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INTELLECTUAL PROPERTY, SURROGATE LICENSING, AND PRECISION MEDICINE

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INTRODUCTION

The fruits of the biotechnology revolution are beginning to be harvested. Recent regulatory approvals of a variety of advanced therapies—Keytruda (pembrolizumab), [1] Kymriah (tisagenlecleucel),[2] and patisiran[3]—have ushered in an age of "precision medicine" treatments that target patients' specific genetic, physiological, and environmental profiles rather than generalized diagnoses of disease. [4] Therapies like these may soon be supplemented by gene editing technologies such as CRISPR, which could enable the targeted eradication of deleterious genetic variants to improve human health. But the intellectual property (IP) surrounding precision therapies and their foundational technology remain controversial.[5] Precision therapies ultimately rely—and are roughly congruent with—basic scientific information developed in the service of academic research.[6] Much of precision medicine's IP, however, is held by academic research institutions that employ for-profit surrogate companies, companies responsible both for

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[1] Letter from Richard Pazdur, Director, Office of Hematology and Oncology Products Center for Drug Evaluation and Research, to Melissa Tice, Executive Director, Global Regulatory Affairs, Merck Sharp & Dohme Corp. (Sept. 4, 2014Sept. 4, 2014) [hereinafter Keytruda Approval Letter], https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/125514Orig1s000ltr.pdf.

[2] Letter from Wilson W. Bryan, Director, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, to Manisha Patel, Novartis Pharmaceuticals Corp. (Aug. 30, 2017) [hereinafter Kymriah Approval Letter], https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM574106.pdf.

[3] Patisiran has, in fact, not yet been approved but recently completed a successful Phase III clinical trial. Approval is likely to be granted in the first quarter of next year. *See* Adam Feuerstein, *Alnylam's Rare Disease Drug Shines in Trial, Paving Way for a Brand-New Class of Medicines*, STAT NEWS (Sept. 20, 2017), https://www.statnews.com/2017/09/20/alnylam-drug-success/.

[4] *See* Euan A. Ashley, *The Precision Medicine Initiative: A New National Effort*, 313 JAMA 2119, 2119 (2015) (defining "precision medicine").

[5] *See, e.g.*, Dan L. Burk, *Patents as Data Aggregators in Personalized Medicine*, 21 B.U. J. SCI. & TECH. L. 233, 239–240 (2015); John M. Conley, Robert Cook-Deegan & Gabriel Lázaro-Muñoz, *Myriad After* Myriad*: The Proprietary Data Dilemma*, 15 N.C. J.L. & TECH. 597, 613–616 (2014); W. Nicholson Price II, *Black-Box Medicine*, 28 HARV. J.L. & TECH. 419, 421 (2015).

[6] Jacob S. Sherkow, *Cancer's IP*, 96 N.C. L. Rev. 297, 361 (2018) (describing the informational nature of precision cancer therapy).

commercially developing university research and sublicensing university IP to others.[7] This creates an uneasy tension between the public missions of universities and the commercial motives of surrogates, particularly universities' goals of producing and disclosing scientific information, and surrogates' goals of exploiting that information for commercial gain.[8]

This essay examines the challenges that surrogate licensing poses for the future of precision medicine. It begins by providing a brief summary of precision medicine and its recent developments. Next, it provides an overview of university patenting and the shift toward surrogate licensing. It then explores some of the difficulties concerning surrogate licensing in the context of precision medicine and, later, suggests modified licensing approaches and best practices that may better promote scientific discovery, the development of human therapies, and overall social welfare. Lastly, the essay discusses some larger doctrinal and theoretical implications arising from surrogate licensing in informationally intensive fields, like precision medicine.

I. PRECISION MEDICINE

Ironically, "precision medicine" itself is an imprecise term, a flexible phrase used to incorporate a host of therapies and diagnostics considered to be the "next generation" of medicine.[9] Nonetheless, the most accurate understanding of precision medicine—and the one used in this essay—defines precision medicine as "precisely tailored therapies to subcategories of disease, often defined by genomics."[10] The thrust of precision medicine is largely informational: it unites basic scientific information, patient-specific data, and algorithms that allow physicians to diagnose and treat the root causes of a patient's condition.[11]

Precision medicine treatments thus focus on an individual's "genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations."[12] For example, Keytruda's new indication focuses not on a specific diagnosis, but on the existence of and level of expression of a particular protein, PD-L1, in patients' tumors.[13] Practically speaking, this means that each patient's biopsy undergoes diagnostic testing to measure levels of PD-L1.[14] Where PD-L1 is present in sufficient quantities, Keytruda is indicated for treatment, independent of the broader type of cancer diagnosed or of the original location of the tumor.[15] This stands in stark contrast to traditional cancer therapy that largely focuses on broad categories such as the organ in which cancer was found, e.g., "breast cancer" for

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[7] Jorge L. Contreras & Jacob S. Sherkow, *CRISPR, Surrogate Licensing, and Scientific Discovery*, 355 SCIENCE 698, 698 (2017).

[8] *See infra* Part III.

[9] Adam A. Friedman, Anthony Letai, David E. Fisher & Keith T. Flaherty, *Precision Medicine for Cancer with Next-Generation Functional Diagnostics*, 15 NATURE REV. CANCER 747, 747 (2015); J. Larry Jameson & Dan L. Longo, *Precision Medicine—Personalized, Problematic, and Promising*, 372 NEW ENG. J. MED. 2229, 2229 (2015) (questioning the cost savings of precision medicine).

[10] Ashley, *supra* note 4, at 2119.

[11] *See* Price II, *supra* note 5, at 421 (examining the role of "black box" algorithms in precision medicine); Sherkow, *supra* note 6.

[12] Jameson & Longo, *supra* note 9, at 2229.

[13] *Id.*

[14] List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools), FDA, https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm (last updated Oct. 19, 2017) (noting the approval of PD-L1 IHC 22C3 pharmDx for PD-L1 assessment for Keytruda).

[15] *Id.*

tumors found in the breast.[16] Treating cancer in this fashion—by assessing and targeting particular molecular variants in individual patients—stands as the quintessential example of precision medicine, medicine using "molecular scalpels" rather than simplistic clinical presentations of constellations of symptoms.[17] In a similar vein, Alnylam's patisiran product is claimed to silence the expression of a defective copy of a specific gene, *TTR*, that causes a form of amyloidosis.[18] And, perhaps most impressively, Novartis's Kymriah consists of a modified form of a patient's own white blood cells, uniquely tailored to that patient's tumor genetic profile.[19]

Techniques such as these come on the heels of an explosion of information on human molecular genetics, beginning with the Human Genome Project and continuing today through a multitude of decentralized next-generation DNA sequencing efforts.[20] As a result, there have been numerous initiatives recently establish to bring precision medicine to the fore. Most notably, the National Institutes of Health established, in 2015, a Precision Medicine Initiative (the human cohort development portion of which is now known as the "All of Us" program), a long-term research project aimed at funding research directed to "detecting, measuring, and analyzing a wide range of biomedical information—including molecular, genomic, cellular, clinical, behavioral, physiological, and environmental parameters."[21] Relatedly, the 21st Century Cures Act (2016) has established a Cancer Moonshot, a precision medicine program aimed ambitiously at curing cancer within a decade (or, at least, establishing a broad informational knowledge base to help).[22] Besides these federal efforts, individual states such as California have established their own precision medicine initiatives, as have research institutions, like Columbia University and the University of Utah.[23] But at their core, all of these research programs are similar: public-private molecular biology research imbued with the hope of translating genetic knowledge into clinical, commercial therapies.[24]

II. UNIVERSITY PATENTING AND SURROGATE LICENSING

The enactment of the Bayh-Dole Act in 1980 and the subsequent rise of the biotechnology industry have made academic research institutions the gatekeepers for many foundational biotechnology discoveries and their accompanying patents.[25] Today, the paths of major "breakthroughs" in biotechnology routinely run through academic research institutions and their

[16] D. Heim, J. Budczies, A. Stenzinger, D. Treue, P. Hufnagl, C. Denkert, M. Dietel & F. Klauschen, *Cancer Beyond Organ and Tissue Specificity: Next-Generation-Sequencing Gene Mutation Data Reveal Complex Genetic Similarities Across Major Cancers*, 135 INT'L J. CANCER 2362, 2362 (2014).

[17] PETER W. HUBER, THE CURE IN THE CODE 85 (2013).

[18] *See* Feuerstein, *supra* note 3.

