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INTRODUCTION

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Innovation breeds uncertainty. New health technologies often promise to revolutionize medical care by improving outcomes[1] and empowering patients.[2] Yet for all their alleged benefits, these new tools always carry risks — some known, others not. This precariousness raises questions for both medicine and law. Nowhere is the problem of medical and legal uncertainty clearer than in the context of emerging genetic technologies, where the science outpaces both integration into clinical care and regulation. Consider polygenic risk scores ("PRSs"), which use big data analytics to predict the genetic risk of complex conditions.[3] Researchers hope that these tools could help physicians detect, delay, or even prevent the onset of disease.[4] However, PRSs are so new that no medical consensus exists regarding how to incorporate them into clinical practice.[5] This medical uncertainty creates legal uncertainty. Should agencies like the Food and Drug Administration ("FDA") rely on existing frameworks to regulate PRSs or adopt new ones? How should patients negotiate the uncertainty of new technologies like PRSs for purposes of informed consent? And, if a patient brings an unsolicited PRS to their appointment, does their doctor commit malpractice by disregarding it during treatment?

Like so many new technologies, one assumption behind PRSs is that more information is always better. Ironically, however, more data

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1. *See* Jin K. Park & I. Glenn Cohen, *The Regulation of Polygenic Risk Scores*, 38 HARV. J.L. & TECH. 377, 382–83 (2024) (describing the potential value of PRSs).

2. *See* Teneille R. Brown, *The Opposite of Empowering*, 38 HARV. J.L. & TECH. 501 (2024); Leah R. Fowler, *The Appification of Genetic Risk*, 38 HARV. J.L. & TECH. 479 (2024) (both explaining narratives around how consumer-generated PRSs are empowering to refute those claims).

3. Park & Cohen, *supra* note 1, at 381 (explaining how PRSs are calculated).

4. *Id.*

5. Jessica L. Roberts & Sonia M. Suter, *Damned If You Do or Damned If You Don't: The Medical Malpractice Implications of Consumer-Generated Polygenic Risk Scores*, 38 HARV. J.L. & TECH. 417, 427 (2024) (describing the lack of a standard of care regarding how to integrate PRSs into medical practice).

can generate more uncertainty.[6] For example, in the context of reproduction, should fertility patients rely on polygenic or other predictive information when deciding among embryos? And if so, should they be nudged to choose the allegedly healthiest embryo, or should they also have the option to select *for* genetic risk to increase the chance that they have a child with a disability? And although PRSs have yet to be widely incorporated into clinical care, patients can buy them directly from consumer health technologies companies.[7] Again, the belief is that access to information empowers.[8] However, those companies may promote products that oversimplify or miscommunicate information, and their focus on genetics and other high-tech explanations for health problems can obscure the role of social factors, like access to nutritious food or affordable housing.[9] What role should the law have in regulating consumer health technologies and the products that they offer?

Finally, PRSs and other emerging technologies have the power to shift our cultural norms, not only around our understanding of health but around our very humanity. Genetic information carries meaning across multiple dimensions, some scientific but others related to identity.[10] How should law- and policy-makers account for the multifaceted nature of this data when deciding how to regulate it? And are some questions better left unanswered? Researchers are already using the same techniques for generating PRSs for disease risk to calculate probabilities related to social and behavioral attributes.[11] While the accuracy of such calculations remains unknown, even if they were completely reliable, they could create or perpetuate discrimination and inequality. For instance, law enforcement might be tempted to rely on PRSs or other predictive tools to assess a person's likelihood of committing a crime.[12] Thus, the regulation of health technologies should not stop at the lab or the clinic. We must ask ourselves how medical and legal uncertainty affects us socially and consider the impact it may have on our culture and its existing hierarchies.

To tackle these questions and more, we assembled leading scholars in law, medicine, and ethics at Harvard Law School for the *Harvard*

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6. *See* Valerie Gutmann Koch, *Previvorship and Medical Uncertainty*, 38 HARV. J.L. & TECH. 401 (2024); Dov Fox, Sonia M. Suter, Meghna Mukherjee, Stacey Pereira & Gabriel Lázaro-Muñoz, *Choosing Your "Healthiest" Embryo After* Dobbs*: Polygenic Screening and Distinctive Challenges for Truth in Advertising and Informed Consent*, 38 HARV. J.L. & TECH. 463 (2024) (both describing how too much information can lead to choice overload).

7. Roberts & Suter, *supra* note 5, at 420.

8. Brown, *supra* note 2; Fowler *supra* note 2.

9. Brown, *supra* note 2; Fowler *supra* note 2.

10. Yaniv Heled & Liza Vertinsky, *Theory of Genetic Dimensions in the Law, Polygenic Risk Scores, and Reproductive Decision-Making*, 38 HARV. J.L. & TECH. 527, 542 (2024).

11. Shawneequa Callier & Anya E.R. Prince, *The Legal Uncertainties of Sociogenomic Polygenic Scores*, 38 HARV. J.L. & TECH. 553 (2024).

