PATENTS

Myriad's impact on gene patents

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A new study examines the impact of the landmark *Myriad* US Supreme Court decision for gene patents at its three-year anniversary. It identifies 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 of *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*.

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

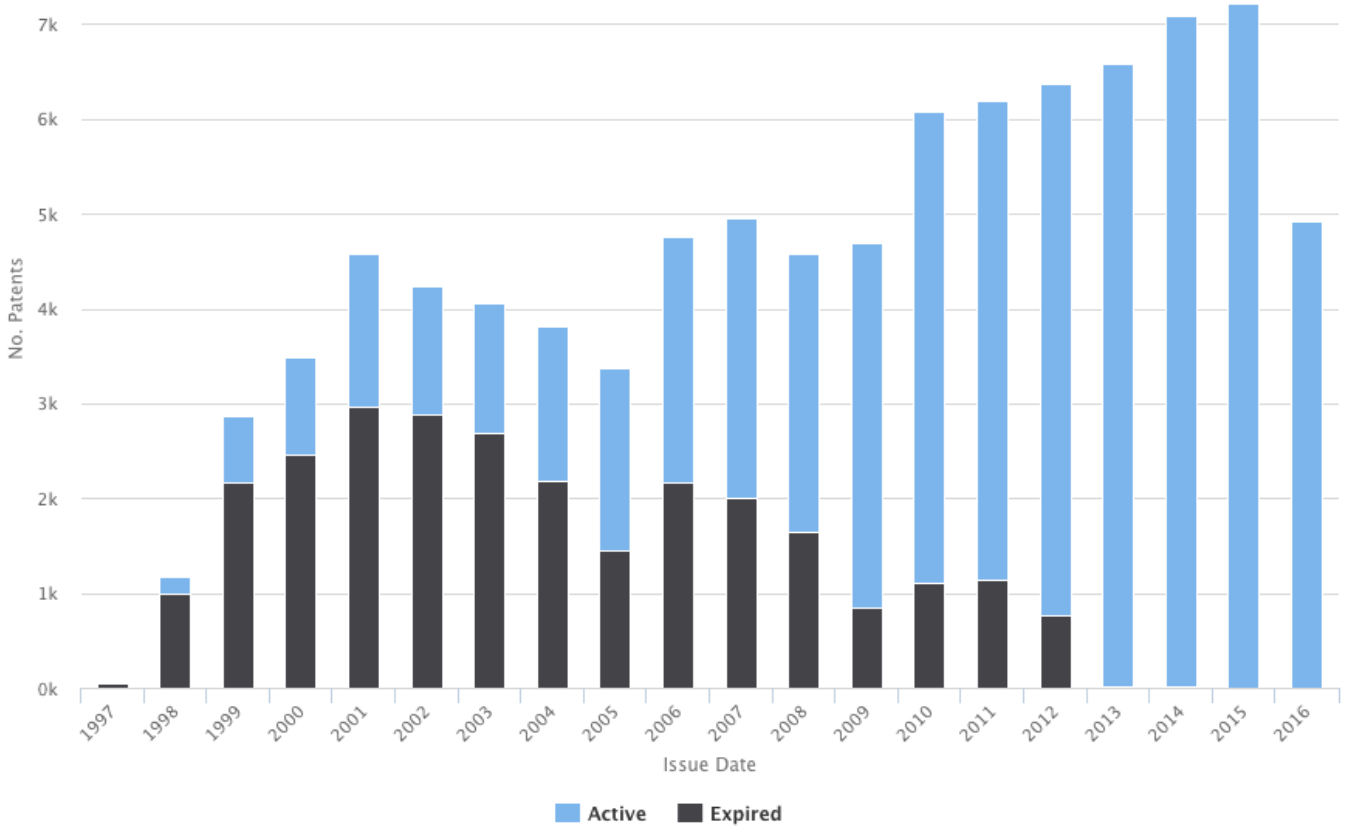

Figure 1 Published granted active and expired patents (1996-2016) with gene-related claims (including the general gene-related search terms identified in search S1 from Table 1). The general shape and total number of gene related patents is consistent with previous studies employing different search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

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, 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**).