[19] Highlights of Prescribing Information (Aug. 30, 2017) [hereinafter Kymriah label], https://www.fda.gov/downloads/BiologicsBloodVaccines/%20CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf.

[20] *See* Jorge L. Contreras, *Constructing the Genome Commons* in GOVERNING KNOWLEDGE COMMONS 99 (Brett M. Frischmann, Michael J. Madison & Katherine J. Strandburg eds., 2014) (discussing the Human Genome Project); Sherkow, *supra* note 6, at 17 (discussing recent efforts).

[21] Francis S. Collins & Harold Varmus, *A New Initiative on Precision Medicine*, 372 NEW ENG. J. MED. 793, 794 (2015).

[22] Sherkow, *supra* note 6, at 2–3 (explaining the Cancer Moonshot program).

[23] California Initiative to Advance Precision Medicine, http://www.ciapm.org; Precision Medicine at Columbia University, https://precisionmedicine.columbia.edu; CCTS Precision Medicine, http://medicine.utah.edu/ccts/precision-medicine/ .

[24] Collins & Varmus, *supra* note 211, at 794 (noting the goal of creating "new therapies").

[25] Daniel J. Hemel & Lisa Larrimore Ouellette, *Bayh–Dole Beyond Borders*, 4 J.L. BIOSCIENCES 282 (2017).

patent estates.[26] As in other areas of academic research, research regarding precision medicine has led to significant patent holdings by universities and other research institutions.[27]

The promises and perils of university patenting have been well-documented.[28] On the positive side of the ledger, university patenting encourages academic scientists to study "translational" technologies—technologies with immediate or near-term practical impact.[29] University patenting also provides academic institutions with an additional revenue stream that, ideally, can be redeployed to serve education and fund further research.[30] On the negative side of the ledger, some argue that university patenting "force[s] US taxpayers to 'pay twice' for patented products: once when they fund the initial grant, and again when they pay supra-competitive prices for the patented product."[31] University patents may also threaten cross-institutional collaboration; skew internal funding, advancement, and promotion decisions; and ultimately stymie follow-on research if enforced against other academic institutions.[32] Whatever the policy considerations, since Bayh-Dole, universities and other research institutions have been obtaining patents in significant numbers, particularly in the biotechnology area.[33]

Biotechnology's marriage of academic and commercial interests has led universities and research institutions to employ a range of methods for commercializing the technologies that they patent. Some university research may be sponsored directly by industrial collaborators, which obtain preferential rights in any technology resulting from that research.[34] Other university research may be licensed directly by the university, commonly through a technology licensing or technology transfer office, to companies granted rights to exploit the technology, usually in

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[26] *See* Rebecca S. Eisenberg, *Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research*, 82 VA. L. REV. 1663, 1666 (1996) (describing this phenomenon).

[27] *See* Rebecca S. Eisenberg, *Diagnostics Need Not Apply*, 21 B.U. J. SCI. & TECH. L. 256, 258–259 (2015) (discussing historical trends with respect to diagnostic patents); Dianne Nicol, Tania Bubela, Don Chambers, Jan Charbonneau, Christine Critchley, Joanne Dickinson, Jennifer Fleming, Alex W. Hewitt, Jane Kaye, Jonathon Liddicoat Rebekah McWhirter, Margaret Otlowski, Nola M. Ries, Loane Skene, Cameron Stewart, Jennifer Wagner & Nik Zeps, *Precision Medicine: Drowning in a Regulatory Soup?*, 3 J. L. BIOSCI. 281, 298 (2016) (noting patents in this area); Arti K. Rai, *Risk Regulation and Innovation: The Case of Rights-Encumbered Biomedical Data Silos*, 92 Notre Dame L. Rev. 1641, 1646 (2016) (describing the fragmentation of such rights in this area). *But see* W. Nicholson Price II, *Big Data, Patents, and the Future of Medicine*, 37 CARDOZO L. REV. 1401, 1401–1405 (2016) (discussing the impotence of patents to incentivize precision medicine research); Rachel E. Sachs, *Innovation Law and Policy: Preserving the Future of Personalized Medicine*, 49 U.C. DAVIS L. REV. 1881, 1906–1922 (2016) (describing the difficulty of getting patents in this area).

[28] *See generally* Hemel & Ouellette, *supra* note 25, at 1–3 (listing praises and criticisms); Wendy H. Schacht, CONG. RESEARCH. SERV., RL32076, *The Bayh-Dole Act: Selected Issues in Patent Policy and the Commercialization of Technology* (2012).

[29] Vicki Loise & Ashley J. Stevens, *The Bayh-Dole Act Turns 30*, 2 SCI. TRANSLATIONAL MED. 52cm27 (2010) (describing this policy objective). *But see* Jerry G. Thursby & Marie C. Thursby, *Has the Bayh-Dole Act Compromised Basic Research?*, 40 RES. POL'Y 1077, 1077 (2011) (empirically refuting this claim).

[30] Rosa Grimaldi, Martin Kenney, Donald S. Siegel & Mike Wright, *30 Years After Bayh–Dole: Reassessing Academic Entrepreneurship*, 40 RES. POL'Y 1045, 1045 (2011) ("[T]here is the potential for promoting technology commercialization and generating revenue for the university, which is typically re-invested in academic research").

[31] Hemel & Ouellette, *supra* note 25, at 283; *see also* Schacht, *supra* note 28, at 14–15.

[32] Jacob S. Sherkow, CRISPR: *Pursuit of Profit Poisons Collaboration*, 532 NATURE 172, 172–173 (2016).

[33] *See*, *e.g.*, Brady Huggett & Kathryn Paisner, *University Biotech Patenting 2013*, 32 NATURE BIOTECH. 512 (2014).

[34] *See* Yong S. Lee, *The Sustainability of University-Industry Research Collaboration: An Empirical Assessment*, 25 J. TECH. TRANSFER 111, 122–123 (2000) (assessing these relationships).

exchange for a royalty based on sales.[35] But a third, and increasingly popular, mode of university technology commercialization is the creation of a new company (a "spinoff" or "spinout") specifically designed for the purpose of commercializing a particular portfolio of the university's technologies and IP. Both the university and the researchers responsible for the relevant technologies often retain an equity ownership stake in the spinout company, which then obtains a license of the relevant IP from the university.[36]

University spinouts are not new; they have been formed to commercialize academic research for more than a century, and have grown substantially in popularity in the wake of the Bayh-Dole Act.[37] According to the Association of University Technology Managers (AUTM), U.S. and Canadian universities formed more than 11,000 start-up companies between 1994 and 2015, contributing to economic growth, job creation, and technology dissemination.[38] Yet, commercial product development and IP licensing are not traditionally part of universities' larger translational research efforts. Ideally then, spinouts enable universities to allocate the responsibility for technology commercialization to external professionals, freeing university researchers to perform basic research.[39] In that vein, spinouts appear to provide an efficient vehicle for raising external capital to fund the translation of scientific discoveries in university laboratories into marketable products.[40] Notable university spinouts over the years have included Google (Stanford University), Bose (MIT), and Myriad Genetics (University of Utah).[41]

Many spinouts leave the university free to license IP to other companies, for other applications, as the university and its researchers see fit.[42] But one variant of this spinout approach uses the spinout as a "surrogate" for the university's broader licensing authority.[43] In a typical transaction of this nature, the surrogate takes an exclusive license to the university's technology, with the charge simultaneously to move the technology toward commercial development, through its own efforts but also through sublicensing the IP to others.[44] In prior work, we termed this licensing approach "surrogate licensing": the spinout company acts as a surrogate for the university, standing in the university's shoes for purposes of commercializing and sublicensing university IP.[45] A significant, recent example of surrogate licensing exists with respect to the IP covering CRISPR-Cas9 gene-editing technology. Separately, the University of California (UC) and the Broad Institute (a joint effort of Harvard, MIT, and Harvard-affiliated research hospitals) have

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[35] *See generally* Jennifer Carter-Johnson, Jeffrey S. Carter-Johnson & Jorge L. Contreras, *University Research and Licensing*, *in* BIOINFORMATICS LAW: LEGAL ISSUES FOR COMPUTATIONAL BIOLOGY IN THE POST-GENOME ERA 98–99 (Jorge L. Contreras & A. James Cuticchia eds., 2013).

[36] *See id.* at 99–100; *see also* Pinaki Nandan Pattnaik & Satyendra C. Pandey, *University Spinoffs: What, Why, and How?*, 4 TECH. INNOVATION MGMT. REV. 44, 44 (2014).

