UNSOLVED MYSTERY (DIAGNOSIS): TREATING RARE DISEASES AS A PUBLIC HEALTH CRISIS

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Rare diseases—conditions that affect no more than 200,000 people—impact an estimated 30 million Americans and 400 million people globally. When rare diseases are examined individually, there are often scarce public health resources available. The result of this reality is that rare disease patients do not have the same opportunities to medical treatments and developments as those with more common conditions. This Note is the first assessment of addressing rare disease through a public health lens, including through public health law and policy.

This framework aims to improve the epidemiologic data surrounding rare diseases, create shared databanks for research and development of therapeutics, develop policies to promote innovation, and use legal interventions to ensure equal rights for rare disease patients. Epidemiologic data on rare disease is scant and a research agenda to clarify rare disease prevalence and incidence, as well as demographic distributions, is vital to understand the scope of this issue. Economic approaches to rare disease therapies have fallen short of providing desperately needed interventions for the vast majority of rare disease patients. Policies, such as creating research initiatives to give researchers access to biological data, are lacking and deserve refreshed attention. Finally, legal principles, such as protection of patient information and availability of remedies in medical malpractice suits, should be altered to better serve rare disease patients.

Until a public health approach using this framework to rare disease is realized, patients with rare diseases will continue to face a world that fails to address their needs.

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I. INTRODUCTION

Suppose you are a family practice physician. You encounter thousands of patients every year.[1] Your patients have respiratory tract infections, hypertension, arthritis, diabetes, depression, anxiety, addiction, pneumonia, back pain, and many other ailments and diseases.[2] For these common conditions, you rely on standard clinical practice guidelines to treat your patients.[3] When a patient

1. *See* Lenny Bernstein, *How Many Patients Should Your Doctor See Each Day?*, WASH. POST (May 22, 2014, 2:09 PM), https://www.washingtonpost.com/news/to-your-health/wp/2014/05/22/how-many-patients-should-your-doctor-see-each-day/ [https://perma.cc/22WN-4PN6] ("[T]he average member of that group has 93.2 'patient encounters' each week—in an office, hospital or nursing home, on a house call or via an e-visit. That's about 19 patients per day. The family physicians said they spend 34.1 hours in direct patient care each week, or about 22 minutes per encounter, with 2,367 people under each physician's care.").

2. *See* Caitlin R. Finley et al., *What Are the Most Common Conditions in Primary Care?*, 64 CANADIAN FAM. PHYSICIAN 832, 832 (2018).

3. *See generally Clinical Practice Guidelines*, NAT'L CTR FOR COMPLEMENTARY & INTEGRATIVE HEALTH, https://nccih.nih.gov/health/providers/clinicalpractice.htm (last visited Nov. 20, 2020) [https://perma.cc/6989-S3NB] [hereinafter *Clinical Practice Guidelines*].

comes into your office with symptoms of pneumonia, for example, you order a chest x-ray, prescribe an antibiotic, and send the patient home with instructions to rest.[4] Your next patient, however, comes in with symptoms you have not seen in your entire career. She complains of symptoms including fainting spells, seizure-like convulsions, extremely low blood pressure, an inability to sweat, "thunderclap" headaches, and irregular heartbeats.[5] You note that she is a young woman in her twenties, experiences stress at work, and recently suffered a miscarriage.[6] You conduct a physical examination and notice no abnormal readings, test results, or indicators of anything serious. Figuring that she is too young to have such serious symptoms, you determine that the cause of her symptoms is merely stress and tell her to find time to "take a vacation."[7]

Now suppose *you* are that patient. You know of nobody else with your symptoms, and you are scared that you may die or live the rest of your life with these chronic, debilitating symptoms. Could it be that whatever is causing your symptoms caused your recent miscarriage? You know you need help, so you go to your family practice physician. You note the puzzled look on your doctor's face as you explain your symptoms and concerns. You are given a physical examination, put through a series of tests, and then told by your doctor that you are under too much stress and to "take a vacation." You leave your doctor's office with no answers. You feel helpless and unheard.

In the real life case, the patient had a rare medical condition: a genetic mutation resulting in a deficiency in the neurotransmitter norepinephrine[8] and subsequent autonomic nervous system dysfunction.[9] Moreover, the disease had yet to be discovered, meaning the patient spent nearly two decades trying to find a diagnosis.[10] There were no clinical guidelines for treating this patient because

4. *See* Lionel A. Mandell et al., *Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults*, 44 CLINICAL INFECTIOUS DISEASES S27, S39 (2007).

5. *See* Hossam I. Mustafa et al., *Dysautonomia: Perioperative Implications*, 116 ANESTHESIOLOGY 205, 205–07, 213 (2012).

6. K. Bourne et al., *Postural Tachycardia Syndrome and Pregnancy: Insights from a Cross-Sectional Community Based Survey*, 28 CLINICAL AUTONOMIC RSCH. 453, 487 (2018).

7. Stories of patients with undiagnosed rare diseases being told to "take a vacation" by their doctor are not uncommon. *See, e.g.*, Mireille Silcoff, *Memoir: No Doctor Could Diagnose My Strange Affliction—So I Did It Myself*, TORONTO LIFE (Sept. 18, 2014), https://torontolife.com/city/memoir-mireille-silcoff-my-strange-affliction/ [https://perma.cc/ZSN6-ZSY5]; *Have You Ever Been Given a False Diagnosis? If So, What Was It?*, QUORA, https://www.quora.com/Have-you-ever-been-given-a-false-diagnosis-If-so-what-was-it (last visited Nov. 20, 2020) [https://perma.cc/RLE8-NLC2].

8. For an accessible description of neurotransmitters and their function, including the role of norepinephrine, see Kayt Sukel, *Neurotransmitters*, DANA FOUND. (Aug. 1, 2019), https://www.dana.org/article/neurotransmitters/ [https://perma.cc/R452-ZACZ].

9. John R. Shannon et al., *Orthostatic Intolerance and Tachycardia Associated with Norepinephrine-Transporter Deficiency*, 342 NEW ENG. J. MED. 541, 541–45 (2000). For an overview of the autonomic nervous system, see Phillip Low, *Overview of the Autonomic Nervous System*, MERCK MANUAL, https://www.merckmanuals.com/home/brain,-spinal-cord,-and-nerve-disorders/autonomic-nervous-system-disorders/overview-of-the-autonomic-nervous-system [https://perma.cc/C9SN-DV2H] (last modified Apr. 2020).

10. *See* Shannon et al., *supra* note 9, at 541–42; MundoVideoMix, *Documentary The Woman Who Kept Falling Down Extraordinary People 2013480pmp4*, YOUTUBE (Dec. 26, 2014), https://www.youtube.com/watch?v=LwMVX4MufD8 [https://perma.cc/6SKW-KBUM].

her condition was only present in her family.[11] Was the family practice physician's missed diagnosis an instance of medical malpractice?[12] After eventually receiving a diagnosis of "norepinephrine transporter deficiency,"[13] how should the patient request social security benefits?[14] How should her employer accommodate her condition, which may require her to work from home and not be subjected to visual stimulation such as a computer screen?[15]

This case study reveals a veiled public health crisis.[16] While this case demonstrates a rare disease afflicting a single individual and her family, there are over 7,000 rare diseases[17] listed by the National Institutes of Health ("NIH").[18] Although rare diseases are "rare," with each disease affecting fewer than 200,000 people in the United States,[19] they collectively affect 25 to 30 million Americans, or about one in ten people.[20] Globally, an estimated 400 million people have a rare disease.[21] Despite the prevalence of rare disease, patients with these conditions are frequently misdiagnosed or treated inappropriately; it takes an average of five years and seven physicians to diagnose a rare disease.[22] Furthermore,

11. *See* Shannon et al., *supra* note 9, at 541.

12. Medical malpractice is broadly defined as "[a] doctor's failure to exercise the degree of care and skill that a physician or surgeon of the same medical specialty would use under similar circumstances." *Malpractice*, BLACK'S LAW DICTIONARY (11th ed. 2019).

13. Shannon et al., *supra* note 9.

14. For a brief description of the Social Security Administration's Compassionate Allowance List (a fast-track process to get disability benefits if the applicant's condition is on the list), see Kenneth Abbott et al., *Automatic Health Record Review to Help Prioritize Gravely Ill Social Security Disability Applicants*, 24 J. AM. MED. INFORMATICS ASS'N 709, 709–10 (2017).

