How do patents affect follow-on innovation?

Evidence from the human genome*

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October 13, 2015

Abstract

We investigate whether patents on human genes have affected follow-on scientific research and product development. Using administrative data on successful and unsuccessful patent applications submitted to the US Patent and Trademark Office, we link the exact gene sequences claimed in each application with data measuring follow-on scientific research and commercial investments. Using this data, we document novel evidence of selection into patenting: patented genes appear more valuable — prior to being patented — than non-patented genes. This evidence of selection motivates two quasi-experimental approaches, both of which suggest that on average gene patents have had no effect on follow-on innovation.

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1 Introduction

Competitive markets may under-incentivize innovation due to the public good nature of new ideas. Intellectual property rights, such as patents, aim to address this under-investment problem by allowing inventors to capture a higher share of the social returns to their research investments. By awarding inventors a temporary right to exclude others from marketing their invention, patents aim to allow inventors to earn quasi-rents — temporarily — as a way to re-coup their research and development costs, thus providing dynamic incentives for investments in new technologies. Dating back at least to analyses such as Nordhaus (1969), optimal patent policy design has traditionally been framed as a trade-off between this benefit of providing incentives for the development of new technologies and the cost of deadweight loss from higher prices during the life of the patent.

Nordhaus-style models of optimal patent policy design have traditionally modeled innovations as isolated discoveries. However, in practice many or most innovations are cumulative, in the sense that any given discovery is also an input into later follow-on discoveries. When innovation is cumulative, optimal patent policy design also depends on how patents on existing technologies affect follow-on innovation. One example that has been prominent in recent policy debates is a patented human gene sequence. Sequenced genetic data is a research input into subsequent follow-on discoveries: by analyzing sequenced genetic data scientists may discover links between genetic variations and diseases, and such knowledge can be applied to commercialize medical technologies such as pharmaceutical treatments and diagnostic tests. If patents on discoveries such as human genes affect follow-on innovation, that effect is a key additional input into optimal patent policy design. In this paper, we investigate whether patents on human genes have affected follow-on scientific research and product development. Our broad goal is to inform whether the Nordhaus-style trade-off between ex ante incentives and deadweight loss is sufficient for optimal patent policy design, or whether — at least in this context — the effects of patents on follow-on innovation need to be considered.

Investigating how patents on existing technologies affect follow-on innovation requires addressing two key challenges. First, in most markets it is difficult or impossible to take a given set of technologies which are claimed as intellectual property in patents and measure follow-on innovation on those technologies. Follow-on innovations require a license from the original innovator. But because licenses are very rarely publicly disclosed, constructing appropriate measures of follow-on innovation for any given patented invention is quite difficult. Second, a priori we may expect a selection bias problem to arise if inventors are more likely to file for and obtain patents on technologies that are inherently more valuable. This type of selection raises the concern that any measured differences in follow-on innovation across patented and non-patented technologies may reflect the selection of which technologies are patented, rather than a causal effect of patents on follow-on innovation.

The contribution of this paper is to construct new data and develop two new quasi-experimental approaches

to address these challenges. To address the first - measurement - challenge, we take advantage of the fact that US patent applications claiming human genes as intellectual property must disclose the exact DNA sequences claimed in the text of the patent. By applying bioinformatics methods (Jensen and Murray, 2005), these DNA sequences can be annotated with gene identifiers, and these gene identifiers can in turn be linked to standard scientific and medical datasets providing measures of follow-on scientific research and product development related to each gene. Specifically, we measure the scientific publications related to each gene as an indicator of scientific research investments, and measure the use of genes in pharmaceutical clinical trials and diagnostic tests as indicators of commercial research investments. Because gene patents have been widely interpreted as sufficiently broad that follow-on inventions require gene patent licenses (see, e.g., Heller and Eisenberg (1998), Doll (1998)), this measurement exercise corresponds closely with the theoretical concept of interest.

Because we observe our measures of follow-on scientific research and product development for all genes, this DNA sequence-based linkage allows us to compare follow-on innovation across patented and non-patented genes. If patents were as good as randomly assigned across genes, this would be sufficient to estimate the causal effect of interest. However, if inventors are more likely to file for and obtain patents on technologies that are more valuable, then this type of simple comparison could reflect the selection of which genes are patented. By taking advantage of the fact that we observe our measures of follow-on innovation both before and after gene patents are granted, we are able to document novel evidence of selection into patenting: genes that will be patented in the future are the focus of more scientific research and more commercial investments prior to being patented, relative to genes that will not be patented. This evidence suggests that estimating a causal effect of patents on follow-on innovation requires constructing an empirical strategy to address this selection bias.

To address the second challenge — selection bias — we develop two new quasi-experimental methods for estimating how patents have affected follow-on innovation. First, we present a simple comparison of follow-on innovation across genes claimed in accepted versus rejected patent applications.[1] In our context, this method is reasonable if — conditional on being included in a patent application — whether a gene is granted a patent is as good as random.[2] Again taking advantage of the fact that we observe our measures of follow-on innovation both before and after gene patents are granted, we document empirically that genes claimed in accepted and rejected patent applications are the focus of similar levels of scientific research and commercial investments prior to the applications being filed, providing evidence for the validity of this empirical approach. Second, we develop a novel instrumental variable for which patent applications are granted patents: namely, the "leniency" of the assigned patent examiner. Patent examiners are charged with a uniform mandate: grant patents to patent-eligible, novel,

[1] Strictly speaking, patent applications are never formally rejected by the USPTO, only abandoned by applicants (Lemley and Sampat, 2008). For brevity, we colloquially refer to such applications as "rejected" throughout the text.

[2] As we will discuss in more detail, this approach does *not* require that patents are as good as randomly assigned across patent applications; rather, the relevant assumption is at the gene level, for genes included in accepted and rejected applications.

non-obvious, and useful inventions. However, prior research has documented that in practice this mandate leaves patent examiners a fair amount of discretion (Cockburn, Kortum and Stern, 2003; Lemley and Sampat, 2010, 2012). We leverage the interaction of this across-examiner heterogeneity with the quasi-random assignment of patent applications to examiners as a source of variation in which patent applications are granted patents. Past qualitative evidence — and new empirical evidence we document — supports the assertion that the assignment of patent applications to examiners is plausibly random conditional on some covariates (such as application year and technology type), suggesting that the leniency of the patent examiner to which a patent application is assigned can provide a valid instrument for whether the patent application is granted a patent.[3]

In contrast with what one would infer from a naïve comparison of follow-on innovation on patented and non-patented genes, both of our quasi-experimental approaches suggest that gene patents have not had quantitatively important effects on either follow-on scientific research or follow-on commercial investments. The estimates from our first quasi-experimental approach — comparing follow-on innovation across genes claimed in successful versus unsuccessful patent applications — document estimates which are economically small and meaningfully precise. While the estimates from our second quasi-experimental approach — using the leniency of the assigned patent examiner as an instrument for which patent applications are granted patents — are less precise, the fact that these two approaches generate similar conclusions provides additional confidence in our estimates.

Our empirical estimates speak most directly to a recent set of high-profile legal rulings on the case *Association for Molecular Pathology v. Myriad Genetics*.[4] The firm Myriad Genetics was granted patents on human genes correlated with risks of breast and ovarian cancer, and in June 2013 the US Supreme Court unanimously ruled to invalidate a subset of Myriad's gene patent claims, arguing that such patents *"would 'tie up'...[genes] and...inhibit future innovation."* That is, the Court argued that gene patents had sufficiently strong negative effects on follow-on innovation that genes should be ineligible for patent protection.[5] While - consistent with that view - there has been widespread concern that patents on human genes may hinder follow-on innovation, as argued by a 2006 National Academies report and by Caulfield et al. (2013) there was essentially no empirical evidence available to either

[3]Importantly, both of our sources of quasi-experimental variation hold the disclosure of inventions constant: both accepted and rejected inventions are disclosed in the published patent applications that comprise our sample. This implies that our analysis corresponds to a partial equilibrium analysis (holding disclosure constant), whereas in general equilibrium firms may choose to protect their inventions with e.g. trade secrecy or other strategies rather than with patents if patent protection is not available. For example, in response to the *Mayo v. Prometheus* ruling discussed below, the law firm Goodwin Proctor issued a "client alert" arguing that the ruling called for "a renewed look at trade secret law for protection of diagnostics innovations as an alternative to patents"; see `http://www.goodwinprocter.com/Publications/Newsletters/Client-Alert/2012/0323_Lessons-from-Mayo-v-Prometheus.aspx`.

[4]Appendix A provides some additional background on this case.

[5]This same line of argument has shaped at least three other recent US Supreme Court rulings which have moved to restrict the set of discoveries eligible for patent protection in other industries (Kesselheim, Cook-Deegan, Winickoff and Mello, 2013). First, in *Bilski v. Kappos* the Court invalidated patent claims on an investment strategy, announcing it supported a "high enough bar" on patenting abstract ideas that it would not "put a chill on creative endeavor and dynamic change." Second, in *Mayo v. Prometheus*, the Court invalidated patent claims on methods of using genetic variation to guide pharmaceutical dosing, expressing concern that "patent law not inhibit further discovery by improperly tying up the future of laws of nature." Finally, in *Alice Corp v. CLS Bank* the Court invalidated patent claims on software based on similar arguments.

support or refute that assertion prior to this paper.[6] Speaking against the US Supreme Court's ruling, our empirical estimates do not provide support for the idea that patents on human genes have hindered follow-on innovation. That is, for the case of human genes, the traditional patent trade-off of ex ante incentives versus deadweight loss may be sufficient to analyze optimal patent policy design, as any effects of patents on follow-on innovation appear to be quantitatively small.

Beyond this specific policy relevance, our estimates also speak to the broader question of how patents affect follow-on innovation. A well-developed theoretical literature has documented ambiguous predictions for how patents will affect follow-on innovation.[7] The only other empirical paper we are aware of on this question is the recent complementary contribution of Galasso and Schankerman (2015). Using the quasi-random assignment of court cases to judges at the US Court of Appeals for the Federal Circuit as an instrument for patent invalidations, the authors investigate the effect of patent invalidations on follow-on innovation as measured by patent citations. On average, they document that patent invalidations lead to a 50 percent increase in citations to the focal patent. A strength of their citation analysis is their ability to analyze the effects of patent invalidations across a wide range of technology fields. However, a limitation of their citation analysis is that it is not clear that citations correspond closely to the theoretical concept of interest, since patent citations can be generated even in cases where a license would not be required. Our analysis is complementary in our construction of measures of follow-on innovation which are more tightly linked to the theoretical concept of interest.[8]

Our empirical results stand in contrast with two prior papers which documented that non-patent forms of intellectual property induced substantial declines in follow-on innovation (Murray et al., 2008; Williams, 2013).[9] Most closely related is prior work by one of the authors (Williams, 2013) which documented evidence that a non-patent form of database protection on the human genome hindered follow-on innovation. That evidence was cited in several briefs filed in the *AMP v. Myriad* case,[10] but as discussed by Marshall (2013) defenders of the patent system had been hesitant to generalize that evidence on gene data protection to the expected effects of gene patents. As we discuss in more detail in Section 6, taken together these results suggest that patents per se did not hinder

[6] Perhaps the best available prior evidence was an oft-cited anecdote that pharmaceutical firm Bristol Myers abandoned research on more than fifty cancer-related proteins due to conflicts with gene patent holders (Pollack, 2001).

[7] We discuss this theoretical literature in Section 6.

[8] Consistent with our results, Galasso and Schankerman find no evidence that patent invalidations increase patent citations in the technology field that includes most of our gene patents. Specifically, the most common patent class in our sample is 435 (Chemistry: molecular biology and microbiology), which is included in the NBER patent technology field "drugs and medical"; Galasso and Schankerman do not find evidence that patent invalidations increase follow-on citations in that subcategory. Unfortunately, the variation used by Galasso and Schankerman (2015) is not directly applicable in our context because very few human gene patents have ever been asserted in court (Holman, 2007, 2008).

[9] We here do not focus on the estimates from Murray and Stern (2007), who documented evidence that patent grants hindered subsequent citations to matched scientific papers (a measure of follow-on innovation), because subsequent work by the authors (Fehder, Murray and Stern, 2014) documented that this result was specific to the first few years after the founding of the journal they analyzed.

[10] See, for example, `http://www.americanbar.org/content/dam/aba/publications/supreme_court_preview/briefs-v2/12-398_pet.authcheckdam.pdf` and `http://www.yaleisp.org/wp-content/uploads/2012/01/31253-BRCA-AMICUS-BRIEF-FINAL.pdf`.

follow-on research on the human genome, but that this non-patent form of intellectual property - which was used after gene patent applications were largely rejected - did hinder follow-on innovation. Taken at face value, this body of evidence highlights that changes to patent policy must be considered in light of what strategies firms will use to protect their discoveries in the absence of patents.

Methodologically, our two quasi-experimental approaches build on similar applications in labor economics and public finance. Our comparison of accepted and rejected patent applications builds on Bound (1989) and von Wachter, Song and Manchester (2011)'s investigations of the disincentive effects of disability insurance on labor supply, and Aizer, Eli, Ferrie and Lleras-Muney (2013)'s investigation of the effects of cash transfers on mortality. Likewise, our approach of using examiner "leniency" as a source of variation in which patent applications are granted patents builds on past work investigating the effects of incarceration length using variation across judges (Kling, 2006), the effects of foster care using variation across foster care case workers (Doyle, 2007, 2008), and the disincentive effects of disability insurance on labor supply using variation across disability insurance examiners (Maestas, Mullen and Strand, 2013). Especially given the relatively small number of patent law changes in countries like the US in recent years, these two new sources of quasi-experimental variation may provide valuable opportunities to investigate the effects of patents in a variety of other applications.

Section 2 describes our data. Section 3 documents evidence of selection in which genes are patented, motivating our two quasi-experimental approaches. Section 4 presents estimates from our first quasi-experimental approach, comparing follow-on innovation across genes claimed in successful and unsuccessful patent applications. Section 5 presents estimates from our second quasi-experimental approach, using the leniency of the assigned patent examiner as an instrumental variable for whether the patent application was granted a patent. Section 6 interprets our empirical results, and Section 7 concludes.

2 Data

This section describes our data construction.[11] To fix ideas, we start by describing an example patent application — USPTO patent application 08/483,554 — claiming intellectual property over the BRCA1 gene, and describe our measures of follow-on innovation in the context of that example (Section 2.1). We then describe in more detail how we construct our sample of USPTO patent applications claiming intellectual property over human genes (Section 2.2), and our gene-level measures of follow-on scientific research and product development (Section 2.3).

