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BRIEF COMMUNICATION

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CRISPR, Patents, and the Public Health

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Patent issues surrounding CRISPR, the revolutionary genetic editing technology, may have important implications for the public health. Patents maintain high prices for novel therapies, limiting patient access. Relatedly, insurance coverage for expensive therapies is waning. Patents also misallocate research and development resources to profitable disease indications rather than those that necessarily impinge on the public health. And it is unclear how CRISPR therapies will figure into the current regulatory framework for biosimilars. Policy makers and physicians should consider these issues now, before CRISPR therapies become widely adopted—and entrenched—in the marketplace.

INTRODUCTION

The gene-editing technology known as clustered regularly interspaced palindromic repeats (CRISPR†), has the potential to revolutionize medicine [1]. Gene therapy—the treatment of disease by modifying the genome of patients' cells—has a long history of scientific and therapeutic complications, as well as failed promises [2]. But CRISPR promises a cheap, precise, high-yield, and—it is hoped—therapeutically tolerable mechanism to edit the genome in living tissue [1]. It is, in the eyes of many, the "holy grail" of genetic engineering [3].

Whether CRISPR will fulfill such promises remains unclear. But in the meantime, CRISPR's basic technology is subject to numerous foundational patents, many of which are licensed by biotechnology and pharmaceutical companies. Those patents, in turn, allow therapeutic developers to control how CRISPR will be developed into therapies and the prices—often high prices—charged to distribute them [4]. To that end, CRISPR is poised to suffer from the same pitfalls as other newly developed biopharmaceuticals. It is unknown, for example, how developers will price CRISPR-based therapies, given both the novelty of the treatment and, it seems, unslakable public demand [5]. It is also unknown—given recent trends and legislation to the contrary—whether insurers will broadly cover CRISPR therapies [6]. Given the high licensing fees associated with CRISPR patents, it is uncertain whether therapeutic developers will focus on high-impact or neglected genetic diseases, or simply turn to more profitable ones [7]. And it is unclear how patents covering CRISPR therapies will fit into the current legal framework concerning follow-on treatments, like generic drugs and biosimilars [8]. This article explores the future impact of CRISPR patents on these important public health issues.

PRICING

The pricing of drugs remains one of the most significant issues to the public interest—and the public health [9]. The public, press, and legislators throughout

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†Abbreviations: CRISPR, clustered regularly interspaced palindromic repeats; FDA, Food and Drug Administration; PBMs, prescription benefit managers; CAR-T, chimeric antigen receptor T-cell.

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the country have responded to recent reports of drug price increases with a staccato of fury and investigations [10]. Patients priced out of or underinsured to receive critical medicines stymie larger public health goals [9].

While the logic behind drug pricing remains almost entirely opaque, one element in its calculus is patent protection. Patents allow drug developers to charge monopoly prices for limited times [11]. This is, indeed, the point. Research and development is expensive and uncertain. So are clinical trials, more of which fail than succeed [12]. In the classic economic account, patents allow developers of biopharmaceuticals to recoup these costs and hedge against the uncertainty of future projects' successes or failures [13].

This logic has historically dictated the extreme cost of gene-therapies. Gene-therapies are difficult to research, inordinately costly to shepherd through clinical trials, and wildly uncertain in their outcomes [14]. Furthermore, even gene-therapies that receive approval from the U.S. Food and Drug Administration (FDA) often serve limited populations—and what revenue developers cannot make up through demand they must make back by restricting supply [12]. Lastly, gene-therapies are often, by their nature, permanent: there is rarely the possibility that patients will pay for the drug, perennially, throughout their lifetimes [15]. These are among the reasons why the sticker-price for Glybera (alipogene tiparvovec)—a gene-therapy used to treat severe familial lipoprotein lipase deficiency—was $1 million [16].

