Services v. Prometheus Laboratories *and* Association for Molecular Pathology v. Myriad Genetics Inc. *caused US and European law on what is patentable subject matter to diverge significantly. Both cases related to molecular tests and changed decades of patent practice. Whether the decisions adversely affect the development of molecular tests in the United States and Europe has been a matter of much speculation but limited empirical investigation. This interview-based study has three main findings. First,* Myriad *and* Mayo *have negatively affected the development of some molecular tests. Notably, half of the US university technology-transfer offices interviewed decided not to develop tests, and many other organizations have found the legal uncertainty following the cases problematic. Second, small "patent-precarious" organizations—those that rely heavily on patents for competitive advantages, such as technology-transfer offices—have been the most affected because patent protection is now often weaker and more difficult*

[*] Senior Research Associate, Centre for Law, Medicine, and Life Sciences, Faculty of Law, University of Cambridge, Cambridge CB3 9DZ, United Kingdom. Corresponding author, jel68@cam.ac.uk.

[**] Senior Lecturer, Centre for Law, Medicine, and Life Sciences, Faculty of Law, University of Cambridge, Cambridge CB3 9DZ, United Kingdom.

[***] Senior Research Scholar, Centre for Law, Medicine, and Life Sciences, Faculty of Law, University of Cambridge, Cambridge CB3 9DZ, United Kingdom. Thanks to Dr. Stuart Hogarth, Dr. Michael Hopkins, and Professor Dianne Nicol for comments on this research. This study was supported, in part, by the awards from the Cambridge Humanities Research Grant Scheme, the Cancer Research UK Cambridge Centre Early Detection Programme (CRUK grant reference C9685/A25117), and a Novo Nordisk Foundation grant for a scientifically independent Collaborative Research Programme in Biomedical Innovation Law (grant number NNF17SA027784).

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to obtain. Third, US-headquartered organizations have been more affected by 35 U.S.C. § 101 case law developments than European organizations, even though both types of organizations file for US patents. This Article refrains from advising law reform, however, because this study only focused on the adverse effects of the decisions and the positive effects remain unexamined.

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I. INTRODUCTION

Patents, which provide inventors with rights to stop others from practicing their invention for twenty years, are commonly justified on the ground that they incentivize research, development, and disclosure of technological breakthroughs.[1] However, two recent US Supreme Court decisions cast doubt on patents' ability to fulfill these functions for molecular tests.

Molecular tests check for various chemical compounds, such as DNA or proteins, that are linked to diseases.[2] Failure to incentivize new tests is a serious issue for medicine because much of the field pivots on results from these tests. It is also a serious issue for the emerging field of precision medicine, which is trying to better tailor medicine to individuals. A core component of precision medicine is providing new and better molecular tests that help prevent, detect, diagnose, provide prognoses, and treat diseases.[3]

These two decisions restricted the subject matter that is eligible for patent protection, a topic commonly known as "patent eligibility," "patentable subject matter," or "35 U.S.C. § 101."[4] *Association for Molecular Pathology v. Myriad Genetics, Inc.*[5] ended the US Patent and

1. *See, e.g.*, WILLIAM M. LANDES & RICHARD A. POSNER, THE ECONOMIC STRUCTURE OF INTELLECTUAL PROPERTY LAW ch.11 (2003); 1 PETER S. MENELL ET AL., INTELLECTUAL PROPERTY IN THE NEW TECHNOLOGICAL AGE: 2018, at 16–20 (2018); Kenneth W. Dam, *The Economic Underpinnings of Patent Law*, 23 J. LEGAL STUD. 247, 249 (1994); F. Scott Kieff, *Property Rights and Property Rules for Commercializing Inventions*, 85 MINN. L. REV. 697 (2001); Edmund W. Kitch, *The Nature and Function of the Patent System*, 20 J.L. & ECON. 265 (1977); Arnold Plant, *The Economic Theory Concerning Patents for Inventions*, 1 ECONOMICA 30, 32 (1934).

2. *NCI Dictionary of Cancer Terms: Molecular Test*, NAT'L CANCER INST., https://www.cancer.gov/publications/dictionaries/cancer-terms/def/molecular-test [https://perma.cc/NH8T-BSKW] (last visited Mar. 23, 2020).

3. *See NCI Dictionary of Cancer Terms: Precision Medicine*, NAT'L CANCER INST., https://www.cancer.gov/publications/dictionaries/cancer-terms/def/precision-medicine [https://perma.cc/J9MT-SZ2K] (last visited Mar. 23, 2020).

4. 35 U.S.C. § 101 (2018). Patentable subject matter is only one of several criteria that must be satisfied for a patent application to be granted. An invention must also be, for example, novel and nonobvious. *See* §§ 102, 103.

5. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576 (2013).

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Trademark Office (USPTO) practice of granting patents on isolated genomic DNA,[6] and *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*[7] ended the USPTO's practice of granting patents on medical relationships between molecules and health outcomes when implemented using conventional scientific techniques.[8]

The new patent-eligibility standards in the United States diverge significantly from those around the world.[9] One prominent commentator argues the changes heralded by *Myriad* and *Mayo* are so significant that molecular tests are no longer patent eligible in the United States,[10] and another asserts that the decisions threaten the next generation of tests.[11] Indeed, in 2019, upon reviewing all relevant decisions, the US Court of Appeals for the Federal Circuit concluded that "[s]ince *Mayo*, we have held every single diagnostic claim in every case before us ineligible."[12]

Concerns surrounding the patentability of molecular tests in the United States have led several organizations to lobby for changes to 35 U.S.C. § 101.[13] The current director of the USPTO and a previous acting

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6. *See id.* at 577, 593–94, 596; Dianne Nicol et al., *International Divergence in Gene Patenting*, 20 ANN. REV. GENOMICS & HUM. GENETICS 519, 529–30 (2019).

7. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66 (2012).

8. *See id.* at 79–82.

9. Nicol et al., *supra* note 6, at 534; *see also* Kevin Madigan & Adam Mossoff, *Turning Gold to Lead: How Patent Eligibility Doctrine Is Undermining U.S. Leadership in Innovation*, 24 GEO. MASON L. REV. 939, 952–60 (2017); David O. Taylor, *The Supreme Court's Revolution in Patent Eligibility Law: Alternative Protections for Biotechnology*, 37 NATURE BIOTECHNOLOGY 227, 229–30 (2019).

10. Rebecca S. Eisenberg, *Diagnostics Need Not Apply*, 21 B.U. J. SCI. & TECH. L. 256, 286 (2015). Eisenberg actually states that "*diagnostic* technology is not patent-eligible." *Id.* (emphasis added). One could argue that Eisenberg's quote is inapt (to this Article) because molecular tests are different from diagnostic technology. However, since molecular tests are a subset of diagnostics, her reference is appropriate. One could also argue that this Article makes a broader claim than Eisenberg, as molecular tests is a broader category than diagnostics because it includes, among other things, prognostic tests—something Eisenberg did not specifically refer to. However, it is very common in the industry to use the term "diagnostic tests" when discussing prognostic tests, and, indeed, this is exactly what Eisenberg did. *Id.* at 260.

11. *See* Christopher M. Holman, *The Critical Role of Patents in the Development, Commercialization and Utilization of Innovative Genetic Diagnostic Tests and Personalized Medicine*, 21 B.U. J. SCI. & TECH. L. 297, 315–16 (2015); *see also* Alice O. Martin & Kimberly K. Vines, *Further Erosion of Patent Protection for Diagnostics: The Federal Circuit Denies En Banc Rehearing in* Ariosa Diagnostics, Inc. v. Sequenom Inc., 44 AIPLA Q.J. 437, 456 (2016); Michael A. Sanzo, *The Patenting of Gene Based Diagnostic Assays in a Post* Mayo *and* Myriad *World*, 16 J. MARSHALL REV. INTELL. PROP. L. 1, 20 (2016).

12. Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 927 F.3d 1333, 1352 (Fed. Cir. 2019).

13. *See* AM. INTELLECTUAL PROP. LAW ASS'N, AIPLA LEGISLATIVE PROPOSAL AND REPORT ON PATENT ELIGIBLE SUBJECT MATTER 2 (2017), https://www.aipla.org/docs/default-source/advocacy/aipla-legislative-proposal---patent-eligible-subject-matter.pdf?sfvrsn=7e208efe_2

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director are generally supportive of such efforts,[14] and this reform is now on several senators' agendas.[15] That said, other commentators argue that *Myriad* and *Mayo* strengthen patent policy because they "[weed] out overly broad patents" by requiring that applicants claim a specific and inventive way of achieving a result, rather than just the result.[16] Their position closely aligns with the rationale offered by the Supreme Court—namely, that patents on medical relationships and isolated DNA risk tying up the tools of future innovation due to their broad scope.[17]

Myriad and *Mayo* have been the subject of much academic commentary, but researchers have yet to study if and how the cases affect the development of molecular tests. Scholars have analyzed the jurisprudence and history of the decisions,[18] as well as how the judicial decisions interact with other US laws that affect the development of molecular tests.[19] Likewise, other scholars have empirically evaluated how the decisions affect many aspects of patent practice, including

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[https://perma.cc/NX7R-4SH7]; Jorge A. Goldstein et al., *The Time Has Come to Amend 35 U.S.C. § 101*, 44 AIPLA Q.J. 171, 173 (2016); Steven Lundberg, *Dave Kappos Calls for Abolition of Section 101*, NAT'L L. REV. (Apr. 14, 2016), https://www.natlawreview.com/article/dave-kappos-calls-abolition-section-101 [https://perma.cc/9RWB-R4WV].

14. *Director of USPTO Addressed Intellectual Property Track Opening Plenary*, BIO: BIOTECHNOW (June 4, 2018), https://www.bio.org/blogs/director-uspto-addressed-intellectual-property-track-opening-plenary [https://perma.cc/CL2F-TAE9]; Joseph Matal, Acting Director, USPTO, Closing Remarks at IP & Diagnostics Symposium (Sept. 29, 2017).

15. Scott McKeown, *Senate Judiciary Leaders Resurrect Long Dormant IP Subcommittee*, ROPES & GRAY: PATENTS POST-GRANT (Feb. 12, 2019), https://www.patentspostgrant.com/senate-judiciary-leaders-resurrect-long-dormant-ip-subcommittee/#page=1 [https://perma.cc/NRF4-D4UU]; Kevin E. Noonan, *Senate Proposal for Section 101 Reform: Effect on Biotech/Pharma Inventions*, PAT. DOCS (May 23, 2019), https://www.patentdocs.org/2019/05/senate-proposal-for-section-101-reform-effect-on-biotechpharma-inventions.html?utm_source=feedburner&utm_medium=email&utm_campaign=Feed%3A+PatentDocs+%28Patent+Docs%29 [https://perma.cc/7ABP-T9RY].

16. U.S. PATENT & TRADEMARK OFFICE, PATENT ELIGIBLE SUBJECT MATTER: REPORT ON VIEWS AND RECOMMENDATIONS FROM THE PUBLIC 24 (2017), https://www.uspto.gov/sites/default/files/documents/101-Report_FINAL.pdf [https://perma.cc/L32W-GXFW].

17. *See* Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 589 (2013); Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 72–73 (2012).

18. *See, e.g.*, Dan L. Burk, *The Curious Incident of the Supreme Court in* Myriad Genetics, 90 NOTRE DAME L. REV. 505 (2014); John W. Cox & Joseph L. Vandegrift, *A Brief History of Supreme Court Interest in Patent-Eligible Subject Matter Under 35 U.S.C. § 101*, 19 J. TECH. L. & POL'Y 181 (2014); Peter Lee, *The Supreme Court's* Myriad *Effects on Scientific Research: Definitional Fluidity and the Legal Construction of Nature*, 5 U.C. IRVINE L. REV. 1077 (2015); Amelia Smith Rinehart, Myriad *Lessons Learned*, 5 U.C. IRVINE L. REV. 1147 (2015); Jacob S. Sherkow & Henry T. Greely, *The History of Patenting Genetic Material*, 49 ANN. REV. GENETICS 161 (2015); Brad Sherman, *What Does It Mean to Invent Nature?*, 5 U.C. IRVINE L. REV. 1193 (2015).

19. Rachel E. Sachs, *Innovation Law and Policy: Preserving the Future of Personalized Medicine*, 49 U.C. DAVIS L. REV. 1881 (2016).

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patent filing and prosecution.[20] These studies provide important macrolevel perspectives, but microlevel data on how the cases affect business decisions surrounding the development of tests are needed in order to see if and how the cases actually affect the development of new molecular tests.

This Article's study conducted thirty-seven semistructured interviews with participants from the United States and Europe. The divergence in US and European patent law provides a natural experiment, enabling an examination of how different patent-eligibility criteria affect the development of molecular tests. Interviews were conducted with executives at molecular-test companies, managers in technology-transfer offices at research institutes,[21] and patent practitioners. The interviews explored how patent prosecution has changed, whether the cases have created problematic levels of uncertainty, and whether development strategies have changed on either or both sides of the North Atlantic.

This Article is organized as follows. Part II provides a more detailed background to the study, including an overview of the relevant US and European law and the research questions pursued in this Article. Part III describes the methodological features of the study. Part IV reports the interview data. Part V distills the interview data to their most valuable components, drawing conclusions on the effects of the cases.

20. *See, e.g.*, Mateo Aboy et al., *After* Myriad*, What Makes a Gene Patent Claim 'Markedly Different' from Nature?*, 35 NATURE BIOTECHNOLOGY 820 (2017) [hereinafter *After* Myriad]; Mateo Aboy et al., Mayo*'s Impact on Patent Applications Related to Biotechnology, Diagnostics and Personalized Medicine*, 37 NATURE BIOTECHNOLOGY 513 (2019) [hereinafter Mayo*'s Impact*]; Mateo Aboy et al., Myriad*'s Impact on Gene Patents*, 34 NATURE BIOTECHNOLOGY 1119 (2016) [hereinafter Myriad*'s Impact*]; Mateo Aboy et al., *Was the* Myriad *Decision a 'Surgical Strike' on Isolated DNA Patents, or Does It Have Wider Impacts?*, 36 NATURE BIOTECHNOLOGY 1146 (2018) [hereinafter *Surgical Strike*]; Gregory D. Graff et al., *Not Quite a* Myriad *of Gene Patents*, 31 NATURE BIOTECHNOLOGY 404 (2013); Elizabeth J. Haanes & Jaume M. Cànaves, *Stealing Fire: A Retrospective Survey of Biotech Patent Claims in the Wake of* Mayo v. Prometheus, 30 NATURE BIOTECHNOLOGY 758 (2012).

21. The exact title of the technology-transfer office interviewees differed, but all interviewees' roles involved managing molecular-test technology and intellectual property. Not all research institution–based organizations involved in the transfer and commercialization of technology identify as "technology-transfer offices." The term is, however, in wide use and serves as a useful label for the activities on which this study focuses.