[37] *See* Jorge Contreras, Kate Eavis, & Susan Newell, *The Dizzying Rise of University Spinouts*, TORNADO INSIDER, Oct. 2002, at 25 (noting the establishment of Cambridge Scientific Instrument Company by Charles Darwin's son in 1881 as a spinout from Cambridge University).

[38] ASS'N U. TECH. MANAGERS, AUTM U.S. LICENSING ACTIVITY SURVEY FY2015 2 (2016).

[39] *See* Lee, *supra* note 34, at 121–122 (discussing the benefits of spinouts to universities).

[40] *See id.*

[41] *From the Garage to the Googleplex*, GOOGLE, https://perma.cc/P7NJ-RZFT; *Myriad Genetics*, TVC, https://perma.cc/PW9A-ERZN.

[42] *See* Jon C. Sandelin, *Dealing with Spinout Companies*, *in* INTELLECTUAL PROPERTY MANAGEMENT IN HEALTH AND AGRICULTURAL INNOVATION: A HANDBOOK OF BEST PRACTICES 1271, 1275 (Anatole Krattiger et al. eds., 2007) (describing university practice in sublicensing when granting spinouts nonexclusive licenses).

[43] *See, e.g.*, Contreras & Sherkow, *supra* note 7, at 698 (coining the term "surrogate licensing" and noting its appearance in the CRISPR context).

[44] *See id.*

[45] *See id.*

exclusively licensed each of their foundational CRISPR patent estates to surrogates: UC to Caribou Biosciences and the Broad Institute to Editas Medicine.[46]

What differentiates surrogates from ordinary spinouts is the breadth of the university's delegation of its IP. In some cases, the field of research ceded by the university to its surrogate is practically universal. In 2007, for example, Harvard University formed Nano Terra, Inc. for the purpose of overseeing the commercialization and sublicensing of more than fifty foundational nanotechnology patents developed by pre-eminent Harvard chemist George Whitesides.[47] The patents covered a variety of nanotechnology innovations with applications in industries ranging from advanced materials to avionics to chemicals to consumer products—broad enough to conjure the "specter . . . [of a] patent thicket . . . in the minds of innovators in this industry."[48]

In the case of CRISPR-Cas9, the field ceded to the research institutions' surrogates encompasses every conceivable application—in the case of UC's license to Caribou—or, as with Editas, every CRISPR-based human therapy directed to any of the 19,000-plus human genes.[49] In either instance, the CRISPR-Cas9 surrogate licenses are so vast as to allow single, for-profit entities to lay claim to a broad universe of the technology's applications in treating human disease.[50] In addition, commercial applications for CRISPR extend beyond human therapies and into the realms of diagnostics, gene screening platforms, and agricultural applications.[51] To the extent that universities abdicate their educational and public missions to for-profit surrogate companies, surrogate licensing casts in stark relief the distinction between universities' core missions as educational institutions and research enterprises and their commercial aspirations.

III. CONCERNS SURROUNDING SURROGATE LICENSING AND PRECISION MEDICINE

Given that precision medicine is likely to advance through information sharing and openness, designating for-profit surrogate companies as gatekeepers for university IP presents several policy challenges. These include tensions between disclosure and secrecy, the "bottlenecking" of commercial research, contributing to the link between IP and rising health care costs, and the erosion of universities' missions as disseminators of information. We discuss each these concerns in turn.

A. Disclosure versus Secrecy

Precision medicine and academic research are largely aligned when it comes to information policy: both thrive on the liberal, broad, and open disclosure of information. Universities, of course, implicitly—and, in some cases, explicitly—inure themselves with the duty to develop and

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[46] *See id.* Editas's license is limited to the field of human therapeutics; Caribou's license has no field restriction. But Caribou has, in turn, exclusively sublicensed human therapeutic applications to Intellia Therapeutics, a publicly-traded corporation that was also formed by University of California to exploit CRISPR technologies.

[47] *See* Barnaby J. Feder, *Harvard Is Licensing More than 50 Patents to a Nanotechnology Start-Up*, N.Y. TIMES (Jun. 4, 2007), http://www.nytimes.com/2007/06/04/technology/04nano.html. Scientists, including former scientists turned lawyers, may be familiar with Whitesides from his seminal primer on how to write a good scientific paper. George M. Whitesides, *Whitesides' Group: Writing a Paper*, 16 ADVANCED MATERIALS 1375 (2004). Note: JLC served as outside legal counsel to Nano Terra.

[48] Mark A. Lemley, *Patenting Nanotechnology*, 58 STAN. L. REV. 601, 621 (2005).

[49] Contreras & Sherkow, *supra* note 7, at 698.

[50] *Id.*

[51] *See* Jennifer A. Doudna & Emmanuelle Charpentier, *The New Frontier of Genome Engineering with CRISPR-Cas9*, 346 SCIENCE 1258096-1, 1258096-7 (2014).

disseminate information to the public.[52] Precision medicine operates in a similar vein. The raw materials required to bring precision medicine from the laboratory to the clinic are genetic and other health-related data—data often developed through academic research.[53] The disclosure of that data—publicly, through government-funded resources such as GenBank, dbSNP, dbGaP and ClinSeq, or even privately, through proprietary databases such as canCORS—drives the discoveries that, when applied to patients, constitute the best form of precision medicine.[54] By contrast, precision medicine crafted under the cloak of secrecy or through impenetrable "black box" algorithms raise a multitude of concerns: scientific irreproducibility, a lack of patient autonomy, and even negative public health consequences.[55]

Openness and access, however, are not primary goals for surrogate companies. Surrogates—running in competitive races to develop therapeutic products—may conclude that secrecy is more valuable than disclosure. For example, Myriad Genetics, the exclusive licensee of breast-cancer risk diagnostic patents from the University of Utah and others, offers a recent example. During the course of its diagnostic work, Myriad developed a database of rare variants of the breast and ovarian cancer risk genes, BRCA1 and BRCA2, with unknown clinical significance—"variants of unknown significance" or VUSs.[56] Concluding that such a database was far more valuable as a trade secret than an open platform, Myriad limited access to it beginning in 2004, leading to public criticism, including a brief, statement of concern from the European Society for Human Genetics.[57]

Relatedly, even where surrogates have committed to data sharing—either at the behest of their parent institutions or of their own accord—they have little incentive to standardize their datasets for sharing and cross-licensing purposes.[58] Difficulties in establishing Hetionet—a cross-platform dataset of cancer genomics information—provide an elucidating example. There, Hetionet's lead researcher, Daniel Himmelstein, faced competing difficulties: making twenty-eight datasets technically interoperable with one another and obtaining sublicenses from each dataset's owner to use one in connection with others.[59] These problems led to at least one dataset being left out of Hetionet's larger platform, with three still floating in legal limbo.[60]

This tension between disclosure and secrecy as profit-maximizing strategies raises what Jonathan M. Barnett calls the "host's dilemma": whether to deploy the "strategic forfeiture" of informational goods when faced with the uncertainty of a technology's future scale and adoption.[61] One traditional hedge against the dilemma—and the one largely employed by surrogates, today—has been the protection of information using a slate of IP protections: copyrights, trade secrets, and

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[52] John C. Scott, *The Mission of the University: Medieval to Postmodern Transformations*, 77 J. HIGHER EDUC. 1, 30–33 (2006).

[53] NAT'N RES. COUNCIL OF THE NAT'N ACAD., TOWARDS PRECISION MEDICINE: BUILDING A KNOWLEDGE NETWORK FOR BIOMEDICAL RESEARCH AND A NEW TAXONOMY OF DISEASE 34–36 (2011).

[54] Samuel J. Aronson & Heidi L. Rehm, *Building the Foundation for Genomics in Precision Medicine*, 526 NATURE 336, 337 (2015).

[55] *See* Conley et al., *supra* note 5, at 613–616; Price, *supra* note 5, at 421.

[56] Conley et al., *supra* note 5, at 600, 612–616.

[57] *Id.* at 614; Privately Owned Genetic Databases May Hinder Diagnosis and Bar the Way to the Arrival of Personalised Medicine, EUR. SOC'Y HUM. GENETICS (Oct. 31, 2012), https://www.eshg.org/477.0.html.

[58] Jorge L. Contreras & Jerome H. Reichman, *Sharing by Design: Data and Decentralized Commons*, 350 SCIENCE 1312 (2015); *see also* Christi J. Guerrini, Amy L. McGuire, & Mary A. Majumder, *Myriad Take Two: Can Genomic Databases Remain Secret?*, 356 SCIENCE 586, 586 (2017),.