There is no reason to believe CRISPR therapies will not be the same. CRISPR, despite its promises of precision and ease, remains difficult to immediately translate into therapeutic products [8]. Juno Therapeutics, for example, spent almost $300 million researching certain immunological-based CRISPR therapies, known as CRISPR CAR-T [17]. CAR-T, short for chimeric antigen receptor T-cell, works by removing T-cells from a patient's blood, modifying them to express a non-native antibody directed to presenting antigens on leukemic B-cells, and reinjecting them back into the patient [18]. Ideally, these modified T-cells then target the patient's cancerous B-cells, providing an elegant way of using the body's own immune system—with modifications—as a cancer treatment. Inexplicable neurotoxicity issues in Juno's trial, however, left 5 out of 38 trial participants dead, forcing Juno to almost entirely strike its research program [19]. Any eventually successful therapy derived from Juno's CRISPR CAR-T platform will likely to be priced in a way to make up for these losses and the costs of developing further research [20]. To that end, patents covering CRISPR in this area are valuable precisely because they function as an asset to command such prices [14].

Similarly, patents would allow developers of CRISPR therapies to price their products in a way that makes up for low patient demand, either because the disease indication sought to be treated is rare or, like Glybera, the treatment is a one-time dose [14]. Glybera, in fact, provides a sterling example of patents covering rare-indication, permanent gene therapies; the treatment is protected by at least eight patent families, covering the viral vector, protein expression systems, and manufacturing processes, with multiple patents and patent applications for each family [21]. CRISPR developers are famously making use of extensive patent families like these, with enormous licensing fees paid to collaborators [4]. The ultimate retail prices of these and related therapies can be astronomical. Novartis's Kymriah (tisagenlecleucel)—the first approved CAR-T therapy, albeit without using CRISPR—costs $475,000 [22]. It stands to reason that such patents will likely make any CRISPR therapies for rare diseases similarly expensive.

The potential price of patented CRISPR therapies also illuminates a larger point about drug pricing: it allows developers to set profit maximizing prices independent of the marginal costs of production [23]. That is, patents allow drug developers to price their products as high as the market will bear regardless of how much therapies cost to make. This is important for CRISPR-based therapies sought to replace expensive-to-produce, multi-dose drugs. Monoclonocal antibody therapy, for example, is typically costly and difficult to manufacture, store, and provide to patients [24]. CRISPR-based alternatives may ultimately be cheaper to produce. But patent coverage of the product allows the therapy's developer to set prices far enough above this manufacturing cost as to make it irrelevant [23]. The ease, cost, and permanency of CRISPR therapies do not necessarily mean they will be cheaper than companion therapies, especially where patents are involved.

INSURANCE COVERAGE

Relatedly, patents covering CRISPR therapies may affect how and whether insurers are willing to cover them. Typically, patents for novel therapies mean only a single source of the therapeutic—the original developer—who, in turn, can price the therapy at extraordinary prices. Insurers, by and large, pick up the tab. This system works to maintain high prices for a number of reasons: insurers rarely refuse to cover novel therapies—and, in some instances, public insurance is prohibited from doing so. Increasingly, insurers often work through prescription benefit managers (PBMs) to receive discounts on drugs' sticker prices [9]. And the American public has become used to the expense of novel therapies [25]. On these points, it would seem that virtually any patented CRISPR therapy would likely be covered by insurers.

But times are changing. In some cases, prices have become so extraordinary that insurers have done the unthinkable: they have refused to cover even novel therapies. Sarepta Therapeutics' Exondys 51 (eteplirsen) provides a shocking example. Sarepta's drug—a novel RNA interference oligonucleotide intended to treat Duchenne muscular dystrophy—showed little promise in clinical trials. A single, twelve-person study—the only post-exploratory study presented to an FDA Advisory Committee—showed no statistically significant clinical benefit in patients [26]. Nonetheless, FDA stunningly approved the drug after a contentious internal debate [27]. Insurers, however, were unpersuaded by the clinical data—or the drug's $750,000 annual price tag, a consequence, in part, of a successful patent campaign against one of its competitors, BioMarin Pharmaceutical [28,29]. As a consequence, a number of insurers have outright refused to cover Exondys 51 or demanded coverage be tied to burdensome testing [24]. A patented, expensive, and clinically questionable CRISPR therapy would likely face the same challenges.