[11] Appendix B describes our data construction in more detail.

2.1 Example: USPTO patent application 08/483,554

On 7 June 1995, Myriad Genetics filed USPTO patent application number 08/483,554: *17Q-Linked Breast and Ovarian Cancer Susceptibility Gene*. This application was subsequently granted a patent on 5 May 1998 (US patent number 5,747,282), and would later become a focus of the US Supreme Court case *Association for Molecular Pathology v. Myriad Genetics*.

This patent claimed intellectual property over an isolated sequence of nucleotide bases (adenine, cytosine, guanine, and thymine), the sequence of which is listed explicitly in the patent (*SEQ ID NO:1: AGC TCG CTG...*). By comparing this sequence of nucleotide bases to the census of human gene sequences, we can uncover that this sequence corresponds to the BRCA1 gene.

The text of the Myriad patent describes how variation in the precise sequence of nucleotide bases in the BRCA1 gene can induce variation in an individuals' risk of developing breast and ovarian cancers. For example, women with certain abnormal types of BRCA1 or BRCA2 genes have a 40 to 80 percent lifetime risk of developing breast cancer, relative to about 12 percent in the general population.[12]

Such links between genetic variation and diseases are referred to as genotype-phenotype links. In the case of the BRCA1 gene, scientific papers have investigated links between BRCA1 and breast cancer (141 publications), ovarian cancer (96 publications), and pancreatic cancer (2 publications).[13] Once scientific knowledge of a given genotype-phenotype link has been documented, this knowledge can be applied to develop medical technologies such as pharmaceutical treatments and gene-based diagnostic tests. In the case of the BRCA1 gene, more than 200 pharmaceutical clinical trials have been conducted that focus on mutations in the BRCA1 gene, and a BRCA1 genetic test is marketed by the firm Myriad Genetics.[14] The goal of our data construction is to trace these measures of follow-on scientific research and product development for each human gene, and to link these data to records of which human genes have been included in USPTO patent applications and granted patents.

2.2 Constructing USPTO patent application sample

Our quasi-experimental approaches require constructing data on the census of published USPTO patent applications that claim intellectual property over human genes — both successful (granted patents) and unsuccessful (not granted patents). Traditionally, unsuccessful USPTO patent applications were not published. However, as part of the American Inventors Protection Act of 1999, the vast majority of USPTO patent applications filed on or after 29 November 2000 are published in the public record — regardless of whether they are granted patents — at or

[12] These statistics are drawn from GeneReviews, published by the US National Institutes of Health (NIH).
[13] These data are drawn from the NIH Online Mendelian Inheritance in Man (OMIM) database, described below.
[14] These data are drawn from the Citeline Pharmaprojects database and the NIH GeneTests.org database, described below.

before eighteen months after the filing date.[15]

From the census of USPTO patent applications, we identify the subset of applications claiming intellectual property over genes. To do this, we follow the methodology proposed by Jensen and Murray (2005), which can be briefly summarized as follows.[16] Since the early 1990s DNA sequences have been listed in USPTO patent applications in a standard format, labeled with the text "SEQ ID NO" (sequence identification number). This standardized format allows for DNA sequences to be cleanly extracted from the full text of USPTO published patent applications. Once extracted, standard bioinformatics methods can be used to compare these sequences against the census of human gene DNA sequences in order to annotate each sequence with standard gene identifiers that can be linked to outside databases.[17]

We apply this Jensen and Murray (2005) methodology to construct two samples. First, we construct a "first stage sample" that aims to include the census of published USPTO patent applications that claim any non-human (e.g. mouse) DNA sequences in their patent claims (Bacon et al., 2006). Second, we construct a "human gene sample" that includes only the subset of published USPTO patent applications that claim human genes (Lee et al., 2007). This human gene sample is the focus of our analysis, given the focus in this paper on investigating how patents on human genes have affected follow-on innovation. However, this sample includes far fewer patent applications than the first stage sample: we have around 1,500 applications in the human gene patent sample, relative to around 14,000 applications in the first stage sample. This matters for our second quasi-experimental design, for which it is (as we will discuss more below) econometrically useful to estimate variation in the grant propensities in a separate sample of patent applications. Hence, we use the first stage sample to estimate the examiner patent grant propensities, and apply those estimates to the examiners in our human gene sample.

Table 1 presents patent application-level summary statistics on our first stage sample and our human gene sample. Our first stage sample includes 14,016 USPTO patent applications with DNA sequences listed in their claims, while our human gene sample includes 1,533 USPTO patent applications with human genes listed in their

[15]For more details, see `http://www.uspto.gov/web/offices/pac/mpep/s1120.html` and the discussion in Lemley and Sampat (2010). Most applications not published eighteen months after filing are instead published sixty months after filing. Some US patent applications opt out of publication: Graham and Hegde (2013) document that around 8% of US applications opted for pre-grant secrecy of patent applications. For the NBER patent technology field "drugs and medical," which includes the most common patent class in our sample, the share was 3.5%.

[16]While we focus on the Jensen and Murray (2005) definition of gene patents, there are many different types of DNA-related patent claims — e.g., protein-encoding sequences, expressed sequence tags (ESTs), single-nucleotide polymorphisms (SNPs), sequence-based claims, and method claims that pertain to specific genes or sequences; see Scherer (2002) and Holman (2012) for more discussion. As one point of comparison, nearly all of the patent applications in our sample are included in the *DNA Patent Database* (`http://dnapatents.georgetown.edu/SearchAlgorithm-Delphion-20030512.htm`), which is constructed using a completely different methodology; we are grateful to Robert Cook-Deegan and Mark Hakkarinen for sharing the patent application numbers included in the *DNA Patent Database*, which enabled this comparison. Our empirical strategies could of course be applied to any empirically implementable definition of gene patents, but we are not aware of data on any other alternative definitions.

[17]Following Jensen and Murray (2005), we focus attention on the subset of DNA sequences that are explicitly listed in the claims of the patent applications (excluding DNA sequences that are referenced in the text of the patent application — and hence listed in the SEQ ID NO format — but not explicitly claimed as intellectual property).

claims. Our data primarily includes US patent applications filed from 2001-2010, given that the requirement for unsuccessful patent applications to be published came into force for patent applications filed on or after 29 November 2000. A small share of our sample has an application year prior to 2000; we retain these observations in our sample in the absence of a clear reason to exclude them. The human gene sample ends with application year 2005, marking the last year of data used as an input into the data construction done by Lee et al. (2007).[18] In both samples, about 30 percent of the patent applications had been granted patents by 2010, although this raw statistic does not account for censoring.[19]

One limitation of our quasi-experimental approaches is that they can only be implemented over the time period when unsuccessful patent applications were published (that is, applications filed after 29 November 2000). Some criticisms of gene patents — such as Heller and Eisenberg (1998) — focused on the subset of gene patents covering expressed sequence tags (ESTs), which Rai (2012) argues were less commonly granted in later years. For the purposes of our descriptive analyses we can (and do) apply the Jensen and Murray (2005) methodology to identify granted USPTO patents that claim human genes but were filed prior to 29 November 2000.[20]

2.3 Measuring follow-on innovation

We collect data on three measures of gene-level follow-on innovation: scientific publications as a measure of scientific research effort; and two measures of product commercialization: gene-related pharmaceutical research, and gene-based diagnostic tests.

We collect data on the scientific publications related to each gene from the Online Mendelian Inheritance in Man (OMIM) database, which catalogs scientific papers that have documented evidence for links between genetic variation and phenotypes. Using this data, we construct a count of the number of scientific papers published related to each gene — across all phenotypes — in each year.

Because of the long time lags between basic drug discovery and the marketing of new drugs, new approvals of drugs that take advantage of sequenced genetic data are just barely starting to enter the market (Wade, 2010). Given these time lags, rather than using drug approvals as a measure of pharmaceutical research, we instead focus on an intermediate measure of drug discovery — namely, drug compounds currently under development, as

[18] Unfortunately, we do not know of a data source which applies the Lee et al. (2007) methodology to later years of data.

[19] This grant rate is also a simple grant rate that does not account for the fact that US patent applications that are rejected can spawn closely related "new" applications (continuations or divisionals). Carley, Hegde and Marco (forthcoming) use internal USPTO data to calculate simple and "family" (including patents granted to continuations or divisionals) grant rates in the universe of new (not related to any previously filed applications) utility patent applications filed at the USPTO from 1996-2005. In this sample, 55.8% of applications were granted patents directly (without the use of continuations), and including patents granted to children increases the allowance rate to 71.2%. For the NBER patent technology field "drugs and medical," which includes the most common patent class in our sample, the progenitor allowance rate is 42.8% and the family allowance rate is 60.7%. This measurement limitation is relevant to our second empirical strategy (which analyzes application-level data) but not to our first empirical strategy (which analyzes gene-level data, and hence captures all patent applications related to each gene).

[20] These data are also drawn from Lee et al. (2007), and include USPTO patents granted through 2005.

disclosed in clinical trials.[21] Specifically, we measure gene-related pharmaceutical clinical trials using the Citeline Pharmaprojects database, a privately-managed competitive intelligence database that tracks drug compounds in clinical trials and — critically for our project — assigns gene identifiers to compounds related to genetic variation on specific genes. Using this data, we construct a count of the number of clinical trials related to each gene in each year.

Finally, we collect data on gene-based diagnostic tests from the GeneTests.org database, a genetic testing registry. Some gene-based tests provide individuals with information about disease risk, such as the BRCA tests related to risks of breast and ovarian cancers; other gene-based tests identify individuals as relatively more or less appropriate for a given medical treatment, such as a test which predicts heterogeneity in the side effects of the widely-prescribed blood thinner warfarin. Using the GeneTests.org data, we construct an indicator for whether a gene is included in any gene-based diagnostic test as of 2012. Unfortunately, this data is only available in a cross-section (not a panel).

A priori, the impact of patents on follow-on scientific research could differ from the impact of patents on product development. For example, many have argued that most patented inventions are made available to academic researchers on sufficiently favorable licensing terms that academics are able to continue their research (USPTO, 2001). Hence, even if transaction costs hinder licensing agreements for commercial applications we could expect to see no impact of patents on measures of follow-on academic research such as scientific publications. Alternatively, patents may change researchers' incentives of whether to disclose the results of their research through academic publications (Moon, 2011), in which case observed differences in scientific publications could be explained by differences in disclosure rather than by differences in the true amount of underlying scientific research. By contrast, we would not expect the product development outcomes we measure to be affected by such disclosure preferences given that the measures we observe are revealed in the natural course of firms commercializing and selling their technologies.

3 Comparison of patented and non-patented human genes

Our interest in this paper is in comparing follow-on innovation across patented and non-patented inventions. To investigate this question, we first examine the selection process in order to investigate which inventions are patented. On one hand, we may expect inventors to be more likely to both file for and be granted patents on technologies that are more valuable: inventors may be more willing to pay the time and monetary cost of filing patent applications for inventions that are more valuable, and patent applications claiming intellectual property over more valuable

[21] Data on clinical trial investments has also been used as a measure of research effort in prior work, starting with Acemoglu and Linn (2004) and Finkelstein (2004).

inventions may also be more likely to "clear the bar" and be granted patents. On the other hand, the USPTO grants patents based on criteria — patent-eligibility, novelty, non-obviousness, and usefulness — that may not closely correspond with measures of scientific and commercial value (Merges, 1988). Hence, it is an empirical question whether inventions with higher levels of scientific and commercial value are more likely to be patented.

There is a remarkable absence of empirical evidence on this question, largely due to a measurement challenge: in most markets, it is very difficult to measure the census of inventions, and to link those inventions to patent records in order to identify which inventions are and are not patented. The only other paper we are aware of which has undertaken such an exercise is Moser (2012), who constructs a dataset of innovations exhibited at world's fairs between 1851 and 1915 and documents that "high quality" (award-winning) exhibits were more likely to be patented, relative to exhibits not receiving awards. Given this dearth of previous estimates, documenting evidence on the selection of inventions into patenting is itself of interest. In addition, if we do observe evidence of selection into patenting, that would imply that any measured differences in follow-on innovation across patented and non-patented genes may in part reflect the selection of which genes are included in patent applications and granted patents (as opposed to an effect of patents on follow-on innovation).

For this exercise, we start with the full sample of human genes (N=26,440). As measured in our data, approximately 29 percent of human genes have sequences that were explicitly claimed in granted US patents (N=7,717).[22] Figure 1 documents trends in follow-on innovation by year separately for genes that ever receive a patent (triangle-denoted solid blue series), and for genes that never receive a patent (circle-denoted dashed red series). For scientific publications (Figure 1(a)), we plot the average log number of scientific publications by year in each year from 1970 to 2012.[23] For clinical trials (Figure 1(b)), we plot the average log number of clinical trials by year in each year from 1995 to 2011.[24]

Because by construction our human gene patents are measured starting in the mid-1990s (when the SEQ ID NO notation was introduced), the cleanest test of selection into patenting is a comparison of pre-1990 follow-on innovation across (subsequently) patented and non-patented genes. While the clinical trials data only starts later (in 1995), the scientific publications data is available prior to 1990 so can be used for this comparison. Looking at the data series in Figure 1(a) from 1970 to 1990 provides clear evidence of positive selection: genes that will later

[22] As a point of comparison, Jensen and Murray (2005) document that as of 2005, approximately 20 percent of human genes had sequences that were explicitly claimed as granted patents. Because our sample includes patent applications that were granted patents after 2005, we would expect our estimate to be mechanically larger.

[23] We focus on the average log number of scientific publications by year because even within a calendar year, the number of publications per human gene is quite right-skewed. The pattern of selection that we document is unchanged if we instead plot the share of genes with at least one scientific publication by year (Appendix Figure D.1 Panel (a)), or the average number of scientific publications by year (Appendix Figure D.1 Panel (c)). Here and elsewhere, we add one to the outcome variables in order to include observations with no observed follow-on innovation.

[24] These years — 1995 to 2011 — are the only years for which the Pharmaprojects data are available. As with the scientific publications measure, we focus on the average log number of clinical trials by year because this variable is quite right-skewed. Again, the pattern of selection that we document is unchanged if we instead plot the share of genes with at least one clinical trial by year (Appendix Figure D.1 Panel (b)), or the average number of clinical trials by year (Appendix Figure D.1 Panel (d)).

receive patents were more scientifically valuable — based on this publications measure — prior to being patented. Moreover, even within the 1970 to 1990 period this positive selection appears not just in the levels of follow-on innovation, but also in the trends: genes that will later receive patents appear to have divergent trends in scientific publications relative to genes that will never receive patents, even before any patents are granted.