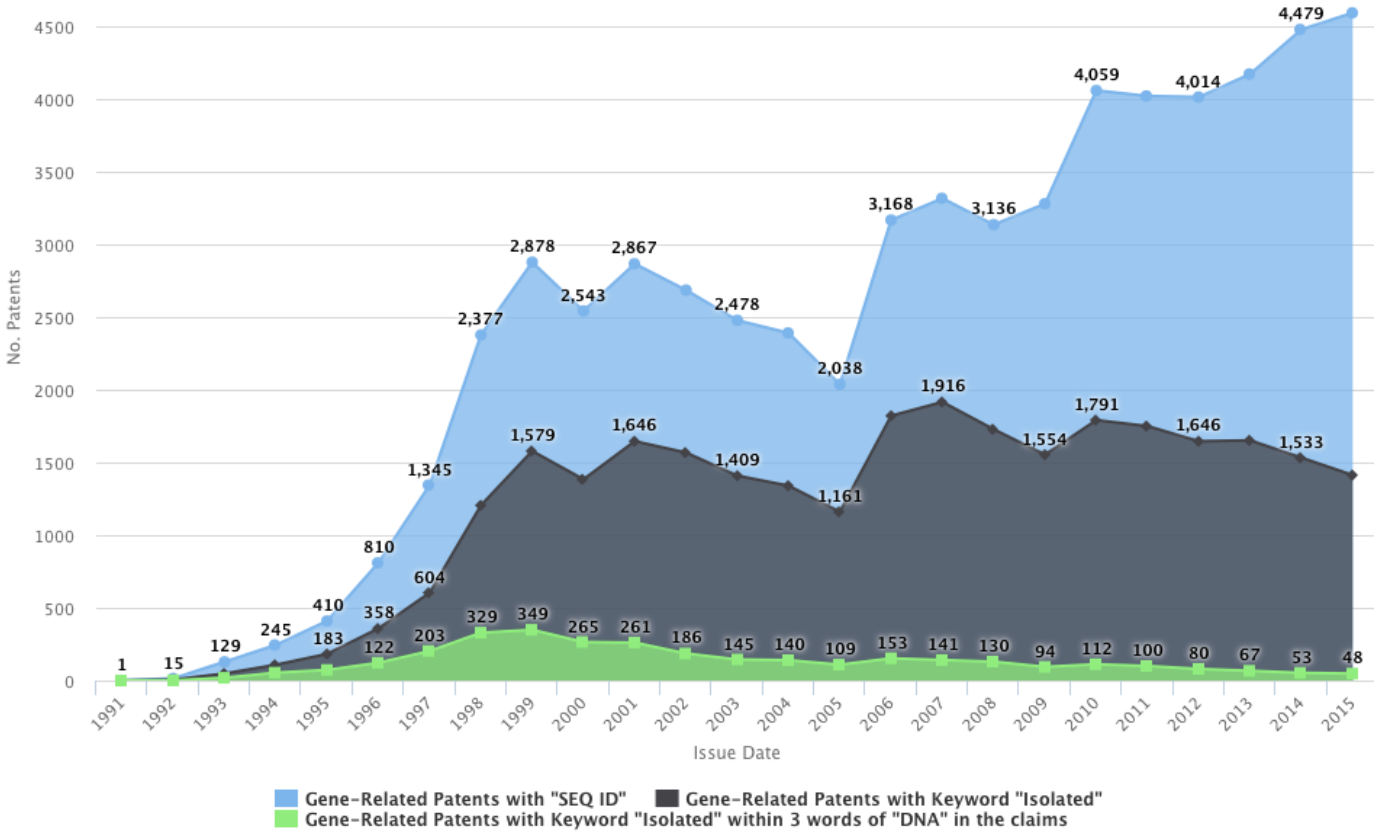

Figure 2 Granted patents with gene-related claims. While issues of gene-related patents in general continue to increase, there is a decrease in isolated gene-related patents regardless of whether the search is conducted by issue (**Fig. 2**) or filing dates (**Table 1**)

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 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

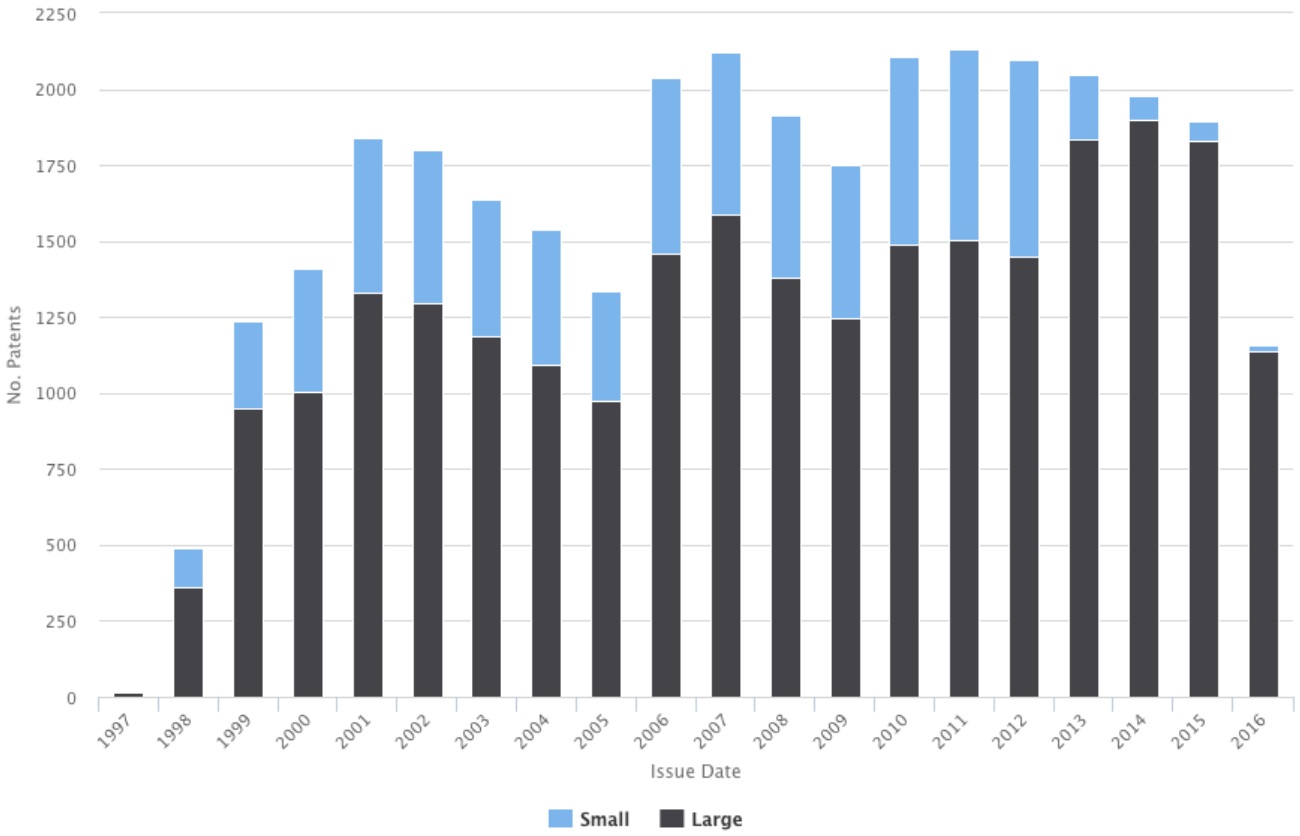

Figure 3 - Granted gene-related patents by small-entities vs large entities (37 CFR definition) based on Search ID S3 in **Table 1** (isolated)

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 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.