15. For a discussion on workplace accommodations for rare disease patients, see *infra* Section II.B.

16. Generally, a "crisis" is "a serious threat to the basic structures or the fundamental values and norms of a social system, which–under time pressures and highly uncertain circumstances–necessitates making critical decisions." Uriel Rosenthal & Alexander Kouzmin, *Crises and Crisis Management: Toward Comprehensive Government Decision Making*, 2 J. PUB. ADMIN. RSCH. & THEORY 277, 279–80 (1997). Nevertheless, a crisis is "not easily described nor measured; there is no formula with a cutoff score. [Rather, a] crisis involves the sense that a great deal is at stake." JOSHUA M. SHARFSTEIN, THE PUBLIC HEALTH CRISIS SURVIVAL GUIDE x (2018). For a more detailed description of how to identify a public health crisis, see *id.* at 61–71.

17. Throughout this Note I will be making references to "rare diseases," "rare disease," "rare conditions," and other synonymous descriptors indicating medical conditions that affect a small percentage of the population. The nomenclature and definitions of "rare disease" are varied, which will be described in greater detail. *See infra* Section II.A; *see also* Trevor Richter et al., *Rare Disease Terminology and Definitions—A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group*, 18 VALUE HEALTH 906, 910–13 (2015).

18. *FAQs About Rare Diseases*, GENETIC & RARE DISEASES INFO. CTR., NAT'L CTR. FOR ADVANCING TRANSLATIONAL SCI., https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases (last visited Nov. 20, 2020) [https://perma.cc/FN2G-M5UV].

19. *Id.*

20. James K. Stoller, *The Challenge of Rare Diseases*, 153 CHEST 1309, 1309 (2018); Robert C. Griggs et al., *Clinical Research for Rare Disease: Opportunities, Challenges, and Solutions*, 96 MOLECULAR GENETICS & METABOLISM 20, 20 (2009).

21. *Rare Facts*, GLOBAL GENES, https://globalgenes.org/rare-facts/ (last visited Nov. 20, 2020) [https://perma.cc/4S2U-SGJ8].

22. *Rare Diseases Create Significant Care and Financial Burdens Among Patients*, AM. J. MANAGED CARE (July 20, 2017), https://www.ajmc.com/newsroom/rare-diseases-create-significant-care-and-financial-burdens-among-patients [https://perma.cc/7B6Y-538K].

most rare diseases have no known treatment.[23] Traditional therapeutic innovation models often focus on more common conditions, as economic incentives are absent for developing therapies for many patients with rare disease.[24]

The case study above is but one example of how a patient navigates through having a rare disease. Individual patients with rare diseases face many obstacles. First, they must maneuver through the rigmarole of the U.S. healthcare system.[25] This includes finding a medical provider—often a specialist located at an urban or academic medical center—to examine and investigate their health concerns, and obtaining affordable health insurance to cover medical expenses,[26] a task which is itself difficult.[27] If a diagnosis is made, the patient may qualify for disability benefits from Social Security,[28] the determination of which is a lengthy process that often requires the hiring of an attorney for representation.[29] Throughout the process, the patient's health status will dominate their lifestyle.[30] Particularly debilitating conditions will render the patient unable to work or leave their home.[31] The patient's prospects that a treatment for their condition will be developed are dim, and the likelihood of a cure is even more minute.[32]

Patient advocacy efforts, while gallant, can struggle for elbowroom within the policymaking process.[33] Indeed, the sum of these issues creates a bleak outlook for most patients with rare conditions.[34] Nevertheless, there is reason for optimism—the most recent summit of the National Organization for Rare Disorders ("NORD") had its highest attendance ever, suggestive of growing support

23. GENETIC & RARE DISEASES INFO. CTR., *supra* note 18.

24. COMM. ON ACCELERATING RARE DISEASES RSCH. & ORPHAN PROD. DEV., INST. MED., RARE DISEASES AND ORPHAN PRODUCTS: ACCELERATING RESEARCH AND DEVELOPMENT 85 (Marilyn J. Field & Thomas F. Boat eds., 2010) [hereinafter INST. MED.].

25. *See generally* Lewis A. Lipsitz, *Understanding Health Care as a Complex System: The Foundation for Unintended Consequences*, 308 JAMA 243 (2012).

26. Stoller, *supra* note 20, at 1309–12.

27. *See, e.g.*, Daniel Marchalik, *The Affordable Care Act Is Still Law. Signing Up for Health Insurance Is Still Hard*, STAT (June 2, 2017), https://www.statnews.com/2017/06/02/afforable-care-act-insurance-signup/ [https://perma.cc/6449-EYYK].

28. *Social Security Disability Programs Available to Eligible Rare Disease Patients*, EVERYLIFE FOUND. FOR RARE DISEASES (Oct. 21, 2016), https://everylifefoundation.org/social-security-disability-programs-available-eligible-rare-disease-patients/ [https://perma.cc/V8QK-8ZKX].

29. *See, e.g.*, *Why Should I Speak to a Disability Lawyer if I Haven't Applied?* DISABILITY BENEFITS CTR., https://www.disabilitybenefitscenter.org/faq/hiring-attorney-before-applying-for-social-security (last visited Nov. 20, 2020) [https://perma.cc/8T4P-RAYF] ("[H]iring a Social Security attorney will maximize your chances of ultimately being successful with your disability claim. . . . [C]laimants who are represented by a lawyer are three times more likely to have their disability claim approved and be awarded disability benefits.").

30. *See infra* Section II.B.

31. *See infra* Section II.B.

32. *See infra* Section III.C (discussing lack of economic incentives to develop therapies for conditions impacting small numbers of patients).

33. *See* STEVEN EPSTEIN, *Measuring Success: Scientific, Institutional, and Cultural Effects of Patient Advocacy*, *in* PATIENTS AS POLICY ACTORS 257, 257 (Beatrix Hoffman et al. eds., 2011) ("The struggle of patient advocates to succeed is complicated by . . . problems of representation, expertise, and incorporation and cooptation.").

34. *See, e.g.*, *Rare Disease by the Numbers*, PHARM. RSCH. & MFRS. AMERICA, https://innovation.org/about-us/commitment/research-discovery/rare-disease-numbers (last visited Nov. 20, 2020) [https://perma.cc/5EGV-SAZC] ("95 percent of rare diseases still do not have any treatment options, representing a significant unmet need for patients.").

within the advocacy community to represent patients with rare disease.[35] In addition, support for increasing rare disease research and therapeutic development has been renewed at the National Center for Advancing Translational Studies ("NCATS"), part of the NIH.[36] The NCATS Director, physician Christopher Austin, stated at the 2019 World Orphan Drug Congress that "NCATS [has] decided that we have real problems with the word 'rare.' The public health implications of rare diseases are poorly understood but profoundly important . . . . Together, they have the same prevalence as type 2 diabetes—about 8% of the population."[37] The goals stemming from that meeting included diagnosing all patients with a suspected rare disease within one year, entering all currently undiagnosable individuals into a globally coordinated diagnostic and research pipeline, and approving 1,000 new therapies for rare diseases, with special focus on disorders without already approved options.[38]

Calls for action to address the issues faced by patients with rare diseases have ranged from promoting economic incentives in order to produce medications to changing federal health policies to better protect these patient populations.[39] One such call to action that has yet to be explored is to consider rare diseases—all 7,000 of them combined—as a public health problem,[40] akin to the comments made by NCATS Director Christopher Austin.[41] Public health consists of addressing health issues affecting populations, involving a collective social effort to ensure the health of all.[42] There are some conditions—namely, infectious diseases—that are rare and fall under the traditional purview of public

35. *2019 NORD Summit Breaks Records with Largest Attendance Ever!*, PR NEWSWIRE (Oct. 23, 2019, 3:30 PM), https://www.prnewswire.com/news-releases/2019-nord-summit-breaks-records-with-largest-attendance-ever-300944254.html [https://perma.cc/HE5G-HFE6].

36. *About NCATS*, NAT'L CTR. FOR ADVANCING TRANSLATIONAL SCIS., NAT'L INSTS. HEALTH, https://ncats.nih.gov/about [https://perma.cc/G6WN-XC3E] (last updated Feb. 4, 2020).

37. Larry Luxner, *Rare Diseases Constitute a 'Public Health Issue,' NCATS Director Warns*, FRAGILE X NEWS TODAY (May 16, 2019), https://fragilexnewstoday.com/2019/05/16/rare-diseases-constitute-public-health-issue-ncats-director-warns/ [https://perma.cc/6AK8-N65A].

38. *Id.*

39. Taeho Greg Rhee, *Policymaking for Orphan Drugs and its Challenges*, 17 AM. MED. ASS'N J. ETHICS 776, 777–78 (015) ("[O]rphan drugs are very expensive and . . . their accessibility can be a huge concern. . . . At least 95 of the . . . 400-plus orphan drugs were for cancer treatment. . . . To improve the accessibility of orphan drugs for patients with rare diseases, relevant policies should be altered in ways that promote fairness and equity.").