12. Natalie Ram, *Polygenic Scoring and the Criminal Legal System*, 38 HARV. J.L. & TECH. 577 (2024).

JOLT symposium on *Medical and Legal Uncertainty in Emerging Genetic Technologies*. We spent the day engaging across disciplines to discuss how to best respond to the many questions posed above. Our agenda consisted of four panel discussions: (1) Regulation and Liability, (2) Reproduction, (3) Consumer Technologies, and (4) Social Implications.

The first panel of the day considered how PRSs and similar technologies would fit into existing legal and regulatory frameworks. It began with *The Regulation of Polygenic Risk Scores* by Jin K. Park and I. Glenn Cohen, which offers a useful introduction to the science behind PRSs, explaining how PRSs calculate genomic risk for complex diseases.[13] However, given their novelty and complexity, PRSs might raise special concerns for regulators. Park and Cohen explain that, while many clinical tests have not undergone approval, the FDA has regulatory authority over genetic tests. Thus, it may seem that the agency could rely on its existing regimes and infrastructures with respect to PRSs. However, the authors propose that certain features of PRSs — while not all necessarily unique to PRSs — combine to demand a novel regulatory pathway. PRSs conceptualize risk differently than traditional genetic tests; their source data is currently evolving; there is no clear consensus on the methodology for calculating them; and the functionality of PRSs depends heavily on context. Park and Cohen, thus, advocate for a unified regulatory framework that increases the burden at either the approval or post-approval stage.

The second paper, *Previvorship and Medical Uncertainty* by Valerie Gutmann Koch, explores the uncertainty that patients encounter when confronted with genetic risk.[14] Because genetic tests and PRSs are predictive, not diagnostic, they communicate the probability of a disease, not its presence. Patients, when confronted with this information, must make decisions around screening, prevention, and even prophylactic treatment. However, Koch demonstrates that the current doctrine of informed consent fails to adequately account for uncertainty. She thus proposes Uncertainty Management Theory as an alternative standard to help address some of the uncertainties associated with genetic risk.

The final paper in the first panel was *Damned If You Do or Damned If You Don't: The Medical Malpractice Implications of Consumer-Generated Polygenic Scores* by Jessica L. Roberts and Sonia M. Suter.[15] Using consumer-generated PRSs as a case study, they explore the precarious position of doctors when patients bring unsolicited, unverifiable health-related information in the clinic. Many PRSs currently have

13. Park & Cohen, *supra* note 1.
14. Koch, *supra* note 6.
15. Roberts & Suter, *supra* note 5.

unknown predictive value and clinical utility, thus physicians lack reliable information regarding whether to integrate PRSs into their decision-making. Moreover, doctors can be held liable for malpractice for both action and inaction. Thus, depending on the circumstances, a physician could be sued for either considering or for ignoring an unsolicited PRS. And because the technology is so new, a standard of care for dealing with such situations has yet to develop. Research implies, however, that doctors may err on the side of considering PRSs, thus running the risk that overtreatment could become the professional custom. To avoid this outcome, the authors advocate for professional guidelines and physician immunity statutes to help doctors mitigate uncertainty.

The next pair of papers considers medical uncertainty in matters of law and reproduction. In *Selecting for Disability: How an Anecdote Can Inspire Regulation of Genetic Reproductive Technologies*, Doron Dorfman explores the ethics of offspring selection when fertility patients pick donors or embryos based on heritable characteristics that they would (or wouldn't) like to see in their kids.[16] He focuses on the particularly thorny question of choosing *in favor of* traits like deafness or dwarfism that, while many regard as undesirable, some people associate with their own familial or cultural belonging. Dorfman's point of departure is a 2002 case in which an American Deaf couple went public with their decision to have two deaf children by selecting a deaf donor. This case got global attention and inspired the United Kingdom's ban on selecting donors or embryos to favor any "serious" "impairment" that could be passed on to a resulting child. Dorfman rejects importing such a prohibition to the United States, especially in the wake of sweeping restrictions on reproductive freedom after the fall of *Roe v. Wade*. In connection with his broader research on moral panics around the meaning and significance of disability, he argues that selecting for disability doesn't warrant policy interventions because it is so rare and context dependent.

In *Choosing Your "Healthiest" Embryo After* Dobbs*: Polygenic Screening and Distinctive Challenges for Truth in Advertising and Informed Consent*, Dov Fox, Sonia M. Suter, Meghna Mukherjee, Stacey Pereira, and Gabriel Lázaro-Muñoz shift the conversation away from how prospective parents make these decisions to the ways in which companies and clinicians communicate with them about the techniques they would use.[17] They examine an emerging tool of prenatal selection called polygenic screening that analyzes embryos for enormous quantities of genomic information to generate risk scores for complex susceptibilities beyond simple one-gene disorders. They argue that this

16. Doron Dorfman, *Selecting For Disability: How an Anecdote Can Inspire Regulation of Genetic Reproductive Technologies*, 38 HARV. J.L. & TECH. 441 (2024).

