

ARTICLES

MEDICAL HARM WITHOUT NEGLIGENCE

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In December 2019, seven women from one family underwent highly invasive surgeries based on genetic test results that indicated that each were at significant risk of developing cancer by age seventy. Subsequently, after procedures that (among other things) permanently scarred and disfigured their bodies and ended their chances of having biological children, they learned that their particular mutation was not, in fact, pathogenic.

This Article focuses on a previously under-recognized problem: what happens when a patient's previously classified pathogenic variant is downgraded to uncertain (or even benign) status? Intuitively, it might seem that the genetic testing company, the surgeons, or others who participated in or influenced the family's decisions should be liable. However, while there is demonstrable harm, no one was negligent. This Article contextualizes the "harm without negligence" problem within the universe of medical harms more generally. It explores a pervasive—but often unrecognized—problem in medicine: harms arise when individuals act in the wake of uncertainty, and common-law negligence rules and current regulations fall short. It concludes by identifying potential tort, regulatory, and intellectual property answers, recognizing that a problem seemingly grounded in tort law may instead have regulatory or other solutions.

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INTRODUCTION

In December 2019, Katy Mathes and six women in her family elected to undergo mastectomies and/or to have their ovaries removed after receiving genetic test results indicating that each had an 84 percent chance of developing cancer by age seventy.¹ Subsequently, after these invasive surgeries and procedures that (among other things) permanently scarred and disfigured their bodies and ended their chances of having more biological children, they learned that their test results signaling a BRCA mutation, which had been obtained from a physician-ordered testing company called Myriad Genetics, had been “downgraded.”² Rather than being pathogenic (and therefore potentially deadly), the mutation was reclassified as a variant of unknown significance (VUS)—meaning that the clinical significance was

1. See Amy Dockser Marcus, *A Genetic Test Led Seven Women in One Family to Have Major Surgery. Then the Odds Changed.*, WALL ST. J. (Dec. 20, 2019, 11:43 AM), <https://www.wsj.com/articles/seven-women-in-a-family-chose-surgery-after-a-genetic-test-then-the-results-changed-11576860210> [https://perma.cc/FHR2-N2DD].

2. See *id.*

uncertain—rendering the highly invasive procedures they underwent contraindicated and unnecessary.³

Genetic variant classification and reclassification is inherently confusing—to patients and physicians alike. Commercial laboratories and diagnostic companies themselves sometimes disagree on how to classify a particular variant,⁴ rendering some test results particularly unreliable.⁵ Despite appearances, even when a patient receives medical test results, these results may not always be reliable or actionable. Not all medical tests, and not all medical test results, are created equal. Ambiguous and changing genetic test results can exacerbate uncertainty in medical decision-making and, in some cases, lead to misguided and contraindicated medical interventions. Individuals who receive genetic test results may feel pressure—internal and external—to undergo prophylactic surgeries that may subsequently be deemed needless. According to one study, 10 to 15 percent of women with pathogenic variants/VUS in genes not associated with a high risk of ovarian cancer still reported undergoing oophorectomies without a clear indication of ovarian cancer.⁶ In short, more information does not always mean more certainty in medical decision-making.

Intuitively, it might seem that Myriad, the surgeons, or others who participated in the Mathes family's decisions to undergo surgical interventions based on the formerly pathogenic test results should be liable. The women underwent aggressive surgeries, had painful and prolonged recoveries, and experienced long-term health sequelae.⁷ They each made irreversible, life-altering medical decisions in reliance on their original test results—decisions they likely would not have made had they learned of their lower risk sooner.

But no one was negligent. The company based its classification determinations on up-to-date criteria and evolving evidence.⁸ Likewise, the

3. *See id.*

4. *See* Sharon E. Plon, Diana M. Eccles, Douglas Easton, William D. Foulkes, Maurizio Genuardi, Marc S. Greenblatt, Frans B.L. Hogervorst, Nicole Hoogerbrugge, Amanda B. Spurdle & Sean Tavtigian, *Sequence Variant Classification and Reporting: Recommendations for Improving the Interpretation of Cancer Susceptibility Genetic Test Results*, 29 *HUM. MUTATION* 1282, 1285 (2008) (describing different protocols that diagnostic laboratories use to classify and report information on variants).

5. In fact, a working group at the American College of Medical Genetics and Genomics (ACMG) recommended *against* reporting variants of unknown significance to patients, recognizing “the challenge of attempting to report and interpret variants of unknown significance as incidental findings.” Robert C. Green, Jonathan S. Berg, Wayne W. Grody, Sarah S. Kalia, Bruce R. Korf, Christa L. Martin, Amy McGuire, Robert L. Nussbaum, Julianne M. O’Daniel, Kelly E. Ormond, Heidi L. Rehm, Michael S. Watson, Marc S. Williams & Leslie G. Biesecker, *ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing*, 15 *GENETICS MED.* 565, 567 (2013).

6. *See* Susan M. Domchek, Jamie Brower, Heather Symecko, Vanessa Marcell, Michael Francis Walsh, Jada G. Hamilton, Fergus Coach, Kenneth Offit, Judy Ellen Garber & Mark E. Robson, *Uptake of Oophorectomy in Women with Findings on Multigene Panel Testing: Results from the Prospective Registry of Multiplex Testing (PROMPT)*, 38 *J. CLINICAL ONCOLOGY* 1508, 1508 (2020).

7. *See* Marcus, *supra* note 1.

8. *See id.*

Mathes family's doctors presumably performed the surgeries and provided care based on current evidence and pursuant to the accepted standard of care.⁹ In short, it may be difficult, if not impossible, to demonstrate that a duty to these individuals had been breached, or that their injuries were caused by the company's or doctors' negligent actions. Thus, no clear negligence claim exists in the reclassification of genetic information based on sound scientific information. But there *is* demonstrable harm.

Recent revelations of false positive results from physician-ordered genetic testing products, particularly in the context of severe diseases such as hereditary breast and ovarian cancers, raise significant questions about fault, compensation, and oversight. Individuals who receive information about their genetic predispositions—even if that information is correct at the time it is shared—are left to make incredibly difficult and complex decisions. Under current legal norms, when that information is unclear or later discovered to be wrong, they may suffer uncompensable harms—both physical and psychosocial.

This Article addresses a question that has been largely undiscussed in legal scholarship: what happens when a patient's previously classified pathogenic variant is downgraded to uncertain (or even benign)? It explores the legal implications of gene reclassification and the harms that arise when individuals act in the wake of uncertainty, an area where common-law negligence rules and current regulations fall short.¹⁰

Current norms effectively punish those who take medical action based on genetic tests for being proactive in the face of uncertainty. Individuals who undergo medical and surgical interventions in response to genetic test results do so based on thoughtful analysis and personal experience. Many have witnessed loved ones suffer from the same disease for which they have just received a positive test result. Thus, these individuals undergo prophylactic interventions not out of ignorance or as knee-jerk reactions. An alternative to being proactive—waiting for the most accurate results—could result in disease and even more costly medical care.¹¹

9. See Jessica L. Roberts & Alexandra L. Foulkes, *Genetic Duties*, 62 WM. & MARY L. REV. 143, 162–74 (2020) (noting that the elements of duty and breach may not be met in cases of genetic variant reclassification).

10. This inquiry does not just implicate whether individuals are able to be autonomous decision-makers; it also raises equity concerns. Researchers have demonstrated significant racial and ethnic disparity in VUS due to historical inequities in genetic research. See Allison W. Kurian, Kevin C. Ward, Ann S. Hamilton, Dennis M. Deapen, Paul Abrahamse, Irina Bondarenko, Yun Li, Sarah T. Hawley, Monica Morrow, Reshma Jagsi & Steven J. Katz, *Uptake, Results, and Outcomes of Germline Multiple-Gene Sequencing After Diagnosis of Breast Cancer*, 4 JAMA ONCOLOGY 1066, 1069–70 (2018).

11. There is a growing amount of literature devoted to the uncertainty associated with patient decision-making after receiving classifications of variants of unknown significance. See, e.g., Lily Hoffman-Andrews, *The Known Unknown: The Challenges of Genetic Variants of Uncertain Significance in Clinical Practice*, 4 J.L. & BIOSCIENCES 648 (2017); Jenny Chang, Sirivan Seng, June Yoo, Pamela Equivel & Sharon S. Lum, *Clinical Management of Patients at Risk for Hereditary Breast Cancer with Variants of Unknown Significance in the Era of Multigene Panel Testing*, 26 ANNALS SURGICAL ONCOLOGY 3389 (2019); Julie O. Culver, C.D. Brinkerhoff, Jessica Clague, K. Yang, Kathryn Elaine Singh, Sharon R. Sand &

Unlike cases that involve downgrading a VUS to “likely benign” or “benign,” in which patients are already (presumably) advised not to take medical action, a pathogenic classification is likely to spur action on the part of the patient.¹² Thus, the circumstances that this Article addresses are unique because a variant classification of “likely pathogenic” or “pathogenic” is generally considered clinically actionable, such that a later downgrading of that classification would indicate that the patient did not need to undergo those interventions. In other words, VUS classifications are not intended to inform clinical management,¹³ while pathogenic classifications are.¹⁴

Importantly, while this Article focuses on a particular set of facts within the context of genetic testing, the “harm without negligence” problem pervades health care.¹⁵ So often, patients are forced to make life-changing medical decisions based on imperfect and constantly changing information. In these situations, patients suffer harm but cannot point to a particular individual’s fault that caused the injury. Patients have devices implanted that turn out to be much riskier than originally expected or even clinically inappropriate.¹⁶ Unanticipated adverse events occur after medications have

Jeffrey N. Weitzel, *Variants of Unknown Significance in BRCA Testing: Evaluation of Surgical Decisions, Risk Perception, and Cancer Distress*, 84 *CLINICAL GENETICS* 464 (2013).

12. Scholars have addressed the legal consequences of either downgrading VUS to benign or upgrading VUS to pathogenic. See generally Roberts & Foulkes, *supra* note 9; Alexandra L. Foulkes, Jessica L. Roberts, Paul S. Appelbaum, Wendy K. Chung, Ellen Wright Clayton, Barbara Evans & Gary E. Marchant, *Can Clinical Genetics Laboratories Be Sued for Medical Malpractice?*, 29 *ANNALS HEALTH L. LIFE SCI.* 153 (2020). However, an original VUS classification carries no recommended medical action. Classifying a variant as unknown means just that: the clinical implications of such a classification are unknown.

13. According to the ACMG: “A variant of uncertain significance should not be used in clinical decision-making. Efforts to resolve the classification of the variant as pathogenic or benign should be undertaken. While this effort to reclassify the variant is underway, additional monitoring of the patient for the disorder in question may be prudent.” Sue Richards, Nazneen Aziz, Sherri Bale, David Bick, Soma Das, Julie Gastier-Foster, Wayne W. Grody, Madhuri Hegde, Elaine Lyon, Elaine Spector, Karl Voelkerding & Heidi L. Rehm, *Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology*, 17 *GENETICS MED.* 405, 423 (2015).

14. Further, this Article focuses specifically on reclassification of genetic variants for patients who sought medical information (i.e., a potential diagnosis upon which to act), rather than reclassification of genetic variants within the research context. See, e.g., Susan M. Wolf, Jordan Paradise & Charlisce Caga-anan, *The Law of Incidental Findings in Human Subjects Research: Establishing Researchers’ Duties*, 36 *J.L. MED. & ETHICS* 361, 365–66 (2008) (exploring the ethical and legal obligations owed to participants in research involving human subjects).

15. For example, Professor Dov Fox notes that tort law does not compensate for reproductive harms, and that the regulatory system is woefully inadequate to avoid such wrongs. See Dov Fox, *Reproductive Negligence*, 117 *COLUM. L. REV.* 149, 149 (2017) (“[E]rrors go virtually unchecked in a profession that operates free of meaningful regulation. Private remedies meanwhile treat reproductive negligence more as trifle than tragedy But in the absence of property loss or physical injury, existing law provides little basis to recognize disrupted family planning as a harm worthy of protection.”).

16. See, e.g., Ed Yong, *Clinical Genetics Has a Big Problem That’s Affecting People’s Lives*, *ATLANTIC* (Dec. 16, 2015), <https://www.theatlantic.com/science/archive/2015/12/why-human-genetics-research-is-full-of-costly-mistakes/420693/> [https://perma.cc/M2S3-JTU2]

been taken.¹⁷ Physicians recommend surgeries that turn out to be unnecessary and potentially dangerous.¹⁸ It is not uncommon for procedures or drugs that the medical community views as initially beneficial based on available evidence to turn out to be either ineffective or even harmful, causing patients to experience “medical whiplash.”¹⁹

In such cases, the patients are the ones who end up paying—physically, emotionally, and financially. Instead, we need to consider how to apportion the risks of these harms in a thoughtful and equitable manner. The fact that patients consented to the intervention should not preclude all recovery when the patient later learns that the harm they suffered turned out to be unnecessary. More information does not always ensure a better outcome.

This Article proceeds as follows: Part I identifies the challenge of genetic variant classification and reclassification. Part II focuses on the central “harm without negligence” problem: that individuals can experience both physical and psychosocial harms due to the reclassification of genetic variants, even in the absence of negligence. After considering the bioethical principles at play, Part III examines the inadequacies in existing tort, regulatory, and intellectual property regimes and explores potential solutions to the “harm without negligence” problem in clinical genomics. What appears to be a problem grounded in tort law may, in fact, have a regulatory fix. In other words, an ideal solution would reduce the likelihood of harms occurring in the first place while providing a possibility of recovery for any injuries that patients sustain. By identifying legal solutions to the harm individuals suffer in these circumstances, we may, perhaps, simultaneously incentivize genetic laboratories to ensure the accuracy and clinical validity and utility of test results, thereby reducing false positives in variant classification.²⁰

(citing cases of patients who “get monitoring devices surgically implanted in their chests on the basis of mutations in heart-disease genes”).

17. See, e.g., VINAYAK K. PRASAD & ADAM S. CIFU, *ENDING MEDICAL REVERSAL: IMPROVING OUTCOMES, SAVING LIVES* 12 (2015) (describing flecainide, a drug intended to suppress premature ventricular contractions and which was later found to also increase patients’ chance of dying).

18. See, e.g., Vinay Prasad, Victor Gall & Adam Cifu, *The Frequency of Medical Reversal*, 171 *JAMA INTERNAL MED.* 1675, 1675 (2011) (defining medical reversal as the “phenomenon of a new trial—superior to predecessors because of better design, increased power, or more appropriate controls—contradicting current clinical practice”). The authors offer, as an example, the 2007 Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, which “found no benefit to support percutaneous coronary intervention (vs optimal medical therapy) in many patients with stable coronary artery disease, an indication that was previously accepted.” *Id.*

19. Abigail Zuger, *Book Review: ‘Ending Medical Reversal’ Laments Flip-Flopping*, *N.Y. TIMES* (Oct. 30, 2015), <https://www.nytimes.com/2015/11/03/science/book-review-ending-medical-reversal-laments-flip-flopping.html> [<https://perma.cc/AY4A-662W>].

20. See Hunter H. Giles, Madhuri R. Hegde, Elaine Lyon, Christine M. Stanley, Iain D. Kerr, Megan E. Garlapow & Julie M. Eggington, *The Science and Art of Clinical Genetic Variant Classification and Its Impact on Test Accuracy*, 22 *ANN. REV. GENOMICS & HUM. GENETICS* 285, 303 (2021).

I. THE CHALLENGE OF GENETIC CLASSIFICATION AND RECLASSIFICATION

Genetic variants are classified by genetic testing companies to allow patients, with guidance from their physicians and genetic counselors, to make informed decisions about future medical care and prevention. However, because data is collected over time, because technology progresses, and because information is accumulated, reclassification of some genetic variants is inherent and inevitable. The utilization of genetic technologies in medicine has incredible potential for better diagnosis, treatment, and prevention, but it is constantly evolving. Experts are increasingly recognizing that “[c]linical genetic variant classification science is hard.”²¹ This part explains how and why this is so.

A. Genetic Testing

Since the success of the first draft of the human genome two decades ago,²² genetic testing for disease predisposition has become almost ubiquitous, particularly for certain cancers. For example, there is a high incidence of mutations in the BRCA genes for individuals of Ashkenazi Jewish descent, which may predispose them to a significantly higher risk of breast, ovarian, and other cancers than the general population.²³ Approximately one in ten breast cancer diagnoses is associated with a pathogenic germline variant, and more than half of those are mutations of BRCA1 and BRCA2.²⁴ Genetic testing extends beyond BRCA to other hereditary cancer syndromes, including Lynch syndrome, Cowden syndrome, Li-Fraumeni syndrome, CDH1 mutations, and multiple endocrine neoplasia type 2,²⁵ as well as hereditary diseases besides cancer, such as Alzheimer’s disease²⁶ and Huntington’s disease.²⁷

While genetic testing is often heralded as the panacea for medical uncertainty because it provides patients and clinicians with targeted information about an individual’s predisposition to disease, it may actually lead to more uncertainty and complications.²⁸

21. *Id.* at 286.

22. See *Initial Sequencing and Analysis of the Human Genome*, 409 NATURE 860, 863 (2001).

23. See Payal D. Shah & Susan M. Domchek, *The Contemporary Landscape of Genetic Testing and Breast Cancer: Emerging Issues*, 26 BREAST J. 1549, 1551 (2020).

24. See THE AM. SOC’Y OF BREAST SURGEONS, CONSENSUS GUIDELINE ON GENETIC TESTING FOR HEREDITARY BREAST CANCER 2 (2019), <https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Genetic-Testing-for-Hereditary-Breast-Cancer.pdf> [<https://perma.cc/VV67-LZE5>].