40. Although there has been some discussion on framing rare disease as a public health problem, this has been limited to academic commentaries with limited analysis on how to incorporate policy-, legal-, or health system-based changes. *See* Rodolfo Valdez et al., *Public Health and Rare Diseases: Oxymoron No More*, 13 PREVENTING CHRONIC DISEASE 1, 1 (2016) ("[W]e have compelling reasons to apply a public health approach to rare diseases: they collectively affect about 25 million people in the United States, about 30 million in Europe, and about 400 million worldwide; most rare diseases begin in childhood and can have devastating health consequences, including premature death. They can severely affect the lives of caregivers; their economic impact is often substantial for patients, their families, and society in general. Although rare diseases are a common cause of neurological and intellectual disabilities and many have no cure, some can be prevented or controlled and the lifespan of patients can be extended into adulthood with opportune medical interventions.").

41. *See* Luxner, *supra* note 37.

42. David Satcher & Eve J. Higginbotham, *The Public Health Approach to Eliminating Disparities in Health*, 98 AM. J. PUB. HEALTH 400, 400 (2008) ("Public health is defined as 'what we, as a society, do collectively to assure the conditions for people to be healthy.'").

health.[43] Rare diseases that are not communicable, however, have usually been addressed through traditional medicine, with a focus on treating the individual patient.[44] Based on their collective prevalence and widespread impact, rare diseases should be treated as a public health crisis. Applying a public health legal framework warrants further investigation as an avenue through which to address the issues facing a large portion of society, both domestically and globally.

This Note will examine rare disease through a public health lens. Part II will provide a background on rare diseases, including an epidemiologic assessment of rare diseases in aggregate—a critical evaluation necessary for an effective public health response.[45] Part II will also describe the societal impact of rare disease, focusing on economic factors, issues with caretakers, workforce issues, and availability of accommodations. Part III will investigate how rare diseases have been addressed in the current legal and policy landscape. Specific focus will be given to the issues faced by rare disease patients in the areas of medical malpractice and tort law, the allocation of government resources, policies promoting the development of novel therapeutics, and modern genetic screening issues. Finally, Part IV will describe new law and policy solutions to address rare diseases like a public health crisis. These solutions will leverage a public health legal framework based on population health models, policy measures, and legal responses.

II. BACKGROUND

Rare diseases are not new.[46] Diagnostic, caretaking, and financial issues faced by rare disease patients and their families are not new.[47] Legislative and legal concerns for patients with rare diseases are not new.[48] Market forces creating barriers to developing rare disease therapeutics are not new.[49] The public health significance of rare disease is not new.[50] In fact, *none* of the issues presented in this Note are new. What *is* new is the idea of treating rare diseases as a public health problem—a policy solution that could provide substantial impact

43. Muin J. Khoury & Wei Yu, *Introducing the Rare Diseases Genomics and Precision Health Knowledge Base*, CTRS. FOR DISEASE CONTROL & PREVENTION: GENOMICS & PRECISION HEALTH (Apr. 4, 2019), https://blogs.cdc.gov/genomics/2019/04/04/introducing-the-rare-diseases/ [https://perma.cc/FLT9-C2AU] ("For many rare infectious diseases, pathogen genome sequencing has substantially affected public health activities in tracking and solving outbreaks, conducting public health surveillance, assessing mechanisms of antimicrobial resistance, and developing better vaccines.").

44. *See, e.g.*, Lorenza Garrino et al., *Living with and Treating Rare Diseases: Experiences of Patients and Professional Health Care Providers*, 25 QUALITATIVE HEALTH RSCH. 636, 642–47 (2015) (discussing health care provider experiences with treating patients with rare diseases).

45. David A. Savitz et al., *Reassessing the Role of Epidemiology in Public Health*, 89 AM. J. PUB. HEALTH 1158, 1158 (1999) (defining epidemiology as "the study of the distribution and determinants of disease frequency in human populations").

46. *See* Caroline Huyard, *How Did Uncommon Disorders Become 'Rare Diseases'? History of a Boundary Object*, 31 SOCIO. HEALTH & ILLNESS 463, 463–64 (2009).

47. *See* discussion *infra* Section II.B.

48. *See* discussion *infra* Section III.D.

49. *See* discussion *infra* Section III.C.

50. *See* Valdez et al., *supra* note 40, at 1.

on vulnerable patients and their families. What *is* new is providing a legal framework to take this action. This Note offers the first of hopefully many such analyses and frameworks.

Essential to any public health response is first understanding the scope of the problem.[51] Once determined, the problem's scope can be shared widely with appropriate officials to both take immediate action and develop long-term solutions.[52] The ongoing global outbreak of the novel *coronavirus*, or "COVID-19," illustrates the importance of this approach.[53] When COVID-19 first appeared in Wuhan in the Hubei Province of China,[54] the Chinese government health officials worked with the World Health Organization ("WHO") to declare a "Public Health Emergency of International Concern,"[55] prompting policy and legal responses as part of the public health response.[56] But the COVID-19 response has not been without flaws. Chinese officials did not report the COVID-19 case to the WHO until December 31, more than three weeks after the virus was first detected.[57] Further, high-level public health leaders have complained about the U.S. response as lacking a "sense of urgency," and thus leading to backlogs in disease testing.[58] The COVID-19 outbreak has been devastating to many and

51. COMM. FOR THE STUDY OF THE FUTURE OF PUBLIC HEALTH, INST. MED., *Public Health as a Problem-Solving Activity: Barriers to Effective Action*, *in* THE FUTURE OF PUBLIC HEALTH 113 (1988), https://www.ncbi.nlm.nih.gov/books/NBK218218/pdf/Bookshelf_NBK218218.pdf [https://perma.cc/9LDR-G27C] ("A foundation stone for public health activities is an assessment and surveillance capacity that identifies problems, provides data to assist in decisions about appropriate actions, and monitors progress. Epidemiology has long been considered the essential science of public health, and a strong assessment and surveillance system based on epidemiologic principles is a fundamental part of a technically competent public health activity.").

52. For a discussion on public health surveillance and response systems, see, for example, INST. MED., THE FUTURE OF THE PUBLIC'S HEALTH IN THE 21ST CENTURY 126–47 (2002), https://www.ncbi.nlm.nih.gov/books/NBK221239/pdf/Bookshelf_NBK221239.pdf [https://perma.cc/X24T-JR3W].

53. For a brief overview of crisis communication in the wake of COVID-19, see Ana Mendy et al., *A Leader's Guide: Communicating with Teams, Stakeholders, and Communities During COVID-19*, MCKINSEY & CO. (Apr. 17, 2020), https://www.mckinsey.com/business-functions/organization/our-insights/a-leaders-guide-communicating-with-teams-stakeholders-and-communities-during-covid-19 [https://perma.cc/76D8-CEDU].

54. *See* Nanshan Chen et al., *Epidemiological and Clinical Characteristics of 99 Cases of 2019 Novel Coronavirus Pneumonia in Wuhan, China: A Descriptive Study*, 395 LANCET 507, 507 (2020).

55. *See Statement on the Second Meeting of the International Health Regulations (2005) Emergency Committee Regarding the Outbreak of Novel Coronavirus (2019-nCoV)*, WHO (Jan. 30, 2020), https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov) [https://perma.cc/SJ9C-RWYR].

56. An example policy response is reflected in the U.S. banking industry, in which banks agreed to cut rates to soften the economic impact of the COVID-19 outbreak. *See* Jeanna Smialek, *Fed Official Says Central Bankers Are Aligned in Coronavirus Response*, N.Y. TIMES (Mar. 5, 2020), https://www.nytimes.com/2020/03/05/business/economy/fed-rate-cut-coronavirus.html [https://perma.cc/WV62-2C5C]. Legal responses have also taken hold, as many states have issued state-of-emergency declarations in order to make funds available to respond to the outbreak. *See, e.g.*, Jesse McKinley & Edgar Sandoval, *Coronavirus in N.Y.: Cuomo Declares State of Emergency*, N.Y. TIMES (Mar. 7, 2020), https://www.nytimes.com/2020/03/07/nyregion/coronavirus-new-york-queens.html [https://perma.cc/U6KZ-9J98].

57. *See Rolling Updates on Coronavirus Disease (COVID-19)*, WHO, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen (July 31, 2020) [https://perma.cc/VQT9-7T5E].