Aside from insurers' reluctance to pay for new, expensive therapies, the nature of health insurance itself is beginning to change. A number of legislative proposals currently before Congress would both shrink the overall insured population in the United States and, in some cases, allow insurers to refuse coverage to patients with pre-existing conditions. These proposals would drastically limit access to new CRISPR therapies. First, legislative proposals to limit the number of patients receiving Medicaid—by some Congressional Budget Office estimates, 15 million patients—would essentially "price out" any patented, expensive CRISPR therapies of poorer, working class Americans, unlikely to be able to afford such therapies out-of-pocket [6].

Even without shrinking Medicaid, private insurers would likely refuse to cover patients' use of CRISPR for pre-existing conditions, if current proposals become law. As gene therapy, CRISPR therapy would be typically indicated for congenital rather than acquired conditions [8]. Current clinical research using CRISPR has consequently focused on congenital diseases, such as sickle cell anemia, that would indeed be considered "pre-existing conditions" under currently pending legislation [30]. As a consequence, insurers may have few covered beneficiaries to use CRISPR therapies in the first instance. And even though CRISPR therapy may, in fact, make some beneficiaries healthy in the long run, insurers would be further encouraged to decline coverage precisely because patents covering such treatments would likely keep prices high [9]. Patents, prices, and pre-existing conditions may make CRISPR unavailable for many Americans.

NEGLECTED DISEASES

Drug development operates under market incentives; therapeutics companies research treatments that stand to make them money. Patents therefore play a significant role in the development of drug candidates. Without some form of intellectual property protection, therapeutics companies often cannot charge the sort of super-competitive prices that generate windfall profits [13]. Indeed, one of the very first checkpoints in the lifecycle of drug development is a "patent screen"—legal rather than scientific research to see how much of the patent landscape can be claimed for a new drug [31].

This patent-based system of therapeutic research and development has both positive and negative consequences for the public health. Generally speaking, therapeutic developers have strong interests to develop therapeutics affecting the greatest number of people [13]. From a high-altitude perspective, this indeed looks like the landscape of drug approvals: out of 22 drugs approved by FDA in 2016, six were indicated for treating cancer, the second-highest cause of disease mortality in the United States [32]. And in 2015, eight of the 45 new drugs approved were indicated for some form of heart disease, the single greatest cause of mortality—disease or otherwise—in the United States [33].

But there are two negative corollaries to this patent-influenced, market-based approach. First, rare diseases are typically woefully under-researched. By definition, the therapeutic market for rare diseases is smaller and, as a consequence, therapeutics developers have fewer incentives to cure or treat patients suffering from them [34]. Programs to bridge this "incentive gap" have had only halting success [35]. Second, where the market is large enough, this encourages developers to focus on, and obtain patents covering, "vanity diseases"—cosmetic conditions that have minimal public health impact [36]. Viagra (sildenafil)—a small molecule drug indicated for the treatment of "erectile dysfunction"—stands testament to this intersection of patents and the public health. Prior to Viagra, erectile dysfunction was not formally classified as a medical condition. But the surprise success of the drug—in combination with a powerful patent estate and broad market appeal—helped chisel "erectile dysfunction" into the medical canon [37]. As a consequence, a number of follow-on drugs, namely, Cialis (tadalafil) and Levitra (vardenafil), were independently developed at great expense, even though the public health benefits of the drugs were scant. In economic terms, "me-too" drugs for vanity conditions "attract more investment than is socially optimal" [32].

These realities of the research enterprise are likely to impact CRISPR therapies as well. Even where the use of CRISPR for orphan diseases may be *socially* optimal,

it may be *economically* inefficient: without broad patents covering the technology, small built-in patient populations may not generate enough revenues to sustain a research program. More specifically, the incentives to develop CRISPR therapies that use known, basic mechanisms to tackle rare diseases may simply be unattractive to shepherd through the rigors of FDA approval if those mechanisms cannot themselves be patented. Further, "passive medicalization" of vanity conditions—such as Latisse (bimatoprost) for eyelash growth—may direct CRISPR research elsewhere. While physicians may view gene therapy as an extreme measure for cosmetic issues, that view may not hold for much longer [38].