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II. LEGAL BACKGROUND

A. Myriad

The key holding in *Myriad*[22] was that *isolated* genomic DNA from the human BRCA1 and BRCA2 genes are not patentable subject matter.[23] The term "isolated" refers to DNA that has been removed from the rest of the genome.[24] Naturally occurring variants in the BRCA1 and BRCA2 DNA sequences correlate with patients' risk of developing cancers,[25] and physicians can use the presence or absence of the variants during diagnosis and prognosis.[26] The Supreme Court has long held that exceptions exist to what is patent eligible, and *Myriad* concerned the judicially created exception for "products of nature."[27] The Court's justification for this exception is that products of nature are the "basic tools of scientific and technological work"; therefore, granting patents on them risks tying up the tools of future innovation.[28]

To determine whether Myriad's claims were patent-eligible products of nature, the Court applied the "markedly different characteristics" test.[29] Pursuant to this test, which was derived from earlier cases including *Diamond v. Chakrabarty*,[30] a nature-based product claim is patent eligible if it has characteristics that differ markedly from naturally occurring products.[31] The Court found that isolated DNA molecules do not exist in nature per se (in the sense that they were man-made),[32] but the Court held that merely separating the DNA from its surrounding genetic material did *not* make it markedly different from naturally occurring DNA.[33] Consequently, Myriad's claims to isolated forms of the BRCA gene were ineligible for patent protection.[34]

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22. *Myriad* was decided after *Mayo*; however, this Article discusses *Myriad* first due to the issues it considered and its likely higher familiarity among readers.

23. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 579–80 (2013).

24. *See id.* at 596.

25. *Id.* at 582–83.

26. *See id.*

27. *Id.* at 589–90 (citing Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980)).

28. *Id.* at 589 (quoting Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 71 (2012)).

29. *Id.* at 590–91 (quoting *Diamond*, 447 U.S. at 310).

30. *See Diamond*, 447 U.S. at 310.

31. *See Myriad*, 569 U.S. at 589–91.

32. *See id.* at 593.

33. *Id.* at 591–93.

34. *Id.* at 596.

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The Court reached a different conclusion in relation to complementary DNA (cDNA).[35] Scientists produce cDNA artificially by working with an RNA template. RNA is an intermediary molecule between DNA and the protein it encodes.[36] cDNA is thus an artificially synthesized DNA strand based on an RNA sequence of interest. The resulting cDNA is similar to genomic DNA, but cDNA lacks intervening sequences of DNA that punctuate long segments of genomic DNA and do not code for proteins.[37] The Court held that cDNA claims were nature based but markedly different from naturally occurring DNA.

Immediately after *Myriad*, some commentators thought that the decision would apply to isolated DNA claims only.[38] This would have meant that the decision affected a relatively small range of inventions on molecules derived from nature. However, it is now clear that the decision applies beyond isolated DNA. One study proved this by analyzing how frequently USPTO patent examiners cite the decision. They found that in 85 percent of the cases where USPTO examiners cite *Myriad* to reject patent claims, the examiners applied the case to subject matter other than isolated DNA.[39] This subject matter included peptides, proteins, antibodies, cells, and pharmaceutical compositions.

B. Mayo

Mayo held that methods to optimize dosages of thiopurine drugs for treating autoimmune diseases such as Crohn's disease were not patentable.[40] Patients metabolize drugs at different rates. The idea underlying the patent for these methods was that medical professionals could tailor the dosage to the individual's rate of metabolism by measuring a metabolite, a compound formed during metabolism of the drug.[41] Tailoring the dosage of thiopurine drugs is important because a low dosage is ineffective and a high dosage can cause harmful side effects.[42]

35. *Id.* at 576.

36. *Id.* at 581–82.

37. *Id.* at 582.

38. *See, e.g.*, E. Richard Gold et al., AMP v. Myriad*: A Surgical Strike on Blockbuster Business Models*, SCI. TRANSLATIONAL MED., July 3, 2013, at 1, 1–2.

39. *Surgical Strike*, *supra* note 20, at 1147–48.

40. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 72–73 (2012).

41. *Id.* at 73–74.

42. *Id.*

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The *Mayo* decision concerned the judicially created exception that "laws of nature" and "natural phenomena" are patent ineligible.[43] The justification for this exception is similar to the justification for the "products of nature" exception from *Myriad*: granting such patents may "preempt" future inventions due to their broad scope.[44] However, all valid patent claims, to some degree, incorporate laws of nature;[45] and the Court stated that claims applying natural laws can be patent eligible if they "contain other elements or a combination of elements . . . sufficient to ensure that the patent in practice amounts to *significantly more* than a patent upon the natural law itself."[46] In the subsequent Supreme Court decision *Alice Corp. v. CLS Bank International*,[47] which concerned a patent for computer-implemented business transactions,[48] the Court helpfully distilled its reasoning in *Mayo* into a two-step test: (i) determine whether a claim is directed to a patent-ineligible concept (e.g., natural laws or natural phenomena); and (ii) if so, determine whether any additional features of the claim (either individually or in combination) transform it into eligible subject matter by claiming significantly more than ineligible subject matter.[49]

In *Mayo*, the Court held that the dosage-optimizing claims were directed to a natural law, stating that the correlation "is a consequence of the ways in which thiopurine compounds are metabolized by the body—entirely natural processes."[50] The Court then considered whether the claims contained "significantly more."[51] The claims included the steps of administering the drug and determining metabolite levels;[52] however, the Court found these steps were "not sufficient to transform unpatentable natural correlations"[53] into patent-eligible claims because they were "well-understood, routine, conventional activit[ies] previously engaged in by scientists who work in the field."[54]

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43. *Id.* at 70–71. The Court reviewed the controlling precedents on this topic. *See id.* at 80–87.

44. *Id.* at 71–73.

45. *Id.* at 71.

46. *Id.* at 72–73 (emphasis added).

47. Alice Corp. Pty. v. CLS Bank Int'l, 573 U.S. 208 (2014).

48. *Id.* at 212.

49. *Id.* at 217.

50. *Mayo*, 566 U.S. at 77.

51. *Id.* at 79.

52. *Id.* at 78–79.

53. *Id.* at 80.

54. *Id.* at 73. For convenience, this Article refers to "well-understood, routine, conventional activities" as "conventional activities."

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Various courts have applied *Myriad* and *Mayo* to invalidate patent claims that protect specific molecular tests.[55] In addition, courts have applied *Mayo* to invalidate molecular-test platform technology that detects DNA. Platform technology refers to technology that has multiple applications (e.g., can be used to perform multiple molecular tests). In *Ariosa Diagnostics, Inc. v. Sequenom, Inc*,[56] the Federal Circuit found the foundational patent for noninvasive prenatal testing (NIPT) invalid. NIPT is a technique that allows medical professionals to genetically test fetuses by drawing blood from a pregnant woman. The technology relies on sequencing cell-free fetal DNA (cffDNA), which exists naturally in maternal blood. The claims in *Sequenom* included the steps of obtaining a blood sample from a pregnant woman and sequencing cffDNA, but the Federal Circuit held the patent invalid because it covered the natural phenomenon of cffDNA and did so using conventional techniques.[57]

Although *Myriad* and *Mayo* cast doubt on the validity of patent claims protecting various types of molecular tests and platforms, they do not cast doubt on patents for "companion tests," which are often but not always a subtype of molecular tests. These tests are, in short, necessary for the safe and effective use of a corresponding drug. They provide information such as dosage or whether a specific patient will respond to a drug.[58] Since *Mayo*, the USPTO has treated claims for companion tests as patent eligible so long as the use of the drug is unconventional or if all the steps in the claim amount to more than merely "diagnosing a patient . . . and instructing a doctor to generically

55. *See, e.g.*, Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 927 F.3d 1333, 1350 (Fed. Cir. 2019); Cleveland Clinic Found. v. True Health Diagnostics LLC, 760 F. App'x 1013, 1016–18 (Fed. Cir. 2019); Roche Molecular Sys., Inc. v. Cepheid, 905 F.3d 1363, 1372 (Fed. Cir. 2018); Cleveland Clinic Found. v. True Health Diagnostics LLC, 859 F.3d 1352, 1356, 1362 (Fed. Cir. 2017); *In re* BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig., 774 F.3d 755, 762–65 (Fed. Cir. 2014); PerkinElmer, Inc. v. Intema Ltd., 496 F. App'x 65, 69–73 (Fed. Cir. 2012). It should also be noted that in *In re BRCA1- & BRCA2-Based Hereditary Cancer Test* and *PerkinElmer* the courts invoked the "abstract idea" or "abstract mental process" exceptions to patent eligibility, also described in *Mayo*. *See, e.g.*, *Mayo*, 566 U.S. at 70–71, 82; *In re BRCA1– & BRCA2–Based Hereditary Cancer Test*, 774 F.3d at 763–64; *PerkinElmer*, 496 F. App'x at 68. As reviewed by Rebecca Eisenberg, these exceptions operate in a similar manner for molecular tests as the "product of nature" and "natural laws" exceptions but may operate in different ways for drug-orientated claims. *See* Eisenberg, *supra* note 10, at 271–74.

56. Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (Fed. Cir. 2015).

57. *Id.* at 1373, 1376; *see also* Martin & Vines, *supra* note 11, at 438–39.

58. *Companion Diagnostics*, FDA, https://www.fda.gov/medical-devices/vitro-diagnostics/companion-diagnostics [https://perma.cc/W29J-7FBT] (last updated July 12, 2018).

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'treat it.'"[59] In 2018, the Federal Circuit in *Vanda Pharmaceuticals, Inc. v. West-Ward Pharmaceuticals International Ltd.*[60] made the § 101 criteria of companion tests easier to meet. The Federal Circuit held that the particular method of treatment in *Vanda* was eligible. The reasoning in *Vanda* can be applied to companion tests. Briefly, a test is patent eligible if it is claimed as a method of treatment that incorporates a molecular test and administers a drug, even if the drug is already known to treat the medical indication.[61] The court's rationale was that a patent claim directed to a method of medical treatment is "not directed to" a natural law and therefore does not fail the first step of the *Mayo* two-step test.[62]

This review of US case law shows how *Myriad* and *Mayo* altered US patent practice for molecular tests. Indeed, both *Myriad* and *Mayo* invalidated patent claims for molecular tests. On the other hand, *Vanda* shows that companion tests incorporating a molecular test are patentable subject matter. As a result, this Article's study focused on molecular tests but excluded companion tests. The next Section contrasts US patent law against European law.

C. European Law

European law permits a broader range of subject matter to be patented than US law. This includes a wider variety of products derived from nature, such as isolated DNA, and methods of in vitro detection and diagnosis based on natural laws and phenomena (i.e., medical correlations).[63] As such, US and European laws have diverged significantly.[64]

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59. *Subject Matter Eligibility Examples: Life Sciences*, USPTO 15 (May 4, 2016), https://www.uspto.gov/sites/default/files/documents/ieg-may-2016-ex.pdf [https://perma.cc/6WND-6S23]. For a brief review of this topic, see Mayo*'s Impact*, *supra* note 20, at 515.

60. Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd., 887 F.3d 1117 (Fed. Cir. 2018). The USPTO immediately reflected the case in an examination guidance memorandum. Memorandum from Robert W. Bahr, Deputy Comm'r for Patent Examination Policy, U.S. Patent & Trademark Office, to the Patent Examining Corps on Recent Subject Matter Eligibility Decision: *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals* 1 (June 7, 2018), https://www.uspto.gov/sites/default/files/documents/memo-vanda-20180607.PDF [https://perma.cc/6TMV-62AM].

61. *See Vanda Pharm.*, 887 F.3d at 1135–36; *see also Memorandum from Robert W. Bahr*, *supra* note 60, at 2.

62. *Vanda Pharm.*, 887 F.3d at 1134–36.

63. *See generally* Nicol et al., *supra* note 6, at 532.

64. *Id.* at 533. For a detailed explanation of the differences between US and European law, see Mateo Aboy et al., *How Does Emerging Patent Case Law in the US and Europe Affect Precision Medicine?*, 37 NATURE BIOTECHNOLOGY 1118 (2019) and Nicol et al., *supra* note 6, at 529–33. Nicol et al. show that, as a result of *Myriad* and *Mayo*, US patent law has diverged

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The core requirement for patent eligibility under the European Patent Convention (EPC)[65] is that the claim involves "technical character."[66] The European Patent Office (EPO) examines EPC patents and also decides "oppositions" that third parties raise against the grant of these patents, while domestic courts determine infringement and revocation disputes.[67] The EPC's implementing rules, which are consistent with the EU Directive on the Legal Protection of Biotechnological Inventions,[68] state that "biological material which is *isolated* from its natural environment or produced by means of a technical process even if it previously occurred in nature" is patent eligible.[69] The EPO has granted many isolated DNA patents on this basis,[70] and the highest patent court in Germany, the Bundesgerichtshof, has confirmed their eligibility.[71]

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significantly from European patent law, as well as from many other patent laws around the world. *See* Nicol et al., *supra* note 6, at 529–33. However, one notable difference to this divergence is Australian patent law, which excludes isolated DNA and cDNA. *See D'Arcy v Myriad Genetics Inc.* (2015) 258 CLR 334; Nicol et al., *supra* note 6, at 531. Aboy et al. confirm significant differences continue to exist between US and European law on the eligibility of biomarkers and medical correlations, despite guidance from the European Patent Office and USPTO at the end of 2018 and early 2019 that converged other areas of the law, including claims incorporating algorithms. *See* Aboy et al., *supra*, at 1125.

65. Convention on the Grant of European Patents, Oct. 5, 1973, 1065 U.N.T.S. 254 [hereinafter European Patent Convention].

66. European Pat. Off., Caselaw of the Boards of Appeal: 9.1.1 Technical Character of the Invention, https://www.epo.org/law-practice/legal-texts/html/caselaw/2019/e/clr_i_d_9_1_1.htm [https://perma.cc/A7RN-7V6V] (last visited Mar. 23, 2020).

67. European Patent Convention, *supra* note 65, arts. 64, 94, 99, 138. For a brief overview, see Nicol et al., *supra* note 6, at 525.

68. Directive 98/44/EC, of the European Parliament and of the Council of 6 July 1998 on the Legal Protection of Biotechnological Inventions, 1998 O.J. (L 213) [hereinafter Biotech Directive].

69. European Patent Convention, Implementing Regulations to the Convention on the Grant of European Patents, Rule 27(a), Oct. 5, 1973, 1065 U.N.T.S. 199 (as amended June 28, 2018), https://www.epo.org/law-practice/legal-texts/html/epc/2016/e/r27.html [https://perma.cc/JRS2-4L5E] [hereinafter EPC Implementing Regulations].

70. *See, e.g.*, Case T 0666/05, Univ. of Utah Research Found. v. Institut Curie, ¶¶ 74–76, at 43 (EPO Boards of Appeal, 2008); Case T 0272/95 Howard Florey Inst. Of Experimental Physiology and Medicine v. Aglietta, ¶¶ 6–9, at 10–11 (EPO Boards of Appeal, 2002).