[59] Simon Oxenham, *Legal Maze Threatens to Slow Data Science*, 536 NATURE 16, 16 (2016).

[60] *Id.*

[61] Jonathan M. Barnett, *The Host's Dilemma: Strategic Forfeiture in Platform Markets for Informational Goods*, 124 HARV. L. REV. 1861, 1865 (2011).

data protection rules.[62] This allows surrogates to selectively parcel off information, lot by lot, if needed, but also to freely give it away in other cases.[63]

This hedge may run counter to universities' larger commitments to the field of precision medicine if placed in the hands of surrogate licensees. If later developments in a surrogate's field mark open-data models as the path to riches, then this tension is largely loosened; the surrogate's interests may very well be aligned with its parent university's values. But if that does not come to pass—if profit-maximization is achieved through secrecy and exclusivity—surrogates have incentives, if not legal duties, to restrict access to their information from downstream competitors. This is all the more complicated—and difficult to square with universities' broader commitments to spreading knowledge—if the surrogate hedges by parceling off some information as public while restricting other information as proprietary. The initial broad assignment of IP rights to the surrogate raises a host's dilemma in ways that would not exist if these rights were retained by the university. Using surrogate licensors to further precision medicine research is, in some senses, an act of irony: the establishment of for-profit licensing structures may ultimately *restrict* information in an effort to commercially *develop* it.

B. Commercial Research Bottlenecks

It is not uncommon in the precision medicine context for patent holders—both commercial developers and universities—to license their patents on exclusive terms, granting, for example, an exclusive license to a downstream company to develop a particular therapeutic product based on a particular genetic target.[64] This is not altogether unreasonable; precision medicine is fraught with uncertainty and failure.[65] Translating what works on LocusZoom—a popular statistical genetics program—into what works in the clinic requires clinical validation and testing, often at an expense of hundreds of millions of dollars.[66] Downstream developers typically balk at conducting such work without some form of exclusive licensing to allow them to recoup these significant up-front costs.[67]

The potential problem with this arrangement—both in the precision medicine context and others—lies in *how much* exclusivity is granted. Exclusive rights beyond those necessary to develop a particular product are a deadweight loss: society will pay a higher price for the end therapeutic product beyond that necessary to bring it to market.[68] If a nonexclusive license would have sufficed, by contrast, this means that other developers did not have the opportunity to enter—

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[62] *See id.* at 1910–1913 (discussing the dilemma in relation to IBM's gargantuan patent estate).

[63] *See id.* Perhaps ironically, this is notable in the CRISPR context: both UC and the Broad Institute are depositors with AddGene, a non-profit repository of CRISPR constructs, made cheaply available to academic researchers, and licensed to them nonexclusively using a standard license, the Uniform Biologic Materials Transfer Agreement. *See* Sherkow, *supra* note 32, at 173.

[64] Carter-Johnson et al., *supra* note 35, at 102–103.

[65] *See* Cassandra Willyard, *Auctioning the Cure*, 17 NATURE MED. 528, 529 (2011) (discussing the commonness of exclusive licenses in precision medicine).

[66] Nicholas J. Schork, *Time for One-Person Trials*, 520 NATURE 609, 611 (2015) ("[C]onventional phase III [clinical] trials . . . can cost between $100 million and $700 million per drug.").

[67] *See* Willyard, *supra* note 65, at 529 (interviewing patent licensors for such a perspective).

[68] Ian Ayres & Lisa Larrimore Ouellette, *A Market Test for Bayh–Dole Patents*, 102 CORNELL L. REV. 271, 284 (2016),; Jerome H. Reichman, Comment, *Compulsory Licensing of Patented Pharmaceutical Inventions: Evaluating the Options*, 37 J.L. MED. & ETHICS 247, 252 (2009) ("[A]s James Love famously observed, deadweight loss tends over time to become dead bodies.").

or at least attempt to enter—the product market.[69] By the same token, exclusivity also deprives the public of the benefit of having multiple firms "race" to develop and test new products, the diversity of pharmaceutical compositions or dosing regimens for the same product, and the differences in approved indications or treatment subclasses.[70] Broad exclusive licenses can thus bottleneck commercial research.[71]

Exclusive surrogate licenses pose particular problems in the precision medicine context. Precision medicine therapy often operates on few genes—if not individual gene variants—as evidenced by Keytruda, Kymriah, and patisiran. Keytruda works by targeting a single protein, PD-L1, expressed on tumor surfaces.[72] Patisiran consists of an RNA molecule that binds, specifically, to a single variant of the TTR gene.[73] And Kymriah is truly specific—a cell therapy designed for each separate instance of treatment to recognize a single variant of CD-19, and unique to each individual patient.[74] Surrogate licenses, however, have been drawn to human therapeutics writ large—to all 19,000-plus known human genes and their attendant medical conditions both known and unknown.[75] Even with the responsibility to sublicense the technology to other competitors, this exclusive grant is far beyond what any surrogate requires to be "induced" to engage in the commercial development of a precision therapy.[76] Competitive, commercial research in related genetic areas—therapies directed to different alleles of the same gene or targets directed to differing points in a protein's cellular pathway—stand to suffer.[77]

The common rejoinder to this criticism is that surrogate companies are expected (and have incentives) to sublicense their rights to others in areas not currently being pursued by the surrogate.[78] This responsibility—at its best—should therefore leave the field open to the rest of the industry, negating the impact of the interposition of the surrogate between the university and

[69] Ayre & Ouellette, *supra* note 68, at 284. This assumes, of course, that other products cannot be substitutes, an assumption that—frankly—may not be an accurate description of reality. In truth, this is an immensely complex question that turns, in part, on a product's indication, physician off-label prescription, and second-order pricing controls, like rebates and insurance coverage—to name just a few of the inputs that go into the question of whether two therapeutic products are really "substitutable" in any economic sense. For purposes of this paper, and for simplicity, we rest on the classical notion that the only true substitutes for a product are generic versions of the same product.

[70] *See* Emily Marden, *Open Source Drug Development: A Path to More Accessible Drugs and Diagnostics?*, 11 MINN. J.L. SCI. & TECH. 217, 251–252 (2010) (comparing this "race" model in open source development to drug development, and noting that its advantages include "multiple decentralized nodes, minimizing space and equipment costs . . . [where] progress is made via the cumulative, potentially more creative, efforts of the participants").

[71] Contreras & Sherkow, *supra* note 7, at 698.

[72] Keytruda Approval Letter, *supra* note 1.

[73] *See* David Adams, Ole B. Suhr, Peter J. Dyck, William J. Litchy, Raina G. Leahy, Jihong Chen, Jared Gollob & Teresa Coelho, *Trial Design and Rationale for APOLLO, a Phase 3, Placebo-Controlled Study of Patisiran in Patients with Hereditary ATTR Amyloidosis with Polyneuropathy*, 17 BMC NEUROLOGY 181, 181 (2017).

[74] Kymriah Approval Letter, *supra* note 2.

[75] *See, e.g.*, Contreras & Sherkow, *supra* note 7, at 698 (documenting this in the CRISPR context).

[76] *See* Michael Abramowicz & John F. Duffy, *The Inducement Standard of Patentability*, 120 YALE L.J. 1590, 1597–98 (2011) (tying the inducement of a patent to deadweight loss in its absence).

[77] *See* Contreras & Sherkow, *supra* note 7, at 699 (describing these difficulties in the CRISPR CAR-T space); Charlie Schmidt, *Negotiating the RNAi Patent Thicket*, 25 NATURE BIOTECH. 273, 273 (2007) (describing Alnylam's licensing position for RNAi).