58. *See, e.g.*, Ken Alltucker & Jayne O'Donnell, '*Should Have Been a Sense of Urgency': Former FDA Chief Warns of Spike in US Coronavirus Cases*, USA TODAY (Mar. 9, 2020, 9:03 PM), https://www.usatoday.com/story/news/health/2020/03/09/former-fda-chief-scott-gottlieb-warns-sharp-increase-u-s-coronavirus-cases/5003087002/ [https://perma.cc/D4AP-WCCM].

caused widespread concern, leading to states of emergency,[59] economic turmoil,[60] strict quarantine measures,[61] and the shuttering of borders.[62] The outlook of the COVID-19 outbreak is worrisome, underscoring the importance of emergency preparedness and a strong public health response to combat against the spread of infectious disease.[63]

Even though public health responses are common for infectious diseases,[64] they also exist for non-infectious conditions.[65] One example is obesity, a key public health problem facing the United States and nations globally.[66] Although obesity does not spread like an infectious disease,[67] the public health response has been widespread. Federal policies have been enacted to curb obesity, including allowing Medicaid funds to be used for weight management counseling and programming.[68] State and local policies have also been implemented, such as nutrition labels on restaurant menus and zoning laws for fast food establishments.[69] Businesses have also been created or tailored to reduce obesity rates.[70]

59. *See* Melissa Alonso, *At Least 8 US States Have Declared a State of Emergency*, CNN (Mar. 8, 2020, 4:02 PM), https://www.cnn.com/asia/live-news/coronavirus-outbreak-03-08-20-intl-hnk/h_1b09bcd8c4b247c893d65b7118353923 [https://perma.cc/6FTY-J5ZY].

60. *See* Stephen Gandel, *3 Market-Panic Signals Point to Global Coronavirus Recession*, CBS NEWS (Mar. 9, 2020, 1:12 PM), https://www.cbsnews.com/news/coronavirus-stock-market-falling-recession/ [https://perma.cc/PD97-PETC].

61. *See* Rachel Donadio, *Italy's Coronavirus Response Is a Warning From the Future*, ATL. (Mar. 8, 2020), https://www.theatlantic.com/international/archive/2020/03/italy-coronavirus-covid19-west-europe-future/607660/ [https://perma.cc/T2WF-CC5S] ("In [the entire Lombardy region], the coronavirus's European epicenter, where the number of cases has been rising rapidly, Italy banned all public gatherings—no weddings, funerals, concerts, sporting events, discos, bingo games, video arcades, or Mass—until April 3. While trains and planes are still operational, and running on time, the government is forbidding people from leaving unless absolutely necessary.").

62. *See id.*

63. Nathaniel Smith & Michael Fraser, *Straining the System: Novel Coronavirus (COVID-19) and Preparedness for Concomitant Disasters*, 110 AM. J. PUB. HEALTH 648, 649 (2020) ("Outbreaks like [] COVID-19 are critical reminders of the significance of public health readiness and the need for continued strengthening of public health agencies' core response capabilities.").

64. *See, e.g.*, Christiana R. Dallas & Curtis H. Harris, *Applying Historical Responses to Infectious Disease for Future Disease Control*, 3 J. INFECTIOUS DISEASES & TREATMENT 1, 1 (2017).

65. *See, e.g.*, Brendan Saloner, *An Overview of Ethics, Public Health, and Noncommunicable Diseases*, *in* THE OXFORD HANDBOOK OF PUBLIC HEALTH ETHICS 489–90 (Anna C. Mastroianni, Jeffrey P. Kahn & Nancy E. Kass eds., 2019).

66. *See, e.g.*, M.J. Friedrich, *Global Health*, 318 JAMA 603, 603 (2017).

67. There is some evidence that obesity can "spread" through social networks, but this is likely the result of myriad phenomena such as genetic precursors, environmental conditions, and shared social experiences. *See* Nicholas A. Christakis & James H. Fowler, *The Spread of Obesity in a Large Social Network Over 32 Years*, 357 NEW ENG. J. MED. 370, 377–78 (2007).

68. *See, e.g.*, *Reducing Obesity*, CTRS. FOR MEDICARE & MEDICAID SERVS., https://www.medicaid.gov/medicaid/quality-of-care/quality-improvement-initiatives/reducing-obesity/index.html (last visited Nov. 20, 2020) [https://perma.cc/BRE5-TFXT].

69. *See* Jamie F. Chriqui, *Obesity Prevention Policies in U.S. States and Localities: Lessons from the Field*, 2 CURRENT OBESITY REPORTS 200, 202 tbl.1 (2013).

70. The roles that businesses can play in curbing obesity rates are still developing, but generally consist of building partnerships, engaging community members, improving community access to healthy eating and living opportunities, and adapting interventions to account for varying socioeconomic statuses. *See* PAUL BAKUS ET AL., NAT'L ACAD. MED.: PERSPECTIVES, WORKING TOWARD ENGAGING LOCAL BUSINESSES IN COMMUNITY

For example, FitBit, Apple, and Garmin are businesses that have created physical activity trackers (e.g. Apple Watch) designed to give user feedback and support for increased activity.[71] National gym chains also engage with people trying to lose weight by frequently offering membership incentives.[72] The obesity epidemic has no signs of slowing down,[73] but the varied public health response may be curbing the rate of obesity compared to no response at all.[74]

With these examples in mind, a critical analysis of the scope of rare diseases is vital before providing a public health framework and response.[75] Determining the scope of rare diseases requires an understanding of basic numbers (or "epidemiology")[76] of rare disease, as well as the broader social impact of these conditions.[77] Like the COVID-19 outbreak and obesity, appropriate responses to rare diseases will require information on epidemiology and social impacts ahead of any concerted policy or legal response.[78] This Part will describe what is known about the epidemiology of rare diseases and illustrate their social impact, while also summarizing current responses from medicine, healthcare, insurers, governments, and advocates.

OBESITY SOLUTIONS: A PRELIMINARY ACCOUNT FROM THE FIELD 3–4 (2017), https://nam.edu/wp-content/uploads/2017/04/Working-Toward-Engaging-Local-Businesses-in-Community-Obesity-Solutions.pdf [https://perma.cc/34NW-GXXD].

71. *See* André Henriksen et al., *Using Fitness Trackers and Smartwatches to Measure Physical Activity in Research: Analysis of Consumer Wrist-Worn Wearables*, 20 J. MED. INTERNET RSCH. 1, 2 (2018).

72. *See, e.g.*, Candice Leigh Helfand, *New Trend: Gyms Banning Slim Clients to Foster Comfort for Overweight Patrons*, CBS SACRAMENTO (June 29, 2012, 6:10 AM), https://sacramento.cbslocal.com/2012/06/29/new-trend-gyms-banning-slim-clients-to-foster-comfort-for-overweight-patrons/ [https://perma.cc/VTG4-NDQ4].

73. *See, e.g.*, Alexandra Sifferlin, *40% of Americans Are Obese—and the Trend Isn't Slowing*, TIME (Oct. 13, 2017, 12:01 AM), https://time.com/4980225/obesity-rates-adults-children/ [https://perma.cc/S3EM-3SCD].

74. Minnesota is one such state in which strong public health measures have reduced the growth rate of obesity, compared to other states. *See* News Release, Minn. Dep't Health, Despite Uptick, Minnesota's Adult Obesity Rate Growing Slower Than Upper Midwest States (Sept. 12, 2018), https://www.health.state.mn.us/news/pressrel/2018/obesity091218.html [https://perma.cc/3HNV-CFEE].

75. *See* Haroutune K. Armenian, *Epidemiology: A Problem-Solving Journey*, 169 AM. J. EPIDEMIOLOGY 127, 128 (2009) ("[A]ddressing the [root problems underlying disease] is our number 1 public health and moral responsibility as health professionals . . . .").

76. "Epidemiology" is defined as "the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems." CTRS. FOR DISEASE CONTROL, PRINCIPLES OF EPIDEMIOLOGY IN PUBLIC HEALTH PRACTICE 1–2 (3d ed. 2006), https://www.cdc.gov/csels/dsepd/ss1978/SS1978.pdf [https://perma.cc/3AKJ-Z4CD].

77. Public health evaluations have traditionally focused on disease impact and preparedness but have started to expand to socioeconomic consequences. *See, e.g.*, Kristine M. Smith et al., *Infectious Disease and Economics: The Case for Considering Multi-Sectoral Impacts*, 7 ONE HEALTH 1, 2–4 (2019).

78. Not having adequate information, such as epidemiologic and social impact information, could lead to unintended consequences with resulting policies. *See, e.g.*, Kathryn Oliver et al., *Understanding the Unintended Consequences of Public Health Policies: The Views of Policymakers and Evaluators*, 19 BMC PUB. HEALTH 1, 6–7 (2019).