71. BGH Jan. 19, 2016, X ZR 141/13, http://juris.bundesgerichtshof.de/cgi-bin/rechtsprechung/document.py?Gericht=bgh&Art=en&Datum=Aktuell&Sort=12288&Seite=2&nr=74097&pos=78&anz=630 [https://perma.cc/Z3GL-HUJQ], *translated in* Allison Felmy, *"Receptor Tyrosine Kinase"*, 49 INT'L REV. INTELL. PROP. & COMPETITION L. 221, 226–27 (2018). It should be noted first that several EU member states have passed legislation that limits DNA claims to the function of the DNA described in the patent specification. *See* SVEN BOSTYN ET AL., FINAL REPORT OF THE EXPERT GROUP ON THE DEVELOPMENT AND IMPLICATIONS OF PATENT LAW IN THE FIELD OF BIOTECHNOLOGY AND GENETIC ENGINEERING 261 (2016), http://ec.europa.eu/DocsRoom/documents/18604/attachments/1/translations/_[https://perma.cc/KWM2-8VTK]. Second, the Court of Justice of the Europe Union in *Monsanto Technology LLC v Cefetra BV* arguably held that all DNA claims are limited to the

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European law is also generous with respect to natural correlations, methods of detection, and methods of in vitro diagnosis.[72] All of these claims are patent eligible provided something in the claim confers technical character. On molecular-test methods and the application of natural correlations, the Bundesgerichtshof in *Rezeptortyrosinkinase* (Receptor Tyrosine Kinase) held that a method claim for detecting a genomic variant, which correlated with an acute form of leukemia, was patentable subject matter.[73] The court reached this conclusion because the method included isolating DNA and other technical processes.[74] In reaching its decision, the Bundesgerichtshof also noted that, unlike US law under *Mayo*, European and German patent law do *not* require an "inventive surplus" or significantly more for the application of a natural law to be patent eligible.[75]

The UK High Court of Justice reached a similar outcome for broad method of detection (essentially a platform technology) patent claims in *Illumina, Inc. v. Premaitha Health PLC*.[76] The case considered several NIPT patents, including the European equivalent of the patent litigated in *Sequenom*. The claims were patent eligible (although several were invalidated for other reasons) because they included creation of analytic samples and detection of cffDNA—steps that do not occur in the natural world and are technical in nature.[77]

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function disclosed in the specification. *See* Claire Baldock, *Insights: The ECJ's Judgement in the Case of* Monsanto v Cefetra BV and Others, BOULT (Aug. 1, 2010), https://www.boult.com/bulletins/the-ecjs-judgement-in-the-case-of-monsanto-v-cefetra-bv-and-others/ [https://perma.cc/TJ7C-AXGN].

72. European law is stricter in relation to methods of in vivo diagnosis and methods of medical treatment. *See* EUROPEAN PATENT OFFICE, GUIDELINES FOR EXAMINATION IN THE EUROPEAN PATENT OFFICE pt. G, ch. II–4.2 (2019), http://documents.epo.org/projects/babylon/eponet.nsf/0/8654640290C2DBE7C12584A4004D2D9A/$File/epo_guidelines_for_examination_2019_hyperlinked_en.pdf [https://perma.cc/46VZ-C3E2].

73. BGH Jan. 19, 2016, X ZR 141/13, http://juris.bundesgerichtshof.de/cgi-bin/rechtsprechung/document.py?Gericht=bgh&Art=en&Datum=Aktuell&Sort=12288&Seite=2&nr=74097&pos=78&anz=630 [https://perma.cc/Z3GL-HUJQ], *translated in* Felmy, *supra* note 71, at 227.

74. *Id.*

75. *Id.*

76. *See* Illumina, Inc v. Premaitha Health PLC [2017] EWHC (Pat) 2930.

77. *Id.* at [184]–[189]. Despite Europe's generous rules on patent eligibility, European clinical genetic-testing laboratories have not encountered profound patent problems. *See* Johnathon Liddicoat et al., *Continental Drift? Do European Clinical Genetic Testing Laboratories Have a Patent Problem?*, 27 EUR. J. HUM. GENETICS 997, 1004–05 (2019).

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D. Predictions and Controversies

This Section describes the leading commentary, predictions, and empirical studies analyzing the differences between US and European law.

In the aftermath of *Myriad* and *Mayo*, a senior commentator stated that molecular tests are "not patent eligible" in the United States.[78] This prediction remains untested, but empirical studies have evaluated other effects. For instance, several studies have assessed how *Myriad* and *Mayo* have affected general aspects of patent practice in the United States. With regard to patents granted before the decisions, researchers have found that tens of thousands of patents are now at risk of invalidation.[79] And for patents prosecuted after the decisions, research indicates that the USPTO has issued thousands of office actions with 35 U.S.C. § 101 rejections, citing *Myriad* and *Mayo*.[80] Applicants have opportunities to overcome rejections, and many do; the data indicate, though, that patent-eligibility rules in *Myriad* and *Mayo* result in claims with narrower scope.[81]

Studies of USPTO patent examination and prosecution also show that a high proportion of applicants are abandoning applications with *Myriad*-related claims[82] and that applications that receive *Mayo*-based rejections spend much longer in prosecution (compared with claims that do not receive a *Mayo*-based rejection).[83] Scholars suggest that high rates of abandonment and long prosecution times indicate there is a high level of uncertainty surrounding the cases—in particular, uncertainty regarding how to draft patent-eligible claims.[84] A USPTO report, which elicited view from the public on § 101 law, reinforces this argument. The report details how practitioners have found the law "unworkable," creating excessive "unpredictability in the [granting of] patents."[85]

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78. Eisenberg, *supra* note 10, at 286.

79. *See* Mayo*'s Impact*, *supra* note 20, at 513; Graff et al., *supra* note 20, at 405; Haanes & Cànaves, *supra* note 20, at 758.

80. Mayo*'s Impact*, *supra* note 20, at 515; *Surgical Strike*, *supra* note 20, at 1147.

81. *After* Myriad, *supra* note 20, at 823–25; Alan Douglas Miller & Brian Amos, *Successful Strategies for Diagnostic Method Patents*, 23 J. COM. BIOTECHNOLOGY 39, 40–42 (2017).

82. *After* Myriad, *supra* note 20, at 822; *Surgical Strike*, *supra* note 20, at 1147.

83. Mayo*'s Impact*, *supra* note 20, at 516.

84. *After* Myriad, *supra* note 20, at 822–23; Mayo*'s Impact*, *supra* note 20, at 515. Uncertainty has also been highlighted in news-style articles. *See, e.g.*, Jeffrey L. Fox, *Industry Reels as Prometheus Falls and Myriad Faces Further Reviews*, 30 NATURE BIOTECHNOLOGY 373, 374 (2012).

85. U.S. PATENT & TRADEMARK OFFICE, *supra* note 16, at 30.

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Several commentators argue that *Myriad* and *Mayo* negatively affect the development and commercialization of molecular tests. Their arguments are based on three reasons.[86] First, patents are a useful instrument for coordinating multiple parties with complementary development skills, including marketers and scientific experts.[87] Patents have this effect because "parties know that only those who strike deals with each other involving the patent can avoid being excluded by the patent in court."[88] Second, molecular tests are often easy to imitate and produce at a lower price than the original developer. Such imitating is often called "free riding" and is more likely to arise in the United States under *Myriad* and *Mayo* because patents have a narrower scope or are unavailable.[89] Third, substantial investment, often funded by venture capitalists (VCs),[90] is needed to develop and validate tests, and the weakening of patent protection for molecular tests will inevitably cause VCs to shift their investments to other sectors of the economy that they know have more robust patent protection.[91]

In contrast, some question the need for patent protection. Between 2009 and 2010, the US Secretary's Advisory Committee on Genetics, Health, and Society studied the role of patents in the development of genetic tests.[92] The committee "concluded that patent-derived exclusive rights are neither necessary nor

86. James E. Daily & F. Scott Kieff, *Anything Under the Sun Made by Humans: Patent Law Doctrines as Endogenous Institutions for Commercializing Innovation*, 62 EMORY L.J. 967, 980 (2013). The authors do not specifically discuss molecular tests, referring instead to "biotechnology." However, it is quite clear that their analysis included it. For example, the authors discuss how *Mayo* affected *Myriad Genetics, Inc. See id.* at 978–80. It should also be noted that the authors published this article before *Myriad* was decided, meaning that they could not have considered the Supreme Court's decision. The authors' thesis in the article, however, makes it quite clear that they would have opposed the decision. *See also* Kieff, *supra* note 1, at 724–27.

87. Daily & Kieff, *supra* note 86, at 973–74; *see also* F. Scott Kieff, *On Coordinating Transactions in Intellectual Property: A Response to Smith's* Delineating Entitlements in Information, 117 YALE L.J. POCKET PART 101 (2007), http://yalelawjournal.org/forum/on-coordinating-transactions-in-intellectual-property-a-response-to-smiths-delineating-entitlements-in-information [https://perma.cc/XJN8-VX25].

88. Daily & Kieff, *supra* note 86, at 973.

89. *Id.* at 973, 980; *see also* Kieff, *supra* note 1, at 742, 747–48.

90. Holman, *supra* note 11, at 308.

91. *Id.*; *see also* Sanzo, *supra* note 11, at 20. Given Eisenberg stated that tests are not patent eligible, one might expect that she would then predict various specific harms to the development of tests. Interestingly, she didn't. Rather, she "hope[d]" that the cases will do more to enhance test development than to suppress it. Eisenberg, *supra* note 10, at 286.

92. SEC'Y'S ADVISORY COMM. ON GENETICS, HEALTH, & SOC'Y, U.S. DEP'T OF HEALTH & HUMAN SERVS., GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON PATIENT ACCESS TO GENETIC TESTS (2010), https://osp.od.nih.gov/wp-content/uploads/2013/11/SACGHS_patents_report_2010.pdf [https://perma.cc/R2V6-RR2N].

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sufficient conditions for the development of genetic test kits and laboratory-developed tests."[93] By "test kit," the committee was referring to commercial products made for sale to multiple laboratories.[94] Kits often include generic scientific materials (e.g., test tubes) as well as test-specific reagents (e.g., DNA test panels, software). However, this conclusion was based on estimated development costs of around $10,000,[95] an unrealistically low assumption given that diagnostic executives estimate the cost to fully develop a test, including clinical education, between $20.1 and $106 million in the United States alone.[96] That said, several factors do indicate that patent protection may not be important for development. For example, (i) developing molecular tests costs considerably less than developing pharmaceutical drugs;[97] (ii) multinationals are increasingly supportive of open-science initiatives for genomics research;[98] and (iii) patent holders often do not pay maintenance fees, meaning their rights lapse and become part of the public domain before the full twenty years of patent life is realized.[99]

Other commentators have different predictions about how *Myriad* and *Mayo* could affect test development. Some argue that innovators would turn to trade secret protection instead of patents,[100]

93. *Id.* at 35.

94. *Id.* at 12.

95. *Id.* at 94.

96. Doug Dolginow et al., *Mystery Solved! What Is the Cost to Develop and Launch a Diagnostic?*, DIACEUTICS (Jan. 15, 2013), https://www.diaceutics.com/?expert-insight=mystery-solved-what-is-the-cost-to-develop-and-launch-a-diagnostic [https://perma.cc/QB7Z-HJ39]; *see also* Sachs, *supra* note 19, at 1894–95.

97. *See* JORGE MESTRE-FERRANDIZ ET AL., OFFICE OF HEALTH ECON., THE R&D COST OF A NEW MEDICINE (2012), https://www.ohe.org/publications/rd-cost-new-medicine [https://perma.cc/EFZ2-JJWW]; Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 20 (2016); *cf.* Donald W. Light & Rebecca Warburton, *Demythologizing the High Costs of Pharmaceutical Research*, 6 BIOSOCIETIES 34 (2011).

98. KATHLEEN LIDDELL, REALISING GENOMIC MEDICINE: INTELLECTUAL PROPERTY ISSUES 4 (2015), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3102224 [https://perma.cc/RTX4-7BHA].

99. Johnathon Liddicoat et al., *Are the Gene-Patent Storm Clouds Dissipating? A Global Snapshot*, 33 NATURE BIOTECHNOLOGY 347, 350 (2015).

100. *See, e.g.*, Arti K. Rai & Jacob S. Sherkow, *The Changing Life Science Patent Landscape*, 34 NATURE BIOTECHNOLOGY 292, 294 (2016); Kevin E. Noonan, *Roche Molecular Systems, Inc. v. Cepheid (Fed. Cir. 2018)*, PAT. DOCS (Oct. 10, 2018), https://www.patent-docs.org/2018/10/roche-molecular-systems-inc-v-cepheid-fed-cir-2018.html?utm_source=feed-burner&utm_medium=email&utm_campaign=Feed%3A+PatentDocs+%28Patent+Docs%29 [https://perma.cc/ZTG7-MTU6]; *see generally* Derek E. Bambauer, *Secrecy Is Dead - Long Live Trade Secrets*, 93 DENV. L. REV. 833, 838 (2016); Chris Palmer, *The* Myriad *Decision: A Move Toward Trade Secrets?*, 22 NIH CATALYST, Mar.–Apr. 2014, at 9; Taylor, *supra* note 9, at 229.

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with the negative effect that innovations would be kept from society.[101] One study explored this prediction by interviewing patent practitioners, legal academics, and scientists involved with genetic technology.[102] It found increased interest in trade secrets but no instances of parties using trade secrets instead of patents.[103] That said, the study interviewed people who might advise others to rely on trade secrets, not those who would actually make the decision.[104]

The divergence between US and European patent-eligibility law led some commentators to question whether there would be ripple effects for Europe.[105] Would European organizations be advantaged by the more generous European patentable subject-matter laws? Most commentators predicted that the effect, if any, would be negligible.[106] The reasoning here was that US patent law applies equally to US and European organizations and that the United States is likely the most lucrative market for most tests.

This Section describes the leading commentary, predictions, and empirical studies analyzing the differences between US and European law. In particular, this Section focuses on commentators' predictions of how *Myriad* and *Mayo* would adversely affect the development of molecular tests. These predictions build on orthodox justifications for patents and suggest that test developers now avoid developing tests due to narrower scope of protection and increased uncertainty that patents are valid.

III. RESEARCH QUESTIONS AND METHODS

This Part describes the research questions and methods in this Article. The research questions build on the predictions in the previous Section, and the methods primarily concern how the interviews were arranged and conducted.

101. Anna B. Laakmann, *The New Genomic Semicommons*, 5 U.C. IRVINE L. REV. 1001, 1013–16 (2015); Noonan, *supra* note 100; *see also* Robert Cook-Deegan et al., *The Next Controversy in Genetic Testing: Clinical Data as Trade Secrets?*, 21 EUR. J. HUM. GENETICS 585, 585 (2013).

102. Christi J. Guerrini et al., *Constraints on Gene Patent Protection Fuel Secrecy Concerns: A Qualitative Study*, 4 J.L. & BIOSCIENCES 542, 546 (2017).

103. *Id.* at 553.

104. *Id.* at 562.

105. LIDDELL, *supra* note 98, at 6–7; Nicol et al., *supra* note 6, at 535.

106. LIDDELL, *supra* note 98, at 6–7.

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A. Research Questions

This Article's study set out to explore whether any of the negative effects and consequences predicted by the commentators were evident in the development of molecular tests. The study also explored whether the effects were felt equally by US- and European-headquartered organizations.