[78] Contreras & Sherkow, *supra* note 7, at 699; *see also Information About Licensing CRISPR Genome Editing Systems*, BROAD INSTITUTE, https://www.broadinstitute.org/partnerships/office-strategic-alliances-and-partnering/information-about-licensing-crispr-genome-edi [hereinafter Broad Institute Licensing Statement].

the rest of the industry.[79] But this does not hold in practice. The surrogate arrangement—by design—makes surrogates competitors with the same companies to which they are expected to offer sublicenses.[80] This creates some obvious conflicts between surrogates and their potential sublicensees that counsel against favorable licensing: restrictions on entry, patent litigation, and former employee non-compete agreements are but a few examples.[81]

These conflicts are particularly problematic in the context of precision medicine, where multiple companies often pursue different strategies to tackle the same genetic problem. Juno Pharmaceuticals, for example—a sublicensee of the Broad Institute's surrogate Editas—has been engaged in patent litigation with Kite Pharmaceuticals concerning one particular aspect of chimeric antigen receptor T-cell therapy, or CAR-T, the underlying technology behind Kymriah.[82] And BioMarin Pharmaceutical and Sarepta Therapeutics—two companies exploring differing approaches to modifying *DMD*, a gene, certain variants of which give rise to forms of muscular dystrophy—have fought fiercely over patent claims to broaden implementations of their respective therapies.[83] These cases suggest that surrogates, far from treating competitors as friendly occupants of unrelated therapeutic niches, view their rivals as challengers to their territories. In the extreme, surrogates' quashing of competition runs the risk of reducing overall welfare.[84]

To their credit, some research institutions have attempted to guard against such behavior. The Broad Institute, for example, has reserved for itself an "escape hatch" of sorts in its license to Editas.[85] Were a competitor of Editas to petition the Broad Institute to license aspects of the CRISPR patents developed by Editas, Editas could not prevent the transaction unless it demonstrated it was actively developing a therapy concerning the same target or had plans to do

[79] *See* Broad Institute Licensing Statement, *supra* note 78 ("The goal of our inclusive innovation model is to enable Editas to devote sufficient investment to develop CRISPR-based genome editing technology to treat human diseases, while supporting broad development of medicines to reach many patients.").

To offer a broader, numerical example: Suppose that there are 100 realistic drug targets contained within the field and twenty companies that could feasibly develop them. If the university were to grant licenses directly to qualified developers and assuming a superhuman technology licensing office, it could conceivably license all 100 targets to the twenty industry participants. This will result in R&D programs for each of the 100 targets. Now, however, suppose that the university licenses all 100 targets to one surrogate company. The surrogate believes that it can successfully develop five targets. It is thus in the surrogate's interest to sublicense the remaining ninety-five targets to other industry participants, each of which is also equipped to develop five targets. The net result is that all 100 targets are licensed, and overall welfare remains the same.

[80] Contreras & Sherkow, *supra* note 7, at 699.

[81] *Id.* To further our numerical example, let us suppose these conflicts would potentially reduce the overall pool of licensees from twenty to, say, fifteen (a reduction of 25%). As a result, the surrogate might not be able to license all ninety-five remaining targets for development. Reducing the licensable targets proportionally, let us assume that only seventy-one targets (75% of the ninety-five remaining targets) are licensed. While the competitive advantage to the surrogate may be increased, overall social welfare is reduced because twenty-four targets are no longer being developed.

[82] *See* Complaint, Juno Therapeutics, Inc. v. Kite Pharma, Inc., No. 2:17-cv-6496 (C.D. Cal. Sept. 1, 2017). Interestingly, Juno's license from Editas actually operates as a cross-license to Juno's CAR-T technology, raising additional potential conflicts concerning the breadth of its license.

[83] *See* Complaint, Univ. of W. Austr. v. Academisch Ziekenhuis Leiden, No. 1:16-cv-109 (D. Del. Feb. 25, 2016) (listing Sarepta and Biomarin as co-plaintiffs and co-defendants, respectively).

[84] Continuing our numerical example: Assume that instead of reserving for itself the five targets that it can feasibly develop, the surrogate decides to reserve for itself ten targets, even though development programs for the last five cannot possibly be commenced for at least several years. This brings the total number of targets available to the field down from ninety-five to ninety, at best delaying the development of five potentially valuable therapies.

[85] *See* Broad Institute Licensing Statement, *supra* note 78.

so.[86] But "active development," not to mention plans to develop, are boundless concepts subject to the vagaries of science, funding, and the manner in which investigators *view* their research at the time. Furthermore, the license is unclear as to how disputes concerning the interpretation of "active development" are to be resolved.[87] The Broad Institute's "clawback" model appears, on its face, to be a good faith attempt to check the indulgences of its surrogate licensee, but it is incomplete and leaves significant discretion to the surrogate itself.

Lastly, surrogate licensing, even if well-intentioned and narrowly tailored today, may become overly broad tomorrow as the science of precision medicine develops. Novartis's approval of Kymriah, for example, comes on the heels of failures by Juno, including the unexpected death of a number of subjects in clinical trials.[88] As CAR-T develops, researchers are beginning to learn the complexities of genetically optimizing the technology, put on kaleidoscopic display by the Adaptive Immune Receptor Repertoire (AIRR), a robust database of such variation.[89] An exclusive license to a single developer to use CAR-T against, say, the CD28 protein—while seemingly narrow several years ago—may now seem like a massive fiefdom. It may therefore be unclear how scientifically narrow a particular precision medicine product must be to develop future therapies, and broad, exclusive surrogate licenses do this little favor. Surrogates are simply ill-equipped—and poorly incentivized—to assess the appropriate level of exclusivity for tomorrow's downstream applications.[90]

C. Institutional Mission Erosion

If the development of precision medicine is the ideal union between universities' educational and research missions, surrogate licensing seems to erode them both. Most research universities and institutions operate under charters that embody a variety of missions directed to the public good: the education of students, the expansion of knowledge through research, the alleviation of human suffering, the fostering of economic growth, or other means for improving overall social welfare.[91] These public-spirited goals affect many aspects of institutional governance and

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[86] *See id.*

[87] Contreras & Sherkow, *supra* note 7, at 700.

[88] Alex Lash, *After Trial Deaths, Juno Pivots and Scraps Lead CAR-T Therapy*, EXOME, (Mar. 1, 2017) https://www.xconomy.com/seattle/2017/03/01/after-trial-deaths-juno-pivots-and-scraps-lead-car-t-therapy/.

[89] Felix Breden, Eline T. Luning Prak, Bjoern Peters, Florian Rubelt, Chaim A. Schramm, Christian E. Busse, Jason A. Vander Heiden, Scott Christley, Syed Ahmad Chan Bukhari, Adrian Thorogood, Frederick A. Matsen IV, Yariv Wine, Uri Laserson, David Klatzmann, Daniel C. Douek, Marie-Paule Lefranc, Andrew M. Collins, Tania Bubela, Steven H. Kleinstein, Corey T. Watson, Lindsay G. Cowell, Jamie K. Scott & Thomas B. Kepler, *Reproducibility and Reuse of Adaptive Immune Receptor Repertoire Data*, 8 FRONTIERS IMMUNOLOGY art. 1418, at 1 (2017).

[90] Contreras & Sherkow, *supra* note 7, at 700. Beyond the CRISPR setting, another telling example concerns the licensing of DNA diagnostic patents. The University of Michigan, which isolated and patented the *CFSR* gene responsible for cystic fibrosis, broadly licensed its *CFSR* patent at minimal cost. The University of Utah, which obtained patent rights covering the *BRCA1/2* genes indicating breast and ovarian cancer, exclusively licensed its patents covering these genes to Myriad Genetics, which monopolized the market for BRCA diagnostic testing for fifteen years (until the patents were invalidated by the Supreme Court). *See* Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013); DEP'T OF HEALTH & HUMAN SERVS., THE INTEGRATION OF GENETIC TECHNOLOGIES INTO HEALTH CARE AND PUBLIC HEALTH A PROGRESS REPORT AND FUTURE DIRECTIONS OF THE SECRETARY'S ADVISORY COMMITTEE ON GENETICS, HEALTH, AND SOCIETY (Jan. 2009), https://osp.od.nih.gov/wp-content/uploads/2013/11/SACGHS%20Progress%20and%20Priorities%20Report%20to%20HHS%20Secretary%20Jan%202009.pdf.

[91] *See* Scott, *supra* note 52, at 30–33.

operation, including the development and exploitation of IP.[92] As observed by the National Academies of Science,

> Universities have a lengthy track record of providing dynamic environments for generating new ideas and spurring innovation, and for moving advances in knowledge and technology into the commercial stream where they can be put to work for the public good . . . .[93]

Along these lines, in 2007 a group of prominent research universities, including Harvard, MIT and UC Berkeley, developed a set of guidelines to reconcile university IP licensing practices with their public missions.[94] The resulting document, *In the Public Interest: Nine Points to Consider in Licensing University Technology*, addresses a broad range of university IP management and licensing issues, such as the preservation of academic research rights, meeting the medical needs of neglected populations, and promoting fair licensing principles to encourage their technologies' broadest dissemination.[95] The *Nine Points* document has now been signed by more than 100 universities and research institutions around the world.[96]

But *Nine Points* is an ideal, not a command, and universities have concurrently aspired to and violated its principles.[97] What's more, the *Nine Points* in no way bind university surrogates in letter or spirit.[98] It is expected, in some instances, for university licensees to develop university technology with an eye toward profit, indifferent to any social consequences.[99] Commercial licensees have, indeed, used university technology to develop tobacco products, surveillance dragnets, and instruments of war.[100] Universities may wish to use the *Nine Points* principles to impose their values on licensees. But that—as with many university IP practices—depends on the desires of the licensees themselves.