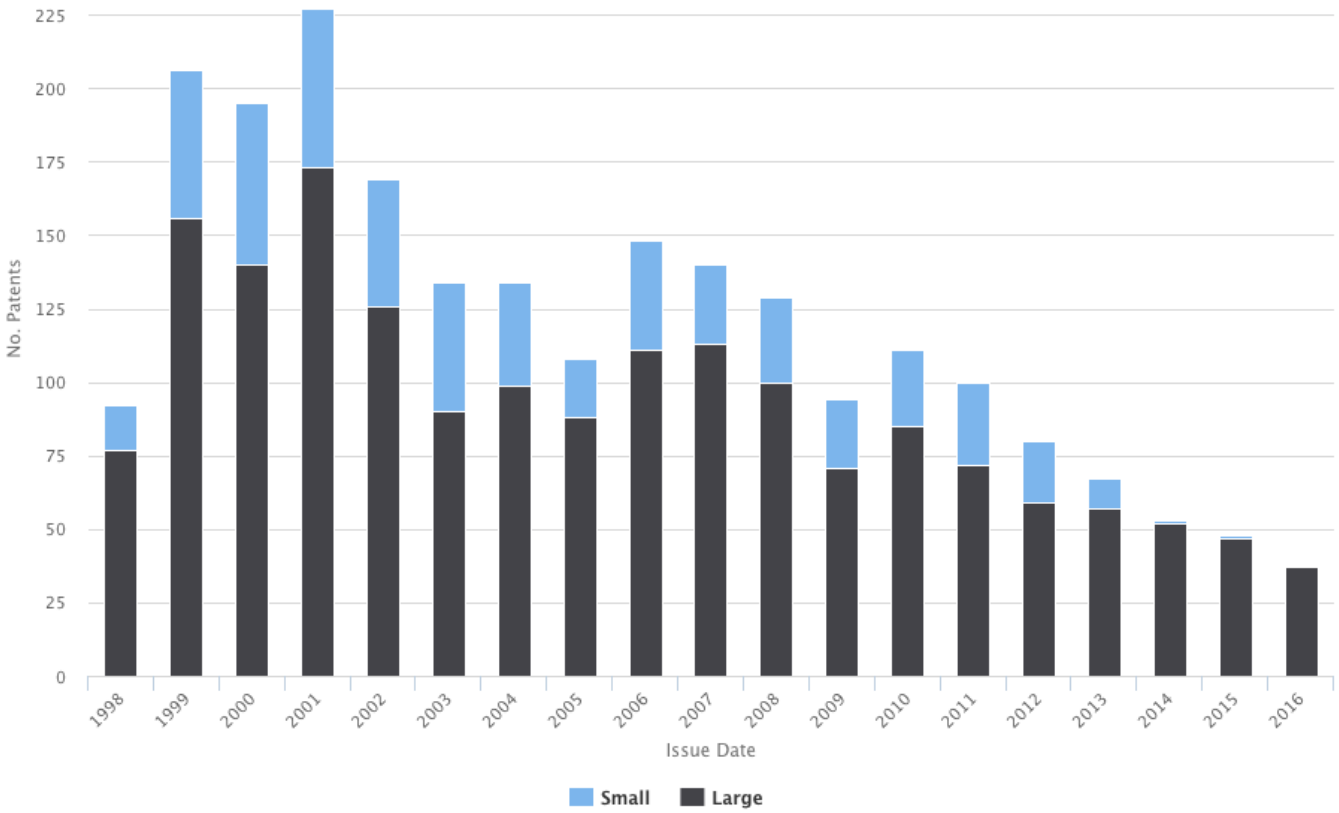

Figure 4 - Granted isolated-gene rated patents by small-entities vs large entities (37 CFR definition) containing "isolated" within 3 words of DNA in the claims.

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 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).

[15] Gold. R.E., Cook-Deegan R., & Bubela. T., *Sci. Transl. Med.* **5**, 192ed9 (2013).

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

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

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

[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).

PATENTS -
SUPPLEMENTAL INFORMATION FIGURES

The codeless myriad of precedent and the wilderness of single instances: An analysis of the impact of Myriad on the myriad of gene patents

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A new study address the status of gene patents on three-year anniversary of the landmark *Myriad* US Supreme Court decision.