A. Epidemiology of Rare Diseases

In the United States, reported numbers of rare diseases have increased substantially due to the development of genetic analysis and screening.[79] Roughly 80% of rare diseases are genetic in origin, discovered principally in the wake of the human genome project.[80] Further, rare diseases are frequently "ultra-rare," with roughly 80% of rare diseases being unique to an individual or to an individual family.[81] These genetic conditions are often congenital, or expressed at birth,[82] but may also be expressed later in life.[83] Indeed, the impact on those with a rare disease and their families can be severe: 50% of rare diseases affect children, 30% of whom will die before the age of five.[84]

Rare diseases can be relatively well-known. One example is Cystic Fibrosis ("CF"), a genetic condition impacting over 30,000 people and characterized by an inability of the body to create healthy mucus, leading to persistent lung infections and severe breathing problems that worsen over time.[85] Life with CF can be particularly difficult[86]—gastrointestinal issues such as obstruction and ulcers are common, as is pancreatic tissue damage and fatty liver.[87] Without reproductive assistance, male patients with CF are unable to have children, and female CF patients may have difficulty with pregnancy.[88] Currently, the median survival age for those with CF is roughly thirty-seven years, although dedicated efforts to research and develop therapies has allowed for many to live enriching lives into their fifties.[89]

79. Jennifer E. Posey, *Genome Sequencing and Implications for Rare Disorders*, 14 ORPHANET J. RARE DISEASES 153, 153 (2019).

80. *Rare Genetic Diseases*, NAT'L INSTS. HEALTH: NAT'L HUM. GENOME RSCH. INST., https://www.genome.gov/dna-day/15-for-15/rare-genetic-diseases (Apr. 13, 2018) [https://perma.cc/5H7K-GWCB].

81. Stéphanie Nguengang Wakap et al., *Estimating Cumulative Point Prevalence of Rare Diseases: Analysis of the Orphanet Database*, 28 EUR. J. HUM. GENETICS 165, 168 (2019) ("A total of 3585 RDs with point prevalence data were included in this analysis, representing 67.6% of the RDs for which point prevalence is the pertinent epidemiological indicator: 745 RDs annotated with a point prevalence figure or class (20.8%), 2496 RDs described by reports of single cases (69.6%), and 344 described by reports of families (9.6%).").

82. *See, e.g.*, Sarah Stevens et al., *Development and Progress of the National Congenital Anomaly and Rare Disease Registration Service*, 103 ARCHIVES DISEASE CHILDHOOD 215, 215 (2018) ("Most congenital anomalies are rare . . . .").

83. *See, e.g.*, Ingrid Lobo, *Same Genetic Mutation, Different Genetic Disease Phenotype*, 1 NATURE EDUC. 64, 64 (2008) ("For many inherited diseases, the same mutation is not always expressed in all individuals who carry it; moreover, when the mutation is expressed, it is not always expressed in the same way. . . . Some diseases, such as Huntington's disease, may have an earlier onset with more severe symptoms in subsequent generations.").

84. *Spotlight on Rare Diseases*, 7 LANCET DIABETES & ENDOCRINOLOGY 75, 75 (2019).

85. *About Cystic Fibrosis*, CYSTIC FIBROSIS FOUND., https://www.cff.org/What-is-CF/About-Cystic-Fibrosis/ (last visited Nov. 20, 2020) [https://perma.cc/BDK7-S3RV].

86. *See, e.g.*, Kyle Swenson, *Claire Wineland, Who Inspired Millions on YouTube Chronicling Her Cystic Fibrosis Battle, Has Died After a Lung Transplant*, WASH. POST: MORNING MIX (Sept. 4, 2018, 2:58 AM), https://www.washingtonpost.com/news/morning-mix/wp/2018/09/04/claire-wineland-who-inspired-millions-on-social-media-chronicling-her-cystic-fibrosis-battle-has-died-after-a-lung-transplant/ [https://perma.cc/SM82-HHJB].

87. Girish D. Sharma et al., *Cystic Fibrosis*, MEDSCAPE, https://emedicine.medscape.com/article/1001602-overview#a6 (Sept. 28, 2020) [https://perma.cc/B4DV-Q6NV].

88. *Id.*

89. *See id.*

Narcolepsy is another well-known rare disease,[90] involving chronic and excessive daytime sleepiness, sudden and extreme muscle weakness, severely disrupted nighttime sleeping patterns, hallucinations when trying to fall asleep, and sleep paralysis.[91] Without treatment, narcolepsy can be particularly devasting to the patient—job or school performance suffers, behavioral health issues become prominent, and significant social stigmatization and relationship issues arise.[92] One study found that 24% of narcoleptic patients had to quit working, and 18% were terminated from their jobs specifically because of their disease.[93]

Lesser-known conditions are often unnamed or simply named after the location on the specific gene where the mutation occurs.[94] One example includes the A457P allele gene mutation, which results in severely excessive levels of the neurotransmitter norepinephrine,[95] ultimately producing autonomic nervous system dysfunction and symptoms such as syncope (fainting), low blood pressure, and tachycardia (fast heart rate).[96] This genetic mutation was the central cause of the patient's issues described in the case study at the beginning of this Note.[97] Another example is ATR-16 Syndrome, so named to indicate a mutation on the sixteenth chromosome that results in alpha-thalassemia, a blood condition.[98] Because the disease is so rare, researchers have had difficulty establishing "core" symptoms of the disease.[99] Notwithstanding, those born with ATR-16 Syndrome often have anemia, intellectual disability, facial and skeletal malformations (e.g. club foot, short neck, etc.), and potential tumor growth.[100]

90. For an example of narcolepsy portrayed in popular culture, see Julie Kliegman, *The Simpsons Shows Why Narcolepsy Is No Laughing Matter*, WEEK (Sept. 27, 2015), https://theweek.com/articles/576595/simpsons-shows-why-narcolepsy-no-laughing-matter [https://perma.cc/63F5-TV4P].

91. *Narcolepsy*, NAT'L ORG. FOR RARE DISORDERS, https://rarediseases.org/rare-diseases/narcolepsy/ (last visited Nov. 20, 2020) [https://perma.cc/ZXZ9-WQNF].

92. Sagarika Nallu et al., *Narcolepsy*, MEDSCAPE, https://emedicine.medscape.com/article/1188433-overview#a5 [https://perma.cc/CL65-ZPT6] (Aug. 3, 2020).

93. *Id.*

94. *See, e.g.*, PROCEDURAL DOCUMENT: RARE DISEASE NOMENCLATURE IN ENGLISH, ORPHANET 16 (2020), https://www.orpha.net/orphacom/cahiers/docs/GB/eproc_Disease_naming_rules_in_English_PR_R1_Nom_01.pdf [https://perma.cc/89H8-D7GK].

95. For a description of neurotransmitters and norepinephrine, see Sukel, *supra* note 8. The effect of the A457P mutation is a defect in the norepinephrine transporter (or "NET"), which is a protein that controls concentrations of norepinephrine in the brain. This process is discussed in detail in Tahir Tellioglu & David Robertson, *Genetic or Acquired Deficits in the Norepinephrine Transporter: Current Understanding of Clinical Implications*, 3 EXPERT REVS. MOLECULAR MED. 1, 1–10 (2001).

96. *Solute Carrier Family 6 (Neurotransmitter Transporter, Noradrenaline), Member 2; SLC6A2*, ONLINE MENDELIAN INHERITANCE MAN, https://omim.org/entry/163970?search=a457p&highlight=a457p (last visited Nov. 20, 2020) [https://perma.cc/CKM6-2DL2].

97. *See supra* Part I.

98. *ATR-16 Syndrome*, NAT'L ORG. FOR RARE DISEASES, https://rarediseases.org/rare-diseases/atr-16-syndrome/ (last visited Nov. 20, 2020) [https://perma.cc/BP3L-NUSE].