Each interview was semistructured, meaning they were organized around a series of questions that permitted in-depth exploration of the various issues under research:

1. What role do patents and other intellectual property (IP) play in the development of molecular tests?
2. How (if at all) have patent prosecution strategies changed after *Myriad* and *Mayo*?
3. Does *Myriad* or *Mayo* create problematic uncertainty?
4. In what ways (if any) have developmental strategies altered due to *Myriad* and *Mayo*?
5. Does *Myriad* or *Mayo* create a disadvantage for US-headquartered organizations compared with European counterparts?

B. Methods

This study was designed to complement the results of previous empirical studies, which analyzed the impact of *Myriad* and *Mayo* at the macro level, by conducting semistructured interviews at the micro or organizational level. Semistructured interviews, which do not follow a rigorous set of questions but do cover the same set of topics with each interviewee, permit deep analyses of issues and flexibility based on interviewees' responses. Thus, semistructured interview-based research is particularly useful in obtaining complex information about experiences and decision-making, especially from individuals who share similar interests and respond to the same events.[107] Indeed, interview-based research, notwithstanding small sample sizes, has some advantages over other empirical methods, such as surveys, because it can identify and obtain context-rich data to explain previously unknown responses.[108] These attributes of interview-based

107. NATASHA MACK ET AL., QUALITATIVE RESEARCH METHODS: A DATA COLLECTOR'S FIELD GUIDE 1–4 (2005); HERBERT J. RUBIN & IRENE S. RUBIN, QUALITATIVE INTERVIEWING: THE ART OF HEARING DATA 1–18 (2d ed. 2005).

108. RUSSELL K. SCHUTT, INVESTIGATING THE SOCIAL WORLD: THE PROCESS AND PRACTICE OF RESEARCH 328–29 (7th ed. 2012).

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research are particularly important in the molecular-test industry, where little is known about how organizations use patents in their development strategies[109] and the development of tests can be complex.[110]

C. Interviewee Inclusion Criteria and Characteristics

This Section gives an overview of the people that were interviewed, including the criteria that were used to determine if someone should be interviewed.

Three different categories of industry participants were interviewed: patent practitioners, executives at molecular-test companies, and technology-transfer office (TTO) managers at research institutes or universities. At least six interviews were conducted in each category in both the United States and Europe. Thirty-seven interviews were conducted in total.

Four interviews were conducted face-to-face and thirty-three were conducted via phone. Thirty-five interviewees agreed to have the interview recorded and transcribed. The other two interviewees agreed to have notes taken during the interview, which were supplemented immediately after the interview. The interviews were coded using NVivo 11 for Mac, according to the research questions, in order to perform thematic analysis, which refers to analyzing the data to find patterns and themes in responses to the questions, as well as latent content analysis, which looks to draw greater meaning from the interviews by combining responses from different questions.[111]

Recruitment began in February 2017, and the last interview was conducted in July 2018. This seventeen-month period was primarily due to protracted recruitment of companies. Making contact with them was challenging, especially in the United States where contact details for potential interviewees are infrequently published online. Before any individual was invited to participate, their profile was checked to ensure they dealt with molecular-test technology and IP. No

109. *See* Ashish Arora & Suma Athreye, *Introduction to the Special Section on Patent Use*, 45 RES. POL'Y 1323, 1323 (2016). Some of the better explorations of how patents fit into organizations' development strategies have been performed by the US Department of Health and Human Services. *See* SEC'Y'S ADVISORY COMM. ON GENETICS, *supra* note 92, at 20–35.

110. *See* Aleksandr Ivanov, *Barriers to the Introduction of New Medical Diagnostic Tests*, 44 LAB MED. e132 (2013); Rosanna W. Peeling et al., *A Guide for Diagnostic Evaluations*, 4 NATURE REVIEWS MICROBIOLOGY S2 (Supp. 2006); Sachs, *supra* note 19; D. L. Sackett & R. B. Haynes, *The Architecture of Diagnostic Research*, 324 BMJ 539 (2002).

111. *See* MARIA J. MAYAN, ESSENTIALS OF QUALITATIVE INQUIRY 93–94 (2009).

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interviewee was offered an inducement to participate, and all were assured anonymity. All interviewees gave verbal consent to participate.

The average interview lasted forty-eight minutes, with a range of twenty-nine to seventy-six minutes. Although the interview times varied considerably, all topics were explored with each interviewee. Two reasons account for the range of interview times: (i) interviewees had varying experience with *Mayo* or *Myriad*, and (ii) interviewees engaged in discussion to varying degrees of detail.

Interviewee recruitment varied depending on the category. Patent practitioners were identified from lists of highly ranked practitioners.[112] US practitioners were recruited from across the country, and European practitioners were recruited from the United Kingdom only. US practitioners included agents and attorneys, and UK practitioners included attorneys and solicitors. Interviewees with different training and different skills (e.g., drafting patents or drafting transactions) were included in order to ensure that all of the various issues at stake here were covered. All practitioners interviewed were partners except one who was an associate with seven years' experience and was described by a partner as an expert in the field. All invitations to practitioners were sent via email.

Companies were recruited via online searches, attendee lists from conferences, and a specialized website.[113] The companies interviewed were headquartered across Europe and the United States. The size of the companies interviewed varied: one company from the United States and one company from Europe identified as large; two from each territory identified as medium-sized; and the other companies identified as small. One small company in the United States and two from Europe had yet to launch a molecular test. All companies (from both territories) had at least one test they were developing that was "highly innovative" in the sense that it offered insights not currently available to medical practitioners and was based on new biomarkers or scientific techniques. Such tests would, for example, identify patients that would not benefit from surgery but are currently treated as patients that would.

TTOs were recruited only from leading biological science institutes, as indicated in research rankings (e.g., The Times Higher

112. CHAMBERS & PARTNERS, https://chambers.com [https://perma.cc/6AUN-PSDU] (last visited Mar. 23, 2020); IP STARS, https://www.ipstars.com [https://perma.cc/W37Y-8NF8] (last visited Mar. 23, 2020); LEGAL 500, http://www.legal500.com [https://perma.cc/JJ25-YKR7] (last visited Mar. 23, 2020); LMG LIFE SCI., https://www.lmglifesciences.com [https://perma.cc/Y9EM-CMFD] (last visited Mar. 23, 2020).

113. BIOPHARMGUY, https://biopharmguy.com [https://perma.cc/LWT5-UTXT] (last visited Mar. 23, 2020).

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Education World University Rankings). US TTOs were recruited from across the United States, and European TTO managers were recruited from the United Kingdom only, due to proximity and familiarity with English. All invitations to TTOs were sent via email.

IV. RESULTS: INTERVIEW DATA

This Part describes the results from the interviews, largely following the order of the research questions.[114]

A. What Roles Do Patents and Other Intellectual Property Play in the Development of Molecular Tests?

To appreciate properly the importance of patents for molecular-test development (and therefore the implications of *Myriad* and *Mayo*), this Section begins by summarizing the responses on the technical and economic environment in which test developers operate. This Section then proceeds to describe how TTOs and companies use patents and other IP when developing molecular tests.

1. Background on Developing Molecular Tests

Companies and TTOs described developing tests as generally a high-risk proposition. No interviewee gave specific data on the chances of a new test making it to market, but they estimated a test had a worse chance of successfully reaching market than, for example, new mechanical equipment, but a better chance than a drug. Several companies also described how costs could vary substantially from $1 million to $150 million for the full development and launch of a test in multiple countries and could vary in duration from two to thirty years. These figures roughly align with the literature.[115] They also explained that developing new molecular tests that rely on new biomarkers or new technical instruments is normally at the more expensive end of the spectrum. The novelty of the biomarker or instrument means that there is little scientific support at the outset; it must be generated.

114. Due to privacy concerns, the interviews cited in this Article are confidential. They remain on file with the Authors.

115. *See* JOSH MAKOWER ET AL., FDA IMPACT ON U.S. MEDICAL TECHNOLOGY INNOVATION: A SURVEY OF OVER 200 MEDICAL TECHNOLOGY COMPANIES 28 (2010), https://www.advamed.org/sites/default/files/resource/30_10_11_10_2010_Study_CAgenda_makowerreportfinal.pdf [https://perma.cc/RTQ9-3ETH]; Dolginow et al., *supra* note 96; *see also* Aaron V. Kaplan et al., *Medical Device Development*, 109 CIRCULATION 3068, 3069, 3072 (2004).

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One company provided a relatively precise account of costs, based on the money it had raised for the development of a new test using a new platform. Overall, it had spent €130 million over ten years. Approximately 80 percent of that was spent on technical development, including clinical trials and scaled-up production. The remainder was spent on commercialization, including marketing, development of supply chains, and clinical education. On clinical education, the company commented that it is expensive and challenging to inform medical professionals about new tests and convince them to implement tests into their workflows, even with data showing the test is cost-effective and improves patient outcomes.[116] Indeed, that company commented that it launched its product after five years of technical development but had continued to invest in work to demonstrate utility and to educate professionals.[117]

The companies mentioned various other challenges surrounding the development of tests and their patent positions. Two challenges were described by every company, indicating common importance: regulation and reimbursement. In the United States, diagnostic kits are regulated by the Food and Drug Administration (FDA), and the regulatory challenges center on the data needed for FDA authorization (clearance or approval). Companies described various issues in obtaining authorization, including difficulties with clinical trial design and recruitment,[118] not to mention results, which may or may not support authorization. Companies also described how it could take years to receive market authorization, especially in the case of technology and biomarkers unfamiliar to the FDA. This finding is echoed in the literature.[119] European regulation for market authorization of molecular-test kits was considered a lower hurdle, although several companies said it could still pose a challenge because the regulator might ask for different data.[120] They also said European regulation is set to change, with the In Vitro Diagnostic Medical Devices

116. *See* Ivanov, *supra* note 110, at e135.

117. The Authors did not interview people responsible for incorporating tests into medical practice. However, various sources describe the myriad concerns and evaluations that are often considered before a test is incorporated. *See id.*; Peeling et al., *supra* note 110; Steven M. Teutsch et al., *The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: Methods of the EGAPP Working Group*, 11 GENETICS MED. 3 (2009).

118. *See* Sackett & Haynes, *supra* note 110 (describing specific challenges at trials).

119. CAMBRIDGE CONSULTANTS, THE FUTURE OF DIAGNOSTICS: A CONSUMER DRIVEN WORLD?: THE US PERSPECTIVE 9 (2007), http://www.medevien.com/landing/pdfs/US_Diagnostics_Report.pdf [https://perma.cc/6L52-ATKE]; MAKOWER ET AL., *supra* note 115, at 6.

120. *See* MAKOWER ET AL., *supra* note 115, at 6; Kaplan et al., *supra* note 115, at 3071–72.

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Regulation ushering in higher standards.[121] Analysts suggest that under the earlier law the "majority" of test kits are self-certified, but under the new regime 80 percent will be reviewed by a regulator.[122]

In many cases, the need for FDA clearance or approval can be avoided if companies choose to launch a laboratory-developed test (LDT) instead of a test kit. LDTs need to comply with less onerous clinical-laboratory laws.[123] This means LDTs can generally be developed faster and cheaper than kits, but there are tradeoffs that may affect supply or demand.[124] One tradeoff is that LDTs require a reference laboratory, where clients must send samples for processing. This might be inconvenient, or samples might degrade when they are sent to the reference laboratory for testing. Companies also described how LDTs typically have lower reimbursement rates, in part because the FDA has not reviewed them.

The respondents described reimbursement challenges as just as important, if not more important, than all other challenges. "Reimbursement" refers to the processes by which physicians and hospitals receive payments (usually from insurers) for the products and services they provide patients, such as molecular tests.[125] Reimbursement determinations are made by private or public payors after analyzing clinical and economic data to determine the clinical value and effectiveness of a test.[126] All companies with experience in US reimbursement determinations (five of six companies in the United States, and four of six in Europe) described them as complex and

121. Regulation 2017/746, of the European Parliament and of the Council of 5 April 2017 on In Vitro Diagnostic Medical Devices and Repealing Directive 98/79/EC and Commission Decision 2010/227/EU, 2017 O.J. (L 117) 176.

122. *See* RONALD BOUMANS, EMERGO, UNDERSTANDING EUROPE'S NEW IN VITRO DIAGNOSTIC MEDICAL DEVICES REGULATION: WHAT MANUFACTURERS NEED TO KNOW AHEAD OF IVDR IMPLEMENTATION 1 (2016), https://www.emergobyul.com/resources/articles/white-paper-eu-ivdr [https://perma.cc/LG9M-NVFD]; HOWARD BROADBRIDGE, NSF HEALTH SCIS. MED. DEVICES, NEW EU MEDICAL DEVICE REGULATION ADOPTED APRIL 5TH 2 (2017), https://www.nsf.org/newsroom_pdf/NSF_MD_EUMDR_Industry_Forum_Whitepaper_LT_EN_LMD-748-0417_REF.pdf [https://perma.cc/6Z4E-GLXF].

123. *Laboratory Developed Tests*, FDA, https://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/laboratorydevelopedtests/default.htm [https://perma.cc/C3WH-PH74] (last updated Sept. 27, 2018). *But see* Ivanov, *supra* note 110, at e132 (describing an exception to this position).

124. *See* Roger D. Klein, *Intellectual Property and Regulation of Molecular Pathology Tests*, 20 CANCER J. 85, 88–89 (2014).

125. Martin Gold, *Getting Reimbursement for Your Product in the United States*, NATURE: BIOENTREPRENEUR (June 23, 2003), https://www.nature.com/bioent/2003/030601/full/bioent738.html [https://perma.cc/BQ7R-PZSF].

126. *Id.*

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time-consuming,[127] especially due to the different approaches for determining reimbursement. Companies noted that similar challenges were faced between European countries, due to different systems, and that some individual European countries presented US-like issues, but not on the same scale of complexity.[128]

The molecular-test industry distinguishes between three types of data for molecular tests: (i) analytic validity, the ability to measure accurately and reliably the marker of interest; (ii) clinical validity, the strength of association between the biomarker(s) and the clinical outcome(s); and (iii) clinical utility, the effect the test has on patient management coupled with economic value.[129] Companies noted that it was possible to launch tests in the United States and Europe without clinical-utility data and with no plans to produce any, thereby avoiding the cost and inconvenience of generating the data; but they advised that this was often not a prudent commercial decision, primarily because payors would be less willing to reimburse the test or only do so at a relatively low rate.[130] All companies described how they conducted clinical trials and combined this data (or at least planned to) with economic analyses to produce clinical-utility data.

2. TTOs

TTOs stated unanimously that patents were core to their work. None aimed to launch a test themselves, and it was important to them to transfer the technology fairly early in its development to another organization either by licensing or assigning the technology. They described patents as core because they offered definable, exclusive, and transferable rights. Patents helped attract partners and VC funding for early development.[131] Without patent protection, TTOs said they had little to offer in a deal because their researchers' work would be

127. *See id.*

128. *See* Kaplan et al., *supra* note 115, at 3071–72.

129. Teutsch et al., *supra* note 117, at 6; Gold, *supra* note 125.

130. *See generally* Julia R. Trosman et al., *Health Technology Assessment and Private Payers' Coverage of Personalized Medicine*, 7 J. ONCOLOGY PRAC. 18s (2011); Gold, *supra* note 125. Similarly, FDA clearance does not guarantee clinical update either, especially without clinical-utility data. *See Recommendations from the EGAPP Working Group: Testing for Cytochrome P450 Polymorphisms in Adults with Nonpsychotic Depression Treated with Selective Serotonin Reuptake Inhibitors*, 9 GENETICS MED. 819 (2007).

