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

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

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.

While nearly four years have passed since the US Supreme Court's decision in *Association for Molecular Pathology v. Myriad Genetics*, 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 US Patent and Trademark Office (USPTO) has published an updated examination guidance on patent-eligible subject matter every year since 2014 (refs. 3–5). This guidance comments on and gives examples of eligible and ineligible claims after *Myriad*[1], *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*[6] and *Alice Corporation v. CLS Bank International*[7] but 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]. Still others argue that the impact of *Myriad* remains uncertain[11] because, even considering USPTO guidelines and the Supreme Court decision, there is considerable ongoing legal debate about the criteria for eligible gene patents and what makes a claim "markedly different" from ineligible natural products[8,12,13].

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 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. Instead, the results empirically confirmed more moderate predictions of impact, such as those made by Graff *et al.*[15] However, although they enable analysis of 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 cannot typically answer detailed questions such as what types of claims, amendments and legal arguments in originally published patent applications for isolated nucleic acids result in allowable subject matter after examination proceedings by the USPTO. Manual claim analysis is thus needed to address currently unanswered questions of significant practical and legal importance, such as whether it is possible to draft around *Myriad* and obtain claims with equal (or very similar) scope[10,13,16], whether the decision has driven patent applicants toward narrower claims[17], what types of claim amendments have transformed ineligible isolated nucleic acid claims into patent-eligible claims in examination proceedings before the USPTO and, relatedly, whether *Myriad* has failed to provide a workable legal test of subject-matter eligibility[18]. The answers to these questions are also important in debates about whether *Myriad* has caused a problem such that subject-matter legislation (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 as 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 (**Box 1**, **Fig. 1**), inspired by other claim-level empirical studies[22], that identifies and systematizes concrete post-*Myriad* examples of granted gene patents that were applied for with at least one isolated nucleic acid claim. These examples highlight what the USPTO considers to make a claim "markedly different" from naturally occurring genomic DNA (gDNA).

We focused on three empirically based research questions: (i) what proportion of human gene–related patent applications published during the three-year period preceding *Myriad* contained an isolated nucleic acid product claim (i.e., a claim similar to the isolated gDNA claim in contention in *Myriad*), (ii) what proportion of these applications matured into a granted patent and (iii) how simple

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

Box 1 Methods

Search strategy and 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 13 June 2010 to 13 June 2013). Furthermore, we restricted our study to applications with biological claims directed to *Homo sapiens*. A search algorithm (S1, **Supplementary Data**) was applied in the online, publicly available Lens patent resource[26] (http://www.lens.org). This search algorithm (**Fig. 1,** step (1)) is designed to identify patent applications with at least one claim containing a SEQ ID and the keyword 'isolated' within five words of 'nucleic acid' (or synonyms). The algorithm was intended as a pre-processing step before manual expert claim review and consequently was designed for optimal sensitivity to isolated nucleic acid patents as opposed to specificity, since the latter is achieved through expert manual claim review[27].

With these inclusion criteria, 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 applications that were examined after *Myriad*, at which point the applicant and USPTO would have needed to consider carefully the legal arguments and amendments required for the isolated nucleic acid claims to meet patent eligibility.

Patent application classification. The output of the automated S1 search algorithm (**Supplementary Data**) was used as the input for the first step in the expert claim review and manual classification (**Fig. 1,** steps (2–4)). These steps involved manually analyzing the claims in each of the applications retrieved and classifying them as containing (i) at least one simple isolated genomic nucleic acid product claim (i.e., claims akin to those litigated in *Myriad*) (M1a); (ii) no M1a-satisfying claims but at least one claim to more complex isolated nucleic acids (e.g., isolated nucleic acids in vectors or sequences encoding monoclonal antibodies) (M1b); or (iii) 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*.

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 subclassified them as (i) granted (M1aG); (ii) rejected or abandoned (M1aR) or (iii) pending (M1aP) (**Fig. 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 they included at least one simple isolated genomic nucleic acid product claim when initially published 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 whether the originally submitted claims had been amended before examination on the merits (**Fig. 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 before 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 nonisolated gene claims (e.g., method claims, systems claims, etc.) for examination on the merits. Amendments were classified as occurring (i) before examination on the merits, meaning the amendment was initiated by the applicant before 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 greatest interest to us, 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 (**Fig. 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 before 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 nonisolated 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 and final rejections), examiner interview summaries and advisory actions (**Fig. 1,** steps (11), (13) and (15)). Each patent application was coded to indicate whether it received a 35 USC §101 (subject-matter eligibility) *Myriad*-based rejection (**Fig. 1,** step (13)). Each applicant's response to a non-final office action, final office action or advisory action and to examiner interview summaries and appeal briefs was also reviewed (**Fig. 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 (**Fig. 1,** step (16)). The **Supplementary Data** provide further details about the methodology and coding notation used in this study.