99. *Id.*

100. *Id.*

Non-genetic rare diseases include conditions such as bubonic plague and other infectious diseases, as well as rare cancers such as certain forms of leukemia.[101] Rare infectious diseases are treated differently than other rare conditions, in part because a rare infectious disease can become widespread (an "epidemic" if contained within a country or a "pandemic" if crossing national borders).[102] An illustrative example is found in the 2014–2016 Ebola outbreak.[103] Ebola virus disease is characterized by fever, sore throat, muscle pain, vomiting, diarrhea, rash, internal and external bleeding, and kidney and liver failure.[104] Death is common—fatality rates of those infected hover at 50%, but range from 25% to 90%.[105] Despite the fact that only eleven people were treated for Ebola in the U.S. (and only two people—both healthcare workers who treated the first Ebola patient—acquired Ebola in the U.S.),[106] the domestic public health response was swift and expansive.[107] The Centers for Disease Control and Prevention ("CDC") trained 6,500 American providers on how to respond to and treat Ebola virus disease,[108] and local public health departments worked together to develop response protocols and inform the public with Ebola-related updates.[109] Hospitals also moved quickly to set up quarantine and treatment units in anticipation of high Ebola infection rates.[110] Like COVID-19, Ebola is an example of how infectious diseases—even rare ones—can be addressed by concerted public health efforts.[111]

The epidemiology of rare diseases can be hamstrung definitionally.[112] While the United States defines "rare conditions" as diseases affecting 200,000

101. *See* Genetic and Rare Diseases Info. Ctr., *Find Diseases by Category*, NAT'L CTR. FOR ADVANCING TRANSLATIONAL SCIS., https://rarediseases.info.nih.gov/diseases/categories (last visited Nov. 20, 2020) [https://perma.cc/6MJH-GTNM].

102. *Introduction to Epidemiology*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/csels/dsepd/ss1978/lesson1/section11.html (last visited Nov. 20, 2020) [https://perma.cc/JZS6-SRG5].

103. *Ebola Virus Disease*, WHO (Feb. 10, 2020), https://www.who.int/en/news-room/fact-sheets/detail/ebola-virus-disease [https://perma.cc/XK5W-D2F6].

104. *Id.*

105. *Id.*

106. *2014–2016 Ebola Outbreak in West Africa*, CTRS. FOR DISEASE CONTROL & PREVENTION (Mar. 8, 2019), https://www.cdc.gov/vhf/ebola/history/2014-2016-outbreak/index.html [https://perma.cc/3LZH-JED8].

107. *See id.*

108. *Id.*

109. *What Local Health Departments Need to Know About Ebola*, NAT'L ASS'N CNTY. & CITY HEALTH OFFS.: VOICE, https://www.naccho.org/blog/articles/what-local-health-departments-need-to-know-about-ebola (last visited Nov. 20, 2020) [https://perma.cc/4M34-3KAJ].

110. *See* Maggie Fox, *U.S. Names 35 Ebola-Certified Hospitals*, NBC NEWS (Dec. 2, 2014, 11:25 AM), https://www.nbcnews.com/storyline/ebola-virus-outbreak/u-s-names-35-ebola-certified-hospitals-n259896 [https://perma.cc/Q9QY-PWT8].

111. Both COVID-19 and Ebola were considered "rare diseases," per the U.S. definition. Although COVID-19 has far surpassed the upper prevalence threshold to be classified as a rare disease, the novel viral infection met the definition of a rare disease through the end of March 2020. *See* Kif Leswing et al., *US Coronavirus Cases Top 200,000, Georgia Issues 'Shelter-in-Place' Order*, CNBC (Apr. 1, 2020, 9:47 PM), https://www.cnbc.com/2020/04/01/coronavirus-latest-updates.html [https://perma.cc/8F9B-MHCP]. In contrast, only eleven cases of Ebola were reported in the U.S. during the 2014–2016 outbreak. *SEE* CTRS. FOR DISEASE CONTROL, *supra* note 106.

112. GENETIC & RARE DISEASES INFO. CTR., *supra* note 18.

people or less,[113] the European Union defines them as those affecting no more than fifty people per 100,000 population.[114] These differences in definitions can create problems when trying to determine global prevalence of rare disease because using one definition may undercount the total prevalence while a different definition may overcount.[115] Moreover, prevalence (or the proportion of population living with a disease in a given time period)[116] can be difficult to capture and may change dramatically year-to-year. For example, pancreatic cancer diagnoses were estimated at 33,730 in 2006, while thyroid cancer diagnoses were estimated at 30,180.[117] Nevertheless, thyroid cancer has a higher survival rate than pancreatic cancer, so the prevalence (or total volume) of thyroid cancer was 410,404 while pancreatic cancer was at 31,180.[118] In other words, these two cancers—thyroid and pancreatic—affect roughly the same amount of people each year, but because those with pancreatic cancer typically survive for shorter periods than those with thyroid cancer, the overall number of people with pancreatic cancer is much lower than the number of people with thyroid cancer.[119] Thus, pancreatic cancer is considered a rare disease, while thyroid cancer is not, despite similar rates of diagnosis per year.[120]

Without reliable data on the epidemiology of their conditions, the rare disease community faces substantial hurdles in galvanizing action to address their conditions.[121] Without data on the prevalence and incidence of rare diseases in both national and global populations, support for a public health response may be difficult to get.[122]

113. *Id.*

114. *Id.*

115. One study investigating rare disease definitions found staggering differences in prevalence thresholds indicating whether a disease was "rare." On average, a rare disease in Korea, for example, is fewer than five cases per 100,000 people; meanwhile, the average rare disease in China has a prevalence of fewer than seventy-six cases per 100,000 people. Richter, *supra* note 17, at 910–13.

116. *See* Nat'l Inst. Mental Health, *What Is Prevalence?*, NAT'L INSTS. HEALTH (Nov. 2017), https://www.nimh.nih.gov/health/statistics/what-is-prevalence.shtml [https://perma.cc/H5H4-ZUQ2].

117. INST. MED., *supra* note 24, at 47.

118. *Id.*

119. This definitional issue has come up in federal rulemaking. For example, the U.S. Department of Health and Human Services adopted an interim rule to alter the definition of a "rare cancer" while tailoring the List of World Trade Center-Related Health Conditions; the new definition was based on "incidence." World Trade Center Health Program, 79 Fed. Reg. 9,100, 9,102–03 (U.S. Dep't Health & Hum. Servs. Feb. 18, 2014) (to be codified at 42 C.F.R. pt. 88).

120. *Id.*

121. STEPHEN C. GROFT & MANUEL POSADA DE LA PAZ, *Rare Diseases: Joining Mainstream Research and Treatment Based on Reliable Epidemiological Data, in* RARE DISEASES EPIDEMIOLOGY: UPDATE AND OVERVIEW 4 (Manuel Posada de la Paz, Domenica Taruscio & Stephen C. Groft eds., 2d ed. 2017).

122. *See, e.g.*, *id.*

B. Social Impact of Rare Diseases

The social impact of rare diseases is substantial. To start, there is a sizeable financial impact related to rare disease.[123] Orphan drugs—drugs used to treat, prevent, or diagnose a rare disease, but which pharmaceutical companies have no economic incentive to develop—underscore the financial costs in developing treatments for rare diseases.[124] The average cost for a patient in the U.S. to treat their condition with an orphan drug increased by 33% from 2014 to 2017, from $140,731 annually to $186,758 annually.[125] Meanwhile, the costs to develop an orphan drug are substantial, typically exceeding $100 million per patient trial[126] and $291 million for approved drugs.[127] Despite these costs, pharmaceutical companies that make rare disease drugs are more profitable than companies that do not produce these treatments, seeing a 10% higher return on assets.[128] Nevertheless, rare disease patients are increasingly bearing greater costs for their limited treatment options—between 1998 and 2017, the average annual costs for orphan drugs increased 26-fold,[129] compared to a twofold increase for traditional drugs.[130]

An example highlighting the staggering costs of orphan drugs can be found with spinal muscular atrophy ("SMA").[131] More than half of the approximately 10,000 SMA patients in the United States have SMA1 or SMA2, the most severe

123. Neil Khosla & Rodolfo Valdez, *A Compilation of National Plans, Policies and Government Actions for Rare Diseases in 23 Countries*, 7 INTRACTABLE & RARE DISEASES RSCH. 213, 213 (2018); Erin Smith, *The Hidden Costs of a Rare Disease*, RARE DISEASE REV. (Sept. 7, 2017) ("[C]osts are much higher for patients with rare diseases. Not only are prescription drugs often more expensive because they are orphan drugs but there can also be specialized medical equipment required, needed full-time care for the patient, and visits to multiple specialists.").

124. An orphan drug is "[a] drug used to treat, prevent, or diagnose an orphan disease. An orphan disease is a rare disease or condition that affects fewer than 200,000 people in the United States. Orphan diseases are often serious or life threatening. In 1983, the U.S. government passed a law, called the Orphan Drug Act, to give drug companies certain financial benefits for developing orphan drugs that are safe and effective." *Orphan Drug*, NAT'L CANCER INST.: NCI DICTIONARIES, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/orphan-drug] (last visited Nov. 20, 2020) [https://perma.cc/7W3Q-RV9A].

125. AM.'S HEALTH INS. PLANS, THE RISE OF ORPHAN DRUGS 5 (2019), https://www.ahip.org/wp-content/uploads/IB_OrphanDrugs-1004.pdf [https://perma.cc/Z5ZJ-3PFS] [hereinafter AHIP].