BIOSIMILARS

The public health is best served not just by the development of new drugs, but access to them once developed. Counterintuitively, one of the more faithful creatures to drug access is a product of the patent system itself: generic drugs and biosimilars. Both generics and biosimilars are copies of an FDA-approved therapeutic. But because the same product has already been approved by FDA, generics and biosimilars path to regulatory approval is easier: their manufacturers can rely on a pioneers' clinical trial data to prove safety and efficacy. At the same time, approval is also predicated on the pioneer's patents covering the "reference listed drug" expiring or, more frequently, successfully challenging those patents in court [39]. Once launched, generic companies of new drugs often sell for less than 20 percent of the brand's price, and in some instances, as low as marginal cost—the cost, say, of physically manufacturing the pill [40]. In this sense, generics and biosimilars can be thought of as function of patent system: they exist because the law ties together regulatory approval with patents.

This idealized version of the generic drug system gets more complicated for biologics, large molecule, biologically manufactured therapies, like monoclonal antibodies. Biosimilars—analogous to generic drugs—cannot entirely rely on pioneer manufacturers' clinical data for FDA approval; they must also conduct smaller clinical trials demonstrating the two products are "highly similar" and that there are "no clinically meaningful differences" between them. Patent challenges, too, are more complicated. Unlike brand-generic patent litigation—typically, a single *Götterdämmerung* of litigation in federal court—biosimilar patent litigation is a complicated process, consisting of multiple rounds of negotiations and lawsuits [35]. In addition, because manufacturing biologics is so complex, a biologic product is typically covered by more patents than a small molecule drug [41]. The average small molecule drug, for example, is covered by 3.5 patents [42]; Humira (adalimumab), the world's best-selling biologic, is covered by over 100 [43]. As a consequence, the availability of biosimilars—from a patient perspective—is significantly more restricted than generic drugs.

It is unclear where a given CRISPR therapy would fit into this model, although given the nature of the technology, most CRISPR therapies are likely to fall on the biologic side of the divide. To that end, the complex interaction of patents and biosimilar products are likely to hinder the availability of biosimilar CRISPR therapies once they come online. Like Humira's patent fortress, the CRISPR patent estate is growing—and with multiple players competing for influence and licensing arrangements. Simply resolving the patent claims for a CRISPR biosimilar is likely to be arduous. Even more perniciously, the same companies developing specific CRISPR therapies also hold foundational patents required to practice basic elements of the technology [4]. Should these companies ever put a CRISPR product on the market, it seems unlikely they would license these patents to direct, biosimilar competitors.

Any path forward to developing not only novel CRISPR therapies but biosimilars to those therapies must find its way through this thicket of foundational and ancillary CRISPR patents. While the current biosimilar patent regime contemplates patents covering specific therapies, it seems ill-fitted to patents covering foundational aspects of a "platform technology"—a technology broadly used to develop specific downstream applications [4]. Humira's patent estate, for example, has only the potential to block the development of a narrow class of biosimilars, *i.e.*, other anti-tumor necrosis factor α antibodies. It would be unlikely to slow the approval of other antibody therapies, generally. But the CRISPR patent estate—with patents covering virtually limitless classes of CRISPR therapies—could be used, in the context of the biosimilar patent regime, to delay biosimilars directed to any CRISPR-based therapy, regardless of therapeutic application or molecular target. Whether the foundational CRISPR patents will be wielded that way remains to be seen. But the interaction of these regimes—the biologics patent regime and the CRISPR patent thicket—suggests that even if CRISPR therapies were developed, cheaper CRISPR biosimilars are unlikely to be developed, much like expensive biologics today.

CONCLUSION

The patent issues likely to arise for CRISPR-based therapies present some difficult challenges for the public health, writ large. Pricing patented CRISPR therapies to make them broadly affordable while ensuring insurance coverage of those therapies will require a careful balancing of the significant commercial risk in

the therapies' development with the clinical reward to patients. Encouraging therapeutic developers to focus their research efforts on clinical needs, rather than monetary desires, will similarly require careful—and creative—thinking. And assessing what role generic competitors can play in CRISPR-based precision medicine needs further regulatory and legislative attention. These challenges are, in a way, good problems to have. Revolutionary gene-therapy technology does not come along frequently. But it is precisely the novelty and power of CRISPR—and the potential effects of its patent landscape on the public health—that counsel us to solve these problems before it is too late for patients.

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