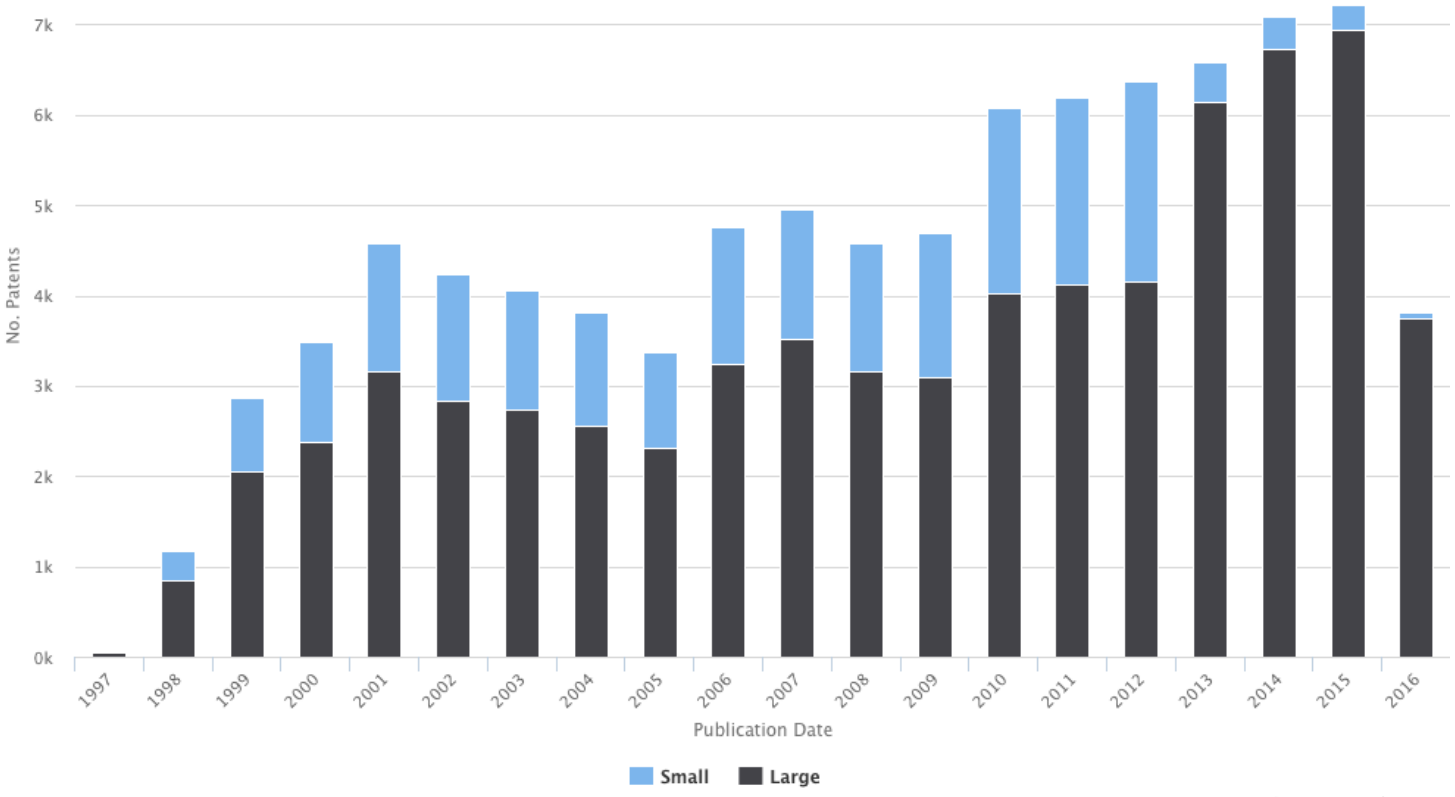

Figure S1 - General gene-related patents by type of entity (large and small)

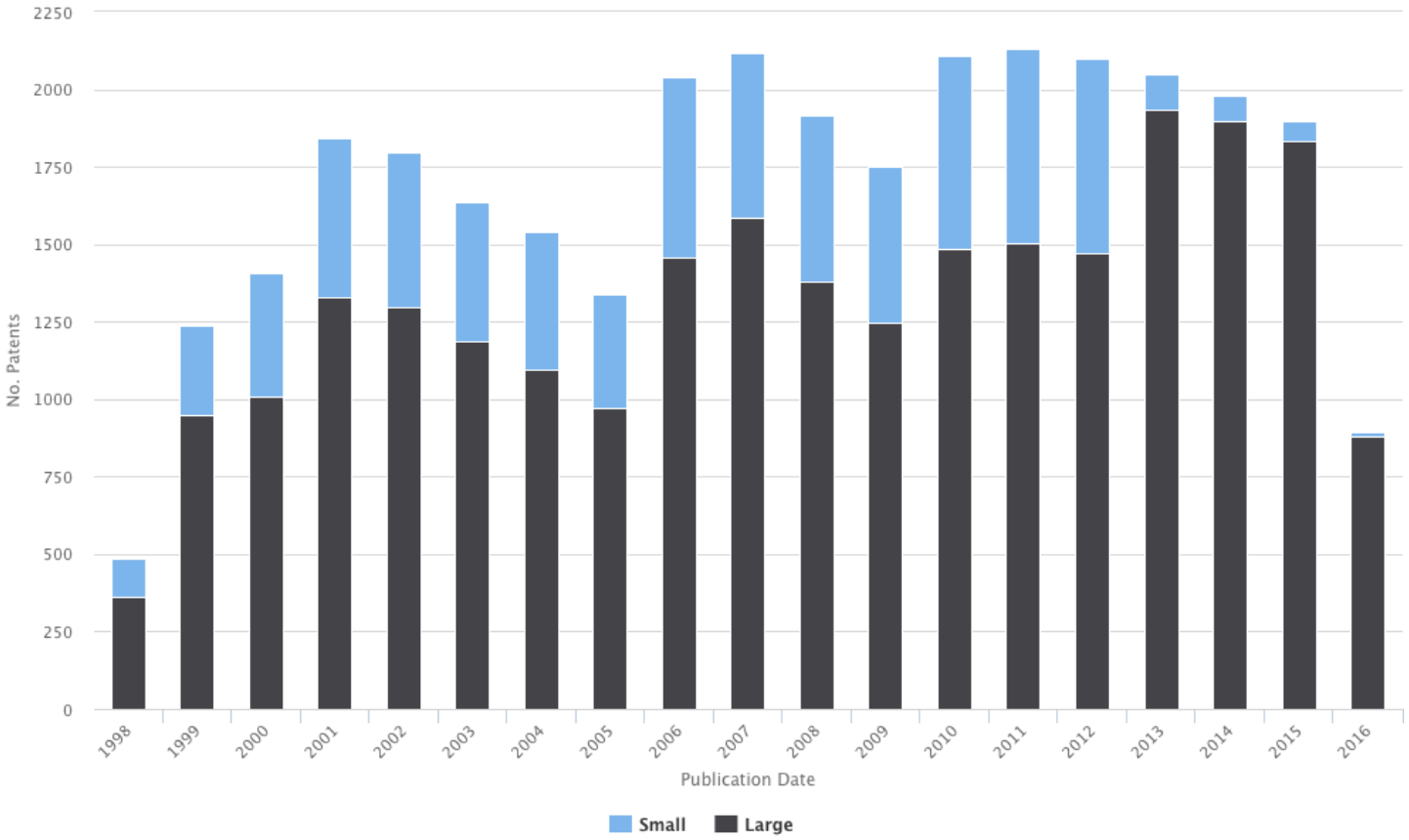

Figure S2 - Isolated gene-related patents by type of entity (large and small)