131. *See* Jason Owen-Smith & Walter W. Powell, *To Patent or Not: Faculty Decisions and Institutional Success at Technology Transfer*, 26 J. TECH. TRANSFER 99, 108 (2000); George Poste, *Molecular Diagnostics: A Powerful New Component of the Healthcare Value Chain*, 1 EXPERT REV. MOLECULAR DIAGNOSTICS 1, 2 (2001).

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published. Indeed, all TTOs thought that transferring test technology without a patent was unlikely.

TTOs also stated unanimously that they tended to avoid licensing strategies based on trade secret protection but did value know-how. The problem with licensing strategies based on trade secrets was that they could compromise researchers' abilities to publish for the duration of the deal.[132] Know-how, which refers to practical knowledge or skill, is different because although researchers might not keep it a secret, the industry norm is not to write about it. Know-how can retain value because often only a few people know about it; examples included details of how to use a specific instrument or optimize an assay.[133]

TTOs discussed other types of IP but only occasionally identified them as valuable. For instance, copyright might sometimes play an important role, particularly if it protected compilations of data or algorithms. Generally, however, they said copyright conferred only a weak advantage because, as a matter of collaborative behavior, data were often shared and combined with other data without intending the use to be exclusive (especially in large research consortia) and, as a legal matter, copyright protection did not prevent similar algorithms being produced using the underlying ideas. Other forms of IP, including European database rights and trademarks, were briefly discussed but dismissed as generally not useful.

TTOs also discussed competitive advantages other than IP. Four TTOs describe how physical property could be important in deals. For example, they might have a reagent or instrument important for the molecular test that was known and used by their organization only or at most by a small number of other people worldwide. The TTOs acknowledged that other parties could probably make the property with a degree of effort, but given the TTOs' existing expertise, the property could form a valuable competitive advantage. Other competitive advantages included scientific lead time and star scientists.[134] Without these, competitors would find it difficult to imitate tests. Star scientists with a track record of successful innovations added extra value.

132. One TTO did describe licensing a test based on confidential data without a patent. They admitted, though, that this was the exception to the rule, and it arose as a concomitant of the research rather than a deliberate strategy.

133. The importance of know-how (otherwise known as "tacit knowledge") has been described elsewhere. *See, e.g.*, Ashish Arora, *Contracting for Tacit Knowledge: The Provision of Technical Services in Technology Licensing Contracts*, 50 J. DEV. ECON. 233 (1996).

134. *See* Lynne G. Zucker & Michael R. Darby, *Star Scientists and Institutional Transformation: Patterns of Invention and Innovation in the Formation of the Biotechnology Industry*, 93 PROC. NAT'L ACAD. SCI. U.S. AM. 12709 (1996).

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However, in all circumstances, the TTOs described how the value of these advantages varied and were not necessary for a deal.

The core nature of patents prompted discussions about patent prosecution strategies. The TTOs used slightly differing strategies but also shared some common elements. All TTOs preferred to transfer technology as early as possible in the patent's lifecycle. One TTO said they preferred to license before a provisional application expired and before they had to make the more expensive full patent application, enabling them to pass on the patent filing costs.[135] A number of TTOs described that they were generally happy to hold patents filed via the Patent Cooperation Treaty (PCT)[136] until national-phase entry[137]—that is, usually thirty months from the earliest priority date.[138] The reason for this was that national-phase costs are significantly higher than those incurred when initially filing.[139] Only two TTOs commented that they held patents longer than this on a regular basis without interest from a potential licensee.

One difference between US and European TTOs' patenting strategies was the jurisdiction where protection was sought. All the US TTOs said they focused on the United States as their primary market and would always seek patent protection there. Five US TTOs added they would look at Europe as well as other territories (e.g., Canada, China, Japan, Australia) as secondary considerations. Obtaining foreign protection, however, depended on many variables, including

135. A US practitioner stated that the practitioner knew of several TTOs that often used the date of a full application as a deadline for some projects. That is, if the test was not licensed by then, the TTOs' role in developing the test would cease.

136. Patent Cooperation Treaty, June 19, 1970, 28 U.S.T. 7645, 1160 U.N.T.S. 231.

137. "National phase" is "the second of the two main phases of the PCT procedure. It follows the international phase and consists in the processing of the international application before each Office of or acting for a Contracting State that has been designated in the international application." *See Chapter 2: Entry into the National Phase (General)*, WIPO, https://www.wipo.int/pct/en/guide/np02.html#_chapt2 [https://perma.cc/E9X7-ATTL] (last visited Mar. 23, 2020).

138. *PCT FAQs – Protecting Your Invetions Abroad: Frequently Asked Questions About the Patent Cooperation Treaty (PCT)*, WIPO, https://www.wipo.int/pct/en/faqs/faqs.html [https://perma.cc/YHZ2-HLTD] (last updated Oct. 2017); *Time Limits for Entering National/Regional Phase Under PCT Chapters I and II*, WIPO, https://www.wipo.int/pct/en/texts/time_limits.html [https://perma.cc/4PRN-MA3Z] (last updated Jan. 2, 2020).

139. Anthony de Andrade & Venkatesh Viswanath, *Estimating the Cost for Filing, Obtaining and Maintaining Patents Across the Globe*, IPWATCHDOG (Aug. 28, 2016), https://www.ipwatchdog.com/2016/08/28/cost-filing-obtaining-maintaining-patents/id=72336/ [https://perma.cc/XH5H-ZKEJ]; *Delaying the Costs Associated with National Stage Entry*, RWS (Apr. 9, 2013), https://www.rws.com/insights/delaying-the-costs-associated-with-national-stage-entry/ [https://perma.cc/CC5D-YP4U]; *The Financial Realities of Patent Protection*, DEHNS, https://www.dehns.com/site/information/information_sheets/the_cost_of_a_patent/ [https://perma.cc/PE8Q-Y3H3] (last visited Mar. 23, 2020).

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potential markets and potential licensees. The remaining TTOs stated they would consider patent protection outside the United States only if a licensee had shown interest in the test technology. All European TTOs, by contrast, stated that European and US patent protection were of similar importance. TTOs (in both territories) also stated there were exceptions to these strategies, such as when the test is specifically designed for use in developing countries. In general, however, European TTOs were likely to obtain both US and European patents as a top priority, whereas US TTOs would always obtain US protection and consider European patents (or patents elsewhere) as a secondary consideration.

TTOs described that their decisions on international patent protection were mostly determined by a sense of where profits could be made. Indeed, all interviewees, not just TTOs, commented that if a molecular test was launched around the world (or at least in the territories mentioned), US profits would be the most valuable, with sometimes half of the overall profit made there.

3. Companies

The companies interviewed were united in their view that patents were important for the development of molecular tests.[140] None of them were developing a test without patent protection. However, they had different views on the role patents played, and they also relied on patents less than TTOs.

Companies often used patents in more than one role. The most common roles were that they could attract partners and investment (VC, private equity, or strategic investors). Eleven companies noted that patents were key for this function. Nine of these eleven companies also said that patents blocked, or potentially blocked, competitors from entering their markets and that the exclusive rights provided by a patent attracted partners and VCs.

All companies had some experience producing clinical-utility data and were able to speak about the connection between such data and patents. Five said that there was a direct connection between obtaining patents, funding, and partners (where necessary) and that, therefore, patents affected their ability to produce clinical-utility data.[141] Another three companies also thought that patents had some

140. *See* Sibylle Gaisser et al., *The Phantom Menace of Gene Patents*, 458 NATURE 407, 408 (2009).

141. *See also* Kathleen Liddell et al., *Patents as Incentives for Translational and Evaluative Research: The Case of Genetic Tests and Their Improved Clinical Performance*, 2008 INTELL. PROP.

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bearing on the production of clinical-utility data but that this work actually depended to a greater extent on other factors, such as the team behind the test, the potential profit of the test, and other competitive advantages.

Three of the companies that saw a connection between patents and the resources that went into producing clinical-utility data were critical of the emphasis that some partners and VCs placed on patents. In their experience, by the time products were launched, the patents offered limited or no protection. They also commented that competitors could often "invent around" patents and produce similar tests without infringing. At the same time, however, these companies acknowledged that patent protection was useful for deterring others from simply copying the test. They also noted that knowing in advance whether patent protection will be important for the test's final market is often difficult; generally only in hindsight are there indications of whether patent protection was necessary or not. The final test market is often different from the market that was envisaged at the time of application for patent protection.

Two companies also thought that patents gave them confidence that they had freedom to operate (FTO). Part of the patenting process is to generate search reports and prior art analyses, and, in doing this, those companies become more confident that they are not infringing other patents. Other companies (and practitioners) were critical of this approach, insisting that conclusions about FTO should be drawn only after a formal FTO analysis and that search reports should not be used as proxies.

Corporate views about the jurisdictions for seeking patent protection followed a similar pattern to the TTOs. That is, US companies primarily focused on US patents, while European companies focused on both US and European patents. Three examples illustrate these approaches: (i) a US start-up let its European patents lapse because the company did not think it had the resources to pursue a European launch and because the patents were expensive to maintain; (ii) a midsize US company said it had launched in Europe but had not been able to make substantial profits there, despite holding a patent; and (iii) a midsize European company launched first in Europe and then in the United States, and then subsequently moved the bulk of its operations to the United States, where it was generating the most profit.

Q. 286, 287 (discussing whether the patent system provides an effective incentive for producing and disseminating genetic diagnostic tests with good clinical validity).

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A distinguishing characteristic between TTOs' and companies' use of IP was that companies thought, in addition to patents, trade secrets could be particularly valuable. For example, they foresaw useful and valuable trade secrets in data, algorithms, reagents, methods, and ways to optimize tests. A trade secret reported by one company was a "dummy" component inserted into its kit to make copying more challenging and infringing activity easier to identify. One company even rated a trade secret as more valuable than its patents because, in its opinion, the trade secret was the key to copying the test.

Companies described several other types of competitive advantage. Like TTOs, they referred to star scientists, scientific lead time, and physical property, and they described how their approach to these advantages did not differ substantially. In addition, two companies commented that a type of clinician inertia gave them some advantage. That is, competitors had to convince medical professionals to "switch" to a new test kit, which could be difficult for them due to the goodwill in the test and the technology platform they had generated. These companies even admitted their technology was open to copying; the scope of their patent protection did not completely cover their tests, which had changed since the original patent applications, but no competitors had yet entered.

Other forms of competitive advantage available to companies included negotiating reimbursement rates and overcoming regulatory hurdles. Six companies described how these steps required significant time and expertise and that competitors could not enter their markets unless they too could address these challenges. These companies acknowledged that LDT providers could compete with kit providers but said that, in many ways, these were different markets. For example, a laboratory would be reluctant to send a test to a reference laboratory if it could perform the test more quickly and at a similar price using a kit.

B. Adapting to Myriad*: Drafting Claims, Uncertainty, and Development Strategies*

This Section details how interviewees adapted to issues presented by *Myriad*. It focuses on changes to drafting patent claims, certainty regarding the validity and the grant of patents, and changes to commercial strategies for developing molecular tests.

1. Practitioners

US practitioners stated that, in principle, they had a clear idea about what amounted to an eligible claim for molecular-test technology

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in compliance with *Myriad*. This means that they thought they could draft claims that examiners were likely to consider patentable subject matter or that, if given a claim, they had a confidence in their assessment of whether it was valid. A consequence of *Myriad*, however, was that they generally thought that the individual claims were narrower in scope and thus offered less valuable protection.[142] One practitioner agreed with this comment from the viewpoint of individual claims, but they also argued that the variety of different claims that they could obtain for nature-based products often meant that, cumulatively, their clients obtained a similar breadth of protection. One practitioner thought that there was still some uncertainty for some nature-based products, and another admitted to being "very cautious" when approaching claims that raised *Myriad* issues. Yet both were relatively confident in what they considered eligible.

The picture differed for patents granted before *Myriad* was decided. The practitioners thought that many patents were likely invalid, but only one practitioner had advised on one. That practitioner explained that the patent was identified in an infringement dispute. The litigants accepted it was invalid, so the case continued based on other patents. The practitioner also added that, even if valid, the patent was unlikely to have a bearing on the dispute because the technology was now quite old and had been superseded by noninfringing technology.

On test development strategies, all US practitioners described how *Myriad* had prompted more discussions with clients on trade secrets, but none knew of clients that had decided to use trade secrets *instead of* patents. Similarly, none of the practitioners knew of a client who had changed a development strategy due to the case.

European practitioners' experience with *Myriad* was similar to their US counterparts, albeit they added that they probably encountered fewer *Myriad*-related issues because clients could raise them with US practitioners without involving European advisers. None of the European practitioners reported particular difficulties advising on *Myriad*-related issues. Likewise, none of the European practitioners reported that a client had changed development strategies due to the case.

Two European practitioners reported substantial issues with *Myriad* for nature-based products *unrelated* to molecular tests. One practitioner described how they had encountered ongoing difficulties obtaining claims for a cell-based therapeutic, elaborating that if the

142. Many of the ways to draft *Myriad*-compliant claims have been described. *See, e.g.*, *After* Myriad, *supra* note 20, at 823–24.

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claim to the compound was not granted, then third parties might be able to imitate the drug. The practitioner added that the method claims they were pursuing were probably valid and would probably provide their client with enough protection; nevertheless, the practitioner thought the case created an unnecessary risk for the drug's development. The other practitioner reported that a US pharmaceutical client had abandoned development of a drug because *Myriad* limited the protection available for the compound and therefore made the project too risky.

2. Companies

Of the six US companies interviewed, four had *not* encountered *Myriad*-related issues. They commented that they had not needed to seek patent protection for products merely isolated from nature; therefore, the case passed largely unheeded. One of these companies recalled a situation when it could have obtained patent protection for a biomarker, assuming it was not recorded in prior art databases, but the respondent noted that the point was moot because it had obtained sufficient patent protection with other claims.

The remaining two US companies had encountered *Myriad* issues, but only one said its business operations had been affected by it. The company that had not been affected explained that, during the due-diligence process for a business deal, it found patent claims that were probably invalid pursuant to the case. However, it also decided that this had little consequence because even if the claims were valid, the patents would have provided limited protection for the molecular tests.

The sixth company had a much more complex story. It described a situation where it had a number of patents granted on *Myriad*-related subject matter before the decision, plus several pending patents where the examination process commenced before the decision and carried on afterwards. It also said that it had continued to apply for similar patents after the decision. The company said that, immediately after the case, patent examiners raised *Myriad*-based rejections that narrowed the pending patents. It lost claims the company desired for its business and thought that, even after examination concluded, there was a higher-than-normal degree of uncertainty about the validity of some claims. As for the patents granted before the decision, the company recognized that many of the claims had doubtful validity, but it had not amended them because of the difficulties and risks in that process. It also added there was some value in leaving these patents on the register, as the patents might discourage competitors from

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researching in the area or encourage potential partners to contact the company. Despite the fact that *Myriad* had narrowed and introduced risks to its patent protection, the respondent said that this had not altered the company's business strategies. That said, it was quite sure that the value of its deals had decreased. It was difficult, the company said, to quantify the impact because such deals included a variety of factors of which patents are only one part, albeit an important one.