25. And the list continues to grow.

26. For example, an individual may receive genetic testing results that indicate an increased risk of developing late-onset Alzheimer’s disease due to the presence of an APOE mutation. See *APOE Gene*, MEDLINEPLUS, <https://medlineplus.gov/genetics/gene/apoe/#conditions> [<https://perma.cc/8CRR-QNHH>] (last visited Nov. 7, 2022).

27. The mutation that causes Huntington’s disease increases the size of a segment in the HTT gene. See *HTT Gene*, MEDLINEPLUS, <https://medlineplus.gov/genetics/gene/htt/#conditions> [<https://perma.cc/88GC-KT4T>] (last visited Nov. 7, 2022).

28. See Sharon C. Zehe, *Genetic Testing: Legal and Ethical Issues and Duties for Providers*, 7 J. HEALTH & LIFE SCI. L. 94, 94 (2014) (“Genetic testing now provides patients

B. How Are Variants Classified?

Despite the increasing popularity of genetic testing, “genetic variant classification science is in its infancy.”²⁹ There is a dearth of oversight of genetic testing laboratories and companies with regard to variant classification.³⁰ Further, credible variant classification has been impeded by certain companies’ virtual monopoly on genetic data and the failure of clinical laboratories and researchers to share data.³¹ Against this backdrop, in order to standardize evidence requirements and make classification algorithms more discerning, the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) have issued guidance for genetic testing laboratories on the classification of sequence variants.³² The ACMG guidelines, first issued in 2000³³ and revised in 2007³⁴ and 2015,³⁵ classify variants in one of five tiers from lowest to highest pathogenicity: benign, likely benign, variant of uncertain significance, likely pathogenic, and pathogenic.³⁶ According to the guidelines, “initial classifications should be based on all available information regarding variant pathogenicity, including population frequency, functional data, segregation analysis, and phenotype analysis.”³⁷

The 2015 guidelines surveyed the germline clinical-genetics community and determined that 90 percent certainty in either direction was sufficient to describe a variant as either likely pathogenic or likely benign.³⁸ In the clinical setting, pathogenic or likely pathogenic results “are considered positive results that may alter care.”³⁹ Thus, based on pathogenic or likely

who historically faced complicated information about their current health with even more complicated information about future and potential risks for themselves, their children, and family members.”).

29. Giles et al., *supra* note 20, at 286, 287 (“Variants are discovered by comparing sequenced DNA to a reference sequence, where any deviation from the reference sequence is considered a variant.”).

30. *See infra* Part III.C (discussing deficiencies in the regulation of genetic testing companies, particularly with regard to variant classification).

31. *See infra* Part III.D.

32. *See* Richards et al., *supra* note 13, at 406; Giles et al., *supra* note 20, at 288.

33. *See generally* ACMG Recommendations for Standards for Interpretation of Sequence Variations, 2 GENETICS MED. 302 (2000).

34. *See generally* C. Sue Richards, Sherri Bale, Daniel B. Bellissimo, Soma Das, Wayne W. Grody, Madhuri R. Hegde, Elaine Lyon & Brian E. Ward, ACMG Recommendations for Standards for Interpretation and Reporting of Sequence Variations: Revisions 2007, 10 GENETICS MED. 294 (2008).

35. *See generally* Richards et al., *supra* note 13.

36. *Id.* at 407.

37. Jacqueline Mersch, Nichole Brown, Sara Pirzadeh-Miller, Erin Mundt, Hannah C. Cox, Krystal Brown, Melissa Aston, Lisa Esterling, Susan Manley & Theodora Ross, Prevalence of Variant Reclassification Following Hereditary Cancer Genetic Testing, 320 JAMA 1266, 1267 (2018).

38. *See* Giles et al., *supra* note 20, at 288.

39. *Id.*; *see also* Richards et al., *supra* note 13, at 423 (explaining that no variant category implies 100 percent certainty, and that “a variant classified as ‘likely pathogenic’ has sufficient evidence that a healthcare provider can use the molecular testing information in clinical decision making when combined with other evidence of the disease in question”).

pathogenic test results, patients may be advised to undergo surgical interventions, take medications, or take other precautions to prevent illness.

1. Variants of Unknown Significance

Individuals who seek genetic testing often receive results indicating that certain mutations are variants of unknown significance.⁴⁰ Unlike known pathogenic or benign mutations, VUS are genetic test results for which the clinical significance is not yet determined, meaning that the mutation may or may not increase the risk of disease. In other words, a VUS is a genetic variant that has an unknown effect on protein function and phenotype.⁴¹ According to the ACMG guidelines, variants unable to be classified as pathogenic, likely pathogenic, benign, or likely benign remain VUS until enough evidence is collected or evidentiary conflicts are resolved.⁴²

The concept and meaning of VUS are confusing to physicians and patients alike. In fact, a working group of the ACMG recommended *against* reporting VUS to patients, recognizing “the challenge of attempting to report and interpret variants of unknown significance as incidental findings.”⁴³ Knowledge of a VUS can exacerbate uncertainty in medical decision-making and, in some cases, lead to misguided and contraindicated medical interventions. In fact, because commercial laboratories and companies make their own classifications based on data available to them, the companies themselves sometimes disagree on how to classify a particular variant. And in some cases—like that of the Mathes family—these classifications can be based on evidence from a single study.⁴⁴ As Lily Hoffman-Andrews describes it, “[t]he current approach to VUS can sometimes seem like the passing of a hot potato from the lab to the clinician on to the patient, who is ultimately the one who has to live with the uncertainty of the result—and who is generally least equipped to understand it.”⁴⁵

2. Reclassification of Genetic Variants

Variant classification is not set in stone. Over time, as more individuals are tested for a particular variant, genetic testing companies may reclassify the test result.⁴⁶ Reclassification can mean upgrading from benign to VUS, or from VUS to pathogenic. Or it can mean downgrading the variant from VUS to benign, or—like in the case of the Mathes family—pathogenic to VUS. In the absence of specific regulations related to the classification of

40. See Moriah Wright, Vijay Menon, Lindsay Taylor, Maniamparampil Shashidharan, Twilla Westercamp & Charles Terner, *Factors Predicting Reclassification of Variants of Unknown Significance*, 216 AM. J. SURGERY 1148, 1148 (2018).

41. See *id.*

42. See Richards et al., *supra* note 13, at 411.

43. Green et al, *supra* note 5, at 567.

44. See Marcus, *supra* note 1.

45. Hoffman-Andrews, *supra* note 11, at 656.

46. See Mersch et al., *supra* note 37, at 1267 (“[G]enetic test results are based on the best scientific information at a given moment, which may change as scientific knowledge evolves.”).

genetic variants, the 2015 ACMG guidelines “encourage” genetic testing laboratories “to consider proactive amendment of cases when a variant reported with a near definitive classification (pathogenic or benign) must be reclassified.”⁴⁷

Reclassification is rather common. In one study in which 1,816 variants were analyzed, 17.3 percent were reclassified at least once.⁴⁸ Reclassification is more common for certain diseases than others. For example, “[g]enetic testing in clinical areas other than cancer may have a greater likelihood of generating both variants of unknown significance and erroneous determinations of pathogenicity.”⁴⁹ And reclassification can take years; one study found that the median time for reclassification is over three and a half years⁵⁰—ample time for individuals to weigh their options and take prophylactic action to avoid potential illness.

Currently, clinical laboratories do not regularly reinterpret data. Rather, physicians usually only request this after an intervening event, such as the onset of new symptoms.⁵¹ Further, while “iterative reclassification policies are considered best practices by experts in this type of analysis,” they are not standard practice for most genetic testing labs.⁵² Notably, variant reclassification depends greatly on the testing laboratory.⁵³ While “some commercial genetic testing laboratories employ an *active* variant reclassification process,” notifying the providers that originally ordered the genetic tests for their patients of updates, “[o]ther laboratories use *passive* reclassification processes, in which the providers must supply new information to help determine whether a specific variant is benign or pathogenic.”⁵⁴

While most reclassification involves downgrading a VUS to benign,⁵⁵ in some instances, a variant that was initially classified as pathogenic might be downgraded to a VUS. Working with Myriad Genetics data over a ten-year period, researchers found that reclassification from pathogenic to unknown

47. Richards et al., *supra* note 13, at 420.

48. See Thomas P. Slavin, Sophia Manjarrez, Colin C. Pritchard, Stacy Gray & Jeffrey N. Weitzel, *The Effects of Genomic Germline Variant Reclassification on Clinical Cancer Care*, 10 *ONCOTARGET* 417, 419 (2019).

49. Wylie Burke, *Making Sense of the Genome Remains a Work in Progress*, 320 *JAMA* 1247, 1247 (2018).

50. See Slavin et al., *supra* note 48, at 419 (“Variant reclassification occurred between 63 days and 20.2 years after initial classification, with a median of 3.55 years.”).

51. See Ellen Wright Clayton, Paul S. Appelbaum, Wendy K. Chung, Gary E. Marchant, Jessica L. Roberts & Barbara J. Evans, *Does the Law Require Reinterpretation and Return of Revised Genomic Results?*, 23 *GENETICS MED.* 833, 834 (2021).

52. See Turna Ray, *Genetic Testing Challenges in Oncology: BRCA1 Variant Downgraded After Risk-Reducing Surgery*, *PRECISION ONCOLOGY NEWS* (Sept. 29, 2021), <https://www.precisiononcologynews.com/cancer/genetic-testing-challenges-oncology-brca1-variant-downgraded-after-risk-reducing-surgery> [https://perma.cc/XGA3-KFXW].

53. See Slavin et al., *supra* note 48, at 421.

54. *Id.* at 422 (emphasis added).

55. See *id.*

significance occurred in less than 1 percent of pathogenic variants.⁵⁶ In another study analyzing reclassification of variants associated with dilated cardiomyopathy (DCM), five of 106 variants of unknown significance were reclassified as likely pathogenic.⁵⁷ The authors concluded that “[e]xisting inaccurate variant-disease associations pose a challenge for clinical variant interpretation and indicate a critical need for an iterative, systematic reassessment of previously classified genetic variation.”⁵⁸

Based on findings such as these, even before the Mathes family’s story came to light, there were already cases reported of pathogenic variants that had been downgraded to VUS, likely benign, or benign.⁵⁹ Cases, like those of Nancy Seegar and the unnamed woman and her mother discussed in Part II.B.1 below, demonstrate that the Mathes family’s plight is not unique and that the harms are real. And while variant reclassification from pathogenic to VUS may be rare, the effects of taking avoidable prophylactic action can be devastating.⁶⁰ We, as a society, have determined that low incidences of certain adverse events related to decision-making that, on the whole, benefit the community, should still be compensable.⁶¹ Further, throughout medicine, patients make decisions, with the support of their physicians, in the wake of uncertainty that turn out to be unnecessary.

In response to the case of the Mathes family, Susan Manley, senior vice president of medical services at Myriad, explained: “We know these are very difficult situations. We make these reclassifications very carefully. The science is evolving.”⁶² She noted that changing a classification from harmful to uncertain “is a rare event, but I understand that rare is of no consolation to the patient when it happens to them.”⁶³

56. Mersch et al., *supra* note 37, at 1270 (finding that, out of 44,777 unique variants of hereditary cancer genes, 6.4 percent (2,861) were reclassified into new clinical categories).

57. See Trevor J. Pugh, Melissa A. Kelly, Sivakumar Gowrisankar, Elizabeth Hynes, Michael A. Seidman, Samantha M. Baxter, Mark Bowser, Bryan Harrison, Daniel Aaron, Lisa M. Mahanta, Neal K. Lakdawala, Gregory McDermott, Emily T. White, Heidi L. Rehm, Matthew Lebo & Birgit H. Funke, *The Landscape of Genetic Variation in Dilated Cardiomyopathy as Surveyed by Clinical DNA Sequencing*, 16 GENETICS MED. 601, 602–03 (2014).

58. *Id.* at 601.

59. See generally Yvonne Bombard, Kyle B. Brothers, Sara Fitzgerald-Butt, Nanibaa’ A. Garrison, Leila Jamal, Cynthia A. James, Gail P. Jarvik, Jennifer B. McCormick, Tanya N. Nelson, Kelly E. Ormond, Heidi L. Rehm, Julie Richer, Emmanuelle Souzeau, Jason L. Vassy, Jennifer K. Wagner & Howard P. Levy, *The Responsibility to Recontact Research Participants After Reinterpretation of Genetic and Genomic Research Results*, 104 AM. J. HUM. GENETICS 578 (2019) (noting that recontacting patients is most compelling in such cases); Yong, *supra* note 16.

60. See *infra* Part II.A.

61. See *infra* notes 199–203 and accompanying text.

62. ‘I Would Have Had Another Kid’: How an Imperfect Gene Test Led to Major Surgery and Big Regrets, ADVISORY BD. (Jan. 7, 2020), <https://www.advisory.com/daily-briefing/2020/01/07/brca-test> [<https://perma.cc/9BQ9-YCAJ>].

63. *Id.*

II. DIAGNOSING THE “HARM WITHOUT NEGLIGENCE” PROBLEM

In some cases, genetic testing—and specifically, variant reclassification—can, in fact, give rise to negligence and medical malpractice claims.⁶⁴ Medical malpractice law is a part of tort law, and thus a claim alleging medical malpractice must prove the classic four elements of a tort claim: (1) a duty of care owed by the defendant to use reasonable care to prevent harm to the plaintiff, (2) breach of that duty by failing to adhere to the standard of care, (3) harm or injury to the plaintiff, and (4) a causal link between the injury and the breach of duty.⁶⁵ Professors David M. Studdert, Michelle M. Mello, and Troyen Brennan have explained that the goals of malpractice litigation are “to deter unsafe practices, to compensate persons injured through negligence, and to exact corrective justice.”⁶⁶

In theory, the harms experienced by the Mathes family seem to be exactly the types of harms that medical malpractice claims are intended to address. And it might seem that Myriad, the surgeons, or others who participated in the Mathes family’s decisions to undergo surgical interventions because of the formerly pathogenic test results should be liable. However, this part will demonstrate that, although there is no clear negligence in the reclassification of genetic information based on sound scientific information, there is a demonstrable harm.

64. See, e.g., Foulkes et al., *supra* note 12, at 155 (noting that as labs work to reclassify and understand variants, “which may—or may not—gain clinical significance as science reveals more about genetic risk, the potential for legal liability raises the stakes of accurate variant interpretation in an environment of uncertainty”); Jennifer K. Wagner & Michelle M. Meyer, *Genomic Medicine and the “Loss of Chance” Medical Malpractice Doctrine*, 2 HUM. GENETICS & GENOMICS ADVANCES, no. 3, 2021, at 1, 1 (“Genomic medicine malpractice caselaw is only beginning to emerge, with approximately 200 reported cases over four decades that involve alleged failures to diagnose a genetic disorder, interpret genetic test results appropriately, offer genetic screening when indicated, return results to patients, or treat a genetic condition properly.”). Professors Wagner and Meyer warn that when a test result is overturned by new data, but not told to the patient, there are

concerns about when and how individuals might ultimately learn this information and whether the discovery will be too late for those individuals to avoid (1) the progression of a condition for which prevention or treatment was available, or (2) unnecessary harms, such as ineffective treatments for which substitutes were available.

Id.; see also Pilar N. Ossorio, *Product Liability for Predictive Genetic Tests*, 41 JURIMETRICS J. 239, 243 (2001) (“Companies that manufacture or sell genetic tests are subject to liability for negligence If a company fails to use due care in manufacturing, conducting a test, or reporting test results, and this failure causes harm to a test user, then the company may be liable.”).

65. See JESSICA W. BERG, CHARLES W. LIDZ, LISA S. PARKER & PAUL S. APPELBAUM, *INFORMED CONSENT: LEGAL THEORY AND CLINICAL PRACTICE* 133 (2d ed. 2001); David M. Studdert, Michelle M. Mello & Troyen Brennan, *Medical Malpractice*, 350 NEW ENG. J. MED. 283, 283 (2004) (“The standard traditionally used to evaluate whether the breach in question rises to the level of negligence is medical custom—the quality of care that would be expected of a reasonable practitioner in similar circumstances.”).

66. Studdert et al, *supra* note 65, at 283.

A. Harm

1. Physical Harms

In response to their original genetic test results, the members of the Mathes family underwent aggressive surgeries, had painful and prolonged recoveries, and experienced long-term health sequelae.⁶⁷ They each made irreversible, life-altering medical decisions in reliance on their original genetic test results, decisions they likely would not have made had they learned of their lower risk sooner. Some had oophorectomies, triggering early menopause and eliminating their opportunity to have more biological children.⁶⁸ Some had prophylactic mastectomies, an invasive and complex surgery that causes patients substantial pain with an extended recovery period.⁶⁹ Katy Mathes, who underwent a double mastectomy, recalled: “It was nine months before I was cleared to pick up my child I wasn’t able to do bathtime with him. I wasn’t able to make dinner for him.”⁷⁰

According to science journalist Ed Yong, “[m]any geneticists have similar tales where mistakes in the scientific literature have led to wrong—and sometimes harmful—diagnoses.”⁷¹ In October 2021, The Pew Charitable Trusts identified “real risks” associated with genetic tests, explaining that “[a]ccording to FDA, inaccurate tests could cause patients to undergo unnecessary, costly, and risky treatment when tests return false-positive results.”⁷²

When a patient receives notification of a pathogenic variant, they often take prophylactic measures to reduce their risk. For example, in the case of BRCA1 or BRCA2 mutations, bilateral prophylactic mastectomy is considered to be the single most effective prevention method to reduce breast cancer risk, as it lowers the chances of developing breast cancer by at least

67. See Marcus, *supra* note 1.

68. See *id.*

69. See *id.*

70. *After Cancer-Prevention Surgeries, Women Learn BRCA Gene Test May Have Been Wrong*, CBS NEWS (Dec. 24, 2019, 7:54 AM), <https://www.cbsnews.com/news/brca-mutation-after-cancer-preventative-surgeries-women-learn-genetic-test-may-have-been-wrong/> [<https://perma.cc/6XJM-8U8N>].