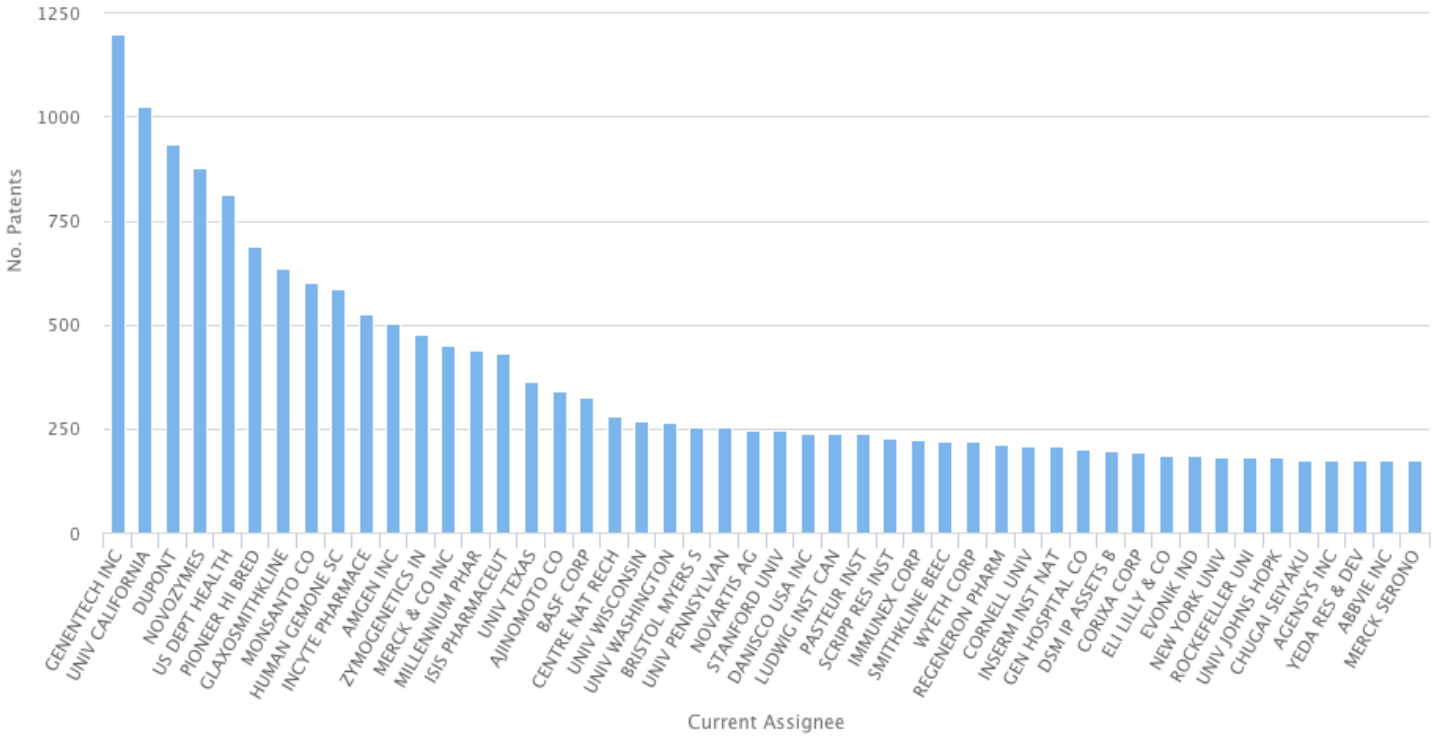

Figure S3 - General gene-related patents current assignee

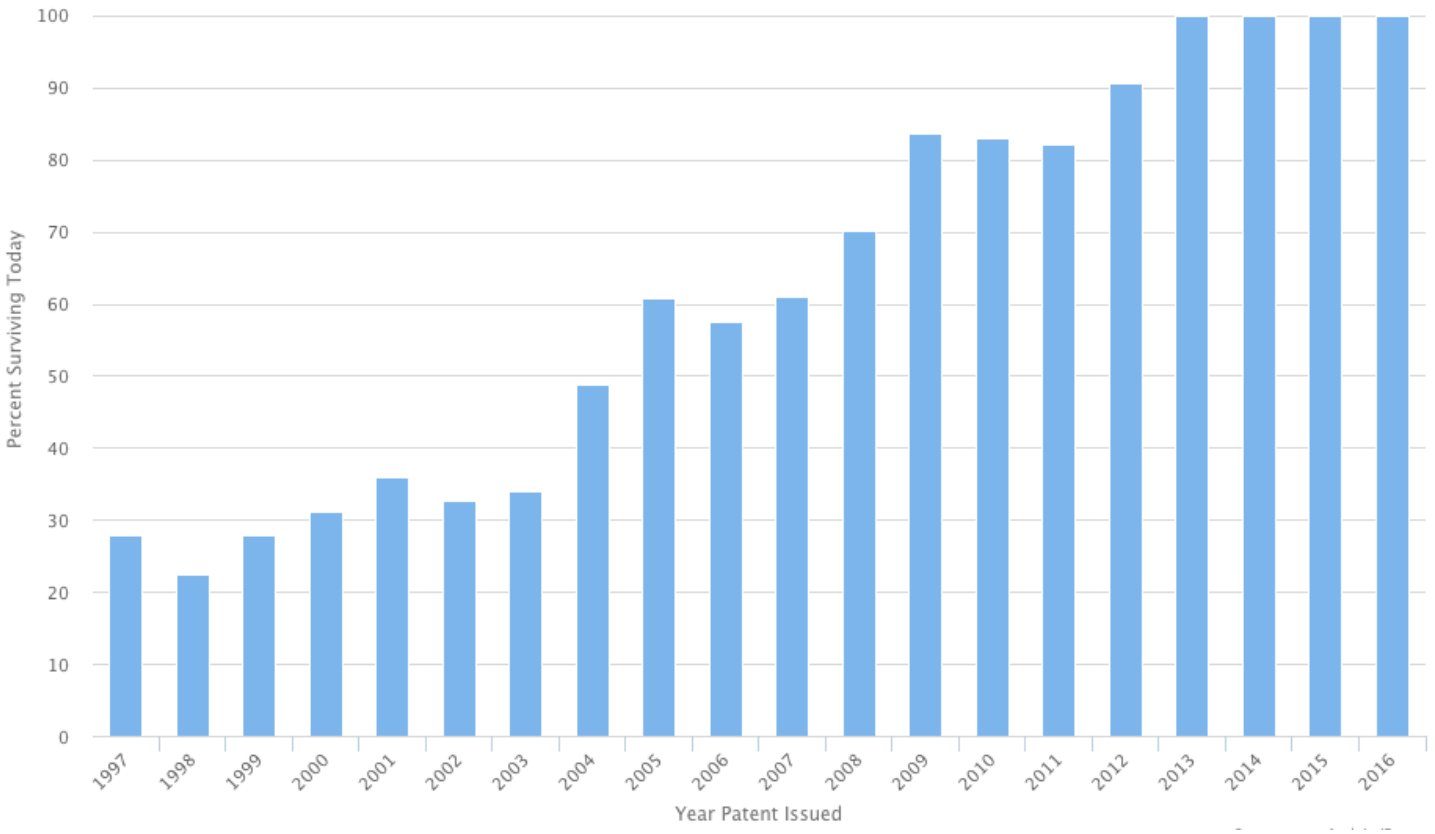

Figure S4 - General gene-related patents survivorship rate

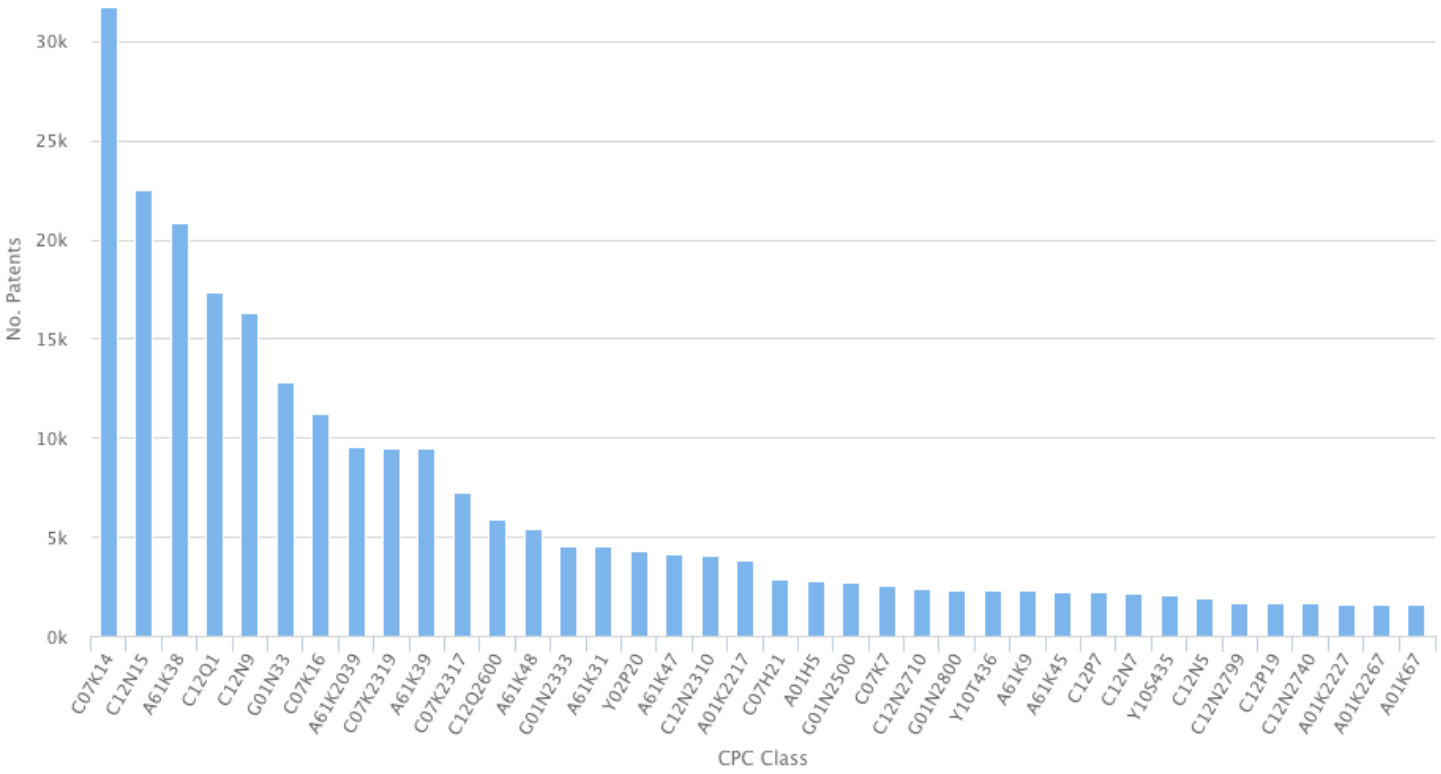

Figure S5 - General gene-related patents CPC class analysis

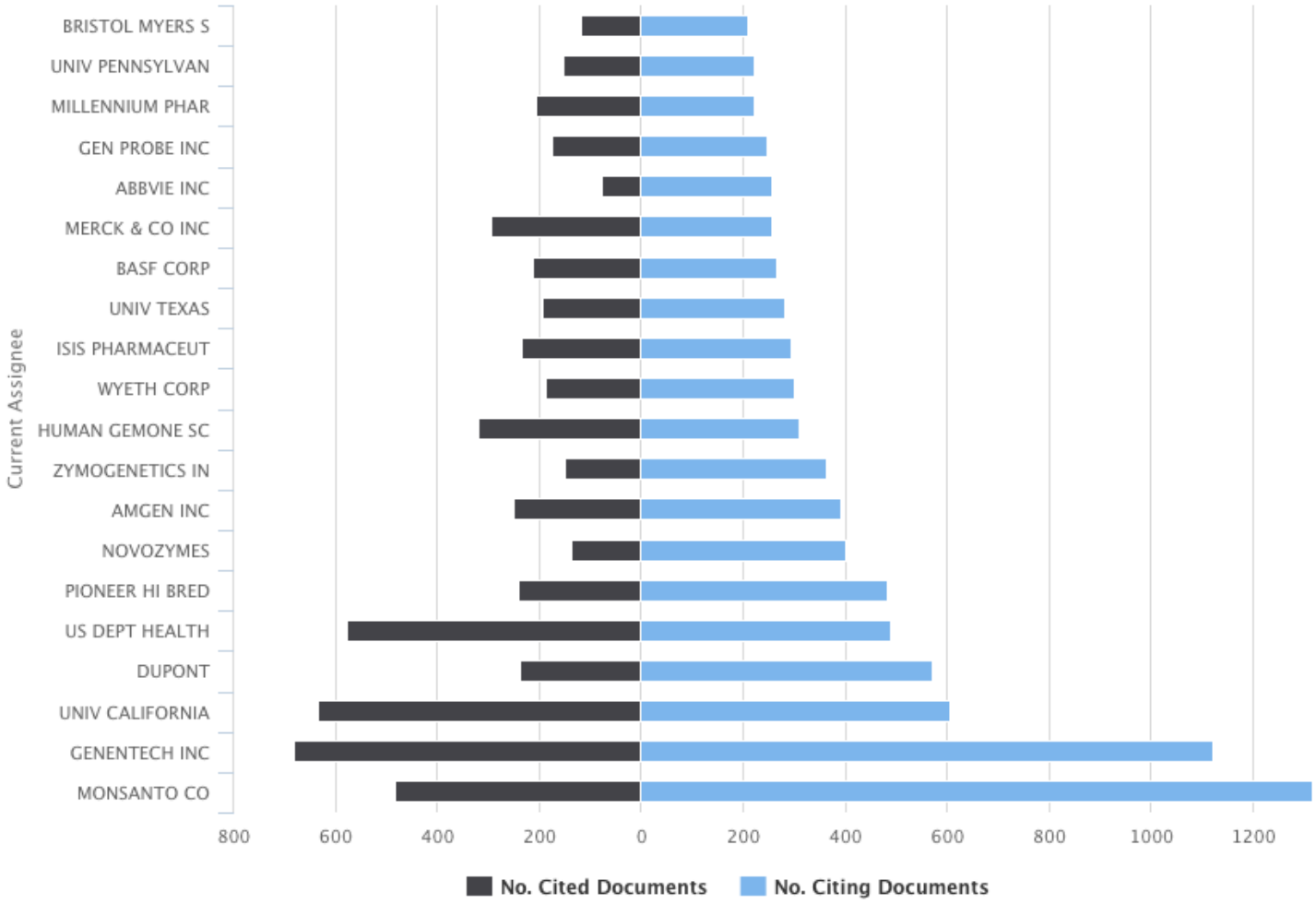

Figure S6 - General gene-related patents combined forward and backward citation analysis

SUPPLEMENTAL INFORMATION

TABLE S1 Key Empirical Research on DNA-related patent protection[i]

Author	Focus/Type of study	Key Findings
Scherer[ii]	Broad economic analysis of granted US 'DNA patents', focussing on those directed to human genes. Patents were initially identified by searching abstracts of patents issued between Sept 1999–June 2001 with broad search terms.	Identified 1,770 patents (with 1,150 of US origin) and estimated these to be 5-10% of all DNA patents. Of the US originating patents, 363 of them claimed 'human DNA sequences' but only 68 claimed human DNA without any explicit use (i.e. as compositions of matter).
Thomas, Hopkins and Brady[iii]	Count of international patent application families 'claiming' human DNA sequences listed on the GENESEQ database[iv] as at August 2002). Focused on applications filed between 1996-1999. This count included patents filed up to the end of 2001.	Identified 18,174 patent applications that 'claimed' human DNA sequences, with 6,485 applications filed between 1996 and 1999. On interpreting the 'main use' of the applications filed between 1996-1999, found that the three most common uses were as: research