In that vein, surrogate companies in the precision medicine space are not constrained by these public missions. Surrogates' decisions concerning which research to prioritize, how to protect their innovations, and to whom they should award sublicenses may not be not aligned with universities' broader commitments to the public. Sublicenses to develop a precision therapy targeting a gene variant prevalent in affluent countries may not, in fact, best serve universities' commitments to treat neglected populations of disease sufferers. But they may be profitable.[101] Similarly, expensive

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[92] *See* In the Public Interest: Nine Points to Consider in Licensing University Technology, ASSOCIATION OF UNIVERSITY TECHNOLOGY MANAGERS (AUTM) (Mar. 6, 2007) http://www.autm.net/AUTMMain/media/Advocacy/Documents/Points_to_Consider.pdf [hereinafter Nine Points].

[93] NATIONAL RESEARCH COUNCIL, MANAGING UNIVERSITY INTELLECTUAL PROPERTY IN THE PUBLIC INTEREST 14 (Stephen A. Merrill & Anne-Marie Mazza eds., 2011).

[94] Nine Points, *supra* note 92.

[95] *Id.*

[96] Signatories, AUTM, https://www.autm.net/advocacy-topics/government-issues/principles-and-guidelines/nine-points-to-consider-when-licensing-university/ [https://perma.cc/RF5F-A7BE].

[97] *See* Mark A. Lemley, *Are Universities Patent Trolls?*, 18 FORD. INTELL. PROP. MEDIA & ENT. L.J. 611, 611 (2007) (noting that universities may be bad actors in the patent system despite their ideals).

[98] That is, the Nine Points apply only to universities—not their licensees.

[99] *See* Lemley, *supra* note 97, at 611.

[100] *See, e.g.*, U.S. Patent No. 9,560,830 (claiming hybrid tobacco plants and assigned to North Carolina State University); U.S. Patent No. 7,095,027 (claiming an infrared remote sensing system for military applications, and assigned to the University of Central Florida Research Foundation, Inc.); U.S. Patent No. 7,609,743 (claiming a robust laser for military purposes, and assigned to the University of Central Florida Research Foundation, Inc.).

[101] *See* Jacob S. Sherkow, *CRISPR, Patents, and the Public Health*, 90 YALE J. BIOL. & MED. 607 (2017) (discussing this problem in the CRISPR context).

patent litigation and prosecution practice may run counter to universities' desires to engage in precision medicine's ideal of data-sharing. But paying for lawyers does preserve marketable value.[102] Universities' initial decisions to grant broad, exclusive licenses to surrogates is a first step—a significant one—in universities' abdication of their responsibilities under the *Nine Points* for precision therapies.

More granularly, the relationship between universities' missions and surrogates' development of precision therapies for low-income populations is particularly fraught. The *Nine Points* require that "[u]niversities should strive to construct licensing arrangements in ways that ensure that . . . underprivileged populations have low- or no-cost access to adequate quantities of . . . medical innovations."[103] This commitment—which arose after some public ire against universities that failed to constrain their profit-seeking licensees—now characterizes many university licensing deals in the pharmaceutical sector.[104] But these development and cost decisions for precision therapies lay at the feet of the surrogates, not their parent universities. Surrogates are entrusted to make decisions concerning whether development targets will focus on underprivileged populations or typically privileged ones. And surrogates ultimately decide whether and to what extent they will mediate cost arrangements of developed therapies for the poor.[105] Surrogates may well act in the public interest in these regards. But they are obligated, as matter of first principles, to generate profits for their shareholders rather than hew to the public missions supported by documents like the *Nine Points*.[106]

Granting surrogate licenses for the development of precision therapies may also erode universities' broader educational missions. Universities often couch these aspirations in terms of the free and open dissemination of knowledge to the world.[107] Columbia University's Mission Statement, for example, states that it "expects all areas of the university to advance knowledge and learning at the highest level and to convey the products of its efforts to the world."[108] But surrogate licenses in the precision medicine context traditionally restrict this free and open exchange of information, especially for broader platform technologies.[109] In some cases surrogates vie to protect their valuable data as trade secrets.[110] And in others, surrogates impose significant restrictions on what data outside researchers can access and how the data can be used in further

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[102] *See* Sharon Begley, *CRISPR Patent Fight: The Legal Bills Are Soaring*, STAT NEWS (Aug. 16, 2016), https://www.statnews.com/2016/08/16/crispr-patent-fight-legal-bills-soaring/ [https://perma.cc/SGY3-RVG7] (quoting a representative from Editas as saying "Investing in intellectual property is one component how we are building the company to be a leader in genomic medicine.").

[103] Nine Points, *supra* note 92, at 8 (Point 9).

[104] In 2001, Yale University came under intense pressure by its students, alumni and the public after licensing its patents covering the antiretroviral AIDS drug stavudine to Bristol-Myers Squibb, which refused to make the drug available to thousands of patients in Africa. *See* Donald G. McNeil, Jr., *Yale Pressed to Help Cut Drug Costs in Africa*, N.Y. TIMES (Mar. 12, 2001).

[105] *See* Sherkow, *supra* note 101.

[106] Risa L. Lieberwitz, *The Marketing of Higher Education: The Price of the University's Soul*, 89 CORNELL L. REV. 763, 790 (2004) ("By adopting for-profit corporate structures, universities choose a corporate structure explicitly intended for the private financial interests of shareholders, whether the shareholders are venture capitalists or the university itself. Further, for-profit corporate partners and shareholders in university spinoff corporations become participants in the core university function of education.").

[107] Scott, *supra* note 52, at 30–33.

[108] *University Mission Statement*, COLUMBIA UNIVERSITY, https://www.columbia.edu/content/about-columbia [https://perma.cc/QHA3-JY6N].

[109] Breden, et al., *supra* note 89, at 1 (cautioning against this problem); *cf.* Lemley, *supra* note 48, at 621 (discussing this problem for platform nanotechnology).

[110] Guerrini, McGuire, & Majumder, *supra* note 58, at 586.

studies.[111] As with Hetionet, these restrictions can detrimentally affect scientific education.[112] Surrogates also have no obligation to engage in the most basic process of public education: publication in peer-reviewed scientific journals.[113] Outside researchers are therefore deprived of the best opportunities to learn, test, and critique surrogates' research.[114] Broad licenses to surrogates ultimately cast a pall over the bright lights of universities' scientific and educational missions.

D. Health Care Costs

Universities may also be victims of their surrogates' successes: by furthering the marketability of profitable precision therapies, surrogates' development work may well contribute to increased health care costs. These increases are linked to a series of more complex issues governing drug pricing, therapeutic value, and insurance coverage.[115] But surrogates—as opposed to restrictive university licensing—can exacerbate the rush to develop high-cost precision therapies.[116]

It is important to understand, first, that while precision medicine seeks to improve clinical outcomes, such improvements do not necessarily bring cost savings.[117] Patients that once had meager options to manage their illnesses may now have the opportunity to pay—in some instances, dearly—for treatment.[118] In other cases, illnesses that were previously treated with inexpensive palliative care may now have expensive therapies that can manage or even cure their underlying etiologies.[119] A telling example concerns fetal fibronectin: Prior to the development of a test for fetal fibronectin—a protein of some value in assessing the chances of preterm birth—expectant mothers were subject to a cheap, albeit inaccurate, vaginal exam, including a transvaginal cervical

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[111] Sherkow, *supra* note 6, at 356–57 (discussing canCORS).

[112] Oxenham, *supra* note 59, at 16.

[113] By way of example, a recent search on PubMed, the NIH's scientific paper database, showed that Intellia Therapeutics—the exclusive sublicensee of Caribou Biosciences, UC Berkeley's surrogate for CRISPR applications in humans—has only two scientific papers to its credit, neither about CRISPR. *See* Thomas J. Povsic, Timothey D. Henry, Jay H. Traverse, F. David Fortuin, Gary L. Schaer, Dean J. Kereiakes, Richard A Schatz, Andreas M. Zeiher, Christopher J. White, Duncan J. Stewart, E. Marc Jolicoeur, Theodore Bass, David A. Henderson, Patricia Dignacco, Ziangoiong Gu, Hussein R. Al-Khalidi, Candice Junge, Adel Nada & Douglas W. Losordo, *The RENEW Trial: Efficacy and Safety of Intramyocardial Autologous CD34$^+$ Cell Administration in Patients With Refractory Angina*, 9 JACC: CARDIOVASCULAR INTERVENTIONS 1576 (2016); *see also* Zhiji Ren, Isana Veksler-Lublinsky, David Morrissey, Victor Adams, *Staufen Negatively Modulates MicroRNA Activity in* Caenorhabditis elegans, 6 G3 1227 (2016).