Claim amendment typology. We used the results of steps (1–16) in **Figure 1** to establish a typology of claim amendments that overcame *Myriad*-based rejections (**Fig. 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.

isolated nucleic acid claims that received a *Myriad*-based rejection were amended to become patent-eligible subject matter before the USPTO.

Results

Table 1 shows the primary results from this study. With regard to the first question, we found 653 applications with at least one claim to a simple isolated genomic nucleic acid product. This constitutes approximately 50% of the 1,292 human gene–related applications found by our S1 search algorithm (**Supplementary Data**).

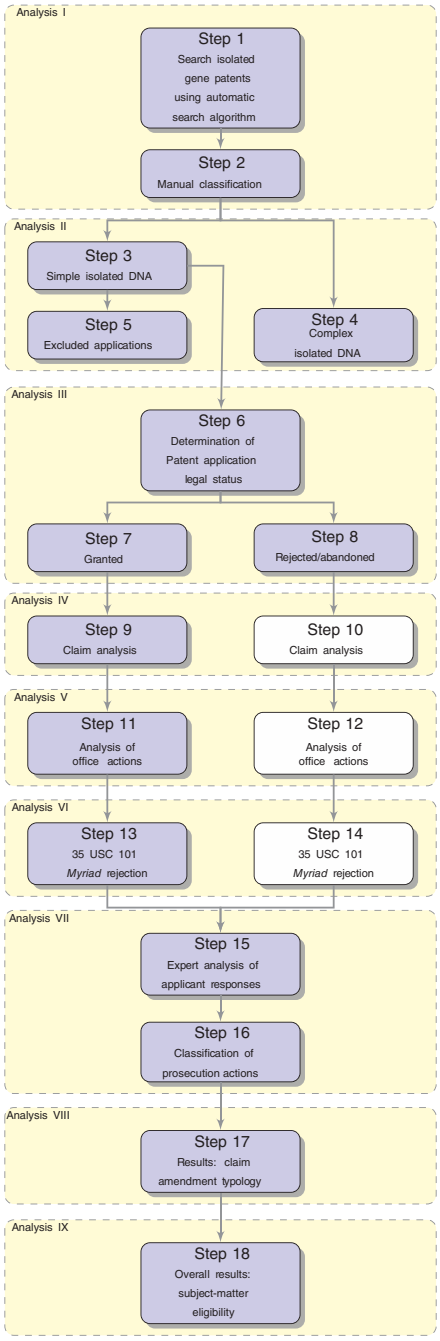

Figure 1 Methodological overview, including automated search, manual classification and expert prosecution history review steps.

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 (we refer to these as M1aG applications), 311 (47.6%) were wholly rejected or abandoned (M1aR), and 29 (4.4%) were, as of January 2017, pending (M1aP).

We then looked more closely at the M1aG subset (n = 313). We wanted to see how these patents had survived 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 that had been published before the *Myriad* decision. The M1aGC cohort, combined with the M1aR applications (where the simple isolated nucleic acid claims were abandoned or rejected along with every other claim), reveals 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). We discuss the significance of this result below, along with our view that it may be time dependent and the result of legal uncertainty.

Only 14 (4.5%) applications were granted without substantive amendments to the originally published isolated nucleic acid claims (M1aGU). 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 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 1,292 applications identified in our S1 search algorithm.

The third question asked how the isolated nucleic acid product claims that received a *Myriad*-based rejection changed during prosecution in order to become 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, 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 before 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 ultimately succeeded.

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 typically employed one of eight prosecution strategies: (i) amending to cDNA, (ii) amending to nucleic acids with non-naturally occurring sequence variations, (iii) amending to nucleic acids recombinantly linked with heterologous sequences, (iv) amending to labeled nucleic acids, (v) amending to a nucleic acid in a vector, (vi) amending to a nucleic acid recombined with a nonspecific regulatory sequence, (vii) amending with a type 2 change and a negative-claim clause and (viii) amending to a nucleic acid so short that it does not naturally occur.