European companies' experiences with *Myriad* were similar to their US counterparts. Two described that they had never patented nature-based products, so the case had not affected them. A third company thought that it *may* have acquired some US patents covering isolated DNA in a deal five to ten years ago, but this had not become a prominent business issue, as the patents were *not* part of their current development strategies.

The remaining three European companies described more substantial interactions with the case. Two said they had prosecuted biomarker patents in Europe and the United States before and after *Myriad* was decided and, as a resulted of the decision, had amended US applications to obtain granted patents with narrower scopes of protection compared with the European patents. Despite the narrower US claims, they stated that their test development strategies remained unaltered. Part of the explanation was that, overall, the breadth of their US patent protection remained similar before and after *Myriad* when one considered the narrowed claims in combination with other claims. They also added that they had a normal degree of confidence (and doubt) in the validity of their granted US patents. The sixth company described a similar experience with the case, involving narrower US claims but unchanged development strategies. This company, however, raised another issue—namely, the narrower protection might devalue commercialization licenses in the United States, resulting in a lower royalty stream. The company considered that it might be overstating this possibility, as it had other types of patent protection and many other factors influence royalty calculations. Nevertheless, the company still thought this was a valid concern.

3. TTOs

US TTOs were more aware of, and more affected by, *Myriad* than the European TTOs. All the US TTOs commented that, after a short learning period, they were relatively confident applying the court's ruling in *Myriad* and knowing what was and was not eligible. Four added, though, that claims to isolated naturally occurring

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compounds were not particularly valuable or common (even prior to the case) and that the case had *not* affected their development strategies.

In contrast, two US TTOs described situations where the decision had affected their development strategies. The first said that a scientist had disclosed a molecular test based on a naturally occurring compound and that, together, they had decided that without a patent on the molecule they would have insufficient protection to develop the test. In response, they decided the scientist should conduct additional experiments to try to develop a slightly different test for which they could obtain commercially valuable claims. Possible claims included *Myriad*-compliant compounds (i.e., nature-based compounds that were markedly different from naturally occurring equivalents) and methods that covered different ways of performing the test and were *Mayo*-compliant. The TTO reported that this research had generated positive results; however, a patent was yet to be drafted. The other TTO stated that an invention was disclosed to them that could not be patented due to *Myriad*, and, therefore, they had forgone developing the test. The TTO thought it may have been possible to conduct additional experiments that could pave the way to a commercially valuable patent, but the scientist did not have the interest, funding, or time to commit to that possibility.

One US TTO also recounted a problem created by the *Myriad* decision for a patent that had been previously granted. The TTO described how a licensee contacted them shortly after the decision, informing them they would stop paying royalties on a patent because it was now invalid. The TTO expressed frustration at the fact that, in hindsight, they probably could have drafted *Myriad*-eligible claims but, due to the difficulties with reissue, this was never a viable option.

Echoing problems reported by European practitioners, two US TTOs described problems stemming from *Myriad in relation to* development of drugs. One described how the case stopped them from applying for a patent on a molecule, and, therefore, research had been redirected to assess whether they could produce a related molecule with markedly different characteristics from the naturally occurring molecule. The other TTO said that *Myriad* meant they could not patent an active ingredient, and, therefore, development of it had ceased.

European TTOs were, in contrast, relatively unaffected by *Myriad*. Two European TTOs were only vaguely aware of the case and said it had not affected their activities. A third was quite familiar with the case but only because it made headlines, not because the TTO had noticed a business impact. Another two, who had filed biomarker patents recently, said that issues surrounding the case had probably arisen during US prosecution and were dealt with by outside counsel,

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but they could not recall any specific details. Both added that they had not altered their development strategies as a result.

The sixth European TTO described how *Myriad* had affected one development strategy but in an equivocal way. They narrowed some claims as a result of *Myriad*-based rejections, and this altered their business strategy for "deploying" the product. The interviewee chose not to describe how exactly deployment had changed but noted that the commercial value of the product and the patent claims had probably not changed.

C. Adapting to Mayo*: Drafting Claims, Uncertainty, and Development Strategies*

This Section details how interviewees adapted to issues presented by *Mayo*. It focuses on changes to drafting patent claims, certainty regarding the validity and the grant of patents, and changes to commercial strategies for developing molecular tests.

1. Practitioners

US practitioners were resoundingly clear that *Mayo* had a more significant impact on patent practice than *Myriad*. In particular, they pointed out the difficulties they had applying the case to new tests due to the legal uncertainty surrounding the decision and the need to narrowly draft claims that undermined potential commercial value. In response to these difficulties, the practitioners described what one practitioner called a "toolbox" of strategies for obtaining claims or delaying prosecution until a time when, they hoped, an event (e.g., a legal decision or change in USPTO practice) would allow the prosecution of claims with more clarity. The delay tactics involved filing continuation and divisional applications.[143]

The various strategies US practitioners deployed to obtain claims had drawbacks. One strategy was to draft more independent claims in a type of scattergun approach, hoping an examiner would grant one. A second strategy was to seek additional interviews with examiners to better understand the "idiosyncratic" way the examiner was applying the case and even, hopefully, to agree on valid claims. Other claim strategies focused on overcoming the "significantly more" element from the second limb of the *Mayo* test. This built on the principle that method claims directed to natural laws could be eligible if they include activities that are *not* well understood, routine, or

143. Guerrini et al., *supra* note 102, at 550.

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conventional. Practitioners reported drafting claims that incorporated reagents or scientific techniques or, alternatively, a series of conventional steps that on the whole created an unconventional method.[144] The drawbacks to these fall into two categories. First, practitioners noted that drafting a large number of claims increased the cost of prosecution, as did seeking interviews with examiners. Second, they commented that including activities that were *not* well understood, routine, or conventional usually resulted in a quite narrow scope and, therefore, did not always confer broad protection;[145] for example, a competitor could supply a similar test by using a conventional reagent (not the patented unconventional reagent) or replacing one of the steps with a different step (or perhaps simply skipping the step).[146]

The uncertainty of drafting claims that an examiner would accept as *Mayo*-compliant flowed into uncertainty about the validity of granted claims. The US practitioners accepted that any granted claim could be invalid if challenged in court, but, in their view, there was a higher-than-normal risk that a court would disagree with examiners' views on *Mayo*-related issues.

Despite the legal uncertainty, the US practitioners described few instances where the case had affected clients' development strategies. None could think of an instance in which a client had abandoned development of a test. Likewise, none knew of a client that had abandoned pursuing patent protection for a test, although two described protracted, ongoing prosecutions that had not yet been resolved. None of the practitioners knew of a client that had decided to use trade secrets *instead of* patent protection. On the other hand, one described an instance where a client chose not to litigate to enforce a patent granted before the *Mayo* decision because of the risk of

144. These and other drafting techniques have been previously reported. *See, e.g.*, Miller & Amos, *supra* note 81, at 40–41; Nicholas J. Landau, *Patenting Diagnostics and Biomarkers Six Years After* Mayo, PAT. 213 (Nov. 29, 2018), https://www.patent213.com/2018/11/patenting-diagnostics-and-biomarkers-six-years-after-mayo/ [https://perma.cc/W7ZG-BMMZ].

145. Three US practitioners also raised challenges regarding the drafting of molecular-test claims that incorporated algorithms complying with the abstract ideas exclusion from *Alice*. This topic was not pursued in this Article's study, however, because there are not clearly different patent practices for abstract ideas and algorithms in the United States and Europe. *See* Aboy et al., *supra* note 64, at 1125.

146. Two practitioners raised the possibility that competitors might be able to avoid infringement-of-method claims by arranging performance of the test by more than one actor. The law concerning this issue has changed significantly in recent years. For a review, see Johnathon E. Liddicoat, *Divided Performance of Patented Methods in Australia: A Call to Codify Procured Infringement*, 41 U. NEW SOUTH WALES L.J. 252, 255–62 (2018). The issue has been raised briefly elsewhere in the context of molecular tests. *See, e.g.*, Guerrini et al., *supra* note 102, at 551; Sachs, *supra* note 19, at 1913–19. The practitioners commented that they raised this issue with clients but stated it was considered ancillary to obtaining valid claims.

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invalidity. They chose instead to leave the granted patent "on the books." Two practitioners thought the legal uncertainty reduced the value of business deals, but another two disagreed with this, stating that patent rights often played only a small role in the ultimate value of test transactions. The other three practitioners had no experience with this topic.

Mayo affected European practice as well, although not as profoundly. Only one patent attorney described consistent issues obtaining US patents for clients. They described similar concerns to those expressed by the US attorneys: (i) ongoing difficulties with drafting *Mayo*-compliant claims, (ii) concerns that the claims were too narrow, and (iii) concerns that the granted claims were actually invalid. Despite these issues, however, the practitioner said their clients had not adjusted their development strategies. A second practitioner explained that on one occasion when assisting with the filing of a US patent, a *Mayo*-based rejection had arisen but the test involved an unconventional technical step, and, therefore, they were able to overcome the rejection (on the second step of the *Mayo* test) and draft commercially valuable claims. A third practitioner noted that they were in the process of prosecuting a US patent and expected to receive a *Mayo*-based rejection, and they thought there was a high chance of protracted prosecution. The remaining European practitioners were aware of the issues *Mayo* raised but said they had not needed to study the decision.

2. Companies

US companies generally commented that *Mayo* had been a significant case for their businesses. Only one reported *not* being affected by *Mayo*. The company in question, a start-up, was granted patents after the decision but, prior to the interview for this study, was unaware of the case. After a brief discussion of the case with the interviewer, the company thought its patents were *Mayo*-compliant because the claims applied a sophisticated, unconventional algorithm that probed a range of relatively unknown biomarkers.

Each of the other US companies had been affected by *Mayo*, but the magnitude of impact varied. One company, when prosecuting its patents, described a similar scenario to the start-up mentioned in the preceding paragraph. When acquiring a test from another business, however, it took the view during due diligence that several key patents were probably invalid under *Mayo*, and, in response to this risk, the company abandoned the deal. Although quite an extreme response to the risk of invalidity, it decided it was necessary because the test, once

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developed, would probably have been easy to imitate without patent protection.

The other four US companies encountered prosecution difficulties similar to those described by the US practitioners—for example, protracted prosecution, narrow claims, and inconsistent examiner application of *Mayo*. Despite these difficulties, though, none said that the lack of patent protection or uncertainty surrounding protection had stopped them from acquiring or developing a test. One company even stated that it is "unlikely any company would kill a product due to a patent."

Although these four companies continued developing their tests, they reported other more nuanced effects. A common concern was that the value of their patents had decreased. The companies struggled to assign a numerical value, but their tone suggested it was a nontrivial amount. One of these companies, a small company yet to launch a test, explained that although it was content to develop its tests on a weak patent position, it was conscious that potential acquirers might have a different development strategy in mind requiring strong patents and that, in the absence of strong patent protection, these companies would no longer be interested.

The remaining three companies described different effects. The second company described how the narrower claims it obtained after *Mayo* led to lower reimbursement rates. It invests heavily in developing novel tests with large amounts of clinical-utility data. Prior to *Mayo*, the company used its patents to charge a premium by excluding competitors. Since *Mayo*, however, narrower claims has meant less certainty of excluding competitors. Therefore, when negotiating reimbursement rates, payors are more likely to refuse premiums because competitors could offer a similar test at a lower price.

The third company described how it had decided to use trade secrets instead of patents. It said that prior to *Mayo* it would have patented certain methods, but given the legal uncertainties of *Mayo* for these types of claims, it had decided to keep the methods secret. The company also noted that since it provides the test as an LDT, secrecy was feasible. On the other hand, trade secrecy made it more difficult to publish performance information about the test lest it reveal the secrets, which in turn made it more difficult to convince payors to pay a higher price or persuade medical professionals to use it.

For the last of these four companies, *Mayo* and a consequent shift to trade secret protection influenced its decision-making about releasing the test as an LDT or a kit. The company's formal strategy was to launch a kit in addition to the LDT version of the test it already offered. The interviewee explained, however, that since *Mayo* had

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weakened the company's patent position, it was now advantageous to offer the test solely as an LDT to keep technical aspects of the test "hidden from view." The company was hence contemplating abandoning the kit launch to preserve its trade secrets.

Mayo affected the European companies interviewed less than their US counterparts. Three had dealt with *Mayo*-related issues during prosecution. One company described how it had avoided a *Mayo* rejection by preemptively drafting narrower claims. The company's test incorporated an unusual technique, and it explained that in these circumstances *Mayo* had not prevented it obtaining US patent claims that were sufficiently valuable for the company to develop its test. The other two companies described more drawn-out patent prosecution, but neither was particularly affected by the case. One thought that the narrower claims it obtained meant it might get a lower license rate in the United States but also that this was hard to predict. The other company was yet to obtain its US patent (it was still pending at the USPTO after two or three rejections) but was not perturbed. It intended to launch its test in Europe before the United States and expected this would provide other competitive advantages, including scientific lead time, comprehensive data, and goodwill in the test. In the company's opinion, these advantages meant that any uncertainty or narrowness in its US claims would have a relatively trivial effect. Furthermore, its algorithm was still a trade secret. The company considered this particularly valuable because competitors would face difficulties trying to reverse engineer the algorithm despite its plans, by the time of launch, to publish on it and provide data to regulatory and reimbursement bodies.

The other three European companies had obtained US patents after *Mayo* was decided but were not aware of the case. After explaining the case and asking why they had not heard of it, all three suggested it was because their technology included clear advances over known techniques. Accordingly, the USPTO probably reached a swift view that the patent application included unconventional advances and fell outside the *Mayo* exception to patent eligibility. One company also opined that a reason why its patent did not receive a *Mayo* rejection may have been because the company directed its claim to an assay that detected the presence or absence of a pathogen. This may have been sufficient to avoid the first limb of the *Mayo* test because the patent was not directed to a medical correlation.

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3. TTOs

Similar to the US companies and practitioners, US TTOs found *Mayo* a difficult case. As a starting point, all US TTOs echoed the points made by US practitioners in relation to prolonged prosecution, narrow claims, and uncertain validity of granted claims. Four TTOs also drew attention to the fact that patent costs for protecting molecular tests had increased substantially due to lengthier prosecution times.

They described a variety of drafting strategies to overcome *Mayo*-related issues, but none were uniformly adopted. One TTO described how they had claimed an assay for detecting a specific biomarker by focusing on specific "mechanical aspects" of the assay, instead of a diagnostic test that relied on a medical correlation. They even thought that the claims were probably as broad as they would have obtained pre-*Mayo*. The TTO noted, however, that this approach was not always feasible, as some tests could *not* be described as an assay.[147] Five TTOs also discussed overcoming *Mayo*-related issues by incorporating tests into methods of medical treatments. One TTO described that they were able to obtain claims with minimal fuss by adopting this approach. Another two TTOs were critical of this approach, however, commenting that it was not feasible for them because they would need more data to support these types of claims and their researchers had no interest or capacity to redirect their research in this manner. The last two TTOs described this approach as feasible, but only when a researcher was interested and had the resources for the extra research.