17. Fox et al., *supra* note 6.

tool poses distinctive ethical and legal challenges for truth in advertising and informed consent. It's marketed directly to consumers, sometimes in ways that oversell its advantages and efficacy. Fertility patients are invited to "choose your healthiest embryo" and "protect your future child from genetic risks." The authors say that these claims trade on norms of children's health and good parenting and invite risks of decision fatigue and choice overload. They argue that inflated advertising could exacerbate other legal and social forces to expand its use after the fall of *Roe*.

The third panel examined the challenges of PRSs being offered directly to consumers. Leah R. Fowler presented her paper, *The Appification of Genetic Risk*, and Teneille R. Brown discussed her contribution, *The Opposite of Empowering*.[18] While both papers touch on the issue of obfuscation, they take contrasting perspectives. Fowler views "appification" as a reality and metaphor for direct-to-consumer PRSs. She argues that by design, presenting complex genetic data in app form creates difficulties in interpretation and limits genomic literacy and must be accounted for. Brown criticizes PRSs for promoting a neoliberal, individualistic approach that obscures the pressing need to address the social and environmental determinants of mental health. While Fowler suggests gaining a better understanding of the various sources of obfuscation in direct-to-consumer technologies could lead to improved products, Brown challenges the very development and marketing of PRSs, which she views as conveying false messages of empowerment rather than tackling the root societal and structural causes of mental illness.

The final set of papers explores the social implications of polygenic risk scores, including their use beyond the clinic. In *Theory of Genetic Dimensions in the Law, Polygenic Risk Scores, and Reproductive Decision-Making*, Yaniv Heled and Liza Vertinsky offer a model for identifying and balancing the varied interests that arise when polygenic risk scores are used in reproductive decision making.[19] They apply a conceptual framework for legally recognizing interests stemming from the multiple dimensions of genetics, developed in earlier work, to questions arising from the use of polygenic risk scores in preimplantation genetic testing. Heled and Vertinsky use their theory to explore a series of hypothetical scenarios, highlighting some of the complex legal questions that are likely to arise as polygenic preimplantation genetic testing moves rapidly from research to clinical use and even to consumer markets. This movement is already occurring — and doing so largely in the absence of public oversight despite the profound implications of such testing for a broad range of different stakeholders with competing and

18. Brown, *supra* note 2; Fowler, *supra* note 2.
19. Heled & Vertinsky, *supra* note 10.

sometimes conflicting interests. Heled and Vertinsky's approach serves as a roadmap that could assist and guide legal decision-makers' decisions on how best to respond to the questions that are likely to arise as polygenic testing continues to expand in scope and reach and its applications in preimplantation testing continue to proliferate.

In *The Legal Uncertainties of Sociogenomic Polygenic Scores*, Shawneequa Callier and Anya E.R. Prince consider a broad range of legal uncertainties that are likely to arise as polygenic risk scores are developed for "sociogenomic" traits.[20] "Sociogenomics" describes a growing field that seeks to identify polygenic scores for complex social and behavioral phenotypes, including "educational attainment, social mobility, well-being, risk-seeking behavior, and more." While proponents of sociogenomic PRSs envision their work improving our understanding of the interactions between genes and the environment to eventually create a more equitable world, Callier and Prince are less convinced, identifying reasons to worry that, given the problematic history of genomics, PRSs could lead to discrimination and inequality. They survey the interaction of sociogenomic PRSs and law across five domains: in vitro fertilization, anti-discrimination law, education, consumer genetic testing, and the criminal legal system. In so doing, Callier and Prince identify the current state of regulation and observe that many uses of sociogenomic PRSs are likely to lie beyond current legal frameworks. Moreover, across these domains, the fact that PRS models are constructed largely from genetic data from individuals of European ancestry both limits the reach of their validated benefits and risks imposing misidentification harms on those of other ancestral populations. Callier and Prince exhort policy makers to enact safeguards around sociogenomic PRS development and use, explaining that in the absence of such safeguards, it could harm vulnerable individuals both now and in the future.

Finally, in *Polygenic Scoring and the Criminal Legal System*, Natalie Ram zooms in on the possible use of PRSs in the criminal legal system, whether for identifying "high-risk" individuals for proactive surveillance or informing "recidivism risk scores" that may influence sentencing decisions.[21] Ram highlights two prior examples of science designed to predict violent or criminal behavior as a model for how law enforcement might want to incorporate behavioral PRSs into the criminal legal system. The first is the "candidate gene" era of behavioral genetics, in which researchers sought to associate a specific gene with a specific observed behavior — most famously, a variant of the MAOA gene and violence — which ultimately fell into disrepute due to methodological and other flaws. The second is the still-growing reliance on

20. Callier & Prince, *supra* note 11.
21. Ram, *supra* note 12.

recidivism risk assessment tools, that is, big data tools purporting to identify individuals at higher (or lower) comparative risk of reoffending. While Ram notes that PRSs might address some of the shortcomings of the candidate gene approach that proceeded them, she nonetheless identifies four reasons that PRSs might do more harm than good. PRSs do not tell a causal story; they are not intended for individual-level prediction; they are population specific and largely cannot at present be applied to populations of non-European ancestry; and they are black box tools, both because they are enormously complex and because they may well be developed as proprietary algorithmic systems. Ram concludes that PRSs are not ready for law enforcement use and may never be.

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