Definitions for each of these strategies and details about the amendments made in each of the 21 cases, including some of the arguments made by applicants and examiners, are provided in the **Supplementary Data**. Also recorded there are three applications that received a *Myriad*-based rejection and were canceled as a result.

As described below, some of the eight strategies may appear obvious in hindsight, but 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. The most common way to amend and overcome a *Myriad*-based rejection was to claim cDNA, which occurred in seven of the 21 instances.

Is it easy to draft around *Myriad*?

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

When we commenced this study, we expected to see more amending activity to overcome *Myriad* rejections; we did not expect as many cancellations of entire patents, or canceled claims that excised a nucleic acid claim without attempting to amend the claim to

Table 1 Results of isolated DNA patent claim analysis

Results of automated S1 patent search algorithm

Manual classification (M1 analysis)	*N*	Percentage
Simple isolated DNA (M1a)	653	50.5
Complex isolated DNA (M1b)	561	43.4
Excluded (M1c)	78	6.0
Total	**1,292**	100
Patent status of M1a applications	***N***	**Percentage**
Granted (M1aG)	313	47.9
Rejected/abandoned (M1aR)	311	47.6
Pending (M1aP)	29	4.4
Total	**653**	100
Patent claim analysis of M1aG applications	***N***	**Percentage**
Canceled (M1aGC)	183	58.5
Amended (M1aGA)	116	37.1
Unchanged (M1aGU)	14	4.5
Total	**313**	100
Fate of M1a patents	***N***	**Percentage**
M1aR	311	49.8
M1aGC	183	29.3
M1aR+M1aGC	**494**	79.2
Amended isolated gene claims	**116**	18.6
Granted as originally filed (unchanged)	**14**	2.2

closely related subject matter–eligible claims. There are many possible reasons for the large proportion of discontinued isolated nucleic acid product claims; the view that such claims were ineligible and difficult to draft around after *Myriad* was undoubtedly one of them. No guidelines were initially issued, and even after guidelines were issued, detailed information about addressing *Myriad*-based rejections in relation to isolated nucleic acids was unavailable. There were reasons other than patent eligibility as well; 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"[23].

It is important to note that canceled *Myriad*-type claims could in some cases be resurrected and amended in the future while claiming the original priority date—as, for example, a divisional, continuation or continuation-in-part patent application. So some applicants that discontinued *Myriad*-type claims may be 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 has and has not worked is the sort of information that patent practitioners may find helpful. In particular, the file wrappers disclose important nuances that applicants have learned only 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 Data**). 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 Data**). 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 Data**).

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

In the immediate aftermath of the *Myriad* ruling, it may turn out that applicants have preferred canceling claims over trying to draft around *Myriad* because there is not enough of a business case to warrant the effort. Or it may be that applicants have delayed drafting around *Myriad* owing to current legal uncertainty. This will be clearer in a few years, when we can see how many canceled *Myriad*-type claims are resurrected as continuations or divisionals and whether the amendments are successful.

After *Myriad*, what is markedly different from nature?

In the *Myriad* and *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[3–5]. The primary guidance, published in the *Federal Register* on 16 December 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): a claim to an exons-only cDNA, where the naturally occurring gDNA also includes introns. On the same day, the USPTO issued three further examples[24] to explain where a claim directed to a nucleic acid is markedly different: (i) the claimed nucleic acid includes a non-naturally occurring nucleic acid substitution, (ii) the claimed nucleic acid includes a non-naturally occurring fluorescent label and (iii) the claim is limited to vectors comprising a non-natural combination.

We 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, given that it was explicitly mentioned in the Supreme Court opinion and the *Myriad* and *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[25].

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 the rejection because "complementary DNA sequence" could be interpreted as "any DNA sequence that is complementary to some other sequence" (case 14, **Supplementary Data**). By contrast, in a different example, a claim to "complementary nucleic acid (cDNA)" was sufficient to overcome a *Myriad*-based rejection (case 2, **Supplementary Data**). 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 that 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 *Myriad* and *Mayo* guidance from 2014 (ref. 24); however, this guidance was issued 18 months after *Myriad*. Moreover, we observed some important nuances in the arguments raised and accepted by USPTO examiners about what would 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 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 that have moieties that confer nuclease resistance (and do not occur in nature) (case 10, **Supplementary Data**). 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 Data**).