71. Yong, *supra* note 16. For example, in a study of over 60,000 people, a team from Massachusetts General Hospital analyzed 200 gene variants that were classified as pathogenic in two widely used databases and found enough evidence to classify only nine of them as pathogenic. *Id.* Yong also reported another study by Dr. Stephen Kingsmore at the National Center for Genome Resources in Santa Fe, Arizona, which found that a quarter of mutations linked to childhood genetic diseases were debatable because the claims “were based on papers that contained extremely weak evidence” or “were plain wrong.” *Id.*

72. THE PEW CHARITABLE TRS., *DIAGNOSTIC TESTS NOT REVIEWED BY FDA PRESENT GROWING RISKS TO PATIENTS* (2021), <https://www.pewtrusts.org/-/media/assets/2021/10/diagnostictestsnotreviewedbyfdapresentgrowingriskstopatients.pdf> [<https://perma.cc/J6GR-MGS4>].

90 percent⁷³ and reduces breast cancer–specific mortality.⁷⁴ BRCA-positive individuals may seek to reduce their risk of developing ovarian cancer by undergoing bilateral prophylactic salpingo-oophorectomy (the surgical removal of the fallopian tubes and ovaries) or regular screening, including regular ultrasounds and CA-125 blood tests.⁷⁵

While each of these strategies offers significant risk reduction, they also carry with them significant health implications and side effects, many of which can be lifelong. For example, bilateral prophylactic oophorectomy induces early menopause, increased risk of cardiovascular disease, osteoporosis, and cognitive impairment.⁷⁶

Variant reclassification can lead to revised clinical recommendations for patients and their families.⁷⁷ One study found that 12 percent of reclassifications resulted in a change in the major reporting category, “with a potential to impact patient management.”⁷⁸ Another observed that the “downgrade of variants may have also led to substantial changes in management.”⁷⁹ Earlier recommendations to undergo prophylactic surgery, “in retrospect, may be clinically inappropriate.”⁸⁰ For example, according to the report in Precision Oncology News discussed in Part II.A, “[t]he mother . . . was understandably shaken to learn that the test result that led her to have risk-reducing surgeries, a decision that carries significant health, reproductive, and quality-of-life consequences, was no longer valid.”⁸¹

Further, variant classification and reclassification can influence reproductive decision-making. Based on the results of genetic tests, individuals may make important and irreversible medical choices. Ms. Mathes herself grieved over the fact that had she not undergone an

73. See Therese B. Bevers, John H. Ward, Banu K. Arun, Graham A. Colditz, Kenneth H. Cowan, Mary B. Daly, Judy E. Garber, Mary L. Gemignani, William J. Gradishar, Judith A. Jordan, Larissa A. Korde, Nicole Kounalakis, Helen Krontiras, Shicha Kumar, Allison Kurian, Christine Laronga, Rachel M. Layman & Loretta S. Loftus, *Breast Cancer Risk Reduction, Version 2.2015*, 13 NAT'L COMPREHENSIVE CANCER NETWORK 880, 893 (2015).

74. See N.E. Carbine, L. Lostumbo, J. Wallace & H. Ko, *Risk-Reducing Mastectomy for the Prevention of Primary Breast Cancer (Review)*, COCHRANE DATABASE SYSTEMATIC REVIEWS, Apr. 2018, at 1, 27 (gathering studies and concluding that bilateral mastectomy was effective in reducing death from breast cancer). Other prophylactic options include the use of selective estrogen receptor modulators, such as tamoxifen and raloxifene, as chemoprevention agents. See Tasleem J. Padamsee, Celia E. Wills, Lisa D. Lee & Electra D. Paskett, *Decision Making for Breast Cancer Prevention Among Women at Elevated Risk*, 19 BREAST CANCER RSCH., no. 34, 2017, at 1, 2. Individuals may also seek to minimize breast cancer risk through increased surveillance (including frequent mammograms and/or MRIs) or “watchful waiting.” *Id.* at 3.

75. See Marleah Dean & Carla L. Fisher, *Uncertainty and Previvors' Cancer Risk Management: Understanding the Decision-Making Process*, 47 J. APPLIED COMMUN RSCH. 460, 462 (2019).

76. See Padamsee et al., *supra* note 74, at 2.

77. See Scott A. Turner, Smita K. Rao, R. Hayes Morgan, Cindy L. Vnencak-Jones & Georgia L. Wiesner, *The Impact of Variant Classification on the Clinical Management of Hereditary Cancer Syndromes*, 21 GENETICS MED. 426, 429 (2019).

78. *Id.*

79. Slavin et al., *supra* note 48, at 421.

80. *Id.*

81. Ray, *supra* note 52.

unnecessary oophorectomy, she could have had more children.⁸² Members of the Mathes family were not the only individuals to undergo invasive medical interventions based on (at the time) actionable genetic test results, only to learn that those actions were unnecessary. In 2015, it was reported that a pathogenic result for a prenatal genetic test for Noonan syndrome, a genetic disorder that prevents normal development throughout the body, led a couple to terminate their pregnancy.⁸³ Subsequent research showed: “[T]he mutation is so common in certain ethnic groups that it couldn’t possibly be responsible for a rare disease like Noonan syndrome. It wasn’t pathogenic after all.”⁸⁴

Another study of variant reclassification noted that “[s]ome individuals may choose not to conceive children based solely on knowing there is a cancer-causing mutation in the family.”⁸⁵ Thus, “[i]f variants are initially misclassified, prospective parents may either unnecessarily opt for, or fail to engage in, medically appropriate and preference sensitive reproductive decision making.”⁸⁶

However, by the time patients learn that their mutations have been downgraded, it is often too late. In many cases in which a patient receives a report indicating the existence of a pathogenic mutation, time is of the essence. In such cases, people *do* act—often quickly—on the results they receive from genetic testing companies. One study observed: “Many . . . genetic test results are accompanied by significant medical management recommendations as well. . . . [I]n some of these cases, significant medical management decisions may have already been made.”⁸⁷ The study found that “[m]any prophylactic surgeries take place within 2 years after someone has been diagnosed with a hereditary cancer syndrome, and the majority of women with pathogenic *BRCA1/2* variants elect for a risk-reducing bilateral salpingo-oophorectomy.”⁸⁸

2. Emotional Harms and Uncertainty

Changes in variant classification can lead to significant uncertainty and mental anguish.⁸⁹ Genetic testing is rife with uncertainty, and “what sounds

82. See Marcus, *supra* note 1.

83. Yong, *supra* note 16. The genetic test revealed a mutation in *PTPN11*, a gene that affects the risk of Noonan syndrome. See *id.*

84. *Id.* Upon learning of the downgrading of the mutation, Heidi Rehm, the original scientist, “immediately contacted the physician to find out the story with that baby,” at which point she “found out that the parents had terminated it.” *Id.*

85. Slavin et al., *supra* note 48, at 421.

86. *Id.*

87. Sarah Macklin, Nisha Durand, Paldeep Atwal & Stephanie Hines, *Observed Frequency and Challenges of Variant Reclassification in a Hereditary Cancer Clinic*, 20 *GENETICS MED.* 346, 349 (2018).

88. *Id.*

89. Gina Kolata, *When Gene Tests for Breast Cancer Reveal Grim Data But No Guidance*, N.Y. TIMES (Mar. 11, 2016), <https://www.nytimes.com/2016/03/12/health/breast-cancer-brca-genetic-testing.html> [<https://perma.cc/LTH9-4BZE>] (“[P]atients need to be prepared for ambiguities.”).

like a simple test can leave patients with frightening information but no clear options or guidance for treatment decisions.”⁹⁰ In the context of BRCA mutations, some patients have described receiving pathogenic test results as “feeling like a ticking time bomb.”⁹¹

When a variant is reclassified from pathogenic to VUS or benign, uncertainty and confusion are exacerbated, particularly when individuals have already made medical decisions based on the earlier results. If a person decides to take prophylactic action based on a genetic test result, only to later learn that the variant had been downgraded, the devastation they may experience cannot be understated. There is something particularly profound about receiving a report that classifies a mutation as pathogenic and later being told that a mutation is a VUS. One study reported that individuals who had undergone genetic testing for arrhythmogenic right ventricular cardiomyopathy, a progressive, inherited heart muscle disease, displayed specific psychological injuries when variants that were previously classified as pathogenic or likely pathogenic were later downgraded.⁹² The authors observed that “the loss of genetic pathogenicity has important clinical consequences: the misinterpretation of the variant may have introduced unnecessary costs and may have impacted their psychological wellbeing.”⁹³ Even if the patient does not take prophylactic medical action upon receiving the erroneous pathogenic report, such results can still have enormous—and unnecessary—psychological ramifications.⁹⁴

90. *Id.*

91. Marni Vyn, *Taking After My Dad*, SHARSHERET (June 17, 2021), <https://sharsheret.org/taking-after-my-dad/> [<https://perma.cc/AJR7-9TTJ>]. Even when a mutation is correctly identified as pathogenic, uncertainty about the best treatment approach can still exist. The story of Angie Watts is one such case: Ms. Watts was a woman with breast cancer who tested positive for a mutation in a gene required to repair DNA. Kolata, *supra* note 89. One physician cautioned that she should avoid radiation therapy because he worried that the treatment would exacerbate the growth of cancer cells. *Id.* Another physician provided contradictory guidance, advising that the mutation was not harmful and that she should, in fact, undergo radiation therapy. *Id.* In the absence of medical consensus, the experts “left it up to [her] to decide,” and the experience greatly perturbed Ms. Watts. *Id.* (“It was scary. There are times I regret ever having genetic testing.”). Moreover, many patients live with stigma associated with the impact of decisions they make. In one study, a woman who had recently found out she was BRCA positive expressed concern “whether her mutation status and impending surgeries would constrain her potential for finding a life partner and bearing children.” Lindsey M. Hoskins & Allison Werner-Lin, *A Multi-Case Report of the Pathways to and Through Genetic Testing and Cancer Risk Management for BRCA Mutation-Positive Women Aged 18–25*, 22 J. GENETIC COUNSELING 27, 31 (2013). And importantly, “people’s preferences are not stable and well-defined,” and are prone to instability. Wendy Netter Epstein, *Nudging Patient Decision-Making*, 92 WASH. L. REV. 1255, 1275 (2017).

92. See Sarah Costa, Argelia Medeiros-Domingo, Alessio Gasperetti, Deniz Akdis, Wolfgang Berger, Cynthia A. James, Frank Ruschitzka, Corinna B. Brunckhorst, Firat Duru & Ardan M. Saguner, *Impact of Genetic Variant Reassessment on the Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy Based on the 2010 Task Force Criteria*, 14 GENOMICS & PRECISION MED. 49, 55 (2021).

93. *Id.* (concluding that “with 10.1% of patients losing their definite disease status, accurate determination of variant pathogenicity is of utmost importance in the diagnosis of [arrhythmogenic right ventricular cardiomyopathy]”).

94. See Danielle Gould, Rachel Walker, Grace Makari-Judson & Memnun Seven, *Experiences of Individuals with a Variant of Uncertain Significance on Genetic Testing for*

Further, the harms that can occur due to the downgrading of a previously classified pathogenic variant can extend to family members. As the authors of one study on the reclassification of genetic variants stated:

[E]ven when considering just the first degree relatives, the potential impact of the changes in actionability of the reclassified variants is impressive. The reclassifications we followed may have affected the genetic cancer risk assessment/counseling for 150 adult male and female first-degree relatives of the 25 carriers. If half of these individuals are assumed to carry the reclassified variant due to the autosomal dominant transmission of the genes . . . 75 individuals would be at risk of overtreatment or missed opportunities for cancer screening or risk reducing procedures.⁹⁵

While the downgrading of genetic tests from pathogenic to VUS or benign may be relatively rare, it is not wholly uncommon. And when it does occur, the ramifications can be great. Importantly, the questions of whether and how we compensate individuals who have suffered harm in medicine in the absence of identifiable negligence is much more universal. People make decisions all the time based on current scientific and medical information but can end up harmed as a result. Under current legal norms, when that information is unclear, or later discovered to be wrong, they may suffer incompensable harms—both physical and psychosocial.

B. Negligence

Conventional medical malpractice fails to address these harms. From all accounts, genetic testing companies like Myriad base their classification determinations on up-to-date criteria and evolving evidence.⁹⁶ The Mathes family's doctors presumably performed the surgeries and provided care based on current evidence and pursuant to the standard of care.⁹⁷ In this case, no mistake was made. Instead, new information led Myriad to update its variant classification.⁹⁸

In short, it may be difficult, if not impossible, to demonstrate that a duty to these individuals had been breached by either the genetic testing company or the treating physician, or that the individuals' injuries were caused by the company's or doctors' negligent actions.⁹⁹ In many cases involving the downgrading of pathogenic variants, there is no clear negligence on the part of the genetic testing company or health-care provider. This section will

Hereditary Cancer Risks: A Mixed Method Systematic Review, 13 J. CMTY. GENETICS 371, 376 (2022) (finding a general lack of understanding among individuals with a VUS result and noting that anxiety and distress are linked to forgetting medical information or to the misconception that the information is unimportant).

95. Slavin et al., *supra* note 48, at 421.

96. See Marcus, *supra* note 1.

97. See Roberts & Foulkes, *supra* note 9, at 162–74 (identifying how the elements of duty and breach may not be met in cases of genetic variant reclassification).

98. See Marcus, *supra* note 1.

99. See BERG ET AL., *supra* note 65, at 133–34; Valerie Gutmann Koch, *Eliminating Liability for Lack of Informed Consent to Medical Treatment*, 53 U. RICH. L. REV. 1211, 1218 (2019); Wagner & Meyer, *supra* note 64, at 2.

explore the absence of negligence claims in these cases, first against the genetic testing companies and then against the treating physicians.

1. Against Genetic Testing Companies

There are a variety of reasons why recovery against genetic testing companies for injuries arising from variant reclassification is unlikely. First, and most importantly, patients may find it difficult, if not impossible, to prove breach. Second, even if genetic testing companies have breached a duty to the patient, the plaintiff must still prove that their injuries were caused by the company's negligent actions. Finally, a plaintiff may have particular difficulty overcoming arguments that they assumed the risk.

When clinical laboratories reclassify a mutation, they may not have a legal duty to individuals to whom they render services.¹⁰⁰ While it may be argued that negligence should lie when a laboratory fails to reinterpret and return revised genomic results, “there are no cases, statutes, or regulations at present that support a legal duty to reinterpret clinical genomic tests and return any new analyses.”¹⁰¹ Thus, some scholars have argued in favor of establishing an ethical¹⁰²—or even a legal¹⁰³—duty on genetic testing companies, particularly when the new results could affect treatment. However, at present, scholars have generally acknowledged that there is no recognized legal duty to reinterpret, recontact, or “take any action when a VUS gains clinical significance.”¹⁰⁴

Individuals in circumstances like those of the Mathes family members may argue that there has, in fact, been a mistake for which the genetic testing company can be held liable. Perhaps individuals who receive pathogenic results that are later reclassified as uncertain or benign can make successful negligence claims against the genetic testing companies that administered or developed the tests (e.g., for failure to update their reports to reflect scientific discoveries in a timely manner).¹⁰⁵ They may claim that the company was too hasty in its initial classification, jumping to classify the variant before accumulating enough research and data. In Ms. Mathes's case, the analysis of the BRCA variant present in her and her family may have relied too heavily on the findings of a single study from 2011.¹⁰⁶ However, despite the fact that the study was conducted in 2011, one of the authors explained that

100. See generally Foulkes et al., *supra* note 12.

101. Clayton et al., *supra* note 51, at 833.

102. See generally Karen L. David, Robert G. Best, Leslie Manace Brenman, Lynn Bush, Joshua L. Dignan, David Flannery, Jodi D. Hoffman, Ingrid Holm, David T. Miller, James O'Leary & Reed E. Pyeritz, *Patient Re-Contact After Revision of Genomic Test Results: Points to Consider—A Statement of the American College of Medical Genetics and Genomics (ACMG)*, 21 GENETICS MED. 769 (2019).

103. See generally Roberts & Foulkes, *supra* note 9.

104. *Id.* at 148; see also Foulkes et al., *supra* note 12; David et al., *supra* note 102; Gary Marchant, Mark Barnes, James P. Evans, Bonnie LeRoy & Susan M. Wolf, *From Genetics to Genomics: Facing the Liability Implications in Clinical Care*, 48 J.L. MED. & ETHICS 11 (2020).