tools, diagnostics and anti-tumour therapeutics. Also found that 62% of the applications between 1996-1999 were from US organisations and 20% from countries in the European Union; and that approximately one third of these applications were from public sector organisations and two thirds from private sector organisations.
Jensen and Murray[v]	Count and mapping of all granted US patents that claim *human* genetic sequences. Granted patents were searched using broad search terms and sequences were identified as human using BLAST.	Identified 4,270 patents that claimed human protein-coding sequences and mapped these to the human genome. Estimated that 20% the human, protein-coding genome was 'explicitly claimed'. Also found that 63% of these patents were owned by private firms and that many genes were the subject of numerous patents e.g., up to 20 patents were reported on one gene.
Hopkins et al[vi]	Count of international patent families claiming nucleic acids published between January 1980-December 2003. Focussed on families that had at least one issued patent from the EPO, JPO or USPTO before 2005. Count was performed on the GENESEQ database.[vii]	Identified 15,603 patents families claiming human DNA sequences and that filing rates for these dropped markedly since 2001. Found that only 5,669 applications had been *granted* in either the USPTO, JPO or EPO and that of these 5,669 applications, 94% had been granted at the USPTO but only 750 or ~5% at the EPO and 494 or ~3% at the JPO. Of the 8,278 applications lodged at the EPO, 890 had been granted, 4,180 were still in examination, 2,849 had been withdrawn, 112 refused and 10 lapsed.