These patterns — a level difference, and a divergence in trends — also appear in the clinical trials data presented in Figure 1(b), although it is not possible to cleanly separate selection and "treatment" (that is, any causal effect of patents on subsequent research effort) because that data series starts in 1995. Likewise, if we tabulate the probability that genes are used in diagnostic tests for patented and non-patented genes, 13.45% of patented genes are used in diagnostic tests, compared to 6.39% of non-patented genes.[25]

Taken together, these patterns suggest strong evidence of positive selection: genes that will later receive patents appear more scientifically and commercially valuable prior to being granted patents, relative to genes that will never receive patents. This evidence is important for three reasons. First, this evidence suggests that our measures of value (pre-patent filing scientific publications and clinical trials) are correlated with patenting activity, which provides some evidence that these measures can provide a meaningful basis for assessing selection in our two quasi-experimental approaches. Second, this analysis provides novel evidence on the selection of technologies into patenting, in the spirit of Moser (2012). Third, this evidence implies that a simple comparison of follow-on innovation across patented and non-patented genes is unlikely to isolate an unbiased estimate of how gene patents affect follow-on innovation. While a naïve comparison that did not account for selection would conclude based on Figure 1 that patents encourage follow-on innovation, as we will see in Sections 4 and 5 our two quasi-experimental approaches will suggest a different conclusion.

4 Comparison of accepted and rejected patent applications

Our first quasi-experimental source of variation investigates a simple idea, which is whether genes that were included in unsuccessful patent applications can serve as a valid comparison group for genes that were granted patents.

A comparison of follow-on innovation on genes included in accepted and rejected patent applications will be valid if — conditional on being included in a patent application — whether a gene is granted a patent is as good as random. A priori, it is not clear that this could offer a valid comparison. The USPTO is responsible for assessing whether patent applications should be granted patents based on five criteria: patent-eligibility (35

[25] While we only observe our diagnostic test outcome in a cross-section, for our clinical trial outcomes we can replicate a version of this analysis which focuses on the set of gene patents whose applications were filed in or after 2001, in which case 1995 to 2000 can serve as a "pre-period" that isolates a selection effect. Appendix Figure D.1 Panels (e) and (f) document that we see very similar patterns of selection on levels as well as trends using this alternative sample of gene patents.

U.S.C. §101), novelty (35 U.S.C. §102), non-obviousness (35 U.S.C. §103), usefulness (35 U.S.C. §101), and that the text of the application satisfies the disclosure requirement (35 U.S.C. §112). Any given patent application in our sample will claim intellectual property rights over at least one gene, and what is required for our first quasi-experimental approach to be valid is that conditional on being included in a patent application, whether a gene is granted a patent is as good as randomly assigned. Importantly, this strategy does not require assuming that patents are as good as randomly assigned across applications; rather, the relevant assumption is that genes that are included in patent applications that are granted patents are comparable to genes that are included in patent applications that are not granted patents. Empirically, we will document in this section that genes claimed in successful and unsuccessful patent applications appear similar on observable characteristics fixed at the time of application, providing evidence for the validity of this empirical approach. While this comparison is quite simple, we will see that the resulting estimates are similar to the estimates from our second quasi-experimental source of variation (the examiner leniency variation, presented in Section 5).

4.1 Graphical analysis

For this exercise, we start with the sample of human genes included in at least one patent application in our USPTO patent applications sample (N=15,530; 59% of the full sample of 26,440 human genes). Of this sample, 4,858 genes are claimed in a patent application that is subsequently granted a patent (31%), relative to 10,672 genes that are never observed to be subsequently granted a patent (69%).[26] Figure 2(a) illustrates the time pattern of when the patented group receives its (first) patent grant over time. Over half of these genes have received a patent by 2005, and (by construction) all have received a patent by 2010.

Figures 2(b) and 2(c) document trends in follow-on innovation by year. As in Figure 1, we plot the average log number of scientific publications by year in each year from 1970 to 2012 (Figure 2(b)), and the average log number of clinical trials by year in each year from 1995 to 2011 (Figure 2(c)).[27] The solid blue triangle-denoted line represents genes claimed in at least one granted patent, and the dashed red circle-denoted line represents genes claimed in at least one patent application but never in a granted patent.

As a point of comparison, the dashed green square-denoted line represents genes never claimed in a patent application (N=10,910; 41% of the full sample of 26,440 human genes). Comparing this group of genes to the other two groups of genes, we see clear evidence of selection into patent filing: genes included in successful and unsuccessful patent applications are much more valuable both scientifically (publications) and commercially

[26] Note that this 4,858 figure is mechanically lower than the 7,717 figure in Section 3, because we here focus only on patents granted on patent applications filed after 29 November 2000 (the date when unsuccessful applications began to be published).

[27] Appendix Figure D.2 documents analogous figures if we instead plot the share of genes with at least one scientific publication or clinical trial by year (Appendix Figure D.2 Panels (a) and (b)) or the average number of scientific publications or clinical trials by year (Appendix Figure D.2 Panels (c) and (d)).

(clinical trials) prior to the patent application filing compared to genes that are never claimed in a patent application. In terms of interpreting the results in Section 3, the data suggest that the major source of selection in which genes are patented is selection in which genes are included in patent applications (as opposed to which genes are granted patents, conditional on being included in patent applications).

The key comparison of interest in this section is across the first two data series: genes included in successful patent applications, and genes included in unsuccessful patent applications. Strikingly, we see little evidence of selection in pre-2001 levels or trends of our two follow-on innovation measures once we limit the sample to genes included in patent applications. For scientific publications (Figure 2(b)), the two groups follow each other quite closely from 1970 to 1990, and diverge slightly in trends from 1990 to 2000 — with genes that will subsequently be included in unsuccessful patent applications having slightly more scientific publications.[28] For clinical trials (Figure 2(c)), the two groups follow each other quite closely in both levels and trends over all available pre-2001 years of data. Taken at face value, the similarity of these two groups in pre-2001 outcomes provides evidence for the validity of this empirical approach. A priori, one might have expected genes that were more scientifically or commercially valuable to have been more likely to receive patents. However, conditional on being included in a patent application, this appears not to be the case.

Looking at the post-2001 time period, we see that although these two groups of genes diverge (by construction) in whether they are claimed in granted patents (Figure 2(a)), we do not see any evidence of a divergence in follow-on innovation outcomes. That is, these figures suggest that gene patents have not had a quantitatively important effect on either follow-on scientific research or on follow-on commercialization.

4.2 Regression analysis

We quantify the magnitudes of these differences in a regression framework in Table 2. Because our scientific publication and clinical trial outcomes are quite skewed, a proportional model or binary outcome (measuring "any follow-on innovation") is more appropriate than modeling the outcome in levels. We focus on the log of follow-on innovation and (separately) an indicator for any follow-on innovation.

Given the absence of strong visual evidence for a difference in follow-on innovation across patented and non-patented genes, our focus here is on what magnitudes of effect sizes can be ruled out by our confidence intervals. Across these specifications, our 95% confidence intervals tend to reject declines or increases in follow-on innovation on the order of more than 5-15%. For brevity, we focus on interpreting the log coefficients. For our measures of follow-on scientific research (publications; Panel A of Table 2) and commercialization (clinical trials; Panel B of Table 2), the 95% confidence intervals can reject declines or increases of more than 2%. For our measure

[28] Note that this slight divergence is not apparent in the robustness check documented in Appendix Figure D.2 Panel (c), where we plot the average number of scientific publications by year.

of diagnostic test availability (only measured as a binary indicator; Panel C of Table 2), we estimate that genes receiving patents had a statistically insignificant 0.9 percentage point decrease in the likelihood of being included in a diagnostic test as of 2012 relative to genes included in patent applications but not granted patents. Our 95% confidence interval can reject declines of greater than 2 percentage points and reject increases of more than 0.2 percentage points. Relative to a mean of 12%, this confidence interval suggests that we can reject declines in this outcome of greater than 17%.[29]

5 Analyzing examiner-level variation in patent grant propensities

Our second source of quasi-experimental variation constructs an instrumental variables strategy for predicting which patent applications are granted patents. Our key idea is to build on previous research which has established that although patent examiners are charged with a uniform mandate, in practice examiners have a fair amount of discretion, and this discretion appears to translate into substantial variation in the decisions different examiners make on otherwise similar patent applications (Cockburn, Kortum and Stern, 2003; Lichtman, 2004; Lemley and Sampat, 2010, 2012).[30] In the spirit of prior analyses such as Kling (2006), we leverage these patterns in order to use variation in the "leniency" of different patent examiners as a predictor of which patent applications are granted patents.

The exclusion restriction for this instrumental variables approach requires assuming that the examiner only affects the follow-on innovation through the likelihood that a gene is patented. As we describe below, the institutional context suggests that the assignment of patent applications to USPTO patent examiners should be effectively random conditional on some covariates (such as application year and technology type). While the exclusion restriction is inherently untestable, we will document empirically that - consistent with our qualitative description of the institutional context - genes assigned to 'lenient' and 'strict' examiners look similar on observable characteristics fixed at the time of patent application.[31]

To motivate our empirical specification, Section 5.1 provides some qualitative background on the key institutional features underlying our empirical strategy,[32] after which we present our empirical estimates.

[29] As a point of comparison, only 3% of genes never included in a patent application are included in a diagnostic test as of 2012.

[30] One of the individuals interviewed by Cockburn, Kortum and Stern (2003) described this variation informally by saying: *"there may be as many patent offices as there are patent examiners."* Similarly, a trade publication written by a former USPTO patent examiner and current patent agent (Wolinsky, 2002) described this variation by saying: *"The successful prosecution of a patent application at the USPTO requires not only a novel invention and adequate prosecution skills, but a bit of luck...If you knew the allowance rate of your examiner, you could probably estimate your odds of getting your patent application allowed."*

[31] While conditional random assignment of applications to examiners assuages many potential concerns about this exclusion restriction, some additional issues remain. In particular, while we focus on variation in patent grant propensity, examiner heterogeneity may also manifest itself in other ways, such as the breadth of patent grants (in terms of the number or strength of allowed claims) and time lags in grant decisions (Cockburn, Kortum and Stern, 2003).

[32] The discussion in this section draws heavily on Cockburn, Kortum and Stern (2003), Lemley and Sampat (2012), Frakes and Wasserman (2014), and US General Accounting Office (2005). See Appendix C for more detail on the USPTO patent examination process.

5.1 Assignment of patent applications to patent examiners

A central USPTO office assigns application numbers to incoming applications, as well as patent class and subclass codes detailing the type of technology embodied in the application.[33] These class and subclass numbers determine which of ~300 so-called Art Units — specialized groups of examiners — will review the application.[34] Within an Art Unit, a supervisory patent examiner assigns the application to a patent examiner for review. While the patent application process up to this point is quite structured, from this point forward substantial discretion is left in the hands of individual examiners, who are responsible for determining which — if any — claims in the application are patentable.

Because no "standard" method for the within-Art Unit assignment of applications to examiners is uniformly applied in all Art Units, Lemley and Sampat (2012) conducted written interviews with roughly two dozen current and former USPTO examiners to inquire about the assignment process. While the results of these interviews suggested that there is not a single "standard" assignment procedure that is uniformly applied in all Art Units, these interviews revealed no evidence of deliberate selection or assignment of applications to examiners on the basis of characteristics of applications other than those observed in standard USPTO datasets (which we can condition on). For example, in some Art Units supervisors reported assigning applications to examiners based on the last digit of the application number; because application numbers are assigned sequentially in the central USPTO office, this assignment system — while not purposefully random — would be functionally equivalent to random assignment for the purposes of this study. In other Art Units, supervisors reported placing the applications on master dockets based on patent classes and subclasses, with examiners specializing in those classes (or subclasses) being automatically assigned the oldest application from the relevant pool when requesting a new application. Our key conclusion from this institutional context is that effective conditional random assignment of applications to examiners — within Art Unit and application year — is plausible. Consistent with this assumption, we will document that patent applications assigned to 'lenient' and 'strict' examiners look similar on observable characteristics fixed at the time of patent application.

From a practical perspective, it is worth noting that informational barriers limit the extent to which we would expect patent applications to be systematically sorted across examiners in a way that would be problematic for our empirical specifications. Because of the limited attention given to patents prior to their assignment to a specific examiner, and the judgment required to determine the characteristics of a given invention, it seems plausible that informational barriers would impose real constraints on sorting (this argument has been made in more detail by

[33] There are currently over 450 patent classes, and more than 150,000 subclasses; see `http://www.uspto.gov/patents/resources/classification/overview.pdf`.

[34] See `http://www.uspto.gov/patents/resources/classification/art/index.jsp`. For the current version of the class/subclass-to-Art Unit concordance, see `http://www.uspto.gov/patents/resources/classification/caau.pdf`. The main Art Units in our sample are from the 1600 group (Biotechnology and Organic Chemistry).

Merges (2001)).[35] In particular, the "patentability" of applications is difficult to assess *ex ante*, and there is no evidence that supervisory patent examiners attempt to do so before assigning applications to particular examiners.

5.2 Examiner leniency variation

To the best of our knowledge, Kling (2006) was the first paper to leverage this type of institutional context as a source of variation - in his case, using the random assignment of court cases to judges as an instrument for incarceration length. He adopted the jackknife instrumental variables (JIVE1) approach proposed by Angrist, Imbens and Krueger (1999), which predicts the judge effect for each case based on data for all other cases.[36] However, JIVE estimators have been criticized for having undesirable finite sample properties (see, e.g., Davidson and MacKinnon (2006)). In our case, a natural alternative is to adopt a two-sample two-stage least squares (TS2SLS) variant of Angrist and Krueger (1992)'s two-sample instrumental variable estimator. Specifically, for each patent examiner in our sample, we observe decisions that examiner makes on non-human gene patent applications, and we can use that separate sample to estimate variation in leniency across examiners. Motivated by the institutional context, we condition out Art Unit-by-application year fixed effects, so that we capture an examiner's patent grant propensity relative to other examiners reviewing applications in that Art Unit in that application year, and we use the two-sample instrumental variables estimator standard error correction provided by Inoue and Solon (2010).[37]

5.3 First stage estimates

Figure 3 provides a visual representation of our first stage. For our first stage sample, we calculate the mean grant rate for each examiner, residualized by Art Unit-by-application year fixed effects, and relate this measure of examiner "leniency" to patent grant outcomes.[38] Visually, there is a strong relationship.