105. See Clayton et al., *supra* note 51.

106. See Marcus, *supra* note 1.

it still met the current ACMG standard for deeming a variant deleterious.¹⁰⁷ Thus, Myriad presumably followed the standard of care and relied on the most up-to-date research at the time it reported the pathogenic variant back to the Mathes family.¹⁰⁸

In another example, an unnamed patient underwent genetic testing for mutations in the BRCA1 gene based on the fact that her mother had had a bilateral mastectomy and risk-reducing salpingo-oophorectomy at a young age after genetic testing.¹⁰⁹ Subsequently, the patient's and her mother's mutations were downgraded to VUS.¹¹⁰ Upon learning of the reclassification, the patient's mother was "angry" because she had "gone into debt to have risk-reducing surgeries based on her genetic test result."¹¹¹ This story clearly illustrates that the current standard of care in genetic testing and disclosure practices can nevertheless cause serious injury to patients.¹¹²

The fact that the initial classification was based on up-to-date scientific evidence distinguishes the Mathes family's experience from that of Nancy Seeger, who sued a genetic testing company in 2000.¹¹³ Ms. Seeger had submitted a specimen for genetic testing to the company, who informed her that she had a pathogenic BRCA1 mutation.¹¹⁴ Based on this report, she elected to undergo a prophylactic oophorectomy.¹¹⁵ Eight months later, while she was considering undergoing a double mastectomy to further reduce her risk of breast cancer, the company downgraded her mutation, informing her that she did not, in fact, have the disease-conferring mutation.¹¹⁶ She sued the company for medical malpractice, alleging that the company failed to use reasonable care in maintaining and identifying samples, conducting the test, or reporting the results.¹¹⁷ The company conceded that it had erred in its original interpretation of the data.¹¹⁸

In Nancy Seeger's case, unlike in the Mathes family's case, the genetic testing company acknowledged that it had misreported the test result. In

107. *Id.*

108. Further, it should be noted that voluntary guidelines, like those issued by the ACMG, may be adopted by courts as the standard of care. But it is likely that companies like Myriad are following the ACMG guidelines anyway, thereby strengthening the argument that they are following the appropriate standard of care.

109. *See* Ray, *supra* note 52.

110. *See id.*

111. *Id.*

112. *See id.*

113. *See* Anne Underwood, *When "Knowledge" Does Damage*, NEWSWEEK (Apr. 9, 2000, 8:00 PM), <https://www.newsweek.com/when-knowledge-does-damage-157593> [<https://perma.cc/RB46-XFTR>].

114. *See id.*

115. *See id.*

116. *See id.*

117. *See* Ossorio, *supra* note 64, at 244.

118. *See id.*

Seeger's case, the company had sent her "an erroneous result,"¹¹⁹ thereby failing to use reasonable care in the testing process.

Even when a genetic company misinterprets or misreports genetic test results, many patients may still be unable to prevail in a malpractice claim against them. In *Belser v. Quest Diagnostics, Inc.*,¹²⁰ the genetic testing company classified a child's mutation as a VUS, despite existing medical literature suggesting that the mutation was, in fact, a disease-associated mutation.¹²¹ Due to this misclassification, the child did not receive the necessary treatment for his illness, resulting in his death in 2008.¹²² The child's mother argued that Quest was negligent in its interpretation of the SCN1A variant, which led to erroneous treatments that resulted in the child's death.¹²³ In 2018, the South Carolina Supreme Court, on certification from the *Belser* court, held in *Williams v. Quest Diagnostics, Inc.*¹²⁴ that diagnostic laboratories are categorized under state law as health-care providers, like hospitals, when a treating physician orders a diagnostic test.¹²⁵ However, having left room for the plaintiff, Williams, to also argue ordinary negligence, in November 2020, the *Belser* court then granted summary judgment in favor of Quest, holding that there was insufficient evidence that the variant was erroneously classified, and therefore the plaintiffs were unable to prove that the VUS classification was due to the genetic testing company's negligence.¹²⁶

As the test case for variant misclassification, *Williams* signals courts' reluctance to hold genetic testing companies responsible for imperfect testing. In the absence of clear evidence of classification error, a plaintiff is highly unlikely to prevail on a negligence or medical malpractice claim against a genetic testing company, regardless of the harm suffered by the plaintiff.¹²⁷ Based on this holding, genetic testing companies are unlikely to be held liable for duties to patients to ensure the quality and currency of variant data.

And even if genetic testing companies are found to have breached a duty, the learned intermediary doctrine might cut them off based on physician

119. Rick Weiss, *A Defective Side to Genetic Testing*, L.A. TIMES (July 26, 1999), <https://www.latimes.com/archives/la-xpm-1999-jul-26-he-59830-story.html> [<https://perma.cc/E6QD-YEC9>].

120. No. 16-0972, 2020 WL 6526084 (D.S.C. Nov. 5, 2020).

121. *See id.* at *2.

122. *See id.* at *3.

123. *See id.* at *1, *3.

124. 816 S.E.2d 564 (S.C. 2018).

125. *See id.* The court also held that the plaintiff's lawyers failed to establish "a causal nexus" between the genetic test report and the child's treatment. *See generally* Timothy Nicolette, Williams v. Quest: *The South Carolina Supreme Court's Misdiagnosis of Quest Diagnostics as a Health Care Provider and the Poor Prognosis for Plaintiffs in Medical Malpractice*, 13 CHARLESTON L. REV. 393 (2019) (arguing that the South Carolina Supreme Court misinterpreted a state statute to classify diagnostic labs as health-care providers and, therefore, the opinion should be overturned).

126. *Belser*, 2020 WL 6526084, at *11. The court also held that the medical malpractice claim was time-barred. *Id.*

127. *See id.* at *7.

negligence. The learned intermediary doctrine stems from the idea that health-care providers are best positioned to correctly diagnose and treat their patients' medical problems.¹²⁸ This doctrine recognizes that "many factors, in addition to genetic predisposition, should enter into decisions about which drugs to prescribe and treatments to pursue."¹²⁹ However, as discussed in Part II.B.2, creating physician liability is unlikely to be the solution.

Even if treating physicians or genetic testing companies have breached a duty to the patient, plaintiffs must still prove that their injuries were caused by the company's or doctors' negligent actions. To successfully recover, the plaintiff must prove that the defendant's conduct was both the but-for and proximate cause of the plaintiff's harm. Thus, a plaintiff must show by a preponderance of the evidence that the defendant's negligence more likely than not caused her injury. As Professor Pilar Ossorio explained: "In cases pertaining to predictive genetic tests, causation will be the most difficult negligence element to prove. Genetic tests themselves generally are not medically risky; it is the information obtained from them and the decisions made in reliance on that information that can lead to harm."¹³⁰

When suing a genetic testing company, the plaintiff must prove that the original classification *caused* them to undergo painful and unnecessary medical interventions. But Adrian Thorogood and Professors Robert Cook-Deegan and Bartha Marie Knoppers argued in the context of *Williams*: "This proof is hindered by the intervention of a physician . . . which may break the chain of causation and scientific uncertainty These uncertainties over causation are even more pronounced for misclassified data sharing through a variant database."¹³¹

Finally, there are strong, scientifically based policy arguments against imposing liability for genetic testing companies' incorrect classification of genetic variants. Imposing liability in such cases may disincentivize companies from updating and returning results after the initial return of patients' test results, as this could potentially shield them from liability. From a policy perspective, we want to encourage laboratories to update their

128. See Victoria M. Kumorowski, *Assessing Legal Liability in Pharmacogenetic Cases*, 42 WASHBURN L.J. 623, 625 (2003).

129. *Id.*

130. Ossorio, *supra* note 64, at 243.

131. Adrian Thorogood, Robert Cook-Deegan & Bartha Marie Knoppers, *Public Variant Databases: Liability?*, 19 GENETICS MED. 838, 839 (2017). To the extent that a plaintiff is able to raise a successful claim against a genetic testing company, it might be alleged that the patient assumed the risk. See generally Nadia N. Sawicki, *Defining the Known Risk: Context-Sensitivity in Tort Law Defenses*, 12 J. TORT L. 9 (2019). In such cases, the (most often female) individual may be alleged to have acted impetuously, assuming the risk of (unnecessary) surgical and medical interventions in the face of medical unknowns. However, such a defense would likely be unsuccessful, even in a jurisdiction that has not abandoned the assumption-of-risk doctrine. Under the doctrine of secondary assumption of risk, the plaintiff would have had to have made medical decisions based on knowledge of the defendant's negligent actions. However, patients who decide to undergo invasive prophylactic medical interventions would not have made such decisions if they knew that the test results were incomplete or that the tests were conducted negligently. The act of genetic testing does not create risk; rather, it identifies existing risk.

data in an efficient manner so that patients like those in the Mathes family's position have current and correct information with which to make medical decisions (and, for example, avoid unneeded surgery). In a way, imposing tort liability would create a counterintuitive, and perhaps perverse, incentive for laboratories by insulating them from liability if they do *not* update and return results, and potentially opening them up to liability if they do.

2. Against Treating Physicians

For physicians, the traditional negligence requirements include an established physician-patient relationship, which imposes a duty of care on physicians.¹³² The physician's goal in this relationship is to benefit the patient, either through treatment or preventative care. The doctor-patient relationship gives rise to a duty of the physician to the patient; breach of that duty allows the injured patient to recover for damages in civil suit.

Assuming that the physician followed the standard of care in interpreting the patient's pathogenic test results and advising the patient about appropriate prophylactic therapies, physicians will not be held liable for the harm that occurs due to interventions that are later found to be unnecessary.¹³³ In these cases, medical malpractice claims or even simple negligence claims are unavailable. As Professor Gary Marchant has explained: "We don't hold doctors to perfection. They can't prevent all harm. So, the question is, 'Was their decision reasonable?'"¹³⁴

To the extent that genetic testing companies may be liable for the detrimental decisions that patients make based on their results,¹³⁵ one may argue that liability may be obviated by the physician's guidance and recommendations to the patient based on the learned intermediary doctrine.

132. See Valerie Gutmann Koch, *A Private Right of Action for Informed Consent in Research*, 45 SETON HALL L. REV. 173, 181–82 (2015).

133. And, in some cases, individuals who receive ambiguous genetic test results may feel pressured by their physicians—contrary to medical consensus—to undergo prophylactic surgeries, which may subsequently be deemed "needless." Christina Bennett, *Ambiguous Genetic Test Results Can Be Unsettling. Worse, They Can Lead to Needless Surgeries.*, WASH. POST (Feb. 7, 2021, 8:00 AM), https://www.washingtonpost.com/health/genetic-tests-uncertain-results/2021/02/05/80a06d9a-65a2-11eb-8468-21bc48f07fe5_story.html [<https://perma.cc/55KQ-KFLF>]. In those cases, the plaintiff may be able to prove liability. If a physician did not follow the standard of care, or there was diagnostic error, then negligence could lie. See, e.g., Katrina A. Armstrong, *Expanding the Vision of Quality and Safety in Genomic Medicine*, 37 J. GEN. INTERNAL MED. 453 (2021); Barbara J. Evans, *The Streetlight Effect: Regulating Genomics Where the Light Is*, 48 J.L. MED. & ETHICS 105, 109 (2020) ("[T]he fact remains that a person is unlikely to experience such injuries without the complicity of a clinician who performs unnecessary prophylactic surgery or orders costly tests not justified by the person's symptoms and clinical presentation. Unsophisticated laypeople cannot perform unnecessary surgery on themselves; for bad things to happen, there has to be a clinician in the loop who proceeds without appropriate clinical indications or confirmatory testing.").

134. Turna Ray, *Quest Diagnostics Win in Wrongful Death Case Reveals Ongoing Challenges for Variant Classification*, GENOMEWEB (Nov. 12, 2020), <https://www.genomeweb.com/molecular-diagnostics/quest-diagnostics-win-wrongful-death-case-reveals-ongoing-challenges-variant> [<https://perma.cc/YM6B-ZEFH>].

135. This is an assumption that was undercut by the discussion in Part II.A.1.

However, physicians themselves are notoriously lacking in genetic literacy.¹³⁶ Scholars continue to call for increased education to improve genetic fluency, which would provide needed support for patients.¹³⁷ With such high rates of genetic illiteracy among physicians, they cannot be expected to play an active enough role in interpretation to provide a defense to genetic-test company liability.¹³⁸ It may still lie with the genetic testing companies to adequately interpret test results and the data on which variant classification relies, presuming that physicians who receive the results also pass this information (and any appropriate warnings) to patients.¹³⁹

136. See generally Vu T. Dung Ha, Julie Frizzo-Barker & Peter Chow-White, *Adopting Clinical Genomics: A Systematic Review of Genomic Literacy Among Physicians in Cancer Care*, 11 BMC MED. GENOMICS, no. 18, 2018, at 1, 1; Erin W. Dekanek, Darcy L. Thull, Mylynda Massart, Robin E. Grubs, Aleksander Rajkovic & Phuong L. Mai, *Knowledge and Opinions Regarding BRCA1 and BRCA2 Genetic Testing Among Primary Care Physicians*, 29 J. GENETIC COUNSELING 122 (2020); Joan Stephenson, *As Discoveries Unfold, a New Urgency to Bring Genetic Literacy to Physicians*, 278 JAMA 1125 (1997).

137. See, e.g., Nonie S. Arora, J. Kelly Davis, Christine Kirby, Amy L. McGuire, Robert C. Green, J.S. Blumenthal-Barby & Peter A. Ubel, *Communication Challenges for Nongeneticist Physicians Relaying Clinical Genomic Results*, 14 PERSONALIZED MED. 423 (2017); Stephanie White, Chris Jacobs & Jane Phillips, *Mainstreaming Genetics and Genomics: A Systematic Review of the Barriers and Facilitators for Nurses and Physicians in Secondary and Tertiary Care*, 22 GENETICS MED. 1149 (2020); RaeLynn Forsyth, Weiyi Mu, Laura Gibson, Janet R. Serwint, Nicole Shilkofski & Joann Bodurtha, *A Structured Genetics Rotation for Pediatric Residents: An Important Educational Opportunity*, 22 GENETICS MED. 793 (2020); Ha et al., *supra* note 136.

138. See Ossorio, *supra* note 64, at 256 (“The application of the learned intermediary justification to genetic tests is unclear. Most practicing physicians have inadequate training in medical genetics and may face problems determining the appropriateness of a genetic test for a particular patient.”).

139. See Mitchell S. Berger, *A Tale of Six Implants: The Perez v. Wyeth Laboratories Norplant Case and the Applicability of the Learned Intermediary Doctrine to Direct-to-Consumer Drug Promotion*, 55 FOOD & DRUG L.J. 525, 534 (2000). In practice, physicians have served as the gatekeepers to medical knowledge, making informed decisions to withhold some information when it is in the best interest of the patient to do so. See Giles et al., *supra* note 20, at 290. There is a power asymmetry in the doctor-patient relationship. See Nadia N. Sawicki, *Modernizing Informed Consent: Expanding the Boundaries of Materiality*, 2016 U. ILL. L. REV. 821, 860 (“One of the primary goals of the informed consent obligation is to correct an information asymmetry between physician and patient, an asymmetry that is made even starker by the physician’s position of power.”). In circumstances like those encountered by the Mathes family, it might be argued that withholding the potential pathogenic nature of individuals’ genetic variants might constitute an abrogation of their autonomy. Rather, these patients should have access to all available information related to their particular situations—even if that information is incomplete or imperfect—and be empowered to make, with the support of their physicians, the best medical decisions for them. Based on information asymmetries and vulnerabilities, the tort system, particularly in the medical negligence context, places certain expectations on physicians and sometimes shifts risk to practitioners to avoid risk. See, e.g., *Canterbury v. Spence*, 464 F.2d 772, 780 (D.C. Cir. 1972) (“The average patient has little or no understanding of the medical arts, and ordinarily has only his physician to whom he can look for enlightenment with which to reach an intelligent decision.”); *Cobbs v. Grant*, 104 Cal. Rptr. 505, 513 (1972) (“[T]he patient, being unlearned in medical sciences, has an abject dependence upon and trust in his physician for the information upon which he relies during the decisional process”); *Betesh v. United States*, 400 F. Supp. 238 (D.D.C. 1974); *Payton v. Weaver*, 182 Cal. Rptr. 226 (Ct. App. 1982). Further, physicians may also be expected to demand more scientific evidence from these genetic testing companies to support their classification before returning results to their

Patients could, perhaps, rely on the oft-ignored loss of chance (LOC) doctrine. The doctrine may be relied on when it is impossible to know whether the defendant's medical negligence was the but-for cause of the plaintiff's injury—because had the patient known of the “correct” variant classification, they could have possibly prevented the injury that occurred.¹⁴⁰ Although the doctrine has historically been invoked in medical malpractice cases, “the availability of the LOC medical malpractice doctrine is a potentially important factor to consider when making programmatic decisions for genomic medicine.”¹⁴¹ However, it is unlikely that someone in circumstances similar to that of members of the Mathes family could rely on the loss of chance doctrine to recover from their physician for their harm. Professors Jennifer K. Wagner and Michelle M. Meyer have raised the role of LOC doctrine in proving proximate causation in the context of genetic malpractice cases.¹⁴² Specifically, they observe that “[n]ondisclosed, erroneous, or delayed genetic testing can, in turn, delay treatment that might reduce the risk of the underlying genetic condition.”¹⁴³ Over twenty state courts have recognized the loss of the chance for a better outcome as a form of harm.¹⁴⁴ In applying the LOC doctrine in medical malpractice cases, courts have looked to the specific physician-patient relationship, particularly the expectation that “the physician will take every reasonable measure to obtain an optimal outcome for the patient.”¹⁴⁵

The current medical malpractice jurisprudence therefore indicates that injured patients face a daunting, and possibly insurmountable, challenge to prove either that a breach of duty occurred or that their injuries were caused by a testing company's or physician's negligence. Thus, there is no clear negligence cause of action that arises from the reclassification of genetic information based on sound scientific information, but there is a demonstrable harm.

patients. Withholding judgment—or classification—until sufficient evidence has been accumulated may ultimately benefit patients and their families. However, placing the onus on physicians to make decisions about which results to withhold or disclose is also an insufficient remedy.