126. *See* Earl Gillespie et al., *Orphan Drug Development—What Are the Real Costs?*, HEALTH ADVANCES BLOG (Apr. 10, 2019), https://healthadvancesblog.com/2019/04/10/orphan-drug-development-what-are-the-real-costs/ [https://perma.cc/6AAN-HQYF].

127. Kavisha Jayasundara et al., *Estimating the Clinical Cost of Drug Development for Orphan Versus Non-Orphan Drugs*, 14 ORPHANET J. RARE DISEASES 1, 3 (2019); David Bai, *Orphan Drugs Have Lower Drug Development Costs Compared with Nonorphan Drugs*, AM. J. MANAGED CARE (Feb. 3, 2019), https://www.ajmc.com/view/orphan-drugs-have-lower-drug-development-costs-compared-with-nonorphan-drugs [https:perma.cc/US7G-CAG7].

128. Dyfrig A. Hughes & Jannine Poletti-Hughes, *Profitability and Market Value of Orphan Drug Companies: A Retrospective, Propensity-Matched Case-Control Study*, 11 PLOS ONE 1, 6 (2016).

129. AHIP, *supra* note 125, at 5.

130 . *Id.*

131. A. Gordon Smith, *The Cost of Drugs for Rare Diseases Is Threatening the U.S. Health Care System*, HARV. BUS. REV. (Apr. 7, 2017), https://hbr.org/2017/04/the-cost-of-drugs-for-rare-diseases-is-threatening-the-u-s-health-care-system [https://perma.cc/8X73-39MM].

forms of the disease and the number-one cause of infant mortality.[132] The condition is destructive, causing progressive paralysis in infants and generally results in death by the age of two.[133] A drug developed to treat the condition, called "nusinersen," was found to be effective—so much so that the clinical trials were ended prematurely by the U.S. Food and Drug Administration ("FDA").[134] Unfortunately, the cost of nusinersen is prohibitively expensive.[135] After the drug was approved by the FDA, the drug maker announced that the per dosage cost of the drug would be $125,000.[136] After accounting for the six total doses required in the first year and three doses each following year, nusinersen costs $750,000 per patient in the first year and $375,000 each subsequent year.[137] Thus, a single patient with SMA treated with nusinersen would have to pay $8.25 million in treatment by their twenty-first birthday, $24.75 million by age sixty-five, and $30.38 million by age eighty.[138] Another SMA drug, called Zolgensma, is the most expensive drug in the world, costing $2.1 million for the treatment.[139] The drug was highly effective in clinical trials but is not covered by most insurance policies, leaving desperate families to either foot the bill or watch their loved one die from the condition.[140]

Another example of the high costs of rare disease is found with adrenoleukodystrophy ("ALD"), a rare genetic condition involving the breakdown of nerve fibers in the brain and progressive deterioration of the adrenal glands.[141] The most severe form of the disease affects boys between the ages of four and ten, and involves "visual loss, learning disabilities, seizures, dysphagia, deafness, disturbances of gait and coordination, fatigue, intermittent vomiting and progressive dementia,"[142] eventually leading to a vegetative state and death within two to three years.[143] The only treatment shown to stop the progression of ALD in the brain is an allogeneic blood and marrow transplant,[144] which costs $925,000 on

132. *Id.*
133. *Id.*
134. *Id.*
135. *Id.*
136. *Id.*
137. *Id.*
138. *See id.* The calculations made assumed no changes in price point for the drug, nor any discounts in cost from the pharmaceutical company or coverage amounts from insurance. The formula used was [(cost of single nusinersen dose) x (six doses in first year)] + [(cost of single nusinersen dose) x (three doses in subsequent years) x (number of years lived – one].
139. Emma Court, *'Like We Were Being Forced to Gamble with Our Son's Life': Health Insurers Won't Pay For a $2.1 Million Drug for Kids, and Parents Say They're Running Out of Time*, BUS. INSIDER (July 26, 2019, 8:36 AM), https://www.businessinsider.com/health-insurance-companies-deny-kids-with-sma-gene-therapy-zolgensma-2019-7 [https://perma.cc/H3TE-C9YZ].
140. *See id.*
141. *See Adrenoleukodystrophy (ALD)*, KENNEDY KRIEGER INST., https://www.kennedykrieger.org/patient-care/conditions/leukodystrophy/adrenoleukodystrophy-ald (last visited Nov. 20, 2020) [https://perma.cc/2APE-LRQT].
142. *Id.*
143. *See X-Linked Adrenoleukodystrophy*, NAT'L ORG. RARE DISORDERS, https://rarediseases.org/rare-diseases/adrenoleukodystrophy/ (last visited Nov. 20, 2020) [https://perma.cc/X8GZ-76RX].
144. *See* Pediatric Blood & Marrow Transplant Ctr., *New Advancements for ALD*, UNIV. MINN., https://bmt.umn.edu/new-advancements-ald (last visited Nov. 20, 2020) [https://perma.cc/W8U8-K6YT].

average.[145] The costs of not proactively treating ALD, however, can cost millions due to expensive palliative treatments, lost productivity and income for parents and caregivers, and associated expenditures related to care (e.g. travel costs to get to treatment centers, home modifications, around-the-clock nursing care, and specialized wheelchairs).[146]

Navigating the American health insurance market—a notoriously bewildering experience even for experts in health policy[147]—is a labyrinth for rare disease patients.[148] Before passage of the Patient Protection and Affordable Care Act ("ACA") in 2010, rare disease patients regularly encountered problems with health insurers.[149] For example, insurance companies tailored for individual policies (as opposed to employer-based policies) would screen or underwrite rare disease patients and their family because of their health history.[150] Lifetime caps on coverage were outlawed under the ACA; before the ACA, rare disease patients could quickly hit their caps, even if the maximum lifetime coverage was $2 million or more.[151] Even though the ACA has expanded insurance coverage for many rare disease patients and their families, problems with health insurance persist. For example, health insurance companies do not always cover orphan drugs for rare disease patients,[152] create strict requirements for patients to qualify for coverage,[153] and prioritize cheaper but less clinically effective drugs.[154] Health insurers also rely on International Classification of Disease ("ICD-10") codes to determine how much to pay doctors and healthcare providers,[155] but ICD-10 codes are not currently robust enough to capture most rare diseases,[156]

145. *See* Laura Adams et al., *Redesigning Care to Lower Episode Costs in Bone Marrow Transplantation*, 23 BIOLOGY BLOOD & MARROW TRANSPLANTATION S18, S109 (2017).

146. Telephone Interview with Julia Jenkins, Exec. Dir., EveryLife Found. (June 26, 2020).

147. *See, e.g.*, Austin Frakt, *Choosing a Health Plan Is Hard, Even for a Health Economist*, N.Y. TIMES: THE UPSHOT (Oct. 27, 2014), https://www.nytimes.com/2014/10/28/upshot/choosing-a-health-plan-is-hard-even-for-a-health-economist.html [https://perma.cc/T2SL-MX7W] ("Each year when I shop for coverage through my employer, I feel like I'm buying myself at least as much grief as I am insurance.").

148. *See* Jeremy Schafer, *Exclusions: Adding Complexity for Patients with Rare Diseases*, U.S. NEWS & WORLD REP. (Sept. 19, 2018, 6:00 AM), https://health.usnews.com/health-care/for-better/articles/2018-09-19/exclusions-adding-complexity-for-patients-with-rare-diseases [https://perma.cc/A9ZB-NYTM]; *see also* GLOBAL GENES, RARE TOOLKITS: NAVIGATING HEALTH INSURANCE (2016), https://globalgenes.org/wp-content/uploads/2018/11/Navigating-Health-Insurance_DIGITAL_spread_op.pdf [https://perma.cc/32QV-7PYC].

149. *See* INST. MED., *supra* note 24, at 70.

150. *Id.* at 182.

151. *Id.* at 197–98.

152. *See* James D. Chambers et al., *Variation in US Private Health Plans' Coverage of Orphan Drugs*, 25 AM. J. MANAGED CARE 508, 508 (2019].

153. *See, e.g.*, Emma Court, *Why Health Insurers Won't Cover This $300,000-a-Year Rare Disease Drug*, MARKETWATCH (Dec. 30, 2016, 12:58 PM), https://www.marketwatch.com/story/why-health-insurers-wont-cover-this-300000-a-year-rare-disease-drug-2016-12-29 [https://perma.cc/KC4G-3UC9].