To quantify this relationship, we estimate the following equation for a patent application i examined by patent examiner j filed in year t assigned to Art Unit a:

$$\mathbf{1}\left(\text{patent grant}\right)_{ijta} = \alpha + \beta \cdot Z_{ijta} + \Sigma_{ta}\mathbf{1}\left(\text{art unit}\right)_{ta} + \varepsilon_{ijta}$$

where the outcome variable $\mathbf{1}\left(\text{patent grant}\right)_{ijta}$ is an indicator variable equal to one if patent application i was

[35] Merges (2001) also argues that although sorting of patent applications to examiners may be efficient, an additional barrier to such sorting is the strong "all patents are created equal" tradition at the USPTO, which cuts strongly against any mechanism for separating and sorting patents.

[36] Much of the subsequent literature (e.g. Doyle (2007)) has approximated JIVE through an informal leave out mean approach.

[37] A separate concern is that if we only observed a small number of applications per examiner, our estimate of the variation in leniency across examiners would be overstated. To address this concern, we limit the sample to examiners and Art Unit-years that saw at least ten applications (Heckman, 1981; Greene, 2001). To match our conceptual thought experiment, we also limit the sample to Art Unit-years with at least two examiners.

[38] We will describe the lighter yellow overlaid plot in Section 5.4.

granted a patent, Z_{ijta} is the non-human gene patent grant rate instrument (as defined in Section 5.2), and $\Sigma_{ta}\mathbf{1}\left(\text{art unit}\right)_{ta}$ are a set of Art Unit-by-application year fixed effects.[39]

In our first stage sample, we estimate a β coefficient on our instrument of 0.858, with a standard error of 0.036. This point estimate implies that a 10 percentage point increase in an examiner's average patent grant rate is associated with a 8.6 percentage point increase in the likelihood that a patent application is granted a patent.[40] The F-statistic is on the order of 500, well above the rule of thumb for weak instruments (Stock, Wright and Yogo, 2002).

As a robustness check, in Appendix Table D.1 we replace our Art Unit-by-year fixed effects with Art Unit-by-year-by-class-by-subclass fixed effects, on the subsample for which these finer fixed effects can be estimated. The point estimates from this more stringent specification are very similar to and not statistically distinguishable from our baseline point estimate, suggesting that at least in our context, variation in the measured leniency of different examiners is unlikely to be generated by the systematic sorting of patent applications that are in more versus less 'patentable' technology classes or subclasses.

5.4 Investigating selection

In order for examiner leniency to be a valid instrumental variable for the likelihood that a given gene patent application is granted a patent, it must satisfy the exclusion restriction: the instrument can only affect follow-on innovation outcomes through the likelihood that a gene is patented. The institutional details described in Section 5.1 suggest that the assignment of applications to examiners is plausibly random conditional on Art Unit-by-application year fixed effects, lending some a priori credibility to the exclusion restriction. In this section, we empirically assess whether this assumption is reasonable by investigating whether patent applications assigned to 'lenient' and 'strict' examiners look similar on observable characteristics fixed at the time of patent application.

Ideally, we would empirically assess selection using variables that are correlated with the 'patentability' of the application at the time of filing, so that we could test whether applications that appear more patentable tend to be assigned to more lenient examiners. As discussed by Lemley and Sampat (2012), it is difficult to identify variables that measure the 'patent-worthiness' of an invention.[41] A variety of metrics have been proposed as measures of the value of granted patents: forward citations (Trajtenberg, 1990), patent renewal behavior (Pakes, 1986; Schanker-

[39] We observe 138 patent examiners in 206 Art Unit-years.

[40] Our patent grant outcome is measured as of 2010 and is censored for patent applications that are still in the process of being examined, but this censoring should be less of a concern for earlier cohorts of gene patent applications. The point estimates on a sub-sample of early cohorts of applications are very similar to our baseline point estimates (results not shown), suggesting that censoring appears to not substantively affect the magnitude of the estimated first stage coefficient. Note that this is likely because the Art Unit-by-application year fixed effects largely account for differences in the probability of patent grant that are mechanically related to time since application. Given this similarity, we retain all cohorts of gene patent applications to retain a larger sample size.

[41] In their paper, they show that two observable characteristics fixed at the time of application — the number of pages in the application and the patent family size — are not correlated with a measure of examiner experience (years of employment at the USPTO). That evidence provides some indirect support for our exclusion restriction.

man and Pakes, 1986; Bessen, 2008), patent ownership reassignments (Serrano, 2010), patent litigation (Harhoff, Scherer and Vopel, 2003), and excess stock return values (Kogan, Papanikolaou, Seru and Stoffman, 2013). For our purposes, not all of these measures are appropriate: we need measures of patent value that are defined for patent applications (not just for granted patents), and also want a measure that is fixed at the time of application (and hence unaffected by subsequent grant decisions). For these reasons, we focus on two value measures which fit these criteria: patent family size and claims count.

Generally stated, a patent "family" is defined as a set of patent applications filed with different patenting authorities (e.g. US, Europe, Japan) that refer to the same invention. The key idea is that if there is a per-country cost of filing for a patent, firms will be more likely to file a patent application in multiple countries if they perceive the patent to have higher private value. Past work starting with Putnam (1996) has documented evidence that patent family size is correlated with other measures of patent value. We define patent family size as the number of unique countries in which the patent application was filed.

We use claims count as an alternative value measure that is fixed at the time of patent application, as proposed by Lanjouw and Schankerman (2001). The key idea underlying this measure is that patents list "claims" over specific pieces of intellectual property, and that patents with more claims may be more valuable.

For our purposes, there are two key empirical questions we want to investigate using these measures. First, do patent family size and/or claims count predict patent grant? While clearly imperfect metrics of patentability, these variables are predictive of patent grants: if we regress an indicator variable for patent grant on these two variables, the p-value from an F test of joint significance is <0.001. Second, is the predicted probability of patent grant — predicted as a function of family size and claims count — correlated with our examiner leniency instrument? If we regress the predicted probability of patent grant (predicted as a function of family size and claims count) on our examiner leniency instrument (residualized by Art Unit-by-application year fixed effects), we estimate a coefficient of 0.007 (standard error 0.003). This relationship is displayed non-parametrically in the lighter yellow plot in Figure 3: consistent with our regression estimate, there is no visual relationship between the predicted probability of patent grant and our instrument.

Taken together, the analysis in this section provides indirect support of our exclusion restriction in the following sense: we find no evidence that applications which appear more likely to be patented based on measures that are fixed at the time of filing are differentially assigned to more lenient examiners. Hence, the variation in grant rates across examiners appears to reflect differences in the decisions made on ex ante similar applications.

5.5 Instrumental variables estimates

Table 3 documents our instrumental variable estimates, relating patenting (instrumented by examiner leniency) to follow-on innovation outcomes.

For our measures of follow-on scientific research (publications; Panel A of Table 3) and commercialization (clinical trials; Panel B of Table 3), the 95% confidence intervals on our log estimates can reject declines or increases of more than 6%; the 95% confidence intervals on our binary versions of these outcomes ("any publication" or "any clinical trial") are much less precise. For our measure of diagnostic test availability (Panel C of Table 3), the 95% confidence interval suggests that - relative to a mean of around 9 percent - we can reject declines in this outcome of greater than 20% and reject increases of greater than 4%.

The estimates from our first quasi-experimental approach — comparing follow-on innovation across genes claimed in successful versus unsuccessful patent applications — are more precise than these estimates. Our confidence in interpreting those estimates as causal is strengthened by the fact that the examiner leniency instrument generates similar results, albeit which are much less precise. From an economic perspective, the estimates from our first approach can cleanly reject the effect sizes documented in the prior literature of how non-patent forms of intellectual property affect follow-on innovation (Murray et al., 2008; Williams, 2013), whereas the estimates from our second approach can only sometimes reject these effect sizes.

6 Discussion

A well-developed theoretical literature has documented ambiguous predictions for how patents will affect follow-on innovation. If a patent holder can develop all possible follow-on inventions herself, then all socially desirable follow-on inventions will be developed. However, as stressed by Scotchmer (2004), the patent holder may not know all potential opportunities for follow-on innovation. If ideas are scarce in this sense, and if patents are sufficiently broad that follow-on inventions require a license, then follow-on inventions will require cross-firm licensing agreements. If ex ante licensing agreements can be signed prior to follow-on inventors sinking their R&D investments, all socially desirable follow-on inventions will still be developed. However, if there are impediments to ex ante licensing — such as asymmetric information — then follow-on innovation will be lower than socially desirable due to the problem of how to divide the profit across firms (Scotchmer, 1991; Green and Scotchmer, 1995). This profit division problem could be exacerbated if transaction costs hinder cross-firm licensing agreements (Heller and Eisenberg, 1998; Anand and Khanna, 2000; Bessen, 2004). On the other hand, work dating back at least to Kitch (1977) has argued patents may facilitate investment and technology transfers across firms (Arora, 1995; Arora, Fosfuri and Gambardella, 2001; Kieff, 2001; Gans, Hsu and Stern, 2002, 2008), which may increase incentives for follow-on research and commercialization.

Because gene patents have been widely perceived to be sufficiently broad that follow-on inventions require gene patent licenses (see, e.g., Heller and Eisenberg (1998) and Doll (1998)), many have expressed concern that gene patents would hinder follow-on scientific research and commercial development, either due to the profit division problem or due to transaction costs. As discussed by Marshall (2013), some market observers conjectured that gene patents were deterring follow-on research based on evidence from prior empirical studies which documented that non-patent forms of intellectual property which restricted access to research materials substantially reduced follow-on innovation. Specifically, Murray et al. (2008) analyze a package of patents and other licensing restrictions that the private firm Dupont held on genetically engineered mice, and Williams (2013) analyzes a non-patent form of database protection that the private firm Celera held on their version of the sequenced genome. Importantly, both Dupont and Celera's forms of intellectual property restricted "openness:" in order to gain access to Dupont's genetically engineered mice, or to Celera's sequenced genome, researchers needed to navigate legal contracts and restrictions. This feature stands in sharp contrast with how patents are commonly used in practice. For example, in our context, patented human genes were freely available to researchers with no restrictions — indeed, data on the entirety of the sequenced human genome was available throughout our time period in public open-access databases.

Both theoretical models (Aghion et al., 2008) and other sources of empirical evidence (Furman and Stern, 2011) suggest that limiting access to research materials may discourage basic research as well as the creation of new research lines. However, patents - unlike the non-patent forms of intellectual property analyzed in these past papers - disclose discoveries and generally retain open access to materials (Walsh et al., 2003a,b). Academics report in surveys that they very rarely investigate whether research materials that they already have access to are covered by patents.[42] One interpretation of this is that "tolerated infringement" is a common feature of the use of patented materials by academic researchers (Walsh, Arora and Cohen, 2003b; Walsh, Cho and Cohen, 2005). Empirically, many private firms seem to openly tolerate infringement by academic researchers.[43] Models such as Murray et al. (2008) and Bessen and Maskin (2009) provide rationales for why this behavior may be optimal for firms: if ideas are scarce in the sense that the initial patent holder does not know all potential opportunities for follow-on innovation, then allowing academics open access to research materials may expand the set of possible commercial applications. Of course, once basic research produces new commercial leads, licensing agreements for follow-on inventions must be negotiated. Hence, in order to rationalize our empirical estimates on product market outcomes it must also be the case that licensing markets operate relatively efficiently. Consistent with this is the fact that there has been very little gene patent-related litigation (Holman, 2008).

[42]The Walsh, Cho and Cohen (2005) survey suggested that only about 5% of academic bench scientists reported regularly checking for patents on research inputs.

[43]For example, in the famous case of Human Genome Sciences' CCR5 patent, then-CEO William Haseltine publicly stated: "We would not block anyone in the academic world from using this for research purposes."

Hence, an explanation that is consistent with both our work and the previous literature is that patents per se on basic scientific discoveries neither restrict access to materials for basic researchers, nor generate quantitatively important transaction costs in licensing markets, and hence do not deter either follow-on scientific research nor follow-on commercialization. In contrast, non-patent policies that restrict basic researchers' access to materials can reduce follow-on scientific research, thus reducing the number of research lines that can be pursued commercially (and hence also reducing follow-on commercialization). Consistent with this interpretation, theoretical models such as Murray et al. (2008) predict that private firms should prefer patents to other forms of intellectual property that restrict access to materials, and at least in the case of Celera this seems to be an accurate description of the historical record: Celera attempted (but largely failed) to obtain patents on its sequenced genetic data, and in the absence of patent protection used their non-patent form of intellectual property as the next best available alternative means of capturing returns to their investment in sequencing the human genome.

Of course, this interpretation is at best suggestive, and given the available data it is not possible to rule out two alternative explanations. A first alternative interpretation is that while gene patents have widely been perceived to be sufficiently broad that follow-on inventions require gene patent licenses, it could be that in practice this is not the case. In a now-classic paper Heller and Eisenberg (1998) documented that more than 100 issued US patents included the term 'adrenergic receptor' in the claim language, and pointed to this as an example of the complex biomedical patent landscape. Consistent with this concern, in a comment on the Heller-Eisenberg paper published in the same issue of *Science*, the then-USPTO biotechnology examination unit head John Doll (Doll, 1998) argued that gene patents would be interpreted quite broadly by the USPTO.[44] In contrast, in a second comment on the Heller-Eisenberg paper, Seide and MacLeod (1998) argued that based on a cursory patent clearance review, at most only a small number of licenses might be required.[45] Empirically, this alternative interpretation is difficult to test: patent breadth is determined not only by the text of the patent, but also by courts' interpretations of these claims, and very few gene patents have been litigated in court so we have little data on how broadly these patents would be interpreted in practice. Importantly, from a theoretical perspective narrow patents should not deter follow-on innovation, so to the extent that this alternative interpretation is correct our analysis would be most useful in

[44] For example, Doll wrote: "*A patent is granted to a large fragment of DNA, within which exists a gene of great medical interest, even though the location of the open reading frame with the fragment has not been determined. The person who actually discovers and isolates the gene may also be able to receive a patent. Alternatively, many patented DNA fragments such as ESTs or SNPs may be isolated that turn out to be part of the same gene. In both cases, the second patent holder may have to obtain licenses from or pay fees to the primary patent holder but is not prevented from obtaining the second patent.*" Doll also argued that gene patents would be interpreted broadly from the perspective of different medical applications: "*...once a product is patented, that patent extends to any use, even those that have not been disclosed in the patent.* "

[45] A similar point has been made in the context of gene patents by Holman (2012): although a large number of human genes are claimed by US patents, he argues that a reading of the claims suggests that few licenses would be required for common types of follow-on innovation. Similarly, we can return to the example in the introduction where pharmaceutical firm Bristol Myers reported abandoning research on more than fifty cancer-related proteins due to conflicts with gene patent holders (Pollack, 2001). This example was actually reported as part of a licensing agreement Bristol Myers brokered with another firm (Athersys) for a method enabling the use of protein targets without infringing gene patents.

highlighting that documentation of biomedical patenting frequency (as in Jensen and Murray (2005)) should not necessarily be interpreted as evidence of a problem; analyses such as the one in this paper are needed in order to investigate whether these patents are sufficiently broad to actually be affecting real economic behavior.