140. See, e.g., Elizabeth R. Pike, Karen H. Rothenberg & Benjamin E. Berkman, *Finding Fault?: Exploring Legal Duties to Return Incidental Findings in Genomic Research*, 102 GEO. L.J. 795, 825 n.161 (2014) (noting that injury “consists of the diminished likelihood of achieving a more favorable medical outcome” (quoting *Matsuyama v. Birnbaum*, 890 N.E.2d 819, 832 (Mass. 2008))).

141. Wagner & Meyer, *supra* note 64, at 1.

142. *Id.*

143. *Id.* at 2 (describing loss of chance doctrine). The authors also note that “[t]he factual circumstances in which application of the [loss of chance] doctrine is sought could involve delayed or erroneous diagnoses as well as delayed or erroneous treatments, and they could allege physical health, mental health, or non-health harms.” *Id.*

144. See generally *Smith v. Providence Health & Servs.*, 393 P.3d 1106 (Or. 2017).

145. Pike et al., *supra* note 140, at 827 (citing *Matsuyama v. Birnbaum*, 890 N.E.2d 819, 832 (Mass. 2008)).

III. POSSIBLE “PRESCRIPTIONS”

In an ideal world, genetic information that is returned to individuals would be accurate, reliable, and actionable. When it is not, patients may suffer physical and emotional harms. Thus, the “harm without negligence” problem implicates the bioethical principles of respect for persons, beneficence, and justice.¹⁴⁶

Until the middle of the twentieth century, the practice of medicine appeared to give particular weight to the bioethical principle of beneficence and its corresponding principle of non-maleficence.¹⁴⁷ Non-maleficence is the foundational value enunciated in the Hippocratic Oath, which requires the physician to “above all, do no harm” to the patient.¹⁴⁸ Applying this principle to prophylactic decision-making in response to genetic test results, physicians have an obligation to guide the therapeutic relationship by making professional recommendations based on sound medical evidence.

The second of these values, respect for persons, is often recognized as the core principle of genetic counseling.¹⁴⁹ It addresses the primary ethical imperative that individuals should be respected as autonomous agents.¹⁵⁰ In many ways, access to genetic testing and the opportunity to make informed medical decisions in response to test results is the quintessential case study on furthering autonomy in medical decision-making.¹⁵¹ Genetic counseling has historically been driven by the concept of “nondirectiveness,”¹⁵² which

146. See generally TOM L. BEAUCHAMP & JAMES F. CHILDRESS, *PRINCIPLES OF BIOMEDICAL ETHICS* (4th ed. 1994). The Belmont Report, published in 1979, enunciated these three ethical values by which research involving human subjects should be conducted. See NAT'L COMM'N FOR THE PROT. OF HUM. SUBJECTS OF BIOMEDICAL & BEHAV. RSCH., *THE BELMONT REPORT* (1979), https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf [<https://perma.cc/TKT3-4Q6G>] (describing the three principles of respect for persons, beneficence, and justice).

147. See Akshay Govind, *A Short History of the Current Approach to Ethical Health Care*, SYNAPSE (Nov. 7, 2013, 1:52 PM), <https://synapse.ucsf.edu/articles/2013/11/07/short-history-current-approach-ethical-health-care> [<https://perma.cc/79T6-Z8WE>] (noting that prior to the 1970s, physicians largely aimed to “maximize medical benefits and minimiz[e] risks of harm and disease”).

148. Cedric M. Smith, *Origin and Uses of Primum Non Nocere—Above All, Do No Harm!*, 45 J. CLINICAL PHARMACOLOGY 371, 371 (2005).

149. See Debra J.H. Mathews & Leila Jamal, *Revisiting Respect for Persons in Genomic Research*, 5 GENES, no. 1, 2014, at 1, 2.

150. An autonomous individual can consider and act on personal goals, and to respect an autonomous individual is to accept their opinions and decisions, so long as these actions do not harm others. The value of respect for persons encourages potential participants to be involved in the decision-making process, assuring them that they have an essential role in the research process, and that their opinions and decisions are valued. See Koch, *supra* note 132, at 185.

151. See generally Valerie Gutmann Koch, *Previvors*, 49 FLA. ST. U. L. REV. 643 (2022).

152. Leila Jamal, Will Shupmann & Benjamin E. Berkman, *An Ethical Framework for Genetic Counseling in the Genomic Era*, 29 J. GENETIC COUNSELING 718, 719 (2020) (“In genetic counseling specifically, valuing patient autonomy expresses respect for the emotionally complex and nuanced nature of decisions about reproduction, pregnancy management, living with a genetic condition, and raising children with special needs.”).

has been described as a strategy that supports autonomous decision-making.¹⁵³

However, the “harm without negligence” problem does not just raise questions about whether individuals are able to be autonomous decision-makers; it also raises significant justice concerns. Genetic medicine already has an inclusion and representation problem because variant classification is dependent on understanding the background genetic variation in a population, but “the data that exist largely come from people of European background.”¹⁵⁴ Individuals who belong to racial minority groups have an especially high likelihood of misclassification or reclassification because “most genes were sequenced first in White people, who also tend to have better access to testing.”¹⁵⁵ A significant amount of genetics research has also focused on BRCA1 and BRCA2 mutations, which occur most often in the Ashkenazi Jewish population.¹⁵⁶ Combined with “preference by researchers to analyze data from well-characterized, well-powered European cohorts,” certain groups and communities have enjoyed greater resources to invest in the research enterprise.¹⁵⁷ Eighty-eight percent of people included in large-scale studies of human genetic variation are of European ancestry, as are most participants in clinical trials.¹⁵⁸

Thus, misclassification or later reclassification is more likely to occur in populations for which research has not been conducted. Variant classifications contribute to racial disparities in genetic medicine.¹⁵⁹ These health disparities are increasingly being recognized. In August 2016, a study published in the *New England Journal of Medicine* advocated for sequencing the genomes of diverse populations.¹⁶⁰ The researchers concluded that

153. See Dianne M. Bartels, Bonnie S. LeRoy, Patricia McCarthy & Arthur L. Caplan, *Nondirectiveness in Genetic Counseling: A Survey of Practitioners*, 72 *AM. J. MED. GENETICS* 172, 172 (1997).

154. Hoffman-Andrews, *supra* note 11, at 655; see also Sandra Soo-Jin Lee, *The Ethics of Consent in a Shifting Genomic Ecosystem*, 4 *ANN. REV. BIOMEDICAL DATA SCI.* 145, 146 (2021) (noting that “[s]everal analyses have demonstrated that participation in genetic research is significantly biased toward individuals of European ancestry, and typically includes only a small minority of those who identify as African, Asian, Latinx, or Indigenous”).

155. Bennett, *supra* note 133; see also Jennifer L. Caswell-Jin, Tanya Gupta, Evan Hall, Iva M. Petrovchich, Meredith A. Mills, Kerry E. Kingham, Rachel Koff, Nicolette M. Chun, Peter Levonian, Alexandra P. Lebensohn, James M. Ford & Allison W. Kurian, *Racial/Ethnic Differences in Multiple-Gene Sequencing Results for Hereditary Cancer Risk*, 20 *GENETICS MED.* 234, 236–37 (2018) (showing that among a racially diverse group of people who had multiple-gene panel testing, more than one-third who were not white had a VUS result, whereas one-quarter who were white did).

156. See Sherry I. Brandt-Rauf, Victoria H. Raveis, Nathan F. Drummond, Jill A. Conte & Sheila M. Rothman, *Ashkenazi Jews and Breast Cancer: The Consequences of Linking Ethnic Identity to Genetic Disease*, 96 *AM. J. PUB. HEALTH* 1979 (2006).

157. Chanita H. Halbert & Barbara W. Harrison, *Genetic Counseling Among Minority Populations in the Era of Precision Medicine*, 178 *AM. J. MED. GENETICS* 68, 71 (2018).

158. See Keolu Fox, *The Illusion of Inclusion—the “All of Us” Research Program and Indigenous Peoples’ DNA*, 383 *NEW ENG. J. MED.* 411, 411 (2020).

159. See Hoffman-Andrews, *supra* note 11, at 655.

160. See Arjun K. Manrai, Birgit H. Funke, Heidi L. Rehm, Morten S. Olesen, Bradley A. Maron, Peter Szolovits, David M. Margulies, Joseph Loscalzo & Isaac S. Kohane, *Genetic Misdiagnoses and the Potential for Health Disparities*, 375 *NEW ENG. J. MED.* 655, 663–64

patients of African or unspecified ancestry received misdiagnoses of hypertrophic cardiomyopathy—a disease in which the heart muscle becomes abnormally thick, making it difficult for the heart to pump blood, which can lead to sudden death—due to incorrectly classified variants.¹⁶¹ Thus, nonwhite patients are more likely to suffer unnecessary harms due to an early pathogenic variant classification that is subsequently downgraded to VUS or benign. As Lily Hoffman-Andrews explains, “[t]his means that all of the challenges presented here are disproportionately likely to affect non-White patients, a frustrating and unjust state of affairs.”¹⁶²

This part explores the universe of possible legal solutions and posits that either these individuals should be able to recover in *some* way for the injuries they have sustained, or—ideally—a solution must be adopted that would reduce the likelihood of these harms occurring in the first place. However, any solution may require reliance on various legal regimes. Consequently, the latter approach would not preclude retrospective relief for patients who do suffer injury.

Medicine is always necessarily evolving, and the standard of care must evolve with it. Thus, any potential solution must be careful to avoid swallowing the practice of medicine in its wake. Situations like those experienced by the Mathes family can be distinguished from classic cases on the evolving standard of care, because in the former, the interventions that the patients underwent were not yet the standard of care. In fact, for many hereditary cancers, there is not yet a standard of care,¹⁶³ often adding yet another level of uncertainty to medical decision-making.¹⁶⁴

In evaluating solutions, it is important to keep in mind the myriad of players besides the patient. Among them are genetic testing companies, physicians, regulators, legislators, and the public. Who besides the harmed person should be obliged to help? Who should bear the burden of paying for the harm? If we believe that, all things being equal, the patient should not be the one burdened with the physical and financial harms, then how do we allocate risk?

A. Tort Law Solutions

1. Current Tort Law Solutions Are Inadequate

Tort law is “the law of wrongs.”¹⁶⁵ It addresses “legally *recognized* wrongs of a particular sort.”¹⁶⁶ Fault is the basis for liability in negligence

(2016) (explaining the need for sequencing the genomes of persons of diverse racial and ethnic backgrounds).

161. *See id.* at 659.

162. Hoffman-Andrews, *supra* note 11, at 655.

163. *See* Lisa Campo-Engelstein, *BRCA Preivors: Medical and Social Factors that Differentiate Them from Preivors with Other Hereditary Cancers*, 6 *BIOÉTHIQUE* ONLINE, no. 1, 2017, at 1, 3.

164. *See* Koch, *supra* note 151, at 679.

165. JOHN C.P. GOLDBERG & BENJAMIN C. ZIPURSKY, *RECOGNIZING WRONGS* 2 (2020).

166. *Id.*

cases.¹⁶⁷ However, the types of harms that the Mathes family members suffered are not legally recognized; they have suffered harm in the absence of fault. Cases like that of the Mathes family raise significant questions that strike at the heart of the American tort system. When are harms compensable? What is the purpose of compensation?

Tort law may be inadequate to address harms that arise when genetic testing results are downgraded from pathogenic to a VUS, particularly when individuals have already taken invasive and ultimately harmful action based on the original test results. For one, negligence (or other) cases may be too complicated for attorneys to take on. After the district court's decision in *Williams*, some have opined that "lawyers are still trying to wrap their heads around what variant classification is."¹⁶⁸ One expert stated: "When I've spoken to lawyers about some of the practices that are harming genetics patients, they've all said, 'Oh, no, this is too complicated. There are far easier medical malpractice cases out there.'"¹⁶⁹

However, withholding recovery from individuals who suffer medical harm undermines public trust in medicine. Patients are expected to rely on genetic test results to make life-changing decisions. This process is already rife with uncertainty. At the time they undergo genetic testing, individuals are often at their most vulnerable. They may be struggling with family members' illnesses or deaths and may be concerned that they will have the same fate. In these moments of uncertainty and vulnerability, they are asked to trust the medical system, including the physicians who order genetic tests and the companies that conduct them. And they are expected to trust that, if something goes wrong, it can be fixed, or at least redressed.¹⁷⁰

But as the director of the Division of Cancer Epidemiology and Genetics at the National Cancer Institute observed when interviewed about the Mathes case: "It's not so simple as 'Doctor, do I have to worry or don't I have to worry?' There is a continuum of risk."¹⁷¹ In the absence of reliable answers and without any remedy, patients may be reluctant to rely on medical test results or even to undergo medical testing. This might have a snowball effect, slowing the collection of genetic information that can inform research, thereby making genetic tests less accurate. As one expert tweeted: "We have to make choices about our bodies with incomplete information. Science is an ongoing project, not a fait accompli. That's true of #brca and it's true of health care in general."¹⁷² Faulting patients for making certain decisions

167. See John C.P. Goldberg & Benjamin C. Zipursky, *The Strict Liability in Fault and the Fault in Strict Liability*, 85 FORDHAM L. REV. 743, 745 (2016).

168. Ray, *supra* note 134.

169. *Id.*

170. Others have noted that, generally, medical reversal erodes trust in the medical system. See, e.g., Prasad et al., *supra* note 18, at 1675.

171. Marcus, *supra* note 1.

172. The Risky Body (@theriskybody), TWITTER (Dec. 23, 2019, 9:56 PM), <https://twitter.com/theriskybody/status/1209306801327558656> [https://perma.cc/YAH7-JVTP].

based on current medical information will hinder the advancement of medicine.

Denying recovery to individuals who suffer medical harm, even in the absence of negligence, may therefore result in the inequitable distribution of risk. For one, withholding remedies from individuals who take medical action based on genetic tests that are later downgraded may disadvantage them for being proactive. In other words, the system encourages individuals who receive a pathogenic (and presumably actionable) test result to refrain from taking action in case those test results are later found to be incorrect. However, on the whole, individuals who undergo medical and surgical interventions based on genetic tests results do not do so out of ignorance or as knee-jerk reactions.¹⁷³ An alternative to being proactive—expecting a patient to wait for conclusive results—could result in disease and even more costly medical care.

Thus, our current legal regime effectively puts the moral “blame” on the individual seeking genetic testing (who, in the case of BRCA mutations, is often a woman). As one expert on BRCA mutations described, “[p]eople with known deleterious [BRCA] mutation (like me) are often dismissed as anxious, over cautious by physicians when asking legitimate questions about family history and cancer risk.”¹⁷⁴ A few hours later, she stated, “I hope for a day where we can stop blaming women for facing decisions about” BRCA.¹⁷⁵

2. Tort Law Remedies

When a patient is harmed due to variant reclassification from pathogenic to a variant of unknown significance, they have little legal recourse. Common-law negligence simply falls short. Currently, legal rules do not acknowledge the individuals who rely on up-to-date scientific information to make complex and invasive medical choices, only to discover that those interventions were unnecessary. Despite the fact that it seems that these individuals should be entitled to redress—or be able to avoid risk of unnecessary surgeries and interventions—the system seems to be intentionally hostile to patients’ interests.

173. See, e.g., Andrea Downing (@BraveBosom), TWITTER (Dec. 23, 2019, 4:58 PM), <https://twitter.com/BraveBosom/status/1209231778445021185> [<https://perma.cc/66KQ-F7NU>] (“Consider nuance: patients need evidence about #BRCA to make informed decisions. Instead of blaming our haste to jump into radical procedures or ‘dangers’ of genetic testing. It’s about changing systemic problem rooted in data-sharing and lack of access. Big difference.”).

174. Andrea Downing (@BraveBosom), TWITTER (Dec. 23, 2019, 5:05 PM), <https://twitter.com/BraveBosom/status/1209233472864210944> [<https://perma.cc/N2WK-Q9E8>]. She continued, “[r]espectfully that’s the 99% of us that do not fall into the edge case of this WSJ story.” *Id.*

175. Andrea Downing (@BraveBosom), TWITTER (Dec. 23, 2019, 10:13 PM), <https://twitter.com/BraveBosom/status/1209311169627865089> [<https://perma.cc/CW2J-76ND>].

As an initial matter, it may be useful to briefly consider the primary theories of tort in an effort to address whether these theories may justify redress, even if current tort rules would not allow it. To the extent that a negligence claim could be applicable to variant downgrading after a patient has undergone medical interventions, an economic theory of tort law—which would seek to minimize the costs of injury—may justify redress. In contrast, various theories of justice do not justify compensating these patients. In the absence of wrongdoing, corrective justice, which holds those at fault accountable, is inapplicable. The principle of retributive justice is similarly inappropriate. Perhaps the principle of distributive justice would justify compensating individuals who have undergone invasive medical interventions based on genetic variants that are later reclassified, as it focuses on the fair distribution of resources, including risk.¹⁷⁶ In their analysis of legal duties that might arise when laboratories reclassify a genetic variant, Professor Jessica L. Roberts and Alexandra L. Foulkes recognize that patients bear “a significant number of costs” in the context of variant reclassification.¹⁷⁷ Notably, with the advent of precision medicine, patients are progressively more burdened by shifting risk.¹⁷⁸

Tort law is generally described as having two main goals (or at least two primary effects): deterring harms and compensating those who have been injured by others.¹⁷⁹ But deterrence principles, with their emphasis on fault, have dominated the application of modern tort doctrine.¹⁸⁰ In cases in which individuals suffer medical harm in the absence of negligence, the focus on deterrence becomes moot because of the absence of questions of fault and wrongdoing. Rather, the focus shifts to redress for the individuals who are harmed.