Cook-Deegan and Heaney[viii]	A wide ranging review of US patents in genomics and human genetics including a count of 'DNA patents' and their assignees. Patents were searched for between 1971 and 2009 on Delphion Patent Database,[ix] using a search algorithm from the Georgetown DNA Patent Database.[x]	Found that issued DNA patents peaked in 2001 and that they dropped off thereafter. Analysis of organisations holding issued DNA patents showed that DuPont has the most (approx. 1,600), followed by Roche (approx. 1,400). Overall, 39% of these issued patents were assigned to academic institutions, which was markedly different to the global average of 3% for US patents.
Mills and Tereskerz[xi]	At 2010, collaborated with the USPTO to count granted US patents (*issued* between 1996–2005) claiming 'DNA products specific to *humans*'. Analyses focussed on renewal patterns of these issued patents.	3,226 patents were identified in the period of study. The granting of these patents peaked in 2002 and fell sharply thereafter. Of the patents granted between 1996–1998, 71% were renewed at the third and final stage. Overall, of the 3,266 granted patents identified, 2,440 were still active.
Graff et al[xii]	Count of US patents claiming nucleic acids as 'compositions of matter'. This count included a number of steps: 1. A combination of different sources and query methods to	Found 72,052 granted patents that 'in some way identify or make reference to nucleotide sequences', with 213,128 independent claims; 39% of these claims were to methods.