A second alternative interpretation - argued by Lemley (2008) - is that both researchers and private firms simply ignore patents to a large degree, a view that is also consistent with our data. In order to test among these alternative theories, we would need to measure licensing agreements, data which is almost always kept confidential. Importantly, while these two alternative interpretations are interesting and important to consider from an academic perspective, distinguishing among these three potential interpretations is not required from a policy perspective: the fact that gene patents have not hindered follow-on innovation is sufficient to inform both the Nordhaus-style theoretical question of interest, and the policy-relevant question at the basis of the recent US Supreme Court *AMP v. Myriad* ruling.

7 Conclusion

The contribution of this paper is to investigate whether patents on human genes have affected follow-on scientific research and product development. Using administrative data on successful and unsuccessful patent applications submitted to the US Patent and Trademark Office (USPTO), we link the exact gene sequences claimed in each patent application with data measuring gene-related scientific research (publications) and commercial investments (clinical development). Building on these data, we develop two new sources of quasi-experimental variation: first, a simple comparison of follow-on innovation across genes claimed in successful versus unsuccessful patent applications; and second, use of the "leniency" of the assigned patent examiner as an instrumental variable for whether the patent application was granted a patent. Both approaches suggest that — on average — gene patents have not had quantitatively important effects on follow-on innovation.

This empirical evidence speaks against two existing views. First, there has been widespread concern that patents on human genes may hinder follow-on innovation. For example, in the recent *Association for Molecular Pathology v. Myriad Genetics* case, the US Supreme Court invalidated patent claims on genomic DNA, arguing that such patents "would 'tie up' the use of such tools and thereby inhibit future innovation premised upon them." Our empirical estimates do not provide support for patents hindering follow-on innovation in the context of human genes. Second, dating back at least to the academic work of Kitch (1977), many have argued that patents on basic discoveries play an important role in facilitating subsequent investment and commercialization. This type of argument has been influential in the policy space, informing the structure of public policies such as the Bayh-Dole Act and the Stevenson-Wydler Act in the US. Our empirical estimates do not provide support for patents spurring follow-on innovation in the context of human genes.

Taken together with the prior literature, our evidence suggests two conclusions. First, for the case of human genes, the traditional patent trade-off of ex ante incentives versus deadweight loss may be sufficient to analyze optimal patent policy design, because any effects of patents on follow-on innovation appear to be quantitatively small. Second, our evidence together with the evidence from Williams (2013) on how a non-patent form of intellectual property on the human genome affected follow-on innovation suggests a somewhat nuanced conclusion: while patent protection on human genes does not appear to have hindered follow-on innovation, an alternative non-patent form of intellectual property - which was used by a private firm after its gene patent applications were largely unsuccessful in obtaining patent grants - induced substantial declines in follow-on scientific research and product development. This pattern of evidence suggests that changes to patent policy must carefully consider what strategies firms will use to protect their discoveries in the absence of patents, and that an understanding of the relative costs and benefits of patent protection compared to those outside options is needed in order to evaluate the welfare effects of patent policy changes.

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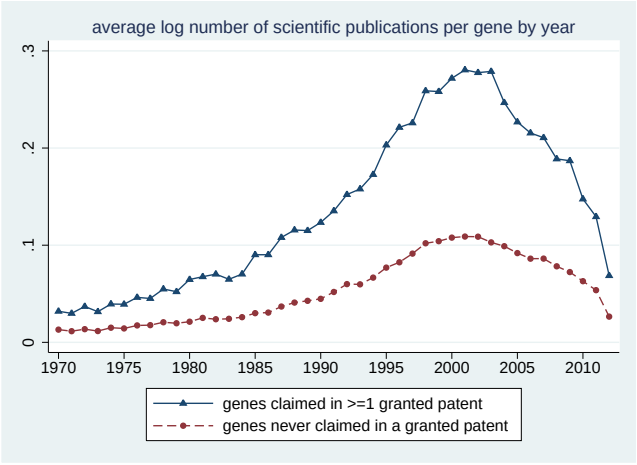
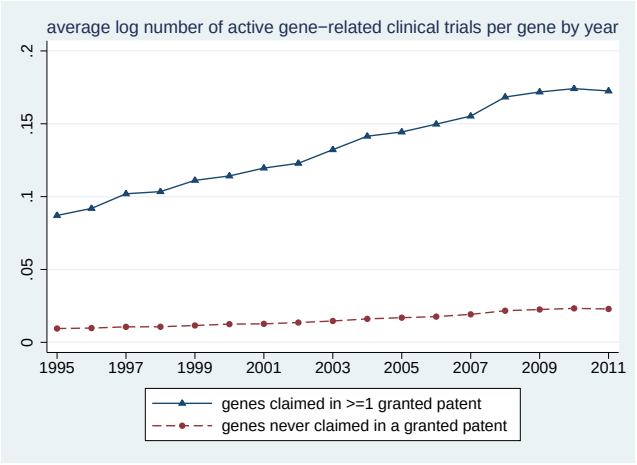
Figure 1: **Follow-on innovation on patented and non-patented human genes**

(a) Gene-level scientific publications



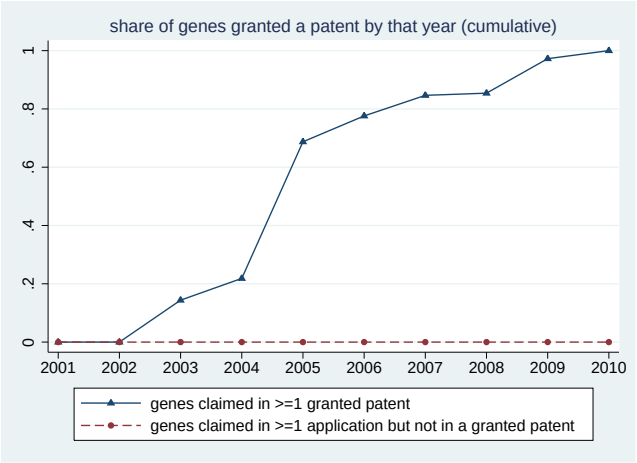
(b) Gene-level clinical trials



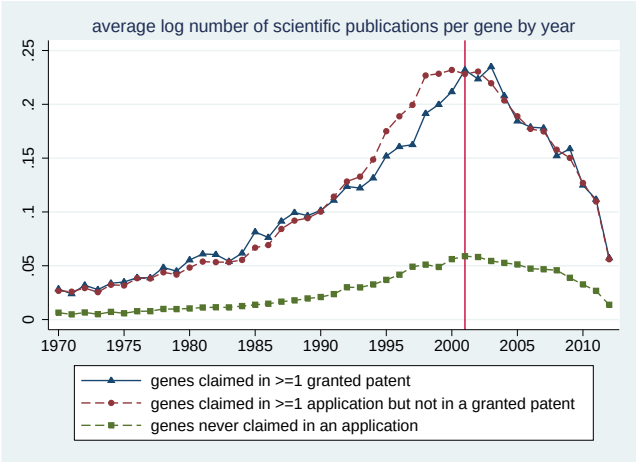
Notes: This figure plots trends in follow-on innovation by year separately for genes that ever receive a patent, and for genes that never receive a patent. The figure is constructed from gene-level data. Panel (a) uses gene-level scientific publications as a measure of follow-on innovation, and plots the average log number of scientific publications by year in each year from 1970 to 2012. Panel (b) uses gene-level clinical trials as a measure of follow-on innovation, and plots the average log number of clinical trials by year in each year from 1995 to 2011. We add one to both outcome variables in order to include observations with no observed follow-on innovation.

Figure 2: **Patents and follow-on innovation on human genes claimed in accepted/rejected patent applications**

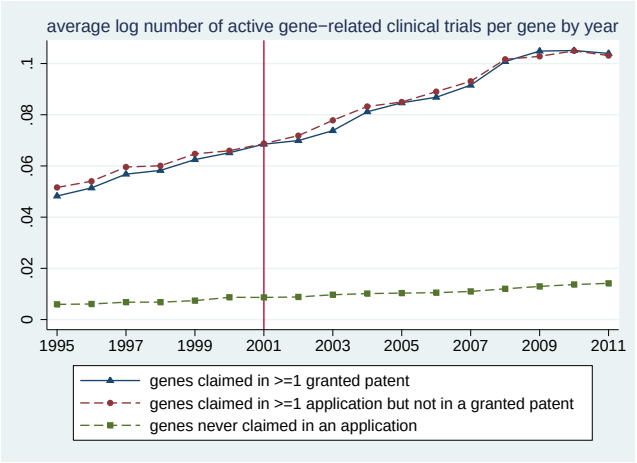
(a) Share of genes receiving a patent grant



(b) Gene-level scientific publications

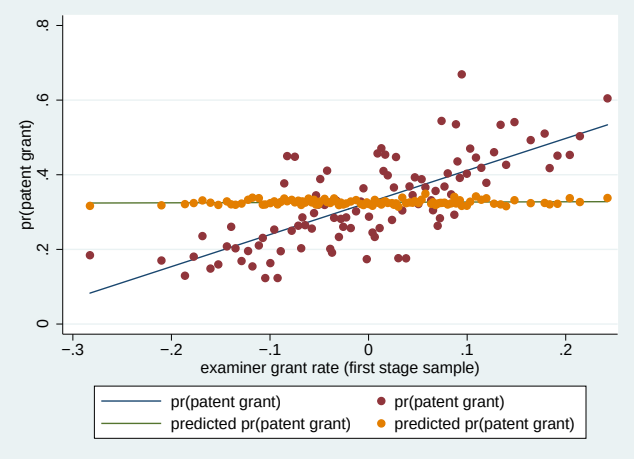


(c) Gene-level clinical trials



Notes: This figure plots trends in patenting and follow-on innovation by year separately for three groups of genes: genes claimed in at least one granted patent; genes claimed in at least one patent application but never in a granted patent; and (in Panels (b) and (c)) genes never claimed in a patent application. The figure is constructed from gene-level data. Panel (a) documents the share of genes receiving a patent grant by year; by construction, this is zero for the circle-denoted red dashed line in all years, is zero for the triangle-denoted blue line in 2001, and reaches one for the triangle-denoted blue line in 2010; the intermediate years simply illustrate the time path of patent grants between 2001 and 2010 for the triangle-denoted blue line. Panel (b) uses gene-level scientific publications as a measure of follow-on innovation and plots the average log number of scientific publications by year in each year from 1970 to 2012. Panel (c) uses gene-level clinical trials as a measure of follow-on innovation and plots the average log number of clinical trials by year in each year from 1995 to 2011. The vertical line in the calendar year 2001 in Panels (b) and (c) denotes that because this figure focuses on patents that were filed in or after 2001, all years prior to 2001 can be considered a pre-period and used to estimate the selection of genes into patenting based on pre-filing measures of scientific research (publications) and commercialization (clinical trials). In Panels (b) and (c), we add one to both outcome variables in order to include observations with no observed follow-on innovation.

Figure 3: **Probability of patent grant, by examiner leniency**



Notes: This figure plots the first stage relationship between the probability of patent grant and our examiner leniency instrument, and plots estimates from two of our selection tests. The figure relates our examiner leniency instrument, residualized by Art Unit-by-application year fixed effects, to two variables: (1) the patent grant rate; and (2) the predicted patent grant rate, where we predict patent grant as a function of our two measures of patent value fixed at the time of application (patent family size and claims count).

Table 1: **Patent application-level summary statistics**

	mean	standard deviation	minimum	maximum	number of observations
Panel A: First stage sample					
application year	2004	2.585	1997	2010	14,016
0/1, patent granted as of 2010	0.3259	0.4687	0	1	14,016
Panel B: Human gene sample					
application year	2002	0.700	1999	2005	1,533
0/1, patent granted as of 2010	0.2564	0.4368	0	1	1,533

Notes: This table shows summary statistics for our patent application-level data in each of our two samples: Panel A for the first stage sample of patent applications, and Panel B for the human gene sample of patent applications.

Table 2: **Patents and follow-on innovation on human genes claimed in accepted/rejected patent applications: Regression estimates**

	Log of follow-on innovation in 2011/12	Any follow-on innovation in 2011/12	
Panel A: Scientific publications			
patent granted	0.0019	-0.0013	
	(0.0060)	(0.0054)	
mean of dependent variable	0.2238	0.1094	
number of observations	15,530	15,530	
Panel B: Clinical trials			
patent granted	0.0008	-0.0012	
	(0.0080)	(0.0043)	
mean of dependent variable	0.5424	0.0657	
number of observations	15,530	15,530	
Panel C: Diagnostic test			
patent granted	-	-0.0091	*
		(0.0055)	
mean of dependent variable	-	0.1199	
number of observations	-	15,530	

Notes: This table estimates differences in follow-on innovation on genes claimed in at least one granted patent relative to genes claimed in at least one patent application but never in a granted patent. The sample for these regressions is constructed from gene-level data, and includes genes claimed in at least one patent application in our USPTO human gene patent application sample (N=15,530). Each coefficient is from a separate regression. In Column (1), we add one to all outcome variables to include observations with no observed follow-on innovation. Estimates are from ordinary-least-squares models. Heteroskedasticity robust standard errors. *: p<0.10; **: p<0.05; ***: p<0.01.