176. See Roberts & Foulkes, *supra* note 9.

177. *Id.* at 183 (arguing that “[s]hould courts opt to impose legal duties related to variant reclassification, laboratories and ordering physicians will have to make updated information available to all potentially impacted patients, not just those who develop symptoms”). Further, with the evolution of the doctor-patient relationship and the advent of new and more advanced technologies, patients also increasingly bear the burden of dealing with uncertainty. See Koch, *supra* note 151, at 666 n.108 (“[T]he sociopsychological burden of uncertainty will be shifted to patients. Paradoxically, the burden of uncertainty inherent in a probabilistic diagnosis will be increased by the expectation that the purportedly ‘precise’ diagnosis will empower patients by giving them the opportunity to make better-informed decisions about future treatment.” (quoting Gil Eyal, Maya Sabatello, Kathryn Tabb, Rachel Adams, Matthew Jones, Frank R. Lichtenberg, Alondro Nelson, Kevin Ochsner, John Rowe, Deborah Stiles, Kavita Sivaramakrishnan, Kristen Underhill & Paul S. Appelbaum, *The Physician-Patient Relationship in the Age of Precision Medicine*, 21 *GENETICS MED.* 813, 814 (2019))).

178. See Koch, *supra* note 151, at 666.

179. See John C.P. Goldberg, *Twentieth-Century Tort Theory*, 91 *GEO. L.J.* 513, 525 (2003). Professors Goldberg and Zipursky posit that deterrence and compensation are not the goals of the tort system, but instead are the “beneficial effects of having tort law.” GOLDBERG & ZIPURSKY, *supra* note 165, at 29. Rather, the purpose of tort is to redress wrongs.

180. See Benjamin Sundholm, *Strict Liability for Genetic Privacy Violations in the Age of Big Data*, 49 *U. MEM. L. REV.* 759, 774 (2019) (“Because fault principles dominate contemporary tort theory, tort law’s deterrence goals have received a disproportionate amount of attention relative to compensation aims.” (citing James A. Henderson, Jr., *Why Negligence Dominates Tort*, 50 *UCLA L. REV.* 377, 377, 380, 404 (2002))).

One potential solution is the establishment of a new negligence claim. However, while courts have historically accepted novel negligence claims,¹⁸¹ doing so here is not a viable solution. Often, when a new tort is established, it usually arises from a newly conceived duty. Here, it is difficult, based on the considerations addressed in Part II.A, to determine what that duty might actually be.

Alternatively, one could imagine proposing a strict liability regime for circumstances in which patients suffer harm due to medical interventions taken before a genetic variant is reclassified. Strict liability, or liability without fault, has been defined as “liability that is imposed on an actor *apart from* either (1) an intent to interfere with a legally protected interest without a legal justification for doing so, or (2) a breach of a duty to exercise reasonable care, i.e., actionable negligence.”¹⁸² Expansion of strict liability has been embraced by theorists and scholars such as Judge Guido Calabresi in order to place “responsibility for injuries with the agent who is best positioned to conduct an analysis regarding the cost of those accidents”¹⁸³ and “who can most readily avoid the potential harms.”¹⁸⁴ So, in a way, strict liability may also have a deterrent effect, by making risky behavior more expensive “and, as a result, making safer alternatives more desirable.”¹⁸⁵

Justice Oliver Wendell Holmes wrote that the general principle of the law is “that loss from accident must lie where it falls, and this principle is not affected by the fact that a human being is the instrument of misfortune.”¹⁸⁶ In a sense, strict liability counteracts this principle.¹⁸⁷ Rather, the doctrine shifts initial liability to the injurer, rather than the injured.¹⁸⁸ In elucidating what he calls the “relational approach to tort law,” Professor Timothy D. Lytton observed that “support for the tort system, despite its gross

181. And other negligence claims have been proposed. In 1985, Professor Marjorie Maguire Shultz recommended “the creation of a distinct and independently protected interest in patient autonomy.” Marjorie Maguire Shultz, *From Informed Consent to Patient Choice: A New Protected Interest*, 95 YALE L.J. 219, 223–24, 229 (1985). Similarly, Professor E. Haavi Morreim has called for the establishment of a “distinct dignitary tort”—those harms that are “caused by conduct that overrides patients’ autonomy,” treats them as less than human, and denigrates them as human beings—for “serious deficiencies of informed consent.” E. Haavi Morreim, *Medical Research Litigation and Malpractice Tort Doctrines: Courts on a Learning Curve*, 4 HOUS. J. HEALTH L. & POL’Y 1, 74 (2003).

182. W. PAGE KEETON, PROSSER AND KEETON ON THE LAW OF TORTS § 75, at 534 (5th ed. 1984) (emphasis added). As a general rule, strict liability applies in three situations: (1) wild animals, (2) abnormally dangerous activities, and (3) products liability. The Restatement (Third) of Torts identifies three types of products liability claims: manufacturing defects, design defects, and information defects. RESTATEMENT (THIRD) OF TORTS: PROD. LIAB. § 2 (AM. L. INST. 1998).

183. Sundholm, *supra* note 180, at 792.

184. Roberts & Foulkes, *supra* note 9, at 187 (discussing GUIDO CALABRESI, THE COSTS OF ACCIDENTS: A LEGAL AND ECONOMIC ANALYSIS (1970)).

185. Sundholm, *supra* note 180, at 795.

186. OLIVER WENDELL HOLMES, THE COMMON LAW 87 (Belknap Press of Harvard Univ. Press 2009) (1881).

187. See Jules L. Coleman, *The Morality of Strict Liability*, 18 WM. & MARY L. REV. 259, 260 (1976).

188. *See id.*

inefficiencies, arises largely from the belief that it clarifies matters of wrongdoing and injustice in addition to providing compensation and deterrence.”¹⁸⁹ According to Professor Lytton, strict liability locates wrongfulness in the outcome of the action, rather than the actor’s state of mind (i.e., intentional torts) or the “inadequacy of a person’s conduct when compared to reasonable behavior” (i.e., negligence).¹⁹⁰

So, could laboratories or physicians have prevented the harm in cases like those of the Mathes family? Perhaps, if the initial classification was not based on sound scientific evidence. However, the holding in *Belser* suggests that a testing company’s inappropriate reliance (or lack thereof) on existing studies is “a failure of administrative oversight, not the exercise of discretion in the practice of genetics.”¹⁹¹

As the authors of one study of the incidence of variant misclassification predicted:

Due to the magnitude of impact that certain genetic test results may bring, laboratory directors may feel a responsibility to not “overcall” variants. Legal questions could arise if a *BRCA1* variant was downgraded to benign after previously being called pathogenic. Women may have performed prophylactic surgery based on this result. It is unclear who, if any group, is responsible for this event or if it is a natural risk of medicine in general. For these reasons, it can be in the best interest of the laboratory and patient to confirm that the laboratory has enough relevant data before they classify a variant as pathogenic.¹⁹²

If strict liability were to be extended to genetic testing companies in such cases, it might spur them to ensure more caution in their variant classification process to minimize subsequent reclassification. However, this potential result may run counter to one of the commonly understood goals of strict liability. Activities subject to strict liability are considered to be valuable while posing inherent risks, such that the tort system compensates victims of the manifestation of those risks, even if there was no way to prevent them. Strict liability is generally imposed when potential liability cannot lead to increased precautions. In the case of reclassification, genetic testing companies may be incentivized to ensure more robust research to guarantee adequate data that supports a likely pathogenic or pathogenic classification before returning results to patients.¹⁹³ However, imposing strict liability in

189. Timothy D. Lytton, *Rules and Relationships: The Varieties of Wrongdoing in Tort Law*, 28 SETON HALL L. REV. 359, 386 (1997).

190. *Id.* at 369.

191. *Belser v. Quest Diagnostics, Inc.*, No. 16-0972, 2020 WL 6526084, at *7, *9 (D.S.C. Nov. 5, 2020) (acknowledging “the difference between an administrative exercise of noting the existence of scientific literature and a professional judgment as to whether the literature has been sufficiently vetted to confirm its reliability and relevance”).

192. Macklin et al., *supra* note 87, at 349.

193. See Mersch et al., *supra* note 37, at 1267 (“Given the clinical implications of genetic testing, accurate and timely variant classification is increasingly important for appropriate long-term patient care. It is, therefore, critical that new information for variants in cancer-risk genes be reviewed by testing laboratories in order to evaluate whether reclassification is appropriate. This is done in an effort to ensure that patients with increased cancer risk receive

these types of cases may induce genetic testing companies to be more careful, thereby leading them to delay classifying variants until full and complete data has been collected, in order to avoid potential liability. While the Mathes family would have benefited from this shift, it might lead others who would have undergone prophylactic interventions under the current regime to not receive actionable results until it is too late.

Providing individuals who experience harm due to an inaccurate variant classification with access to a strict liability claim serves two purposes. First, it eliminates many of the “doctrinal barriers imposed by fault-based tort law,”¹⁹⁴ thereby increasing ability for individuals to be compensated for harms. Second, a strict liability regime may influence genetic testing companies to anticipate the potential downgrading of variants that had been previously classified as pathogenic, thereby ensuring “that at least some form of compensation—fiscal or otherwise—is available” to these individuals and serving as “acknowledgement of the wrong they have suffered.”¹⁹⁵

And while this may not be the type of fact pattern that strict liability was historically intended to redress,¹⁹⁶ it would not be the first time we’ve seen arguments in favor of expanding the scope of strict liability. For example, scholars have recommended it in the context of psychotherapists’ liability for the release of imprisoned people with mental illness.¹⁹⁷ And, significantly, the development of strict liability doctrine in the context of products liability was heavily influenced by the American Law Institute’s recognition, in its restatements, of the need to adopt the doctrine in the case of defective products.¹⁹⁸

Despite the arguments in favor of expanding strict liability to address circumstances like the one the Mathes family faced, doing so may have a fatal flaw: strict liability still requires that the defendant *cause harm* to the

appropriate screening, risk-reducing surgical interventions, or both while those with lower risk avoid unnecessary interventions.”).

194. Sundholm, *supra* note 180, at 796.

195. *Id.*

196. Further, predictive genetic tests are generally not considered “products”; rather, they are defined as “services.” Ossorio, *supra* note 64, at 240 (“Courts have been unanimous in refusing to apply products liability doctrine to professional services, including medical and legal services. Product liability applies, however, to genetic tests sold as kits for use by parties other than the manufacturer.”). Scholars have argued for a more consistent interpretation of “product” that anticipates and includes emerging technologies, based on the policy objectives underlying strict liability law. See David W. Lannetti, *Toward a Revised Definition of “Product” Under the Restatement (Third) of Torts: Products Liability*, 35 TORT & INS. L.J. 845, 887–89 (2000). However, Professor Ossorio observes that “the doctrine concerning liability for medical products has evolved away from liability in the absence of fault.” Ossorio, *supra* note 64, at 242 n.15. Thus, even if genetic tests fall under the definition of “products,” individuals such as the Mathes family members may still be unable to recover without proving wrongdoing.

197. See *Psychotherapists’ Liability for the Release of Mentally Ill Offenders: A Proposed Expansion of the Theory of Strict Liability*, 126 U. PA. L. REV. 204, 239–40 (1977).

198. See Marshall S. Shapo, *In Search of the Law of Products Liability: The ALI Restatement Project*, 48 VAND. L. REV. 631, 632–33 (1995).

plaintiff.¹⁹⁹ As demonstrated in Part II, causation is a difficult element to prove in these cases because there is no recognizable wrongdoing.²⁰⁰ Professor Lytton's conceptualization that strict liability requires wrongdoing would undercut an application of the doctrine to our fact pattern. He argues that "[t]he language of wrongdoing pervades negligence and strict liability claims," as reflected in the "sense of injustice" (in contrast to misfortune) in certain tort claims.²⁰¹

Faced with a case similar to that of the Mathes family, a judge may be reluctant to find that an injustice has occurred. The physicians and laboratory applied the most up-to-date scientific data and followed the standard of care for returning genetic test results. Instead, what happened to these seven family members may more aptly be categorized as an unfortunate and rare confluence of events.²⁰²

B. No-Fault Compensation System

As Part III.A describes, relying on the tort system to redress the harm that individuals suffer after a variant is downgraded is an inadequate approach.²⁰³ In contexts such as these, injured individuals may instead seek recovery outside the tort system. While not universally available, in certain cases, no-fault compensation systems have sometimes been implemented. No-fault compensation systems simplify the process of recovery for plaintiffs while limiting litigation costs and payments for defendants.

No-fault compensation schemes are frequently premised on a specialty-court model, like the "vaccine court."²⁰⁴ The National Vaccine Injury Compensation Program (NVICP) is administered through the Office of Special Masters in the U.S. Court of Federal Claims.²⁰⁵ The NVICP permits individuals injured by vaccines to petition the federal government for

199. See RICHARD EPSTEIN, A THEORY OF STRICT LIABILITY: TOWARD A REFORMULATION OF TORT LAW 15 (1980).

200. See *supra* Part II.

201. Lytton, *supra* note 189, at 385.

202. In an empirical study, Professors Richard L. Cupp Jr. and Danielle Polage found that jurors hearing a case under negligence language (which "may draw on emotionally 'hot' notions of fairness and fault") were more likely to find the defendant liable than jurors hearing a case under the "cold" technical concepts of strict liability. Richard L. Cupp Jr. & Danielle Polage, *The Rhetoric of Strict Products Liability Versus Negligence: An Empirical Analysis*, 77 N.Y.U. L. REV. 874, 874 (2002). The study presents a "challenge to the notion that strict liability is generally a pro-plaintiff doctrine under courts' increasingly dominant approaches to design and warning cases." *Id.* Thus, applying strict liability instead of negligence may not benefit potential plaintiffs like the Mathes family, as their claims may not result in liability for the testing company that returned the misclassified results.

203. See *supra* Part III.A.

204. The National Vaccine Injury Compensation Program (NVICP) established the vaccine court. See National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755 (codified as amended in scattered sections of 21 and 42 U.S.C.).

205. See *Vaccine Claims/Office of Special Masters*, U.S. CT. OF FED. CLAIMS, <https://www.uscfc.uscourts.gov/vaccine-program-readmore> [https://perma.cc/HS2P-563Y] (last visited Nov. 7, 2022).

compensation.²⁰⁶ Claimants present their medical records to the vaccine court to demonstrate that, shortly after they were vaccinated, they developed one of several adverse events listed in a “vaccine injury table.”²⁰⁷ A system like the NVICP’s might similarly address harms such as those experienced by the Mathes family. Harms inevitably arise in such circumstances, lawsuits might be prohibitive, and it behooves the industry to fund a system to obviate risk.²⁰⁸

States have also implemented no-fault compensation systems in some circumstances in which causation is difficult to prove. The Florida Birth-Related Neurological Injury Compensation Association (NICA) provides limited recovery, irrespective of fault, for infants who have sustained a birth-related neurological injury.²⁰⁹ With exceptions, NICA provides the exclusive remedy in cases in which an infant suffers such an injury, and the physician who delivered obstetrical services in connection with the birth participates in the program.²¹⁰ The Florida Board of Medicine requires that physicians who deliver such services pay into NICA unless they fit into specific categorical exemptions.²¹¹

206. *See id.*

207. *See Covered Vaccines*, HEALTH RES. & SERVS. ADMIN., <https://www.hrsa.gov/vaccine-compensation/covered-vaccines> [<https://perma.cc/W6DU-7PKC>] (last visited Nov. 7, 2022) (providing the most up-to-date vaccine injury table and explaining how to determine whether an injury is covered).

208. Other examples of no-fault compensation systems include special victim compensation funds, which provide compensation to victims of major catastrophes. These include the September 11th Victim Compensation Fund, the Deepwater Horizon Oil Spill Trust, and One Fund Boston. *See* SEPT. 11TH VICTIM COMP. FUND, <https://www.vcf.gov/> [<https://perma.cc/A6UU-ZGSR>] (last visited Nov. 7, 2022); Nanciann Regalado, *Historic NRDAR Settlement Reached for Deepwater Horizon Spill*, U.S. DEP’T OF THE INTERIOR (Sept. 3, 2020), <https://www.doi.gov/restoration/historic-nrdar-settlement-reached-deepwater-horizon-spill> [<https://perma.cc/Q4F5-YMGY>]; *Massachusetts Crime Victim Compensation Antiterrorism Program for Bombing Survivors*, OFF. FOR VICTIMS OF CRIME (July 29, 2016), <https://ovc.ojp.gov/funding/awards/2016-rf-gx-0002> [<https://perma.cc/29WT-22N5>]. These funds are often congressionally ordered and administered. In many cases, to recover from these funds, plaintiffs must waive their rights to sue.

209. *See* FLA. STAT. §§ 766.301–766.316 (2022); *CS/CS/SB 1786—Florida Birth-Related Neurological Injury Compensation Plan*, FLA. SENATE, <https://www.flsenate.gov/Committees/bills/summaries/2021/html/2450> [<https://perma.cc/TMG5-QY6M>] (last visited Nov. 7, 2022). Virginia also enacted its Birth-Related Neurological Injury Compensation Act in 1987. VA. CODE ANN. §§ 38.2-5001 to 38.2-5021 (2022).

210. *See* FLA. SENATE, BILL ANALYSIS AND FISCAL IMPACT STATEMENT 2 (2021), <https://www.flsenate.gov/Session/Bill/2021/1786/Analyses/2021s01786.pre.bi.PDF> [<https://perma.cc/V7S2-SVCW>].