Beyond the examination guidance, we found four additional strategies applicants used to successfully respond to *Myriad*-based rejections (types 3, 5, 7 and 8 in the **Supplementary Data**). 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 a naturally occurring nucleic acid (case 13, **Supplementary Data**). 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 Data**).

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 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 had prosecution reopened with a *Myriad*-based rejection (e.g., cases 7 and 24, **Supplementary Data**). In general, our results also indicate the USPTO examiners interpret *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 Data**). Although the position against eligibility is conservative overall, there seems to be inter-examiner variability. For example, an oligonucleotide that did not differ from sequences in nature was granted (case 21, **Supplementary Data**), yet a claim to a pair of primers was rejected (case 23, **Supplementary Data**).

The conservative approach of USPTO examiners probably results in longer prosecution times, and in some cases applicants may be surrendering more patent protection scope than needed in order to satisfy the examiners with regard to 35 USC §101 requirements (depending on one's view of the requirement for a marked difference rather than a mere difference from a naturally occurring nucleic acid). If so, a potential positive side effect is that patents granted are more likely to withstand a validity challenge, should one be made via the courts in the future. On balance, it is unclear whether the conservative approach is beneficial. Longer patent prosecution times could disproportionately affect startups and small companies. They may not have the resources for engaging in complex prosecution involving multiple rounds of examination and requests for continued examination (RCEs), unlike larger companies with more resources. We found preliminary evidence of this effect in a previous empirical study[14]. Strong, reliable patents are typically important for businesses that need to attract investment in a risky R&D environment and firm growth during the term of the patent (i.e., 20 years from the filing date). But strong, reliable patents are particularly important for small and medium-sized enterprises. These companies are important providers of disruptive innovation (e.g., new ventures and substitute and new entrant products), which often require a period of market protection to challenge incumbents. In contrast, larger companies 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, our results offer examples of successful claim amendments that could help applicants with 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 endeavor to produce updated guidelines quickly and with as much detail as possible.

Conclusions and 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 past three years. On the basis of these results, we conclude that there has been no 'drafting around' the legal principles in *Myriad* that has achieved protection of equal breadth to isolated gDNA claims. There has been some drafting to achieve claims that approach the boundary between eligible and ineligible subject matter, and there is still some room for debate about whether applicants are being issued claims directed to products that are different, but not markedly so, from naturally occurring nucleic acids. 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 examination.

Insofar as patent practitioners engaged 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 Supreme Court in *Myriad* and the primary *Myriad*, *Mayo* and *Alice* guidance from the USPTO. Other allowable amendments followed other examples in the USPTO guidance[3–5,8,24], namely sequence variations, labeling and nucleic acids inserted into vector. USPTO examiners were noticeably conservative in what they considered acceptable amendments in these categories. We observed a handful of other amendments—not currently mentioned in USPTO examination guidelines—that 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 the claim was amended during the election process or via preliminary amendment) to see whether any additional strategies for drafting around *Myriad* emerge. Another line of inquiry would be to investigate the US patent 'family members' related to the M1a subset. Such follow-on research could help answer, for instance, whether the *Myriad*-type claims that were canceled in the uncertain aftermath of *Myriad* are being resurrected and filed as 'children' (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 the US patent families, patent family members in other jurisdictions are ripe for further research, especially family members filed with the European Patent Office (EPO). Empirical answers to these questions would help provide further insight in 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 and future court decisions—in short, the passage of time—will resolve some of the uncertainty that still surrounds the *Myriad* distinction between claims directed to products of nature and 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 canceled *Myriad*-type claims in the aftermath of *Myriad* may in time decide to amend the claim in a manner that 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 on whether the canceled, potentially amendable claims are perceived as having economic value. A separate question is 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 we observed in amendments that satisfy current USPTO practice, we conclude that it has not been 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 they see good reason for pursuing related amended nucleic acid claims. As shown here, there are more than half a dozen tried-and-tested claim-drafting strategies that can transform ineligible simple isolated nucleic acid product claims into 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, businesses and patent practitioners) agree on is the need for 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 intellectual property–intensive field.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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