While these experiences were similar to other interviewees' experiences with *Mayo*, the challenges with patenting tests had more serious outcomes for the TTOs. Several TTOs abandoned or considered abandoning the development of tests. Five US TTOs said that they were looking very closely at molecular-test projects and had many concerns, and three of these TTOs had gone as far as abandoning patent filings and development of at least one test. Indeed, one of these TTOs said they were not developing "lots of promising products," and another declared they "don't translate diagnostics." Three TTOs also reported having licensees contact them to cancel licenses because the patents were now invalid. The only TTO that had not lost a license or abandoned a test was the one who described successfully linking their tests to methods of medical treatments.

Although the US TTOs described different approaches for patenting and developing tests, two issues they all agreed on were that

147. The TTO chose not to elaborate on this point.

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they thought fewer VCs were interested in tests[148] and that fewer companies were interested in partnering.

European TTOs described a very different experience with *Mayo* compared with their US counterparts. Their development strategies had not been affected by the case. Five said that they had no specific memory of the case arising during prosecution or development strategy meetings. They thought it was possible that the case had been raised during prosecution but, if it had, presumed it had been dealt with by external practitioners without raising concern. Indeed, two of the TTOs commented they were unaware of the case prior to the interview, even though they regularly dealt with molecular-test technology. One of the TTOs differed from the other four in that they had discussed the case with colleagues; they suggested that one reason the case had not arisen in (or at least had not been significant for) their development strategies was that their claims detailed unconventional instruments or incorporated an unconventional technique, such as a previously unpublished algorithm to diagnose a group of patients.

The sixth TTO described how the case had significantly prolonged the prosecution process for several of their patents, but eventually they obtained commercially valuable US claims and the delay had not affected their development strategies. This TTO outlined similar approaches to drafting claims as described above by the other TTOs. They also mentioned that they typically filed their patents "late" in order to generate more information about the delivery of the tests in medical practice. This strategy had a further advantage. They found it helped them overcome *Mayo*-related issues because the additional information often meant they had worked out unconventional reagents, instruments, or techniques that could be included in claims without affecting the commercial value of the claim.

D. Does Myriad *or* Mayo *Disadvantage US-Headquartered Organizations?*

Prior to this Article's study, opinions differed on whether US-headquartered organizations were more strongly disadvantaged by *Myriad* or *Mayo* compared with European counterparts. It is often argued that patent protection is important to an innovative domestic economy. Yet, patent law applies equally to domestic and foreign organizations. This means that all organizations developing tests can seek patents in Europe, where they will engage with European patent law, which permits a broader range of subject matter. It also means that

148. Taylor, *supra* note 9, at 229.

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all organizations can seek patents in the United States, where they will have to deal with more restrictive patentable subject-matter law, as dictated by *Myriad* and *Mayo*.

As a general rule, US interviewees (practitioners, companies, and TTOs) thought that patentable subject-matter thresholds were easier to meet in Europe than in the United States. However, none thought the differences in patent law disadvantaged US-headquartered organizations compared with European counterparts. Explaining this view, the US interviewees offered four reasons.

First, European patents can be obtained by anyone, including US organizations. Thus, if European patents do confer a benefit, this benefit is available to organizations on both sides of the North Atlantic. Second, organizations that develop tests want, almost always, to launch in the United States because that is where they make most profits. Therefore, all organizations must engage with US patent law. Six US interviewees described this reason as a consequence of the globalized world. Third, although patent applications filed in Europe usually meet patent-eligibility thresholds, problems are often encountered with other patentability criteria (e.g., novelty, inventive step, nonobviousness). Accordingly, any benefit gained through patentable subject matter falls away during other stages of examination. Fourth, successful development of molecular tests involves many challenges, of which obtaining patent protection is only one. So even assuming European patents are broader and granted more easily, this benefit to the organization can be overridden by a milieu of other issues.

Despite such reasons, two US TTOs described how they had considered focusing their development activities in Europe in view of the differences in patent law. However, both went on to say that they had not actioned this plan. One of their primary reasons to continue focusing on the United States was that they had relatively limited knowledge of the potential European licensees or VCs that would be interested in their test.

European organizations had more diverse opinions on whether cross-Atlantic legal differences in patent eligibility brought about by *Myriad* and *Mayo* advantaged European organizations and disadvantaged US organizations. Four European practitioners thought that the cases did not disadvantage US-headquartered organizations, raising the same four arguments mentioned by US organizations. On the other hand, two European practitioners disagreed, taking the view that US organizations were at a disadvantage. One reasoned that US organizations tend to focus on their domestic markets, whereas European organizations tend to focus on territorial markets outside the United States. As a result, European companies could respond to

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Myriad and *Mayo* in a more agile way, focusing attention on substantial, patent-friendly markets such as the United Kingdom and Germany. The other European practitioner, sharing the view that US organizations were at a disadvantage, had a client base with a high proportion of TTOs and start-ups compared to many other attorneys. The practitioner stated confidently that the cases, especially *Mayo*, created a disadvantage for US organizations because organizations working at the early stage of test development (like this practitioner's clients) typically use patents to attract partners and VCs to develop their tests, and this is easier if they can obtain broad patent protection quickly and at low cost.

European companies were evenly split on the question. Two companies thought the cases created a disadvantage for US organizations. One of the explanations offered was that US companies typically regard strong US patent protection as necessary for early-stage test development, while molecular-test organizations in Europe had a more global vision and were content to obtain stronger patents in European markets (as well as other markets outside the United States). The second company articulated its ideas with less precision, merely stating that indirect benefits would flow to European companies because they could obtain patents quicker and often with broader scope. On the other hand, two European companies thought *Myriad* and *Mayo* did not create any particular advantage or disadvantage for European or US companies. One explained this with reference to the concept of the "globalized world," and the other because it thought the extra scope and speed to grant offered minimal advantages. This company added that even if the cases did create a disadvantage for US companies, it was minor and, overall, US companies were still at an advantage because of the high number of VCs there. The remaining European companies did not comment on this topic, explaining that they were not familiar enough with the cases.

European TTOs were the only cohort where a clear majority thought the cases created a disadvantage for US companies.[149] Only one European TTO thought that the cases did not create a disadvantage, basing this on the "globalized world." The other five European TTOs offered several reasons why the legal position after *Myriad* and *Mayo* effectively disadvantaged US companies and advantaged European companies.

First, European organizations are more likely to file for patents in Europe than US organizations. And since patents are typically

149. Although two European TTOs were not familiar with *Mayo* before the interview, they felt they understood the case well enough by the end of the interview to answer this question.

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necessary for the development of tests and procuring patent protection for tests is often easier and cheaper in Europe, European organizations are more likely to obtain the protection needed to develop tests in a protected market.

Second, most VCs and partners they engaged with were: (i) European, (ii) focused on European patent law, and (iii) (largely) oblivious to how severely the US cases had affected patent protection and practice there.[150] Thus, the local European environment for tests had not changed,[151] whereas they were under the impression the US venture-capital environment had changed significantly with media coverage of *Myriad* and *Mayo*.[152]

Third, one of the most important elements for the success of any test is the data supporting it (e.g., data on its analytic and clinical validity), and typically such data are first gathered in an organization's home market. Accordingly, since European organizations could launch in Europe with strong patent positions, then later launch in the United States when their data were stronger, this strategy might avoid the need for strong US patents because they would have the advantage of a good evidence base as well as strong reputation and other competitive advantages.

Fourth, pursuing a Europe-only launch of a test based on strong local patent protection was a legitimate and feasible business objective, particularly as a fallback from a US and European launch. These five TTOs admitted, though, that relative disadvantage for US organizations would not arise for every test, primarily because some test technology was still patent eligible in the United States.

V. DISCUSSION: INSIGHTS FROM THE INTERVIEW DATA

The following three topics distill the interview data and describe how the data provide insights into how *Myriad* and *Mayo* affect the development of molecular tests. The first topic is whether molecular tests can satisfy patentable subject-matter requirements in the United States. The second topic is the adverse effects of *Myriad* and *Mayo* on the development of molecular tests. The third topic is why the data show that organizations in the United States are now at a relative disadvantage compared to organizations in Europe.

150. Taylor, *supra* note 9, at 229.

151. One US practitioner did speculate that if VCs are only aware of local laws, then US VCs might be more reluctant to fund early-stage US organizations because of concerns about patenting, whereas European VCs' activities will remain unchanged. After reflecting further on this possibility, though, the practitioner dismissed it.

152. Taylor, *supra* note 9, at 229.

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A. Molecular Tests and Patent Eligibility

In the immediate aftermath of *Myriad* and *Mayo*, senior legal commentators posited that molecular tests were no longer patent eligible in the United States. The interview data demonstrate that this is incorrect, at least as a blanket statement; many interviewees described a variety of ways to draft valuable claims. Indeed, *Myriad*'s effect on patenting tests appears to be quite limited, with US practitioners in particular describing how they were confident drafting claims that complied with *Myriad*, and all stating confidently that they had been able to obtain commercially valuable claims for clients. Although one US TTO chose not to develop a test because *Myriad* prevented them from patenting some biomarkers, all the other organizations (TTOs and companies) said *Myriad* had not stopped them from obtaining sufficient patent rights when required. These data accord with patent-register data identified by one study. It found that post-*Myriad* the numbers of gene-related patents continued to rise.[153] Although the numbers of patents granted for isolated DNA sequences declined after *Myriad*, it found that these patents were already on a downward trajectory, which probably would have continued even without the *Myriad* decision.[154]

Mayo's impact on patent eligibility was more nuanced. The interview data show that commercially valuable patent claims *can* be obtained after *Mayo*, although experiences differed. Practitioners stated they were able to obtain claims for clients. In contrast, three TTOs stated they had forgone at least one patent application each due to concerns about legal uncertainty and claims being too narrow. One interpretation of these results is that commercially valuable claims are available for only some tests post-*Mayo*. Another interpretation is that valuable claims are generally available for all tests but only after protracted, resource-intensive prosecution. The interview data do not resolve this disagreement. But a consistent point with both interpretations is that *Mayo*'s most significant impact on patent practice was the way in which it increased legal uncertainty.

Uncertainty was a recurrent theme in interviews when discussing *Mayo*. Respondents raised three issues in particular: (i) whether claims could be drafted that were *Mayo*-compliant (and valuable); (ii) how USPTO examiners would apply *Mayo* to a patent application; and (iii) whether granted papers would survive judicial review, a concern which also applied to patents granted

153. Myriad*'s Impact*, *supra* note 20, at 1120.

154. *Id.* at 1120–22.

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before the decision. Uncertainty was also a major finding in the first peer-reviewed study of *Mayo*-related patent filings and prosecutions. The study, analyzing a USPTO art unit related to molecular tests, found an allowance rate of 36 percent for applications that received a rejection citing *Mayo*,[155] indicating that the majority of the applicants could not or chose not to overcome the rejections. Moreover, findings indicated that the number of annual *Mayo*-based rejections remained consistently high in the six years preceding the study, indicating that the patent profession had not worked out how to draft *Mayo*-compliant claims.[156] Thus, from different perspectives, this study's interview data and Aboy et al.'s data confirm that molecular tests remain patent eligible post-*Myriad* and post-*Mayo* but that there is ongoing and substantial uncertainty with the specific claims that are patent eligible. Mostly, the uncertainty stems from *Mayo*.

B. The Adverse Effects of Myriad *and* Mayo *for the Development of Molecular Tests*

This Section considers three types of adverse effects observed in this Article's study. The first type, forgone test development, concerns interview data detailing organizations that abstained from or abandoned developing molecular tests. The second concerns how patents on molecular tests have reduced in financial value. The third concerns whether organizations are now using trade secrets *instead of* patents during the development of tests.

1. Forgone Test Development

Several patent-law theorists predicted that the decisions in *Myriad* and *Mayo* would adversely affect the development of tests. One theorist stressed that molecular tests are expensive to develop and validate and, therefore, typically require investment from VCs.[157] Another stressed that few organizations have the necessary resources and skills in-house to develop tests by themselves and therefore require partners with complementary skills, which patents help attract.[158] Both argued that § 101 law pre-*Myriad* and pre-*Mayo* was necessary for high rates of innovation because broad exclusive patent rights act as a type of security for investments, such as capital injections, as well as other resources, such as labor, and that they help prevent free riding. Thus,

155. Mayo's *Impact*, *supra* note 20, at 515.

156. *Id.* at 516.

157. Holman, *supra* note 11, at 307–08.

158. Daily & Kieff, *supra* note 86, at 973–74.

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Myriad and *Mayo*, which narrowed patent protection, would likely reduce the incentive to invest in test development.

The interview data show that (i) one TTO did not develop a test because of *Myriad*, (ii) three TTOs did not develop tests because of *Mayo*, and (iii) one company abandoned acquiring a test due to *Mayo*. These data, therefore, support the predictions. Furthermore, the data predominantly support their reasons: TTOs said that the most important role patents play in their organizations is attracting partners and VCs. In addition, however, the data bring to the fore some important nuances not mentioned by the patent-law theorists.

One nuance is that the data just summarized show TTOs are more affected than companies. TTOs and universities were not singled out by the theorists. A second detail, closely related to the first, concerns the roles that patents play for companies compared with TTOs. The interview data show that TTOs are more dependent on patents—they have fewer competitive advantages available to them—and, due to constraints on funding, are more sensitive to the cost of protracted patent prosecution. In effect, they are "patent precarious": organizations that are particularly susceptible to changes in patent law that narrow protection or make patents difficult to obtain. This precariousness is exacerbated, too, by the fact that technologies emerging from TTOs are at their most immature and, therefore, their riskiest stage of development for investment.[159]

Patent precariousness also helps explain the difficulties two US companies experienced with transferring tests. One company stated that it abandoned acquiring a test from a start-up due to *Mayo*-related invalidity. The second, a small company, continued test development but anticipated more limited interest from potential partners due to *Mayo*. Both the start-up in the first scenario and the small company in the second scenario were yet to obtain regulatory approval, negotiate reimbursement, or scale up production of a test. The small company kept some trade secrets, but the start-up, according to the interviewee, had none of significance. These companies relied heavily on patents.

The idea that some organizations, particularly small ones, are patent precarious is consistent with other theoretical and empirical work. Economists in 1982 suggested that small companies might rely on patents because they lack other means to protect their development investments.[160] The point is also consistent with foundational literature

159. Bronwyn H. Hall & Josh Lerner, *The Financing of R&D and Innovation*, *in* 1 HANDBOOK OF THE ECONOMICS OF INNOVATION 615 (Bronwyn H. Hall & Nathan Rosenberg eds., 1st ed. 2010).