211. *Am I Required to Pay the Florida Birth-Related Neurological Injury Compensation Association (NICA) Fee?*, FLA. BD. OF MED., <https://flboardofmedicine.gov/help-center/am-i-required-to-pay-the-florida-birth-related-neurological-injury-compensation-association-nica-fee/> [<https://perma.cc/L54Z-ZS3V>] (last visited Nov. 7, 2022) (“You are required to pay the NICA fee unless you meet the following exemption criteria per s. 766.314, F.S.:

- Resident physicians, assistant resident physicians and interns in postgraduate training programs approved by the Board of Medicine
- Retired physicians who maintain an active license, but who have withdrawn from the practice of medicine

Finally, workers' compensation is based on a system in which employers pay into a workers' compensation fund.²¹² Injured employees can recover without having to prove the defendant's fault, regardless of any comparative negligence.²¹³ This type of no-fault compensation system consists of "a self-governed insurance/self-insurance program, rather than a specialty court or nationwide compensation fund."²¹⁴ These plans are intended to "treat like cases alike, offer fair compensation, and disburse compensation with maximum efficiency and minimum administrative cost."²¹⁵

No-fault compensation has frequently been proposed to redress medical injury as an alternative to traditional liability systems.²¹⁶ Recognizing that "with modern medicine's capacity to alleviate disease, injury, and disability comes significant risks that it may independently cause harm,"²¹⁷ scholars have concluded that "a form of no-fault is clearly feasible for at least some medical issues" and "no-fault delivers benefits quite similar in value to tort, but much faster and with far lower administrative costs."²¹⁸

Shifting the burden of responsibility to clinical laboratories would serve multiple purposes. First, these companies are better positioned to take precautions to avoid misclassification in the first place, and when reclassification becomes necessary, they are in the best position "to efficiently redress injuries" and to "internalize the costs of compensation or shift those costs to society downstream."²¹⁹ In other words, individuals who have already undergone invasive unnecessary medical interventions will not also be expected to absorb the costs of decisions that have been made based on results returned to them by genetic testing companies. Instituting a

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- Physicians who hold a limited license, as defined by s. 458.317, F.S., who do not receive any compensation for medical services
 - Physicians employed full-time by the Veterans Administration whose practice is confined to VA hospitals
 - Any licensed physician on active duty with the Armed Forces of the United States
 - Physicians employed full-time by the State of Florida whose practice is confined to state-owned correctional institutions and state-owned mental health facilities").

212. See generally Emily A. Spieler, *Perpetuating Risk?: Workers Compensation and the Persistence of Occupational Injuries*, 31 HOUS. L. REV. 119, 122 (1994).

213. See *id.* at 168–71 (describing the workers' compensation no-fault system).

214. Leslie Meltzer Henry, Megan E. Larkin & Elizabeth R. Pike, *Just Compensation: A No-Fault Proposal for Research-Related Injuries*, 2 J.L. & BIOSCIENCES 645, 648 (2015).

215. *Id.* at 645–46.

216. See, e.g., Randall R. Bovbjerg, Frank A. Sloan & Peter J. Rankin, *Administrative Performance of "No-Fault" Compensation for Medical Injury*, 60 L. CONTEMP. PROBS. 71, 71 (1997). A no-fault compensation system also requires some level of administrative responsibility and bureaucracy. That said, "because individual institutions can implement this system voluntarily, the approach does not require the creation of a new centralized bureaucracy." Henry et al., *supra* note 214, at 657.

217. David M. Studdert & Troyen A. Brennan, *Toward a Workable Model of "No-Fault" Compensation for Medical Injury in the United States*, 27 AM. J.L. & MED. 225, 227 (2001).

218. Bovbjerg et al., *supra* note 216, at 106. The authors analyzed Virginia's and Florida's no-fault compensation systems for birth-related neurological injuries and concluded that they "work[] successfully." *Id.* "That is, premiums are collected, and claims are received, investigated, and paid with not unreasonable results in an area that is very contentious in tort. In this, our interviews and other observations accord with prior study." *Id.*

219. Henry et al., *supra* note 214, at 654.

no-fault compensation system might create incentives for laboratories “to manage and mitigate risks by forcing institutions to internalize the financial costs of . . . harms.”²²⁰

Under these types of insurance-like no-fault compensation systems, however, compensation is generally received in exchange for an agreement not to sue. Often, no-fault compensation funds were established to protect companies, like BP in the case of the Deepwater Horizon oil spill, from going out of business due to tort liability. In contrast, as demonstrated in Part II, in the cases like that of the Mathes family, there is little to no threat of tort liability against the physicians who ordered the genetic test or the clinical laboratories who conducted the test.²²¹ Thus, there is little to incentivize genetic testing companies to voluntarily “buy in” to an insurance program to redress reclassification of genetic variants, since there is a little chance that those who are injured due to the misclassification would be able to sue in the first place.²²² Any no-fault compensation system for harms that arise from prophylactic medical decisions based on information that later turns out to be incorrect should include incentives for companies to “buy in.” Further, most no-fault compensation systems address physical harms alone, rather than emotional damages, including pain and suffering. Therefore, a classic no-fault system may be insufficient to address the types of harms at issue in the present case.

C. Regulatory Solutions

Current regulations are similarly inadequate to address harms that arise when individuals take prophylactic action before genetic variants are reclassified. There is a dearth of regulation related to variant classification because “[v]ariant classification has traditionally been treated as ‘art of medicine’ rather than science.”²²³ As explained in a review of genetic variant classification and its impact on test accuracy, “[a]rt of medicine falls under clinician licensure rather than Clinical Laboratory Improvement Amendments (CLIA) or College of American Pathologists (CAP) accreditation.”²²⁴

Despite the 2015 ACMG guidelines’ determination that a 90 percent certainty in either direction was sufficient to describe a variant as either likely pathogenic or likely benign, “sufficiently large orthogonally validated truth sets are not publicly available to actually quantify laboratories’ certainty of variant classifications; therefore, the certainty concept remains aspirationally

220. *Id.* at 657.

221. *See supra* Part II.

222. Further, no-fault compensation systems like the NVICP intend to serve a dual role: encouraging companies to create and manufacture vaccines and supporting the public to get vaccinated. A no-fault compensation system for genetic tests may not serve these same goals. Although encouraging companies to develop tests based on sound scientific evidence is an important objective, it is not clear that our policies should advance taking action on genetic tests given current levels of uncertainty.

223. Giles et al., *supra* note 20, at 288.

224. *Id.*

qualitative.”²²⁵ Any regulatory solution to the “harm without negligence” problem needs to incentivize accuracy to protect patient safety, ensuring that test results are supported with robust data and research.

Under the authority of the Federal Food, Drug, and Cosmetic Act²²⁶ (FDCA), the U.S. Food and Drug Administration (FDA) regulates medical “devices,” which are defined as instruments and related articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease or intended to affect a bodily structure or function.²²⁷ Depending on how a genetic test is produced and marketed, it can be regulated as either an in vitro diagnostic device (IVD) or a laboratory developed test (LDT). Laboratory developed tests are IVDs designed, manufactured, and used within a single laboratory.²²⁸ According to a 2008 study, IVDs subject to FDA review make up only about 1 percent of the commercially available genetic tests.²²⁹

IVDs that are not LDTs must comply with the FDA’s medical device regulations, which require clearance or premarket approval before they can be legally used.²³⁰ Thus, FDA regulations establish “several layers of oversight” for these types of diagnostics.²³¹ In contrast, the FDA does not hold LDTs to the same standards. While the FDA has taken the position that LDTs are medical devices and are therefore within the agency’s jurisdiction, it has historically exercised enforcement discretion over these tests.²³² Thus, the FDA has not generally required clinical laboratories to comply with IVD requirements for their LDTs.²³³ According to one report, “[t]he fact that a

225. *Id.*

226. Ch. 675, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301–399).

227. 21 U.S.C. § 321(h).

228. U.S. FOOD & DRUG ADMIN., FRAMEWORK FOR REGULATORY OVERSIGHT OF LABORATORY DEVELOPED TESTS (LDTs): DRAFT GUIDANCE FOR INDUSTRY, FOOD AND DRUG ADMINISTRATION STAFF, AND CLINICAL LABORATORIES (2014), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/framework-regulatory-oversight-laboratory-developed-tests-ltds> [<https://perma.cc/3LPZ-KR7X>]. The definition of LDT has always been somewhat murky. See Turna Ray, *Labs Scramble After FDA Loosens Regulations on Some Tests*, MODERNHEALTHCARE (Aug. 31, 2020), <https://www.modernhealthcare.com/supply-chain/labs-scramble-after-fda-loosens-regulations-some-tests> [<https://perma.cc/A9X8-YFB3>] (“The FDA defines LDTs as tests that are developed, validated and performed by the same lab. But there have been times when the lab industry has launched tests expecting to fall under FDA’s enforcement discretion only to be told that they aren’t LDTs and require premarket review.”).

229. See Jennifer A. Gniady, *Regulating Direct-to-Consumer Genetic Testing: Protecting the Consumer Without Quashing a Medical Revolution*, 76 FORDHAM L. REV. 2429, 2438 (2008).

230. See Rachel E. Sachs, *Regulating Intermediate Technologies*, 37 YALE J. REG. 219, 244–46 (2020) (describing the FDA’s process for approving new medical devices).

231. See THE PEW CHARITABLE TRS., *supra* note 72.

232. See Ray, *supra* note 228 (noting that the FDA typically uses its “enforcement discretion” with regard to LDTs, and has “left it up to [the Centers for Medicare & Medicaid Services] to oversee labs under federal standards outlined under the Clinical Laboratory Improvement Amendments (CLIA)”).

233. See Gail H. Javitt & Katherine Strong Carner, *Regulation of Next Generation Sequencing*, 42 J.L. MED. & ETHICS 9, 14 (2014); Patricia J. Zettler, Jacob S. Sherkow & Hank T. Greely, *23andMe, the Food and Drug Administration, and the Future of Genetic Testing*, 174 JAMA INTERNAL MED. 493, 493–94 (2014).

medical professional is involved in ordering genetic tests and providing the results helps move them out of range of FDA regulation.”²³⁴

Whether a genetic test is classified as an LDT or an IVD has enormous ramifications for how they are regulated. Devices are determined to be safe and effective based on three factors: analytic validity, clinical validity, and clinical utility.²³⁵ Analytic validity asks, among other things, whether the test works and whether it is, in fact, testing the correct person’s data.²³⁶ Clinical validity asks whether the presence of the mutation sheds light on whether the person’s health will be affected, or whether there is a valid association between having a variant and having a health implication.²³⁷ And clinical utility inquires whether this knowledge is actionable—i.e., will it actually improve health outcomes?²³⁸ In the case of IVDs, the FDA requires proof of both analytic and clinical validity. The fact that a physician has ordered the test appears to—at least in practice—remove genetic tests out of the FDA’s jurisdiction, despite the fact that such tests are not necessarily more accurate or reliable than other IVDs. Dr. Michael F. Murray of Yale University has explained that “[t]he FDA, rather than choosing to specifically insert itself, has decided that having a licensed medical professional order the test is enough protection for the consumer—patient—whatever you want to refer to that person as—so that [the FDA doesn’t] have to specifically step in.”²³⁹

Instead, companies like Myriad are regulated by the Clinical Laboratory Improvement Amendments of 1988²⁴⁰ (CLIA). The Centers for Medicare & Medicaid Services (CMS) regulate laboratory testing (except research) performed on humans in the United States.²⁴¹ CLIA governs all clinical laboratories operating in or returning test results to individuals in the United States, where clinical laboratories are defined as any laboratory that tests human specimens to provide information for the diagnosis, prevention, treatment of any disease or impairment, or assessment of health.²⁴²

CLIA certification is required for clinical laboratory testing on specimens collected for health purposes (i.e., for the diagnosis, prevention, or treatment of disease or impairment) using minimum quality standards, where research

234. Ike Swetlitz, *Genetic Tests Ordered by Doctors Race to Market, While ‘Direct-to-Consumer’ Tests Hinge on FDA Approval*, STAT (Mar. 16, 2018), <https://www.statnews.com/2018/03/16/genetic-tests-fda-regulation/> [<https://perma.cc/YK5T-9M59>].

235. See Gniady, *supra* note 229, at 2442–46 (describing these three factors).

236. See *id.* at 2442–43.

237. See SARAH A. ROBINSON, ALISON R. CARTER & DAVID A. BRINDLEY, *THE CHANGING REGULATORY LANDSCAPE FOR LABORATORY DEVELOPED TESTS* (2021), https://www.raps.org/RAPS/media/news-images/Feature%20PDF%20Files/21-8_Robinson-et-al.pdf [<https://perma.cc/LDF4-TJMD>] (noting that clinical validity is an “assessment of how well a test can diagnose or predict a clinical condition”).

238. See Gniady, *supra* note 229, at 2446.

239. Swetlitz, *supra* note 234, at 4.

240. 42 U.S.C. §§ 201 note, 263a; see 42 C.F.R. § 493.

241. See 42 C.F.R. § 493.1.

242. See *id.* § 263a(a).

is returned and specimens have a unique identifier.²⁴³ Unlike the FDA regulations, CLIA only requires proof of analytic validity.²⁴⁴

In 2014, the FDA indicated that it was considering premarket review of LDTs by publishing draft guidelines involving a risk-based approach.²⁴⁵ However, in 2016, it became clear that the new guidelines would not be finalized.²⁴⁶ The continued delay in announcing a proposed policy might reflect the inherent difficulty of determining clinical validity for genetic tests. Recently, The Pew Charitable Trusts called for Congress to step in to authorize the FDA to review LDTs, citing the risks that failure to do so presents to patients.²⁴⁷ Specifically, such legislation should allow the “FDA to require that higher-risk LDTs be reviewed for both analytical and clinical validity—both of which are key criteria for ensuring test accuracy, reliability, and usefulness—before they’re used on patients.”²⁴⁸ It opined: “LDTs serve an important role in medicine and public health, but they must be held to the same standards for accuracy and reliability that apply to tests manufactured by device companies. This approach requires risk-based oversight from FDA and increased transparency from the entire diagnostics industry.”²⁴⁹

243. See Susan M. Wolf, Pilar N. Ossorio, Susan A. Berry, Henry T. Greely, Amy L. McGuire, Michelle A. Penny & Sharon F. Terry, *Integrating Rules for Genomic Research, Clinical Care, Public Health Screening and DTC Testing: Creating Translational Law for Translational Genomics*, 48 J.L. MED. & ETHICS 69, 73 (2020).

244. See Thorogood et al., *supra* note 131, at 839 (“The Clinical Laboratory Improvement Amendments regulations that govern clinical laboratories in the United States address analytic validity but do not impose mandatory standards for determining the clinical validity of a particular genetic test.”); see also Michael J. Malinowski & Robin J.R. Blatt, *Commercialization of Genetic Testing Services: The FDA, Market Forces, and Biological Tarot Cards*, 71 TUL. L. REV. 1211, 1230 (1997) (describing “home-brew” tests, which are tests that are performed in-house by its manufacturer and marketer; home-brew tests are services, not products, and are not subject to products liability law); Ossorio, *supra* note 64, at 243 (arguing that marketing the test as a home brew allows companies to avoid routine FDA review and noting that laboratories that perform home-brew testing are subject to regulation and oversight under CLIA; however, because CLIA does not yet recognize genetic testing as a specialty, it contains no regulations designed particularly to assess the accuracy and the reliability of genetic tests).

245. See Letter from Sally Howard, Deputy Comm’r, U.S. Food & Drug Admin., to Tom Harkin, Chairman, U.S. Senate Comm. on Health, Educ., Lab. & Pensions (July 31, 2014), <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM407409.pdf> [<https://perma.cc/C28P-TE9M>]. However, the FDA has since announced that it will delay this plan. See Sheila Kaplan, *FDA Puts off Closing Lab-Test “Loophole,” Leaving Decision to Congress and Trump*, STAT (Nov. 18, 2016), <https://www.statnews.com/2016/11/18/fda-lab-test-loophole/> [<https://perma.cc/2NM2-L9VG>].

246. And, in August 2020, the U.S. Department of Health and Human Services announced that the FDA could not require premarket review of LDTs without notice-and-comment rulemaking, effectively limiting any FDA authority over such tests. See Ray, *supra* note 228 (“However, noting the growth and changing marketing practices within the lab industry, the FDA from time to time has tried to regulate LDTs in a piecemeal fashion through guidance.”).

247. See THE PEW CHARITABLE TRS., *supra* note 72, at 1 (“Congress should pass legislation that would increase the transparency of the market and authorize FDA to review them based on their risks to patients.”).

248. *Id.* at 4.

249. *Id.*

The FDA's reluctance or inability to regulate LDTs and ensure not only analytic validity but also clinical validity and utility may be partly to blame for the ordeals faced by the Mathes family and other patients.²⁵⁰ Because the FDA exercises its enforcement discretion, LDTs "exist in a loophole, and most are not subject to any analysis to gauge their clinical validity before marketing and use."²⁵¹

The FDA is best positioned to ensure that, if a company is going to report a variant as pathogenic, it is, in fact, pathogenic.²⁵² Professor Rachel Sachs has explained that "without FDCA regulation, the question of how accurately Myriad's test is able to predict a woman's risk for cancer is unknown."²⁵³ The FDA, when it regulates medical devices, looks at particular tests and whether they work.²⁵⁴ In contrast, CLIA is more focused on the operations of the laboratory.²⁵⁵ Thus, had the FDA exercised its enforcement authority over the genetic test that the Mathes family members used, both analytic validity and clinical validity might have been ensured, and the variant might have been correctly classified before results were returned to the patients.