	identify all granted patents that 'in some way identify or make reference to nucleotide sequences'; 2. Identifying the independent claims in these patents; 3. Excluding method claims; and 4. Analysing the remaining independent claims using linguistic algorithms to identify nucleic acid molecules claimed as composition of matter. Period of study: up to end of 2010.	Found 36,571 claims to nucleic acids as composition of matter in 15,359 different patents. Estimated that 5,936 (39%) of these patents 'primarily' involved human sequences (compared with 7% to other animals; 12% plant; 21% microbial; and, 21% synthetic). Found that granting of these patents peaked in 1999 and declined since, but stabilised with an average of 623 granted each year since 2005. Estimated that the number of patents with composition-of-matter claims still in force in 2010 was 8,703. Found that of the 15,369 patents that contain composition-of-matter claims, 65% of the assignees were private-sector businesses and 24% were public-sector organisations, and that these proportions have been relatively stable over time.
Jefferson et al[xiii]	A report on the scope and type of US granted patents that disclose and/or claim human sequences. Used the 'Biological Lens' facility as a platform for analysis, which includes the PatSeq toolkits. [xiv]	Found that, depending on the homology threshold used, 26-62% of human genes are referenced – but not necessarily claimed – in granted US patent claims. Found that 2,685 patents referenced 76,910 human genes (with 100% homology). Manual analysis of the claims in these patents showed that: 13% of the sequences were claimed as isolated sequences and 9% were claimed as a probe or primer in a method. Overall, found 927 granted patents that contained claims to isolated human nucleotide sequences with 100% homology. However, only 67-70% of these were maintained for 20 years.
Rosenfeld et al[xv]	Linked US patents that 'claim' nucleotide sequences to genes in the human genome Focused on shorter sequences, down to 15 nucleotides (15mers) .	Found 41% of the genes in the human genome have been claimed, but if this analysis includes 15mers claimed, then 100% of human genes have been claimed. Also found 58 patents with claims to short sequences that map to 10% of all bases in the human genome and one patent linked to 91.5% of all human genes.
The Centre for International Economics[xvi]	A broad, economic report analysing the role of human gene patents in Australia's economy, including a patent count that initially used broad key terms to identify a large collection of patents then interpreted a sample of this collection to estimate the true number patents with claims to isolated gene sequences. Patents were search for up until March 2013.	Estimated that between 3000-4399 patent applications with claims to isolated human gene patents have been filed in Australia (not including modified DNA claims). 68% of these are to genomic DNA and 32% to cDNA or probes/primers. At the time of publication in 2013, estimated that only 284-627 isolated human gene patents were in force and that 76% of these were to partial gene sequences and 24% to full-length gene sequences.
Jefferson et al[xvii]	A comparison of granted US patents that reference plant (maize, rice and soybean) and human genomic sequence in the claims. Study included a count of sequences referenced and mapping of referenced sequences to the genomes in question. Search and analyses were conducted using PatSeq tool. Study included patents granted up until November 2014.	Found that 130,000 human genomic sequences were referenced in patent claims, but that fewer than 11,000 genomic sequences from each of the plant genomes were. Found that 80% of the plant sequences overlapped with sequences in at least one of the other three genomes and that 3,956 sequences overlapped among all four genomes. Of these 3,956 sequences, almost all of them were 1-50bp sequences.

[i] This table excludes stem cell patent studies, and specific diseases
[ii] Frederic M Scherer, 'The economics of human gene patents' (2002) 77 *Academic Medicine* 1348.
[iii] Thomas, Hopkins, and Brady, 'Shares in the human genome: the future of patenting DNA' (2002) 20 *Nature Biotechnology*. 1185.
[iv] GENESEQ, http://sequencebase.com/geneseq-fastalert-patent-sequence-databases/ (accessed 13 July 2016).
[v] Jensen and Murray, 'Intellectual property landscape of the human genome' (2005) 310 *Science* 239; see also, Christopher M Holman, 'Debunking the Myth that Whole-Genome Sequencing Infringes Thousands of Gene Patents' (2012) 30 *Nature Biotechnology* 240.
[vi] Hopkins et al, 'DNA patenting: the end of an era? (2007) 25 *Nature Biotechnology* 185.
[vii] GENESEQ, http://sequencebase.com/geneseq-fastalert-patent-sequence-databases/ (accessed 13 July 2016).
[viii] Cook-Deegan and Heaney, 'Patents in Genomics and Human Genetics' (2010) 11 Annual Review of Genomics and Human Genetics 383.
[ix] The database is now 'retired', see, 'Experience Thomason Innovation', *Thomson Reuters* < http://ip.thomsonreuters.com/maketheswitch>.
[x] Delphion Search Algorithm, *DNA Patent Database*, < https://dnapatents.georgetown.edu/SearchAlgorithm-Delphion-20030512.htm>.
[xi] Mills and Tereskerz, 'Human DNA patent renewals on the decline' (2011) 29 *Nature Biotechnology* 711.
[xii] Graff et al, 'Not Quite a Myriad of Gene Patents' (2013) 31 *Nature Biotechnology* 404.
[xiii] Jefferson et al, 'Transparency Tools in Gene Patenting for Informing Policy and Practice' (2013) 31 *Nature Biotechnology* 1086.
[xiv] PatSeq, Lens <https://www.lens.org/lens/biological_search>.
[xv] Jeffrey Rosenfeld and Christopher E Mason, 'Pervasive Sequence Patents Cover the Entire Human Genome' (2013) 5 *Genome Medicine* 27; see also, Tu et al, 'Response to 'pervasive sequence patents cover the entire human genome' (2014) 6 *Genome Medicine* 14; and, Rosenfeld and Mason, 'Response to "Pervasive' Sequence Patents Cover the Entire Human Genome" – Authors' Reply' (2014) 6 *Genome Medicine* 15.
[xvi] The Centre for International Economics, 'Economic Analysis of Human Gene Patents' (2013) http://www.thecie.com.au/?page_id=358 .
[xvii] Jefferson et al, 'Gene patent practice across plant and human genomes' (2015) 33 *Nature Biotechnology* 1033.