Table 3: **Patents and follow-on innovation on human genes by examiner leniency: Instrumental variable regression estimates**

	Log of follow-on innovation in 2011/12	Any follow-on innovation in 2011/12
Panel A: Scientific publications		
patent granted (instrumented)	-0.0167	-0.0131
	(0.0125)	(0.0098)
mean of dependent variable	0.0797	0.0886
number of observations	292,655	292,655
Panel B: Clinical trials		
patent granted (instrumented)	-0.0233	-0.0156
	(0.0175)	(0.0117)
mean of dependent variable	0.0676	0.0498
number of observations	292,655	292,655
Panel C: Diagnostic test		
patent granted (instrumented)	-	-0.0069
		(0.0052)
mean of dependent variable	-	0.0915
number of observations	-	292,655

Notes: This table presents instrumental variable estimates, relating follow-on innovation to whether a patent application was granted a patent, instrumented by our examiner leniency instrument. The sample for these regressions is constructed from application-gene-level data, and includes patent application-gene-level observations in our human gene sample (N=301,642). Each coefficient is from a separate regression. Estimates are from ordinary-least-squares models and condition on Art Unit-by-application year fixed effects. In Column (1), we add one to all outcome variables to include observations with no observed follow-on innovation. Inoue and Solon (2010) standard errors. *: p<0.10; **: p<0.05; ***: p<0.01.

A Appendix: Additional background on *AMP v. Myriad* case (for online publication)

This appendix provides some additional background information on the recent *AMP v. Myriad* case.

The private firm Myriad Genetics was granted patent rights on human genes correlated with risks of breast and ovarian cancer. In 2009, the American Civil Liberties Union (ACLU) and the Public Patent Foundation filed suit against Myriad, arguing that many of Myriad's patent claims were invalid on the basis that DNA should not be patentable. One technical detail that is critical to understanding the *AMP v. Myriad* case is that two types of nucleotide sequences were at issue: naturally occurring genomic DNA (gDNA), and complementary or cDNA, which is produced in a laboratory using gDNA as a template. After a series of lower court decisions, in June 2013 the US Supreme Court issued a unanimous ruling drawing a distinction between these two types of sequences: "A naturally occurring DNA segment is a product of nature and not patent eligible...but cDNA is patent eligible because it is not naturally occurring."[46]

The question of whether DNA is patent eligible may at first blush seem very far removed from the economics of gene patents. Yet in fact, the US Supreme Court decision was made in part on the basis of the research question examined in this paper: whether patents on human genes would impede follow-on innovation. A brief background on patent eligibility is helpful in clarifying this point. The patent eligibility criteria set out in the US Constitution (35 U.S.C. §101) has long been interpreted to exclude laws of nature, natural phenomena, and abstract ideas from patent eligibility. The *AMP v. Myriad* decision followed this precedent, arguing that "[g]roundbreaking, innovative, or even brilliant" discoveries of natural phenomena should be patent-ineligible, because patents "would 'tie up' the use of such tools and thereby inhibit future innovation premised upon them." As discussed by Rai and Cook-Deegan (2013), the Court decision essentially aimed to draw a line between patent-eligible and patent-ineligible discoveries based on the "delicate balance" between patents prospectively creating incentives for innovation and patent claims blocking follow-on innovation. In the end, the Court drew this line by ruling naturally occurring DNA patent-ineligible, and non-naturally occurring cDNA patent-eligible.

Numerous legal scholars have argued that the distinction between DNA and cDNA is "puzzling and contradictory" (Burk, 2013) given that "both isolated sequences and cDNA...have identical informational content for purposes of protein coding" (Golden and Sage, 2013); in interviews, patent attorneys expressed similar confusion (Harrison, 2013). A recent analysis of gene patent claims by Holman (2012) concluded that most human gene patents claimed cDNA, and would thus be unaffected by the Court ruling.

[46]The earlier decisions were a 2010 ruling by the US District Court for the Southern District of New York (see `http://www.pubpat.org/assets/files/brca/brcasjgranted.pdf`) and a 2011 ruling by the US Court of Appeals for the Federal Circuit (see `https://www.aclu.org/files/assets/10-1406.pdf`); a subsequent re-hearing of the case by the US Court of Appeals at the request of the US Supreme Court did not substantively change this decision.

B Appendix: Data construction (for online publication)

This appendix describes our data construction in more detail. A brief background of application, publication, and patent numbers is useful before describing our data from the United States Patent and Trademark Office (USPTO).

Application numbers: The USPTO assigns patent applications application numbers, which consist of a series code and a serial number.[47] The USPTO states that these application numbers are assigned by the Office of Patent Application Processing (OPAP) immediately after mail has been opened.[48] As suggested by this process, the USPTO and other sources note that application numbers are assigned chronologically.[49] While application serial numbers are six digits, the use and length of application series codes has changed over time: in recent years series codes are two digits, but previously these codes were one digit and historically series codes were not used.[50]

Publication numbers: Traditionally, unsuccessful patent applications were not published by the USPTO. However, as part of the American Inventors Protection Act of 1999, the vast majority of patent applications filed in the US on or after 29 November 2000 are published eighteen months after the filing date. There are two exceptions. First, applications granted or abandoned before eighteen months do not appear in this sample unless the applicant chooses to ask for early publication. Lemley and Sampat (2008) estimate that about 17 percent of patents are granted before eighteen months, of which about half (46 percent) are published pre-patent grant. Second, applications pending more than eighteen months can "opt out" of publication if they do not have corresponding foreign applications, or if they have corresponding foreign applications but also have priority dates pre-dating the effective date of the law requiring publication (Lemley and Sampat, 2008).[51] If the patent application is published, then the USPTO assigns the application a publication number of the form USYEARXXXXXXX: a 2-digit country code, always US; followed by a 4-digit year (denoting year of publication); followed by a 7-digit identifier.

Patent numbers: Applications that are granted patents are assigned patent numbers. The number of characters in the patent number varies by the type of patent.[52] Utility patent numbers are six or seven digits; reissue patents start with "RE" followed by six digits;[53] plant patents start with "PP" followed by six digits; design patents start with "D" followed by seven digits; additions of improvement patents start with "AI" followed by six digits;[54] X-series patents start with "X" followed by seven digits;[55] H documents start with "H" followed by seven digits;[56] and T documents start with "T" followed by seven digits.[57]

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[47] For more details, see `http://www.uspto.gov/web/offices/ac/ido/oeip/taf/filingyr.htm`.

[48] See `http://www.uspto.gov/web/offices/pac/mpep/s503.html`: *"Application numbers consisting of a series code and a serial number are assigned by the Office of Patent Application Processing (OPAP) immediately after mail has been opened. If an application is filed using the Office's electronic filing system, EFS-Web provides an Acknowledgement Receipt that contains a time and date stamp, an application number and a confirmation number."*

[49] See `http://www.uspto.gov/web/offices/ac/ido/oeip/taf/filingyr.htm` (*"In general, patent application serial numbers are assigned chronologically to patent applications filed at the U.S. Patent and Trademark Office."*) and `http://www.thomsonfilehistories.com/docs/RESOURCES_Series_Codes.pdf` (*"US patent applications consist of a 2-digit series code and a 6-digit application serial that is assigned chronologically as they are received at the USPTO."*).

[50] Note that design applications, provisional applications, and reexamination (*ex parte* and *inter partes*) applications are assigned different series codes; reissue patent application numbers follow the utility and design application structures. See `http://www.uspto.gov/web/offices/pac/mpep/s503.html` for details on these series codes.

[51] For more details, see `http://www.uspto.gov/web/offices/pac/mpep/s1120.html` and the discussion in Lemley and Sampat (2010). Most applications not published eighteen months after filing are instead published sixty months after filing.

[52] For more details, see `http://www.uspto.gov/patents/process/file/efs/guidance/infopatnum.jsp`.

[53] For more details on reissue patents, see `http://www.uspto.gov/web/offices/pac/mpep/s1401.html`.

[54] Addition of improvement patents were issued between 1838 and 1861 and covered an inventor's improvement on his or her own patented device. For more details, see §901.04 of `http://www.uspto.gov/web/offices/pac/mpep/s901.html`.

[55] X-series patents were issued between 1790 and 1836. For more details, see §901.04 of `http://www.uspto.gov/web/offices/pac/mpep/s901.html`.

[56] H documents are part of the statutory invention registration series. For more details, see `http://www.uspto.gov/web/offices/ac/ido/oeip/taf/issudate.pdf`.

[57] T documents are part of the defensive publication series. For more details, see `http://www.uspto.gov/web/offices/ac/ido/oeip/taf/issudate.pdf`.

Data on USPTO published patent applications

USPTO Patent Document Pre-Grant Authority files

The USPTO makes available Patent Document Authority Files, including the Pre-Grant Authority files which contain listings of all US published applications beginning 15 March 2001 ("Pre-Grant").[58] Our versions of these files were downloaded on 24 March 2014 and are up to date as of February 2014.

Our version of the Pre-Grant Authority File includes 3,681,468 observations. Nearly all are utility patent applications (kind code=A1; 3,672,723; 99.76% of observations). Of the remaining 8,745 observations, 3,228 (kind code=A9; 0.09%) are corrections of published utility applications; 1,207 (kind code=A2; 0.03%) are subsequent publications of utility patent applications; and 4,310 (kind code=P1; 0.12%) are plant patent applications. One observation is denoted as the USPTO missing a copy of the relevant document images, and 1,025 observations are denoted as applications for which pre-grant publications were withdrawn. The identifier in the Pre-Grant Authority File is the publication number.

USPTO *Cassis* BIB published patent applications data

The USPTO's *Cassis* BIB Applications DVD (Sampat, 2011) includes US patent applications published between 15 March 2001 and 31 December 2010. The data include 2,625,950 observations.

There are two identifiers in the *Cassis* data: publication numbers and application numbers. Publication numbers uniquely identify observations, whereas application numbers do not: 2,744 application numbers appear more than once in the dataset. Of those 2,744 application numbers, most (2,699) appear twice; 40 appear three times; and 5 appear four times. This is not unexpected, as it is known that application numbers can be published under multiple publication numbers.[59] Merging to the USPTO Pre-Grant Authority File reveals that almost all of these cases of non-unique application numbers are explained by subsequent publications of utility applications (697 observations) or by corrections of published utility applications (2,094 observations). The three remaining duplicate application numbers (8957425, 9726661, and 9728294) can be confirmed as having two application numbers on e.g. Google Patents, although the reason is not clear. We retain these duplicate application numbers in our sample in the absence of a clear reason to exclude them.

If we check the *Cassis* data against the USPTO Pre-Grant Authority File, as expected all observations in the USPTO's *Cassis* BIB Applications DVD appear in the Pre-Grant Authority File. As expected given that the *Cassis* BIB Applications DVD includes observations only through 31 December 2010 whereas the Pre-Grant Authority File includes observations through February 2014, many patent applications published between 1 January 2011 and February 2014 appear in the Pre-Grant Authority File but not in the *Cassis* BIB Applications DVD. In addition, 2,241 observations published prior to 1 January 2011 appear in the Pre-Grant Authority File but not in the *Cassis* BIB Applications DVD. These observations are roughly evenly distributed across publication years from 2001-2010; it is not clear why these observations are missing, but we are unable to include them in our analysis.

USPTO full-text published patent application files

Google currently hosts bulk downloads of US patent applications published between 15 March 2001 to present.[60]

USPTO PAIR data

We also use data from the USPTO PAIR (Patent Application Information Retrieval) system. The PAIR data contains the key patent application-level variables needed for our analysis (*e.g.* examiner name). Google is currently crawling the universe of patent documents in the USPTO PAIR system and posts updated versions of the data as

[58] Available at: `http://www.uspto.gov/patents/process/search/authority/index.jsp`.

[59] See, for example, WIPO Standard ST.1: `http://www.wipo.int/export/sites/www/standards/en/pdf/03-01-01.pdf`.

[60] Available at `http://www.google.com/googlebooks/uspto-patents-applications-text.html`.

they become available.[61] Not all of our patent applications were available in this Google data; we collected some additional data from a USPTO posting on ReedTech and entered data on the remaining applications manually from the USPTO PAIR website.[62]

Thomson Innovation published USPTO patent applications data

We use the Thomson Innovation data as an additional source of data on patent applications. Specifically, the Thomson Innovation database provides information on two measures of patent value: claims count (as proposed by Lanjouw and Schankerman (2001)) and patent "family size" (as developed in Jonathan Putnam's 1996 dissertation). Below, we briefly describe these two value measures in more detail.

Claims count. We use claims count as a first proxy for the ex ante value of a patent application that is fixed at the time of patent application, as proposed by Lanjouw and Schankerman (2001). The key idea here is that patents list "claims" over specific pieces of intellectual property, so that patents with more claims may be more valuable. Past work has documented mixed empirical evidence on whether that is a valid assumption based on correlations of claims counts with other value measures.

Patent family size. We use patent "family" size as a second proxy for the ex ante value of a patent application that is fixed at the time of patent application, as proposed by Putnam (1996). A patent "family" is a group of related patents covering the same invention. Conceptually, this includes two types of patents: first, within-country family members include continuations, continuations-in-part, and divisionals; and second, foreign family members include patent applications covering the same technology in other jurisdictions. We here briefly describe each group of patents to motivate our family size measure:

- *Within-country patent families*. Within a country, patent families may include continuations, continuations-in-part, and divisionals. Because our focus is on US patent applications, we focus here on describing within-country patent families only for the US. This description summarizes material in the USPTO's *Manual of Patent Examining Procedure*.[63] A "continuation" is a subsequent application covering an invention that has already been claimed in a prior application (the "parent" application). A "continuation-in-part" is an application filed which repeats some portion of the parent application but also adds in new material not previously disclosed. A divisional application arises when an applicant divides claims in a parent application into separate patent applications. Taken together, the use of continuations, continuations-in-part, and divisionals imply that more than one patent can issue from a single original patent application. Lemley and Sampat (2008) document that among utility patent applications filed in January 2001 and published by April 2006 (a sample of 9,960 applications), 2,016 "children" (continuations, continuations-in-part, or divisionals) had been filed by April 2006: around 30% were continuations, 20% were continuations-in-part, and 40% were divisionals (an additional 10% were of indeterminable types).

- *Foreign patent families*. Patent protection is jurisdiction-specific, in the sense that a patent grant in a particular jurisdiction provides the patent assignee with a right to exclude others from making, using, offering for sale, selling, or importing the invention into that jurisdiction during the life of the patent (subject to the payment of renewal fees). Hence, for any given patent application, applicants must choose how many jurisdictions to file patent applications in, and given that there is a per-jurisdiction cost of filing we would expect patents that are perceived by the applicant as more privately valuable to be filed in a larger number of jurisdictions.[64] The first patent application is referred to as the priority application, and the filing date of the first application is referred to as the priority date; while the priority application can be filed in any

[61] Available at `http://www.google.com/googlebooks/uspto-patents-pair.html`.

[62] The ReedTech data is available at `http://patents.reedtech.com/Public-PAIR.php`; the hand data entry was done based on data available in the USPTO PAIR system, available at `http://portal.uspto.gov/pair/PublicPair`.