The lack of regulation of genetic testing laboratories was highlighted in *Williams*.²⁵⁶ Professor Wagner has explained: "[*Williams*] underscores a problem we have with ensuring adequate quality of genetic testing laboratories Americans currently place heavy reliance upon CLIA accreditations of laboratories for consumer protection. I think this reliance is misplaced."²⁵⁷ And Professor Cook-Deegan has stated that *Williams* "really illustrates how sloppy things can be in reporting a genetic test result in the chain of communication from a lab to the doctor ordering the test, to the doctor taking care of a patient, and to the patient and the family,"

250. See Christi J. Guerrini, Jennifer K. Wagner, Sarah C. Nelson, Gail H. Javitt & Amy L. McGuire, *Who's on Third?: Regulation of Third-Party Genetic Interpretation Services*, 22 GENETICS MED. 4, 4 (2020) ("Government regulation is a traditional mechanism for addressing potential harms of products and services made available to the public, and it is especially prevalent in the health sector given the special responsibilities of governments to protect public health.").

251. Sarah F. Sunderman, *The Need for Regulation of Direct-to-Consumer Genetic Testing in the United States: Assessing and Applying the German Policy Model*, 12 WASH. U. GLOB. STUD. L. REV. 357, 368 (2013); see also Guerrini et al., *supra* note 250, at 7.

252. See Clayton et al., *supra* note 51, at 835 ("Laboratories are the best situated to re-examine both previously reported results and the underlying genomic data to the extent that they retain them.").

253. Rachel Sachs, *The FDA Takes Steps Toward Regulation Laboratory-Developed Tests*, BILL OF HEALTH (Aug. 4, 2014), <https://blog.petrieflom.law.harvard.edu/2014/08/04/the-fda-takes-steps-toward-regulating-laboratory-developed-tests-2/> [<https://perma.cc/L9T6-QB79>].

254. See Rachel Sachs, *Diagnostic Method Patents and Harms to Follow-on Innovation*, 126 HARV. L. REV. 1370, 1378–79 (2013) (explaining the FDA's jurisdiction over diagnostic tests).

255. See *id.* at 1379 (describing CLIA's authority over laboratory operations).

256. See *supra* Part II.B.1.

257. Turna Ray, *In Williams v. Quest, State Supreme Court Leaves Room for Plaintiff to Argue Ordinary Negligence*, GENOMEWEB (July 3, 2018), <https://www.genomeweb.com/molecular-diagnostics/williams-v-quest-state-supreme-court-leaves-room-plaintiff-argue-ordinary> [<https://perma.cc/8NRU-ME7E>].

concluding that “[c]learly, there was a breakdown here, [and] the regulations are not very clear on that.”²⁵⁸

However, it may be argued that the harm that arises in these types of cases is not actually the harm that the FDA is equipped to address when regulating medical devices. For example, harm does not arise from a blood test or cheek swab administered to collect a patient’s biospecimen. Rather, as explored in Part II.B, the patient’s harm is a result of the unnecessary medical intervention that the patient underwent based on the genetic test results (e.g., a double mastectomy that the patient did not, in fact, need based on that patient’s particular level of risk).²⁵⁹ This determination of risk is not the type of risk that the FDA has historically addressed in determining the safety or quality of a device.²⁶⁰

Despite these concerns, appropriately tailored FDA oversight of LDTs may help address the challenges of standardizing the classification of genomic variants and how genetic testing laboratories report results to the patients’ treating physicians. Standardizing the evidence required to classify variants as pathogenic, a VUS, or benign could go a long way in ensuring trustworthy and reliable test results, and potentially avoiding unnecessary medical interventions in response to earlier variant misclassifications.

D. Intellectual Property Solutions

Regulation, however, might not be the (entire) answer. To begin with, Professor Sachs identifies the concerns with overregulating “intermediate technologies” like certain genetic tests.²⁶¹ Putting up regulatory barriers to going to market may stifle needed innovation that, if left less regulated, would make the technology more advanced and reliable. She discusses Myriad’s reduction in VUS classifications over time, despite the fact that the fundamental technology did not change, concluding that its ability to improve and refine the test in a favorable regulatory climate ultimately improved its therapeutic value to patients.²⁶² She states:

The improvements in Myriad’s tests over the years are a success story of an intermediate technology. Myriad was able to bring its test to market when the product was still an intermediate one: it had some predictive value, but significant improvements were still needed, and were foreseen. It had clinical value at the time for some patients, but for nearly half of women receiving the test, their results were inconclusive. However, that

258. Ray, *supra* note 134.

259. *See supra* Part II.B.

260. *See A History of Medical Device Regulation & Oversight in the United States*, U.S. FOOD & DRUG ADMIN. (June 24, 2019), <https://www.fda.gov/medical-devices/overview-device-regulation/history-medical-device-regulation-oversight-united-states> [<https://perma.cc/643M-EKWG>] (noting that, in 1976, Congress amended the Federal Food, Drug & Cosmetic Act to give the FDA the power to “provide reasonable assurance of the safety and effectiveness of medical devices”).

261. *See Sachs, supra* note 230, at 233 (calling Myriad’s test a “paradigmatic example of an intermediate technology”).

262. *See id.*

very act of coming to market was necessary to enable Myriad to construct the database of genetic test results it used to bring down the VUS rate. If regulators had required a lower VUS rate before Myriad came to market, it is not clear when (if ever) Myriad would have been able to aggregate the kind of information necessary to meet that goal.²⁶³

The same might be true of collecting enough data to ensure that, when a patient receives a pathogenic test result, the result is accurate, reliable, and actionable.

The lack of credible variant classification can largely be attributed to certain companies' (like Myriad's) virtual monopoly on genetic data and the failure of clinical laboratories and researchers to share data.²⁶⁴ Myriad remains the market leader for genetic tests, and it still, in many ways, exercises near monopolistic authority in breast cancer screening for clinical cases.²⁶⁵ Significantly, Myriad, the company that performed the Mathes family's BRCA tests, benefits from its history of patent and trade secret protection for the data that it has amassed over the course of many years.²⁶⁶ While the company's BRCA1 and BRCA2 patents were invalidated by the U.S. Supreme Court in 2013,²⁶⁷ the private (and secret) proprietary database of test results and health outcomes it had built up since at least 2005 enabled the company's continued monopoly in the market for such tests. This database includes all past patient information and test results. The advantage of protecting trade secrets is that such protections are not time-limited, in contrast to patent protection, which only grants a temporary monopoly.²⁶⁸ Generally, states develop their own trade secret laws, but almost all have adopted the Uniform Trade Secrets Act²⁶⁹ (UTSA) as its basis for trade secret

263. *Id.* at 231.

264. Myriad has claimed that it can offer patients unparalleled speed and accuracy, most likely due to its "vast and unique interpretive database, derived from a patent-based U.S. testing monopoly going back to the late 1990s and involving more than one million patients." John M. Conley, Robert Cook-Deegan & Gabriel Lázaro-Muñoz, *Myriad after Myriad: The Proprietary Data Dilemma*, 15 N.C. J.L. & TECH 597, 607, 612, 614 (2014) ("Myriad has used its patent-based monopoly as the sole BRCA 1 and 2 test provider to develop, at its own cost, an extensive database that relates VUSs to phenotypes, details the frequency of VUS in various populations, and includes genetic studies on patient families."); see also Robert Cook-Deegan, John M. Conley, James P. Evans & Daniel Vorhaus, *The Next Controversy in Genetic Testing: Clinical Data as Trade Secrets?*, 21 EUR. J. HUM. GENETICS 585, 585 (2013).

265. See Sharon Begley, *As Revenue Falls, A Pioneer of Cancer Gene Testing Slams Rivals with Overblown Claims*, STAT (Nov. 29, 2016), <https://www.statnews.com/2016/11/29/brcacancer-myriad-genetic-tests/> [<https://perma.cc/9T8V-U9MU>] (noting that even three years after its key patents were invalidated, Myriad still had about 85 percent of the U.S. market for BRCA testing).

266. See *id.* (describing how Myriad's "main competitive edge was its proprietary database," which contained much more data than what its competitors had access to).

267. See *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 596 (2013).

268. See *Kewanee Oil Co. v. Bicorn Corp.*, 416 U.S. 470 (1974).

269. UNIF. TRADE SECRETS ACT (amended 1985), 14 U.L.A. 628–830 (2021); see also 18 U.S.C. § 1839(3) ("[T]he term 'trade secret' means all forms and types of financial, business, scientific, technical, economic, or engineering information . . . whether tangible or intangible, and whether or how stored, compiled, or memorialized physically, electronically, graphically, photographically, or in writing if—(A) the owner thereof has taken reasonable

protection, which provides for injunctive relief, damages, and attorneys' fees if violated.

Because, until 2013, Myriad maintained its patent monopoly and was therefore the only entity that had conducted the BRCA1 and BRCA2 screening tests, it has the information necessary to understand the clinical significance of the mutations, particularly VUS. Myriad's patents were therefore "data-generating," allowing the company to collect and create data, thereby extending its monopoly.²⁷⁰ In other words, while companies besides Myriad can now offer diagnostic tests for BRCA1 and BRCA2, they may not have the information that correlates these mutations with the probability of actually developing cancer.²⁷¹ Thus, "Myriad's test is the gold standard," and "[e]veryone goes by what they say."²⁷² It is often alleged that companies like Myriad hoard data, making "evaluation of data by outside parties impossible."²⁷³

In the absence of data sharing among genetic testing companies, the likelihood of initial misclassification is much higher. One study published in the *New England Journal of Medicine* found that "the interpretation of the importance of the same variant by multiple clinical laboratories may differ, so that at least one interpretation must be wrong and could therefore lead to inappropriate medical intervention."²⁷⁴

The stakes for individuals like members of the Mathes family or Nancy Seeger are particularly high; extending trade secret protection in these cases imposes identifiable harm on patients. For the Mathes family, the "lab said it made the change as more people with the same variant were tested and added to Myriad's database," and "[t]he new analysis showed that specific

measures to keep such information secret; and (B) the information derives independent economic value, actual or potential, from not being generally known to, and not being readily ascertainable through proper means by, the public.").

270. Brenda M. Simon & Ted Sichelman, *Data-Generating Patents*, 111 NW. U. L. REV. 377, 379 (2017). Myriad's actions here are not unique to genetics. As Professor W. Nicholson Price has explained, companies "use the interlocking effects of patents and difficult-to-reverse-engineer trade secrets to maintain monopolies long past patent expiration." W. Nicholson Price II, *Expired Patents, Trade Secrets, and Stymied Competition*, 92 NOTRE DAME L. REV. 1611, 1612 (2017).

271. See Price, *supra* note 270, at 1630 ("Although competitors promptly rushed to offer BRCA1/2 genetic tests, and although the testing process was readily duplicable, Myriad maintained—and still maintains—the lion's share of the genetic testing market Over the years of Myriad's monopoly, it collected genetic information on well over a million women, including family histories of cancer incidence.").

272. Marcus, *supra* note 1.

273. Turner et al., *supra* note 77, at 430 ("[M]ost commonly, variants were reclassified due to new proprietary evidence not available to all testing laboratories. The proprietary nature of internal variant databases makes evaluation of data by outside parties impossible. This data should be incorporated into publicly available databases, such as ClinGen, to allow for data aggregation and quicker resolution of rare variants. Ideally, the data should include pathogenic and benign variants.").

274. Heidi L. Rehm, Jonathan S. Berg, Lisa D. Brooks, Carlos D. Bustamante, James P. Evans, Melissa J. Landrum, David H. Ledbetter, Donna R. Maglott, Christa Lese Martin, Robert L. Nussbaum, Sharon E. Plon, Erin M. Ramos, Stephen T. Sherry & Michael S. Watson, *ClinGen—The Clinical Genome Resource*, 372 NEW ENG. J. MED. 2235, 2235 (2015).

variant might carry a lower risk of cancer than one categorized as pathogenic, which increases a person's chance of getting a disease."²⁷⁵ Had Myriad been involved in more data sharing prior to returning the results to the Mathes family, they would have received accurate results much sooner. The increased competition (and ability to obtain second confirmatory testing) may therefore be the impetus for updated (and more accurate) results.²⁷⁶

However, "[h]ealthy competition among isolated entities is no longer sufficient to drive our understanding of human variation, and patient care may be compromised when data are not shared."²⁷⁷ Thus, limiting data monopolies through increased data sharing appears to be a potential solution to ensure that variants are correctly classified the first time. Arguably, harms like those suffered by the Mathes family, as well as those suffered by individuals whose initial VUS results are upgraded to pathogenic (but who are unable to take medical action until it is too late) would be significantly less common if there were more sharing of data and larger, more comprehensive data sets.²⁷⁸

Public efforts to collect and share this data are ongoing. For example, the National Institutes of Health's National Center for Biotechnology Information launched ClinVar, a "public archive for clinical laboratories, researchers, expert panels, and others to archive their classifications of variants across all genes."²⁷⁹ These "public variant databases are increasingly relied on during genomic testing to clarify the clinical significance of variants in support of diagnosis or targeted treatment."²⁸⁰ ClinVar has been billed as a "one-stop shop for disease genes."²⁸¹

The ClinGen consortium then works to develop publicly available tools, procedures, and working groups to advance the field of genetic variant classification.²⁸² ClinGen evaluates genes involved in diseases such as cystic fibrosis and breast cancer and employs "a rating system to show how strongly any particular variant has been linked to a particular disease," thus "creat[ing] a measure of trust for genetic results."²⁸³

However, many companies do not share variant classification data or contribute to databases like ClinVar, despite numerous calls from

275. Marcus, *supra* note 1.

276. Evidence has shown that 17 percent of the variants with clinical interpretations submitted by more than one laboratory had conflicting interpretations. Rehm et al., *supra* note 274, at 2240.

277. *Id.* at 2235–36.

278. See Hoffman-Andrews, *supra* note 11, at 655 ("Functional studies of genes and variants, and population-level data with accurate phenotyping, will improve variant classification and reduce uncertainties.").

279. Giles et al., *supra* note 20, at 290.

280. Thorogood et al., *supra* note 131, at 838.

281. Monya Baker, *One-Stop Shop for Disease Genes*, 491 NATURE 171, 171 (2012).

282. See Giles et al., *supra* note 20, at 291.

283. Yong, *supra* note 16.

organizations such as the ACMG and the AMP to do so.²⁸⁴ For example, the lab that tested Nancy Seeger’s mother does not submit to ClinVar.²⁸⁵

Further, on a practical level, data sharing may not be as straightforward as we would hope. There exist multiple databases with inconsistent and variable data from which it is difficult to extract reliable information.²⁸⁶ As one author observed, “[r]ecent studies have documented that different laboratories may produce discordant interpretations of the same variant.”²⁸⁷ And, even when data is shared, testing results may still be misclassified. In other words, “concordance does not guarantee accuracy.”²⁸⁸

CONCLUSION

Although this Article explores various legal protections to redress harms that occur after a patient has undergone unnecessary medical interventions based on variants previously classified as pathogenic, tort remedies are generally unsatisfactory.²⁸⁹ Our intention should be to reduce harms by limiting the risk of unnecessary medical actions in response to variant misclassification, rather than to reallocate and/or spread that risk.

An ideal solution would reduce the likelihood of harms occurring in the first place by improving reliability and accuracy—both in the genetic tests themselves and in the ability of physicians to interpret the tests and their clinical significance. Thus, FDA regulation coupled with increased data sharing may go a significant way toward ameliorating the “harm without negligence” problem in clinical genomics. However, mistakes may still occur. Thus, any solution may require simultaneous reliance on multiple legal regimes. Consequently, a solution may also be to adopt a strict liability approach for genetic tests, thereby allowing individuals, when they are

284. See Ray, *supra* note 52. Just before this Article went to print, Myriad Genetics announced that it would begin submitting hereditary cancer risk variants to ClinVar in 2023. Turna Ray, *Myriad Genetics to Submit Hereditary Cancer Risk Variants to ClinVar in 2023*, GENOMEWEB (Nov. 1, 2022), <https://www.genomeweb.com/molecular-diagnostics/myriad-genetics-submit-hereditary-cancer-risk-variants-clinvar-2023> [https://perma.cc/NDV7-N6VL] (“[B]y sharing information on hereditary cancer risk variants, the ‘new Myriad’ is attempting to come out from under the shadow of the landmark Supreme Court case that took away its dominance over BRCA1/2 testing and its much criticized decision to maintain its variant data as a trade secret.”).

285. See Ray, *supra* note 52.

286. See Burke, *supra* note 49, at 1247–48 (calling for the creation of a national database to collect data from multiple sources).

287. *Id.* at 1247 (“One study of 9 laboratories found that the concordance rate for interpretation of 99 variants spanning the full range of classification categories was only 34%. After consensus discussions, concordance increased to 71%, underscoring the need for judgment, and, therefore, the potential for disagreement in interpreting data on variant pathogenicity.” (footnotes omitted)).

288. Giles et al., *supra* note 20, at 290.

289. There may also be clinical practice solutions to the “medical harm without negligence” problem, some of which have been discussed in this Article. For example, increased focus on genetic literacy among physicians may help improve decision-making based on genetic test results. See Part II.B.2. Likewise, modification of the ACMG guidance to include stricter rules regarding initial variant classification could potentially reduce the incidence of later reclassifications.

harmed as a result of prophylactic action before a variant is later reclassified, to seek redress. Prioritizing regulatory solutions over tort law solutions may reduce some of the alternative problems that could arise under solely a compensation scheme. While the “harm without negligence” problem may seem intractable in many ways, the law offers approaches to enable individuals to obtain better information upon which to make potentially life-changing medical decisions. And at least some of these solutions²⁹⁰ may have value in other—perhaps even nonmedical—contexts.

290. Importantly, however, FDA regulation of LDTs to address the particular concerns related to the downgrading of previously pathogenic mutations to uncertain or benign will not fix the “harm without negligence” problem in medicine wholesale.