160. Richard C. Levin et al., *Appropriating the Returns from Industrial Research and Development*, 3 BROOKINGS PAPERS ON ECON. ACTIVITY 783, 797, 831 (1987); *see also* Roberto

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on the competitiveness of firms that posits that companies need competitive advantages to gain market traction and that small organizations in resource-intensive industries find it particularly difficult to handle market forces without patent protection since they usually have access to only a small number of possible competitive advantages.[161] At least two lines of empirical research support this idea. First, professors Ashish Arora and Marco Ceccagnoli conducted research on whether patent protection increases companies' ability to license technology.[162] The researchers found that licensing propensity correlated with increased patent protection but only when companies lacked "complementary assets," a type of competitive advantage, which the authors defined as assets that are costly and time-consuming to acquire and which complement the product sold[163] (e.g., trade secrets and manufacturing capabilities).[164] Second, economist Scott Shane's analysis of patents assigned to the Massachusetts Institute of Technology between 1980 and 1996 shows that wide patent scope correlated with new business formation. That is, the wider a patent's scope, the more likely a business will be formed that acquires the patent from the university.[165]

Two further lines of empirical research support the more specific idea that patent precariousness is an issue for small molecular-test organizations. A 2008 survey of US start-ups found that medical device start-ups, a category that includes molecular-test start-ups, rated patents as 3.3 out of 4 on a scale of importance (with 4 being the highest importance) for capturing competitive advantage.[166] The second piece of empirical research shows a different side of precariousness: when the prosecution of patents becomes expensive and difficult, precarious companies stop obtaining them. A study shows that the number of patents granted to small entities, which includes TTOs if they have not

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Mazzoleni & Richard R. Nelson, *The Benefits and Costs of Strong Patent Protection: A Contribution to the Current Debate*, 27 RES. POL'Y 273, 276 (1998); Scott Shane, *Technological Opportunities and New Firm Creation*, 47 MGMT. SCI. 205, 209 (2001).

161. *See generally* Robert M. Grant, *The Resource-Based Theory of Competitive Advantage: Implications for Strategy Formulation*, 33 CAL. MGMT. REV. 114, 133 (1991); Michael E. Porter, *The Five Competitive Forces that Shape Strategy*, HARV. BUS. REV., Jan. 2008, at 78; David J. Teece, *Profiting from Technological Innovation: Implications for Integration, Collaboration, Licensing and Public Policy*, 15 RES. POL'Y 285 (1986).

162. Ashish Arora & Marco Ceccagnoli, *Patent Protection, Complementary Assets, and Firms' Incentives for Technology Licensing*, 52 MGMT. SCI. 293, 294 (2006).

163. *Id.*

164. The cited study focused on manufacturing capabilities. *Id.* at 297.

165. *See generally* Shane, *supra* note 160, at 209.

166. Stuart J.H. Graham et al., *High Technology Entrepreneurs and the Patent System: Results of the 2008 Berkeley Patent Survey*, 24 BERKELEY TECH. L.J. 1255, 1290 (2009).

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licensed the patent,[167] has declined after *Myriad*: prior to the decision, about one-third of applicants were small entities, and this has since dropped to almost zero.[168]

Consequently, although this study's findings—that *Myriad* and *Mayo* had negative effects on small organizations due to the increased precariousness of their patent portfolios—are based on a relatively modest number of interviews, the idea has substantial theoretical and empirical support.

2. Value Reduction

Four US companies reported that the financial value of their patents had reduced due to *Mayo*, and one US company and one European company reported patent value had reduced due to *Myriad*. The legal theorists did not specifically predict this effect, but practitioners did.[169] Each of the companies describing this issue said reduced patent value resulted in reduced value of financial deals, including reimbursement, but none of the companies knew by how much.

This is clearly a negative effect for the individual companies interviewed, but whether it is an adverse effect from a public perspective of technology development is more complex. One could argue that if a transaction is modestly profitable for an organization that develops a test, then the laws influencing the value of the technology are operating sufficiently well. However, since one of the primary drivers of this reduction is the higher-than-normal level of uncertainty surrounding granted and pending patents, then to this extent at least the reduction in value is negative.

3. Trade Secrets

A number of commentators have argued that, from society's perspective, changes in patent law have a negative impact when they fail to incentivize firms to disclose technological information and firms retain it as a trade secret.[170] An interview-based study explored the adoption of this strategy in gene technology but found no instances of it

167. 37 C.F.R. § 1.27 (2019).

168. Myriad*'s Impact*, *supra* note 20, at 1122.

169. *See, e.g.*, Sean Sheridan, *How* Mayo*,* Myriad *and* Alice *May Impact Patent Valuations*, LAW360 (Mar. 4, 2015, 8:48 AM), https://www.law360.com/articles/626370/how-mayo-myriad-and-alice-may-impact-patent-valuations [https://perma.cc/E2NV-8BYF].

170. Guerrini et al., *supra* note 102, at 544–45; W. Nicholson Price II, *Big Data, Patents, and the Future of Medicine*, 37 CARDOZO L. REV. 1401, 1418–19 (2016); *see generally* LANDES & POSNER, *supra* note 1, at 326–28; Bambauer, *supra* note 100, at 837–40.

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occurring. The results of this Article's study confirm increased interest in trade secret protection as a strategy for test development but found only one instance of it occurring. This supports the view that trade secrets hold increasing interest for test developers, but initial uptake appears low.

A related issue emerging from the interview data is that in response to *Myriad* and *Mayo*, companies were choosing to provide a test as an LDT instead of a kit to preserve trade secrets. The study recorded one instance of a US company choosing this strategy and another instance of a US company considering it. Unlike using trade secrets instead of patents, patent theorists have not previously predicted a shift to LDT technology nor the implications of this industry movement. In other fields the issue is familiar,[171] and there is an active debate about whether the FDA should regulate LDTs, especially due to safety and accuracy concerns.[172] In an environment where LDTs are arguably insufficiently regulated, it is a negative effect for *Myriad* and *Mayo* to have underpinned a shift in this direction.

C. Explaining the Relative Disadvantage for US-Headquartered Organizations

As previously mentioned, respondents had mixed views about whether *Myriad* and *Mayo* disadvantaged US-headquartered organizations more than their European counterparts. In the main, US organizations thought there was no noticeable difference. However, quite a number of European organizations, particularly TTOs, thought they were able to deal with the implications of *Myriad* and *Mayo* more easily than US organizations. It is also revealing that four US organizations decided against acquiring or developing a test due to *Mayo* and one decided against developing a test due to *Myriad*, whereas no European organization decided not to develop or acquire a test.

Notwithstanding the small sample size,[173] the results on this issue speak to debates about whether local conditions of patent protection are significant for local innovation. On the one hand, patent

171. *See, e.g.*, Arielle Duhaime-Ross, *Theranos Isn't the Only Diagnostics Company Exploiting Regulatory Loopholes*, VERGE (Nov. 11, 2015, 8:28 AM), https://www.theverge.com/science/2015/11/11/9706356/fda-theranos-health-diagnostics-cancer-tests-regulation-loophole-ldt [https://perma.cc/2TVE-TWDM].

172. *See* Sachs, *supra* note 19, at 1884–99; *see also* Kelly Holloway et al., *Dangerous Diagnostics? Regulatory Reform in the Genomic Era*, 364 BRIT. MED. J. l640 (2019); Jeffrey N. Gibbs, *LDTs: The Saga Continues*, FDLI, https://www.fdli.org/2017/04/ldts-saga-continues/ [https://perma.cc/XBN2-69BW] (last visited Mar. 23, 2020).

173. SCHUTT, *supra* note 108, at 165.

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protection appears to establish a level playing field, since the legal thresholds apply to any organization (local or foreign headquartered) seeking patent protection in the jurisdiction. However, several reasons emerged that support the view that *Myriad* and *Mayo* disadvantaged US-headquartered organization more than European counterparts, even though both groups must meet § 101 thresholds to acquire US patent protection.

First, US organizations commented that they primarily focus on the US market, whereas Europeans focus on US and European markets with roughly equal intensity; and some European organizations entertain business strategies that exclude the United States, whereas no US organization said they would do this. Second, US TTOs and companies described diminished VC and partner interest in molecular tests as a result of the cases,[174] whereas no European organizations described this. The explanation is that local VCs and partners play important roles in innovation,[175] especially for TTOs,[176] and that European VC investors were less perturbed by, or perhaps less aware of, US legal developments.

Third, European organizations described business strategies that mitigated weak US patent rights, including relying on European and other non-US patent rights; relying on European and other non-US VCs; only partnering with European and non-US organizations; and launching tests in Europe before launching in the United States, using strong data generated in Europe. None of these strategies were mentioned by US interviewees.

Fourth, the interview data strongly indicate that *Mayo* generally made patent prosecution lengthier and more costly. This outcome, however, interferes with TTOs' business strategy of prosecuting patents and transferring the technology swiftly and cheaply. European TTOs experienced *Mayo*'s effects on prosecution, but US TTOs were more

174. Taylor, *supra* note 9, at 229.

175. *See generally* David B. Audretsch & Paula E. Stephan, *Company-Scientist Locational Links: The Case of Biotechnology*, 86 AM. ECON. REV. 641, 650–51 (1996); Najoua Boufaden & Anne Plunket, *Proximity and Innovation: Do Biotechnology Firms Located in the Paris Region Benefit from Localized Technological Externalities?*, ANNALES D'ÉCONOMIE ET DE STATISTIQUE, July/Dec. 2007, at 197, 206; Joshua B. Powers & Patricia P. McDougall, *University Start-Up Formation and Technology Licensing with Firms that Go Public: A Resource-Based View of Academic Entrepreneurship*, 20 J. BUS. VENTURING 291, 292, 300 (2005); Kjersten Bunker Whittington et al., *Networks, Propinquity, and Innovation in Knowledge-Intensive Industries*, 54 ADMIN. SCI. Q. 90, 93, 100 (2009).

176. *See generally* M. S. Gertler & Y. M. Levitte, *Local Nodes in Global Networks: The Geography of Knowledge Flows in Biotechnology Innovation*, 12 INDUSTRY & INNOVATION 487, 488–89 (2005).

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sensitive to the effects because they more precariously rely on US patents.

On balance, the results support the view that US organizations, particularly patent-precarious TTOs, have been more strongly disadvantaged by *Myriad* and particularly *Mayo* compared with European counterparts. The results, however, do *not* permit an assessment of how frequently the disadvantages arise.

VI. STUDY LIMITATIONS: REASONS FOR CAUTION PRIOR TO LAW REFORM

This Article's study shows that *Myriad* and *Mayo* have adversely affected the development of some molecular tests and that the cases may create disadvantages for US-headquartered organizations. However, care must be taken before relying on this evidence as a basis for law reform. It is better to see it as indicative, but nonconclusive, evidence of overall trends. There are three reasons for careful reading of this evidence.

First, the sample size for the interviews is appropriate for an interview-based study but is small relative to the entire industry. The methodology does not accurately indicate the percentage of test organizations that have been negatively impacted in the wider population, nor the full number of tests that companies and TTOs chose not to develop, nor the amounts by which the value of molecular-test deals have reduced.

Second, there may have been some selection bias. The invitations sent to potential interviewees stated that this study was investigating the US Supreme Court cases of *Myriad* and *Mayo*. Some organizations may have ignored the invitations because they develop tests with little reliance on patent protection or have little interest in the Supreme Court cases. This is particularly plausible for tests that might be developed, for example, with public money or that build on existing technology, biomarkers, or clinical-utility data. A few interviewees illustrated this idea, pointing out that hospitals have been developing panel tests that are less innovative than their tests because the panels draw primarily on existing technology and publicly available data.

Third, this study was designed to assess the negative effects of *Myriad* and *Mayo*, not the positive ones that might balance out the adverse impacts. The most obvious potential positive effect of the decisions is the one argued by the Supreme Court: the decisions would unshackle "basic tools of scientific and technological work" from patent

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protection, enabling wider and easier use.[177] If the patent practice before the decisions did tie up these "tools," then various fields of innovation may have flourished in the years afterward. To the Authors' knowledge, research has not investigated this topic from an empirical perspective. Three US TTOs in this study volunteered information (it was not pursued by the interviewer) that they were developing projects that, at least in part, incorporated technology that was patented until *Myriad* invalidated the protection.

Previous empirical studies found that biomedical scientists rarely become aware of protective patents and redirect research to avoid patent infringement.[178] In contrast, the interview data suggest it might be more common for researchers to learn something is no longer patented, or that only a narrow patent exists, and subsequently deliberately move into that technical field. Thus, the potentially positive effects of *Myriad* and *Mayo* still need further examination before it can be concluded that the negative effects warrant law reform.[179] Relatedly, *Myriad* and *Mayo* affect more than molecular-test development. For instance, they are having an impact on drug development. Two interviewees stated *Myriad* had stopped development of a drug, one US TTO said *Myriad* had redirected research on a drug, and one European practitioner said *Myriad* posed a serious issue for the development of one of their client's drugs. These points are consistent with a study that indicated that *Myriad* is more frequently cited by the USPTO to reject non-DNA than DNA patent applications. Since *Myriad* and *Mayo* affect scientific research other than molecular-test technology, it would be prudent to understand these effects before devising any law reform.

Proceeding with policy or legislative reform before understanding the effects of the cases better is likely to be premature, poorly targeted, and insufficient and may even lead to more uncertainty. Further research is important.

177. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 589 (2013).

178. Timothy Caulfield et al., *Patents, Commercialization and the Canadian Stem Cell Research Community*, 3 REGENERATIVE MED. 483, 487–89 (2008); CJ Murdoch & Timothy Caulfield, *Commercialization, Patenting and Genomics: Researcher Perspectives*, 1 GENOME MED. 22, 22.4 (2009); John P. Walsh et al., *Where Excludability Matters: Material Versus Intellectual Property in Academic Biomedical Research*, 36 RES. POL'Y 1184, 1194–1201 (2007); John P. Walsh et al., *Working Through the Patent Problem*, 299 SCIENCE 1021, 1021 (2003).

179. How exactly one should weigh innovation that has flourished with, for example, tests that were not developed is quite challenging.

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VII. CONCLUSION

Myriad and *Mayo* significantly changed US patent practice and created significant divergence with European law on patentable subject matter. Previous studies of *Myriad* and *Mayo* have examined macrolevel effects, and this Article's study aimed to examine the negative effects of *Myriad* and *Mayo* at the organizational level by interviewing patent practitioners, executives at molecular-test companies, and managers in technology-transfer offices at research institutes. The sample size of interviewees is small relative to the size of the molecular-test industry, meaning the results are only indicative of overall trends. However, since little is known about the molecular-test industry, this study provides context-rich information on how and when the negative effects arise. This information is vital to understanding the effects of the cases on the molecular-test industry and to developing evidenced-based patent law and policy.

This study has three main findings. First, *Myriad* and *Mayo* have negatively affected the development of tests in several ways. Notably, several organizations deliberately chose to forgo developing tests, and many have found the legal uncertainty following the cases problematic. Second, small patent-precarious organizations (those that rely heavily on patents for competitive advantage) have been more affected by the decisions than other organizations. Third, US-headquartered organizations have been more affected by the cases than European organizations, even though both types of organizations file US patents under the same eligibility law—a result that the majority of interviewees did not expect. The basis for this disadvantage is that European organizations do not, as a general rule, rely on US patents as significantly as US organizations do.

These results show that *Myriad* and *Mayo* have adversely affected the development of some molecular tests and that the cases may create disadvantages for US-headquartered organizations. Yet this Article does not recommend reform. A key reason for this unwillingness is that this study was designed to assess only the negative effects of *Myriad* and *Mayo*, not the positive ones. The most obvious potential positive effect is the one argued by the Supreme Court: that the decisions would unshackle "basic tools of scientific and technological work." Until the positive effects are understood, reform is premature.

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