[63] Available at `http://www.uspto.gov/web/offices/pac/mpep/s201.html`.

[64] Multi-national routes such as applications filed with the European Patent Office or Patent Cooperation Treaty applications are intermediate steps towards filings in specific jurisdictions.

jurisdiction, Putnam (1996) argues that the transaction costs involved with foreign filings (e.g. translation of the application) generally imply that domestic filing is cheaper than foreign filing, and that most priority applications are filed in the inventor's home country. Under the Paris Convention for the Protection of Industrial Property (signed in 1883), all additional filings beyond the priority application that wish to claim priority to the priority application must occur within one year of the priority date. Putnam (1996) argues that most foreign applications — if filed — are filed near the one-year anniversary of the home country filing.

- *Commonly used measures of patent family size.* The term patent family can be used to describe different constructs: a patent family can be defined to include only documents sharing exactly the same priority or combination of priorities, or as all documents having at least one common priority, or as all documents that can be directly or indirectly linked via a priority document.[65] There are three commonly-used measures of family size: Espacenet (produced by the European Patent Office), the Derwent World Patents Index (DWPI; produced by Thomson Reuters), and INPADOC (produced by the European Patent Office).[66] Researchers tend to rely on these measures because collecting data from individual non-USPTO patent authorities would be quite time-consuming.

    1. Espacenet uses a 'simple' patent family definition which defines a patent family as all documents with exactly the same priority or combination of priorities. This family is constructed based on data covering around 90 countries and patenting authorities.[67]

    2. DWPI uses a similar patent family definition which defines a patent family as all documents with exactly the same priority or combination of priorities, but also includes non-convention equivalents (e.g. applications filed beyond the 12 months defined by the Paris Convention). This family is constructed based on data covering around 50 patent authorities and defensive publications (international technology disclosures and research disclosures). Continuations and divisionals are not included in the DWPI family definition.

    3. INPADOC defines a patent family more broadly, defining an 'extended' patent family as all documents that can be directly or indirectly linked via a priority document even if they lack a common priority. This family is constructed based on the same data as the Espacenet measure.

- *Our measure of patent family size*. For the purpose of our study, we would like to use the general concept of family size to develop a proxy for patent value that is fixed at the time the patent application is filed. Given this objective, it is clear that we should exclude continuations, continuations-in-part, and divisionals from our family size measure: these applications arise — by construction — after the filing date of the original patent application. In addition — and potentially more concerning in our specific context — the propensity for applications to develop continuations, continuations-in-part, or divisionals may differ across examiners, and hence could be affected by the examiner. We define patent family size as the number of unique countries in which the patent application was filed (as measured in the INPADOC patent family).

[65] For details and examples, see `http://www.epo.org/searching/essentials/patent-families/definitions.html`.

[66] For details on details on Espacenet, see `http://www.epo.org/searching/essentials/patent-families/espacenet.html`; for details on DWPI, see `http://www.epo.org/searching/essentials/patent-families/thomson.html`; and for details on INPADOC, see `http://www.epo.org/searching/essentials/patent-families/inpadoc.html`.

[67] For a list, see `http://documents.epo.org/projects/babylon/eponet.nsf/0/2464E1CD907399E0C12572D50031B5DD/$File/global_patent_data_coverage_0711.pdf`.

Data on USPTO granted patents

USPTO Patent Document Patent Grant Authority Files

The USPTO makes available Patent Document Authority Files.[68] The Patent Grant Authority Files contain listings of all published or granted patent documents ("Patent Grant") found in USPTO Patent Image databases and not included in the Pre-Grant Authority Files. Our versions of these files were downloaded on 24 March 2014 and are up to date as of February 2014.

Our version of the Patent Grant Authority File includes 9,432,761 observations. The vast majority are utility patents (first character 0; 8,656,513; 91.77% of observations). Of the remaining 776,248 observations, 699,917 (first character D; 7.42%) are design patents; 44,742 (first two characters RE; 0.47%) are reissue patents; 24,257 (first two characters PP; 0.26%) are plant patents; 2,785 (first character X or first two characters RX; 0.03%) are X-series patents; 2,289 (first character H; 0.02%) are H documents; 1,968 (first character T; 0.02%) are T documents; and 290 (first two characters AI; <0.00%) are additions of improvement patents. Following the kind code in the US Patent and Trademark Office data files (listed as I2), we code re-issued X-series patents (which start with "RX" rather than "X") as X-series patents.[69] There are 32,572 observations (0.35%) missing USPTO kind codes; 154 observations (<0.00%) denoted as the USPTO missing a copy of the relevant document images; and 32,572 observations (0.35%) denoted as applications for which pre-grant publications were withdrawn. The identifier in the Patent Grant Authority File is the patent number.

USPTO data on granted patents

In order to observe which US patent applications are granted patents, we use a USPTO administrative dataset covering patents issued from January 1, 1975 to December 31, 2010.[70] The data include 3,995,847 observations.

There are two identifiers in this data: application number and patent number. From the patent grant year variable in this data, we can infer whether and when a patent was granted as of December 31, 2010.

If we check these data against the USPTO Patent Grant Authority File, there are 12,770 reissue patents which appear in this USPTO grant data but not in the USPTO Patent Grant Authority File (none of the reissue patents in the USPTO grant data appear in the USPTO Patent Grant Authority File). There are 5,449,684 patents in the USPTO Patent Grant Authority File which do not appear in the USPTO grant data. Given that the USPTO Patent Grant Authority File includes all patent grants whereas the USPTO grant data includes only patents issued from 1975-2010, presumably these 5,449,684 patents were granted either prior to 1975 or after 2010, but as the USPTO Patent Grant Authority File does not include information on year of grant we have no direct way to verify that.

[68] Available at: `http://www.uspto.gov/patents/process/search/authority/index.jsp`.

[69] For more details on kind codes, see `http://www.uspto.gov/patents/process/search/authority/kindcode.jsp`.

[70] Available at `http://dvn.iq.harvard.edu/dvn/dv/boffindata/faces/study/StudyPage.xhtml;jsessionid=b8224569cfb3e22f8f305fcfdb51?globalId=hdl:1902.1/16412&studyListingIndex=0_b8224569cfb3e22f8f305fcfdb51`; under the "Data & Analysis" tab, select "saved original (stata binary)" from the drop-down menu.

Data on DNA-related USPTO published patent applications

CAMBIA Patent Lens data

The CAMBIA Lens database provides a list of published USPTO patent applications associated with human and non-human protein and DNA sequences appearing in patent claims (Bacon et al., 2006).[71] This data construction was supported by the Ministry of Foreign Affairs of Norway through the International Rice Research Institute for CAMBIA's Patent Lens (the OS4 Initiative: Open Source, Open Science, Open Society, *Orzya sativa*).

Over the time period relevant for our analysis, US patent applications list DNA sequences in patent claims with a canonical 'sequence listing' label, e.g. SEQ ID NO:1 followed by the relevant DNA sequence. The CAMBIA Patent Lens data construction parses patent claims text for lists of SEQ ID NOs to determine which sequences are referenced in the claims. Importantly, CAMBIA makes available several versions of their data; following Jensen and Murray (2005), we focus on the dataset of nucleotide sequences (as opposed to amino acid sequences), and on the 'in-claims' subsample (as opposed to a larger dataset which includes DNA sequences listed in the text of the patent application, but not explicitly listed in the patent claims).

The CAMBIA Patent Lens data is updated over time; our version is current as of 8 February 2012. The level of observation is a patent-mRNA pair indexed by a publication/sequence number that combines the patent publication number and a mRNA sequence number. The patent publication numbers were extracted from the CAMBIA Patent Lens data using a Perl script.[72]

Patome data

Patome annotates biological sequences in issued patents and published patent applications (Lee et al., 2007).[73] This data construction was supported by the Korean Ministry of Science and Technology (MOST).

Although the full Patome dataset contains issued patents and published patent applications from several jurisdictions — including Japan and Europe — in this paper we focus on the subsample of US published patent applications and granted patents. As in the CAMBIA Patent Lens data, the Patome data construction parses patent application texts for lists of SEQ ID NOs to determine which sequences are referenced in patent applications. Following the methodology pioneered by Jensen and Murray (2005), BLAST (Basic Local Alignment Search Tool) searches are used to compare listed sequences against a census of potential matches in order to identify regions of similarity. Using these BLAST searches, the DNA sequences are annotated with mRNA and gene identifiers (RefSeq and Entrez Gene numbers).

The Patome data includes some patent applications which do not correspond to the definition of human gene patents proposed by Jensen and Murray (2005); to follow the Jensen-Murray definition, we impose some additional sample restrictions. First, the Patome data includes sequences which appear in the text of patent applications but are not explicitly listed in patent claims; to follow the Jensen and Murray (2005) definition of gene patents, we exclude observations which do not appear in the patent claims.[74] Second, following Jensen and Murray (2005) we limit the sample to BLAST matches with an E-value of exactly zero; the goal of this conservative E-value is to prevent spurious matches. Finally, following Jensen and Murray (2005) we limit the sample to disclosed sequences that are at least 150 nucleotides in length; the motivation of this restriction is that this is the average length of one human exon and yet still small enough to capture EST sequences.

As in Jensen and Murray (2005), many patents claim multiple variants of the same gene (that is, multiple mRNA sequences corresponding to the same gene). Following their methodology, we focus on variation in patenting across human genes.

[71] Available at `http://www.patentlens.net/sequence/US_A/nt-inClaims.fsa.gz`.

[72] We are very grateful to Mohan Ramanujan for help extracting this data from FASTA format. This Perl script is available on request.

[73] Available at `http://verdi.kobic.re.kr/patome_int/`.

[74] Specifically, we merge the list of patent-mRNA numbers in the Patome data to the CAMBIA Patent Lens data, and drop observations that appear in Patome but not in the CAMBIA data; because our version of the CAMBIA data includes only patent-RNA observations listed in patent claims, this allows us to exclude Patome observations which are not explicitly listed in the claims of the patent applications.

Data measuring innovation on the human genome

Gene-level measures of scientific publications: OMIM data

We collect our measure of scientific research from the Online Mendelian Inheritance in Man (OMIM) database, a catalog of Mendelian traits and disorders. We use the full-text OMIM data and extract our variables of interest using a Python script.[75] One gene can be included in more than one OMIM record, and one OMIM record can involve more than one gene. We tally the total number of publications related to each gene in each year across all OMIM records related to that gene.

Gene-level data on drug development: Pharmaprojects data

We collect data on gene-related drug development from the Pharmaprojects data.[76] According to the company Citeline, which compiles and sells the Pharmaprojects data, "There is continual two-way communication between Pharmaprojects staff and their contacts in the pharmaceutical and biotechnology industries; both to gather new data and importantly, to verify information obtained from other sources." Citeline employees gather drug information from company websites, reports, and press releases; annually every company covered in the database verifies information related to drugs in the development pipeline.

Pharmaprojects annotates a subset of the clinical trials in their data as related to specific Entrez Gene ID numbers. We construct a count of the number of clinical trials in which each gene is used as the basis for a pharmaceutical treatment compound in clinical trials in each year.

Gene-level data on diagnostic tests: GeneTests.org data

We collect our measure of genes being used in diagnostic tests from the GeneTests.org database.[77] This data includes a laboratory directory that is a self-reported, voluntary listing of US and international laboratories offering in-house molecular genetic testing, specialized cytogenetic testing, and biochemical testing for inherited disorders. US-based laboratories listed in GeneTests.org must be certified under the Clinical Laboratory Improvement Amendment of 1988, which requires laboratories to meet quality control and proficiency testing standards; there are no such requirements for non-US-based laboratories.

We use the GeneTests.org data as of September 18, 2012, which lists OMIM numbers for which there is any genetic test available in the Genetests.org directory. As with the OMIM data above, one gene can appear in more than one OMIM record, and one OMIM record can involve more than one gene. We construct an indicator for whether a given gene is used in any diagnostic test as of 2012.

Human genome-related crosswalks

NCBI-generated crosswalks are used to link OMIM numbers indexing genotype-phenotype pairs to Entrez Gene ID numbers,[78] and to link mRNA-level RefSeq accession/version numbers to Entrez Gene ID numbers.[79] We also use an NCBI-generated crosswalk that links discontinued Entrez Gene ID numbers to current Entrez Gene ID numbers, which is useful for linking Pharmaprojects observations that list discontinued Entrez Gene ID numbers to our data.[80]

[75] Available at `http://omim.org/downloads`.
[76] Pharmaprojects data is available for purchase through Citeline or the Pharmaprojects website: `http://www.pharmaprojects.com`.
[77] Available at `ftp://ftp.ncbi.nih.gov/pub/GeneTests/disease_OMIM.txt`.
[78] Available at `ftp://ftp.ncbi.nih.gov/gene/DATA/mim2gene_partial`.
[79] Available at `ftp://ftp.ncbi.nih.gov/refseq/release/release-catalog/release54.accession2geneid.gz`.
[80] Available at `ftp://ftp.ncbi.nih.gov/gene/DATA/gene_history.gz`.

C Appendix: The USPTO patent examination process (for online publication)

In this appendix, we describe the USPTO patent examination process in more detail.[81]

C.1 Overview of the USPTO patent examination process

The USPTO is responsible for determining whether inventions claimed in patent applications qualify for patentability. The uniform mandate for patentability is that inventions are patent-eligible (35 U.S.C. §101), novel (35 U.S.C. §102), non-obvious (35 U.S.C. §103), useful (35 U.S.C. §101), and the text of the application satisfies the disclosure requirement (35 U.S.C. §112).

Patent applications include a written description of the invention (the "specification"), declarations of what the application covers ("claims"), and a description of so-called prior art — ideas embodied in prior patents, prior publications, and other sources — that is known to the inventor and relevant to patentability. Once a patent application is received, as long as it satisfies a series of pre-examination formalities the Office of Patent Application Processing will assign it an application number, as well as a patent class and subclass.[82] These classifications, in turn, determine — based on a concordance between classes/subclasses and Art Units — the Art Unit to which the application is assigned, where Art Units are specialized groups of patent examiners that work on related subject matter.[83] Once assigned to an Art Unit, a supervisory patent examiner (SPE) then refines the patent classification if it is incorrect. In some cases, this means the application needs to be re-assigned to another Art Unit, though that is thought to be rare.