[114] *See* Spencer Phillips Hey & Aaron S. Kesselheim, *Countering Imprecision in Precision Medicine*, 353 SCIENCE 448, 448 (2016) (arguing that precision medicine is only advanced through disclosure and validation).

[115] *See* Rachel Sachs, Nicholas Bagley & Darius N. Lakdawalla, *Value-Based Pricing For Pharmaceuticals In The Trump Administration*, HEALTH AFFAIRS BLOG, (Apr. 27, 2017) https://www.healthaffairs.org/do/10.1377/hblog20170427.059813/full/ [https://perma.cc/4H4Q-J39J] (discussing some of the many drug pricing levers).

[116] Sherkow, *supra* note 101101, at 4.

[117] *See* Joanna C.D. Willis & Graham M. Lord, *Immune Biomarkers: The Promises and Pitfalls of Personalized Medicine*, 15 NATURE REV. IMMUNOLOGY 323, 327 (2015) ("[N]ot all potential immune biomarkers will satisfy health economists in terms of attractive cost- benefit ratios.").

[118] *Id.* ("[N]ovel therapeutic agents for which biomarkers are being developed are extremely expensive; a single course of ipilimumab for the treatment of melanoma costs approximately US $120,000."). The current sticker price for Kymriah is $475,000. Sy Mukherjee, *Is $475,000 Too High a Price for Novartis's "Historic" Cancer Gene Therapy?*, FORTUNE (Aug 31, 2017) http://fortune.com/2017/08/31/novartis-kymriah-car-t-cms-price/ [http://perma.cc/T9J8-XGTL] .

[119] *See* Jameson & Longo, *supra* note 9, at 2229 (discussing precision medicine's cost increases).

measurement.[120] This standard intervention cost pennies per patient; the fetal fibronectin test, by contrast, cost one hospital system $225 per patient.[121] To be clear, the value of precision medicine is a human one—improving health and saving lives—but its cost may be also be high.

Developing precision medicine through surrogate companies—rather than direct university licensing—may exacerbate these cost increases. Surrogates, like other for-profit therapeutic developers, are strongly encouraged to develop revenue-maximizing therapeutic products—therapies that afflict large numbers of patients who can afford treatment.[122] Because surrogate licenses from universities do not, typically, include pricing controls, surrogates may chase therapies on which they can pin high price tags.[123] Two of the CRISPR surrogates—Editas Medicine and Intellia Therapeutics—provide illuminating examples. Editas's primary research platform concerns Leber Congenital Amaurosis, a congenital form of blindness that affects between 3,000 and 6,000 Americans.[124] At a cost of $100,000 per course of treatment, the therapy has a potential market of $3 billion. Other precision medicine ocular treatments—such as Spark Therapeutics' soon-to-be-approved $1 million treatment for inherited retinal disease—could result in markets in the tens of billions.[125] Intellia, meanwhile, has focused on curing sickle-cell anemia, an illness that afflicts roughly 100,000 Americans,[126] and for which the few treatment options—such as hydroxyurea—cost around $1.50 per 500 mg dose,[127] which could yield large profits through its broad reach.

Beyond this intersection, between clinical utility and commercial profitability, surrogates' sublicensing agreements are also expected to be profit maximizing. In the precision medicine context, this may result in layers of sublicenses—each predicated, perhaps, on different genes or disease indications—and all of which are designed to return the maximum possible revenues upon product approval.[128] Payers, therefore, would be paying drug prices set to maximize royalties on at least two fronts: the sublicense to the surrogate, and the surrogate's license to the university.[129] As explored in a loosely analogous context, a series of profit-maximizing sublicenses can create systems of "royalty stacking," ultimately creating end products far more expensive than their cost

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[120] *See, e.g.*, A. Sullivan, N.A. Hueppchen & A.J. Satin, *Cost Effectiveness of Bedside Fetal Fibronectin Testing Varies According to Treatment Algorithm*, 10 J. MATERNAL FETAL MED. 380, 380 (2001).

[121] *Id.*

[122] *See* Contreras & Sherkow, *supra* note 7, at 700.

[123] *Id.*

[124] *See Eye Diseases*, EDITAS MEDICINE, http://www.editasmedicine.com/areas-of-research/eye-diseases [https://perma.cc/33SY-ZB9Y]; *see also* Rando Allikmets, *Leber Congenital Amaurosis: A Genetic Paradigm*, 25 OPTHALMIC GENETICS 67, 67 (2004).

[125] See Emma Court, *Spark Therapeutics' Promising Gene Therapy for Vision Loss Could Cost $1 Million*, MARKETWATCH, (Oct. 16, 2017 8:35 AM ET), https://www.marketwatch.com/story/spark-therapeutics-promising-gene-therapy-for-vision-loss-could-cost-1-million-2017-10-13 [https://perma.cc/XKK8-DUF7].

[126] Emily Mullin, *Sickle-Cell Patients See Hope in CRISPR*, MIT TECH. REV., Aug. 23, 2017, https://www.technologyreview.com/s/608641/sickle-cell-patients-see-hope-in-crispr/ [https://perma.cc/Q6QY-Z62S].

[127] Richard D. Moore, Samuel Charache, Michael L. Terrin, Franca B Barton & Samir K Ballas, *Cost-Effectiveness of Hydroxyurea in Sickle Cell Anemia*, 64 AM. J. HEMATOLOGY 26, 28 (2000).

[128] *Cf.* Mark A. Lemley & Carl Shapiro, *Patent Holdup and Royalty Stacking*, 85 TEX. L. REV. 1991, 1992–1993 (2007) (noting this phenomenon—royalty stacking—in the wireless communications and other technology markets).

[129] This assumes, of course, that the ultimate retail or sticker price paid by payers is a function of these inputs—not simply a single profit maximizing price independent of input. We recognize this is a hotly contested issue in the health economics literature, but do not go into it in more detail here.

of development or production would suggest.[130] Surrogates' profit motivation in sublicensing, therefore, also has the potential to contribute to rising health care costs.[131]

IV. Recommendations for Patent Licensing in Precision Medicine

The issues raised by surrogate licensing for precision medicine should give research institutions cause to rethink such licenses. Given the potential value of precision therapies and universities' broad patent estates in the field, we make several recommendations to better align university patenting licensing with the realities of commercially developing precision therapies: restrictions on exclusive licenses or "claw back" clauses; fair pricing requirements on end products developed from university patent grants; and commitments to data sharing.

A. Exclusivity Restrictions and Claw Back Provisions

When licensing precision medicine IP to for-profit companies, universities and other non-profit research institutions should ensure that they retain rights to make such technology available, in a manner necessary to fulfill their public missions. We believe this can be accomplished in two non-mutually exclusive ways. The first concerns the restriction of exclusive licenses in the first instance. While surrogate licensing presents some potential efficiencies for university management of IP, as discussed above, these exclusive licenses can be overly broad—beyond any commensurate level of efficiency or inducement to develop a specific precision therapy.[132] Solving this problem lies in constructively abandoning the surrogate model—granting companies only the exclusivity they need to develop a particular therapy. As a further inducement, such limitations could be coupled with rights of first refusal on other licenses for specific therapies, assuming the licensee can demonstrate that it is actually furthering development. In other instances, where it does appear that a licensee could effectively develop a technology with a nonexclusive license, universities should readily use such licenses, as Stanford and UCSF famously did for recombinant DNA technology patents in the 1980s.[133] In the precision medicine field, nonexclusivity has the benefit of allowing other nonexclusive licenses elsewhere to ameliorate scientific or regulatory deficiencies in a single company's approach to a specific genetic target or disease indication.[134] Parceling off licenses—exclusive or otherwise—at the university, rather than the surrogate level, better enables universities to fulfill their own public missions.

But even with a surrogate licensing model, universities should structure their licenses to enable them to "claw back" disease indications or genes that are being insufficiently developed by the surrogate. In the CRISPR context, this is akin to the Broad Institute's rights of "relicensing" with

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[130] Lemley & Shapiro, *supra* note 128, at 1992–1993.

[131] *Cf.* Lisa Larrimore Ouellette, Note, *How Many Patents Does It Take to Make a Drug? Follow-On Pharmaceutical Patents and University Licensing*, 17 Mich. Telecomm. & Tech. L. Rev. 299, 307–308 (2010) (discussing the relationship between exclusive patent licenses and drug pricing).

[132] *See* Contreras & Sherkow, *supra* note 7, at 699.

[133] Sally Smith Hughes, *Making Dollars out of DNA: The First Major Patent in Biotechnology and the Commercialization of Molecular Biology, 1974-1980*, 92 Isis 541, 564 (2001).

[134] *Cf.* Marden, *supra* note 70, at 271–272; Ayres & Ouellette, *supra* note 68 (proposing a "market test" to determine whether federally-funded discoveries should be licensed exclusively or non-exclusively); Ana Santos Rutschman, *IP Preparedness for Outbreak Diseases*, 5 UCLA L. Rev. (forthcoming 2018) (suggesting non-exclusive licenses for vaccine development).

Editas, its surrogate.[135] At the same time, such claw back provisions—for what we think are obvious reasons—should not rest entirely on the surrogate's discretion, nor be based solely on the surrogate's own descriptions of the state of its work, or the promises of its success. Retaining an automatic right to reenter areas of the licensed field that the surrogate is not currently working could ensure that universities take seriously the stewardship of their IP, in a manner that is consistent with their public missions.

B. Fair Pricing Requirements

Particularly with respect to precision medicine, universities and other non-profit research institutions should ensure that their IP licensees are bound to price resulting products and treatments in a manner that reasonably affords access to patients. The current pricing system of precision therapies is profit-maximizing; untethered to real costs of the development of any given therapy.[136] For non-essential goods, like video games and sports drinks, this has little effect on universities' greater missions to the public.[137] But for essential goods, like life-saving medical treatments, this brings universities' greater ethical commitments to bear. Importantly, such ethical restrictions have been important features of university licensing in other areas.[138] The Broad Institute's license of its CRISPR patents to Monsanto, for example, prohibits Monsanto from enforcing the use of its covered technology against individual farmers.[139] Other university licenses, in line with the *Nine Points* (Point 9), require that pharmaceuticals be made available for compassionate use, or in developing countries.[140] In a similar vein, universities could—and should—require licensees of their precision medicine IP to ultimately sell their products at "fair" prices, however defined.

Beyond individual cost concerns, there exist serious healthcare reimbursement and coverage concerns that restrictive price licensing could ameliorate. Glybera—a now-discontinued gene therapy that retailed for $1 million per patient while on the market—exemplifies these difficulties.[141] This principle is especially important given that many precision therapies, such as Kymriah, now sell for upwards of $400,000 a year.[142] These, frankly, are unsustainable prices for

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[135] Broad Institute Licensing Statement, *supra* note 78. At the same time, the terms of the clawback are imprecisely defined and likely easily worked around. Contreras & Sherkow, *supra* note 7, at 699.

[136] *See supra* note 129 and accompanying text.

[137] Interestingly, it is in fields such as these that market forces discipline the prices of university-licensed goods through competition. In areas such as pharmaceuticals, where patents grant real exclusivity over substantial fields of activity, the market cannot impose such pricing discipline. *See also supra* note 69 and accompanying text (concerning this article's interpretation of economic substitutes).

[138] *See* Christi J. Guerrini, Margaret A Curnutte, Jacob S Sherkow & Christopher T Scott, *The Rise of the Ethical License*, 35 NATURE BIOTECH. 22, 23 (2017) (discussing these restrictions regarding the Broad Institute's agricultural licenses with Monsanto).

[139] *Id.* Note, however, that this restriction mirrors an earlier pledge made by Monsanto itself with respect to its assertion of patents covering genetically-modified seeds against farmers who inadvertently infringed those patents. *See* Monsanto, *Monsanto's Commitment: Farmers and Patents*, (2017), https://monsanto.com/app/uploads/2017/05/monsantocommitmentfarmsersandpatents.pdf [https://perma.cc/QC29-N3AK]; *see also* Jorge L. Contreras, *Patent Pledges*, 47 ARIZ. ST. L.J. 543, 545–46 (2015) (discussing Monsanto's pledge).

[140] *See* Nine Points, *supra* note 92.

[141] *See* Antonio Regalado, *The World's Most Expensive Medicine Is a Bust*, MIT TECH. REV. (May 4, 2016) https://www.technologyreview.com/s/601165/the-worlds-most-expensive-medicine-is-a-bust/ [https://perma.cc/K65X-G7W7].

[142] *See* Mukherjee, *supra* note 117.

long-term public-payer funding, even if they are currently what the market will bear.[143] In their missions to the broader public, universities should ensure that products developed from their IP can be afforded by the public health system, writ large.[144] Given that much precision medicine technology is developed through academic institutions, those institutions' duty to better the public weal would be well-served by such restrictions.

C. Data-Sharing Commitments

When licensing precision medicine IP, universities and other non-profit research institutions should require that their licensees share any underlying research data with the scientific community. This first and foremost requires licensees to be involved in the scientific enterprise of publishing their results and broadly releasing underlying data for use by other researchers—without significant restrictions.[145] Some university licensees have indeed engaged in this practice, becoming significant contributors to the scientific literature.[146] At the same time, while we recognize that universities have both ethical and legal imperatives to maintain data integrity in ways that protect patient privacy, these concerns should not be a subtext for restricting the use of licensees' data in subsequent research. Deidentifying data is, indeed, difficult but several excellent models of the practice, including the Vanderbilt Genome-Electronic Record project, exist and are ripe for adoption by licensees.[147] Likewise, licensees should not—in an effort solely to preserve market value—restrict access to data more than their parent universities would. Given that many universities' principal goals center on the dissemination of basic information, such data sharing practices best align universities' virtues with their licensees' behavior.

CONCLUSION

Precision medicine—the translation of patient-specific information into patient-specific therapy—presents numerous challenges to both clinical practice and intellectual property management. Universities, as the gatekeepers to much of the foundational IP in this area, have a special responsibility to ensure that precision therapies are developed broadly, and on reasonable terms, for the public. By abdicating that responsibility to surrogate companies, universities threaten

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[143] *See* Nicholas Bagley, *Medicaid Programs Can't Withhold a Hep C Cure.*, INCIDENTAL ECONOMIST, (June 1, 2016, 9:41 AM) https://theincidentaleconomist.com/wordpress/medicaid-programs-cant-withhold-a-hep-c-cure/ [https://perma.cc/P8ZQ-TJ6J] (describing this problem for Solvadi); *see also* Sean M. Flynn, Aidan Hollis & Mike Palmedo, *An Economic Justification for Open Access to Essential Medicine Patents in Developing Countries*, 37 J.L. MED. & ETHICS 184, 184 (2009) (elucidating, and criticizing, economic model for drug pricing that yields highest profits when drugs are priced at such a level that they are affordable only to a small fraction of the population).

[144] Commitments to fair and reasonable drug pricing are already being made by pharmaceutical companies in the wake of recent public outcry and political saber-rattling. *See, e.g.*, Brett Saunders, *Our Social Contract with Patients*, ALLERGAN CEO BLOG (Sep. 6, 2016) https://www.allergan.com/news/ceo-blog/september-2016/our-social-contract-with-patients [https://perma.cc/HN5A-QRX9] ("We commit to making . . . branded therapeutic treatments accessible and affordable to patients.").

[145] Victoria Stodden, *The Legal Framework for Reproducible Scientific Research: Licensing and Copyright*, 11 COMPUTING SCI. ENG'R 35, 36 (2009).

[146] Genentech, for example—one of Stanford and UCSF's licensees—is proud of its scientific publishing, listing more than 10,000 scientific articles published by its researchers. *Publications*, GENENTECH, https://www.gene.com/scientists/publications [https://perma.cc/U5F2-A46D].

[147] Grigorios Loukides, Aris Gkoulalas-Divanis & Bradley Malin, *Anonymization of Electronic Medical Records for Validating Genome-Wide Association Studies*, 107 PROC. NAT'L ACAD. SCI. USA 7898, 7898 (2010).

to limit the very public missions they strive to achieve. Developing precision medicine upon the foundation of university IP will likely require restrictions on the breadth and exclusivity of surrogate licenses and a commitment to making the knowledge generated by the licensees available to all.