The SPE then assigns the application to a patent examiner for review (via a process described in more detail below). While the patent application process up to this point is quite structured, from this point forward substantial discretion is left in the hands of individual examiners. In particular, the examiner is responsible for determining which — if any — claims in the application are patentable in light of prior art disclosed by the applicant as well as prior art found through the examiner's own search. To give a sense of the time involved in the patent examination process, examiners have been estimated to spend an average of eighteen hours working on a given application (Lemley, 2001), although the process of evaluating a patent application takes several years.

As background for our empirical analysis, it is useful to outline the key steps in the examination process that occur from this point forward. The examiner sends a "first action" letter back to the applicant with an initial decision on the patent application. This initial decision can be an allowance, or (more commonly) a "non-final rejection." For non-final rejections, applicants have a fixed length of time (usually six months) during which to revise the application. After receiving the applicant's response, the examiner can then allow the application, negotiate minor changes, or send a second rejection. Counterintuitively, rejections in or after this second round are called "final rejections" but are in fact not final: there can be subsequent rounds of negotiation, and the only final resolution to a patent application that is not granted a patent is abandonment by the applicant (Lemley and Sampat, 2008).

C.2 Within-Art Unit assignment of patent applications to patent examiners

The process outlined above clarifies that the assignment of patent examiners to applications is a function of at least two factors: first, the Art Unit to which the application is assigned; and second, the year the application is filed,

[81] The discussion in this appendix draws heavily on Cockburn, Kortum and Stern (2003), Lemley and Sampat (2012), and GAO (2005), among other sources referenced in the text.

[82] There are currently over 450 patent classes; the most common class in our sample is 435 (Chemistry: molecular biology and microbiology). There are currently more than 150,000 subclasses, which may be repeated among classes. For more details, see `http://www.uspto.gov/patents/resources/classification/overview.pdf`.

[83] There are over 300 Art Units; see `http://www.uspto.gov/patents/resources/classification/art/index.jsp`. For the current version of the class/subclass-to-Art Unit concordance, see `http://www.uspto.gov/patents/resources/classification/caau.pdf`. The main Art Units in our sample are from the 1600 group (Biotechnology and Organic Chemistry).

given that the group of examiners in an Art Unit will vary over time. In this section, we discuss how — within an Art Unit in a given application year — patent applications are assigned to patent examiners.

The USPTO does not publish rules regarding the assignment of applications within Art Units to particular examiners. Given this absence of formal written rules, Lemley and Sampat (2012) conducted written interviews with roughly two dozen current and former patent examiners and supervisory patent examiners to inquire about the assignment process. While the results of these interviews suggested that there is not a single "standard" assignment procedure that is uniformly applied in all Art Units, these interviews revealed no evidence of deliberate selection or assignment of applications to examiners on the basis of characteristics of applications other than those observed in standard USPTO datasets. In some Art Units, supervisors reported assigning applications to examiners based on the last digit of the application number; because application numbers are assigned sequentially in the central USPTO office, this assignment system — while not purposefully random — would be functionally equivalent to random assignment for the purposes of this study. In other Art Units, supervisors reported placing the applications on master dockets based on patent classes and subclasses, with examiners specializing in those classes (or subclasses) being automatically assigned the oldest application from the relevant pool when requesting a new application. Consistent with what we would expect given these types of assignment mechanisms, Lemley and Sampat present empirical evidence that observable characteristics of patent applications are uncorrelated with characteristics such as the experience of the examiner to which the application was assigned. Unfortunately, we do not have information on the specific set of assignment processes used by the Art Units most common in our sample over the relevant time period.[84] In the absence of such information, we rely on the interviews in Lemley and Sampat (2012) as a guide to designing our empirical specifications.

[84] We have tried, unsuccessfully, to track down individuals who were supervisory patent examiners in the Art Units most common in our sample over the relevant time period.

D Appendix: Additional results (for online publication)

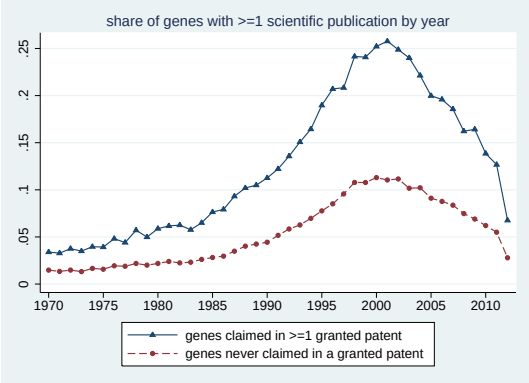
Table D.1: **Robustness of first stage estimates: Patent grants by examiner leniency instrument**

fixed effects included:	Art Unit - by - Application Year		Art Unit - by - Application Year		Art Unit - by - Application Year - by - Class - by - Subclass	
	(1)		(2)		(3)	
0/1, =1 if patent granted (mean = 0.3259)						
examiner leniency	0.8577	***	0.8518	***	0.8413	***
	(0.0357)		(0.0529)		(0.0536)	
number of observations	14,016		6,318		6,318	

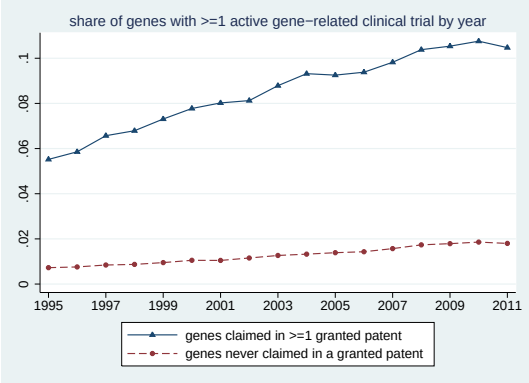
Notes: This table presents robustness checks on our first stage estimates, relating the probability of patent grant to our examiner leniency instrument. Column (1) documents estimates that condition on Art Unit-by-application year fixed effects. Column (3) replaces the Art Unit-by-application year fixed effects with Art Unit-by-application year-by-class-by-subclass fixed effects, estimated on the subsample of data meeting our sample restrictions. For ease of comparability, Column (2) documents estimates that condition on Art Unit-by-application year fixed effects but use the same sample as in Column (3). *: p<0.10; **: p<0.05; ***: p<0.01.

Figure D.1: **Follow-on innovation on patented and non-patented human genes: Robustness**

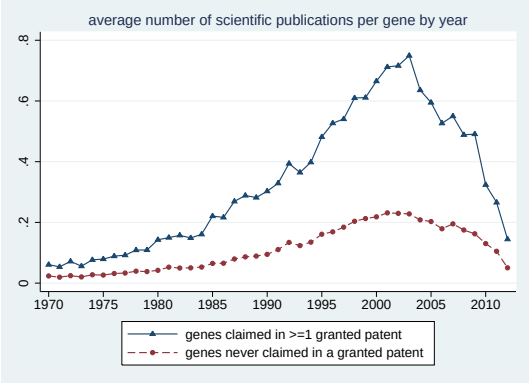
(a) Gene-level scientific publications: Binary



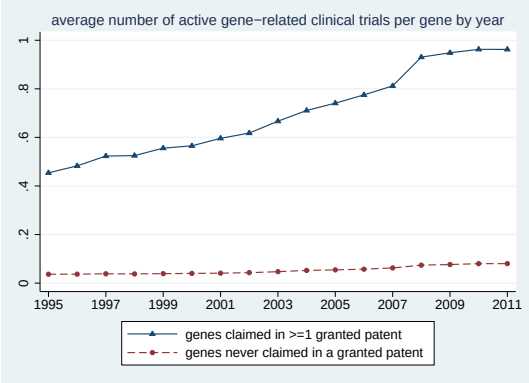
(b) Gene-level clinical trials: Binary



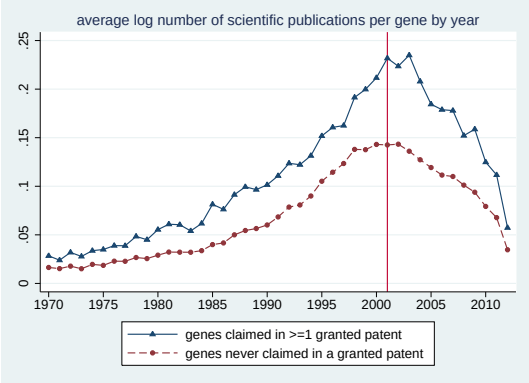
(c) Gene-level scientific publications: Count



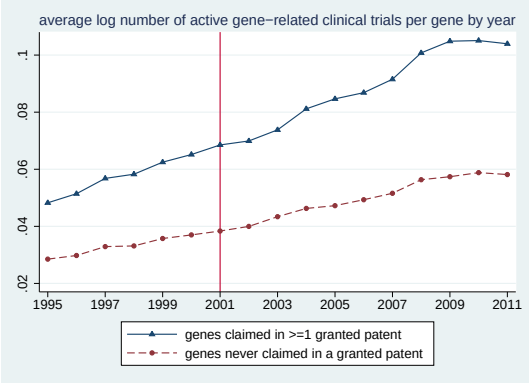
(d) Gene-level clinical trials: Count



(e) Gene-level scientific publications: Patents filed in or after 2001



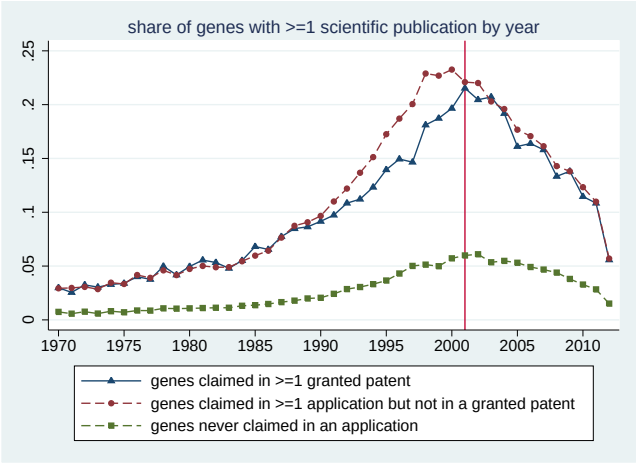
(f) Gene-level clinical trials: Patents filed in or after 2001



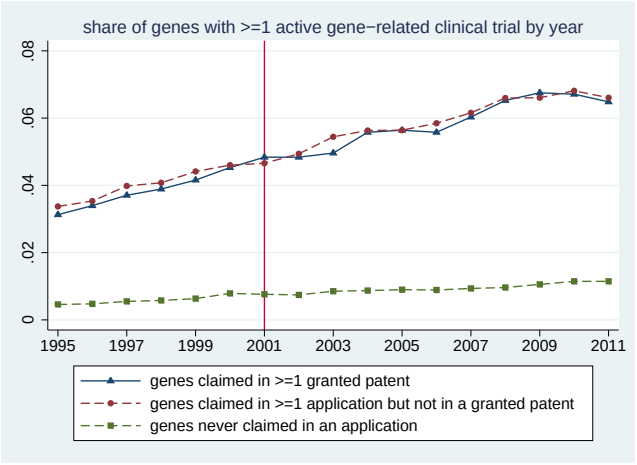
Notes: This figure plots trends in follow-on innovation by year separately for genes that ever receive a patent, and for genes that never receive a patent. The figure is constructed from gene-level data. The left-hand side panels use gene-level scientific publications as a measure of follow-on innovation, and the right-hand-side panels use gene-level clinical trials as a measure of follow-on innovation. The first row of figures plots the average of indicator variables for any follow-on innovation by year; the second row of figures plots the average number of each follow-on measure by year; and the third row of figures limits the sample of patents to patents filed in or after 2001. In the third row of figures, the vertical line in the calendar year 2001 denotes that because this figure focuses on patents that were filed in or after 2001, all years prior to 2001 can be considered a pre-period and used to estimate the selection of genes into patenting based on pre-filing measures of scientific research (publications) and commercialization (clinical trials). In Panels (e) and (f), we add one to both outcome variables in order to include observations with no observed follow-on innovation.

Figure D.2: **Patents and follow-on innovation on human genes claimed in accepted/rejected patent applications: Robustness**

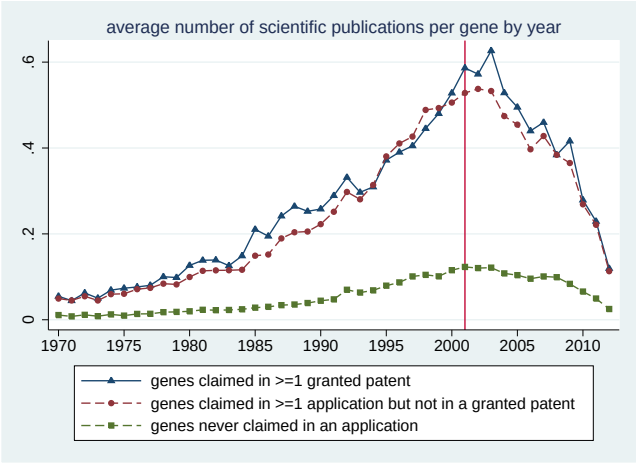
(a) Gene-level scientific publications: Binary



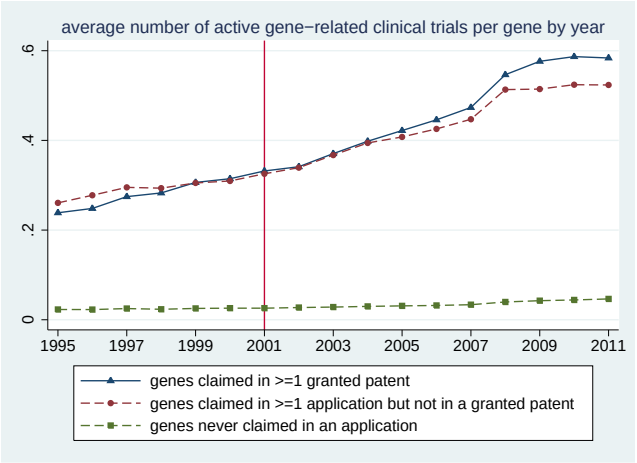
(b) Gene-level clinical trials: Binary



(c) Gene-level scientific publications: Count



(d) Gene-level clinical trials: Count



Notes: This figure plots trends in patenting and follow-on innovation by year separately for three groups of genes: genes claimed in at least one granted patent; genes claimed in at least one patent application but never in a granted patent; and genes never claimed in a patent application. The figure is constructed from gene-level data. The left-hand side panels use gene-level scientific publications as a measure of follow-on innovation, and the right-hand-side panels use gene-level clinical trials as a measure of follow-on innovation. The first row of figures plots the average of indicator variables for any follow-on innovation by year, and the second row of figures plots the average number of each follow-on measure by year.