154. Telephone Interview with Julia Jenkins, *supra* note 146.

155. *See* J. A. Hirsch et al., *ICD-10: History and Context*, 37 AM. J. NEURORADIOLOGY 596, 596–97 (2016); Michael Bihari, *Learn About Insurance Codes to Avoid Billing Errors*, VERYWELL HEALTH (Feb. 16, 2020), https://www.verywellhealth.com/learn-about-insurance-codes-to-avoid-billing-errors-1738628 [https://perma.cc/RR49-LY3E].

156. Ségolène Aymé et al., *Rare Diseases in ICD11: Making Rare Diseases Visible in Health Information Systems Through Appropriate Coding*, 10 ORPHANET J. RARE DISEASES 1, 2 (2015) ("In January 2015, among the over 6,954 clinical entities listed by Orphanet, 355 of them only have a unique specific code in ICD 10 and 162 can be specifically mapped to a set of ICD10 codes.").

leading to inadequate coverage.[157] Thus, the medical community has called for expanding ICD-10 codes to include more rare diseases,[158] and early work on new ICD-11 codes suggests a tenfold increase in rare disease codes compared to the current version.[159]

Rare disease patients can encounter significant opportunity costs.[160] It takes an average of five years and seven physicians to diagnose a rare disease,[161] time during which they will receive no benefits to buoy financial burdens associated with medical care, the costs of caretakers, and the loss of income.[162] Throughout the process of searching for a diagnosis and managing their condition, rare disease patients are often forced to become the expert on their own condition—both general practitioners and physician specialists are unlikely to have advanced knowledge on living with or treating the disease.[163]

Importantly, patients diagnosed with a rare condition will often face the news that there is no known treatment.[164] In fact, 95% of rare diseases have no FDA-approved treatment.[165] Additionally, some rare diseases have treatments that are only approved for use outside of the patient's home country.[166] One study found that the United States has 415 orphan products for 300 rare diseases, while the European Union has 133 products for 122 rare diseases.[167] Thus, a person living in France with a rare condition might only be able to receive treatment in the U.S. if that treatment was approved by the FDA but not the European Medicines Agency.[168] If the market approvals for these drugs were to merge, that same person in France or elsewhere in the European Union would have 362 more

157. Kin Wah Fung et al., *Coverage of Rare Disease Names in Standard Terminologies and Implications for Patients, Providers, and Research*, AM. MED. INFORMATICS ASS'N ANN. SYMP. PROC. 564, 567 (2014).

158. Aymé et al., *supra* note 156, at 1.

159. *Id.* at 6.

160. *See* Nathan Handley & Judd E. Hollander, *Opportunity Cost: The Hidden Toll of Seeking Health Care*, HEALTH AFFAIRS: BLOG (May 1, 2019), https://www.healthaffairs.org/do/10.1377/hblog20190429.592190/full/ [https://perma.cc/CAW5-VFSU].

161. *Rare Diseases Create Significant Care and Financial Burdens Among Patients*, AM. J. MANAGED CARE (July 20, 2017), https://www.ajmc.com/newsroom/rare-diseases-create-significant-care-and-financial-burdens-among-patients [https://perma.cc/RMA9-GXMV].

162. One such example can be found in the case of Early-Onset Dementia ("EOD"), a rare disease in which dementia begins before the patient turns sixty-five years of age. *See* Nobuo Sakata & Yasuyuki Okumura, *Job Loss After Diagnosis of Early-Onset Dementia: A Matched Cohort Study*, 60 J. ALZHEIMER'S DISEASE 1231, 1233 (2017) ("We found that 14% of patients with EOD left their jobs within one year after their diagnosis, which was twice the rate of those without EOD.").

163. *See, e.g.*, Karolina Budych et al., *How Do Patients with Rare Diseases Experience the Medical Encounter? Exploring Role Behavior and its Impact on Patient–Physician Interaction*, 105 HEALTH POL'Y 154, 155 (2012) ("However, due to the low prevalence and the lack of expertise, patients are forced to become knowledgeable about their own disease and related therapies.").

164. *See* Max Bronstein et al., *For Rare Disease Patients, A Pathway to Hundreds of New Therapies*, HEALTH AFFAIRS: DRUGS & MED. INNOVATION BLOG (Mar. 21, 2017), https://www.healthaffairs.org/do/10.1377/hblog20170321.059289/full/ [https://perma.cc/8B7M-PETY].

165. *Id.*

166. *See* Viviana Giannuzzi et al., *Orphan Medicinal Products in Europe and United States to Cover Needs of Patients with Rare Diseases: An Increased Common Effort Is to Be Foreseen*, 12 ORPHANET J. RARE DISEASES 1, 7 (2017).

167. *Id.* at 5.

168. *See id.* at 5–7.

products available, while those in the U.S. would have access to seventy-two additional products.[169]

An additional consideration beyond the limited number of approved treatments is the limited emotional support for those with conditions unique to them or their family.[170] While patients with rare conditions tend to prefer having a diagnosis over not knowing the nature of their health issues,[171] those with unique conditions often feel isolated and can encounter severe emotional and mental health problems associated with their diagnosis and outlook.[172]

Caretakers of those with rare conditions—similar to caretakers of patients with more common diseases—face significant financial and emotional stressors, as well.[173] Consider, for example a hypothetical middle-class American family: a husband, wife, and two children.[174] Both parents work to provide for their chil-

169. *Id.* at 7.

170. *See* Charlotte von der Lippe et al., *Living with a Rare Disorder: A Systematic Review of the Qualitative Literature*, 5 MOLECULAR GENETICS & GENOMIC MED. 758, 766 (2017) ("[A]dults with rare conditions described psychological restraints, such as a lack of autonomy and freedom due to the demands of treatment, uncertainty about the disease evolution, and emotional distress as a consequence of pain or other distressing aspects of the conditions."); *see also* Lemuel J. Pelentsov et al., *The Supportive Care Needs of Parents with a Child with a Rare Disease: Results of an Online Survey*, 17 BMC FAM. PRAC. 1, 1 (2016) ("Fifty-four percent (n = 140/259) of parents were dissatisfied with health professionals' level of knowledge and awareness of disease; 71 % (n = 130/183) of parents felt they received less support compared to other parents. Information regarding present (60 %, n = 146/240) and future services (72 %, n = 174/240) available for their child were considered important. Almost half of parents (45 %, n = 106/236) struggled financially, 38 % (n = 99/236) reduced their working hours and 34 % (n = 79/236) ceased paid employment. Forty-two percent (n = 99/223) of parents had no access to a disease specific support group, and 58 % (n = 134/230) stated that their number of friends had reduced since the birth of their child; 75 % (n = 173/230) had no contact with other parents with a child with a similar disease, and 46 % (n = 106/230) reported feeling socially isolated and desperately lonely. Most frequent emotions expressed by parents in the week prior to completing the survey were anxiety and fear (53 %, n = 119/223), anger and frustration (46 %, n = 103/223) and uncertainty (39 %, n = 88/223).").

171. *See* Rebecca C. Spillmann et al., *A Window into Living with an Undiagnosed Disease: Illness Narratives from the Undiagnosed Diseases Network*, 12 ORPHANET J. RARE DISEASES 1, 1 (2017) ("[T]he majority [of rare disease patients or parents of rare disease patients] felt they had no further healthcare options and hoped the [Undiagnosed Diseases Network] would provide them with a diagnosis, with the adults expecting to return to their previously healthy life and the parents wanting information to manage their child's healthcare . . . [those] living with their undiagnosed illness [expressed] frustration at being undiagnosed . . . . The adults felt they had to provide validation of their symptoms to providers . . . [t]he parents worried that something relevant to their child's management was being overlooked.").

172. Von der Lippe et al., *supra* note 170, at 766 ("[A]dults with rare conditions described psychological restraints, such as a lack of autonomy and freedom due to the demands of treatment, uncertainty about the disease evolution, and emotional distress as a consequence of pain or other distressing aspects of the conditions.").

173. *See* NAT'L ALL. FOR CAREGIVING, RARE DISEASE CAREGIVING IN AMERICA 69 (2018), https://www.caregiving.org/wp-content/uploads/2020/05/NAC-RareDiseaseReport_February-2018_WEB.pdf [https://perma.cc/X5QG-X9DR]; *see also* Brian P. Dunleavy, *The Impact of Rare Disease on Family Caregivers*, EVERYDAY HEALTH, https://www.everydayhealth.com/rare-diseases/rare-disease-takes-toll-on-family-caregivers/ (Feb. 28, 2018) [https://perma.cc/S5ZY-2LEU].

174. The "typical" American family has become much more varied due to numerous sociologic factors. For a detailed analysis of the changing American family, see PEW RSCH. CTR., PARENTING IN AMERICA: OUTLOOK, WORRIES, ASPIRATIONS ARE STRONGLY LINKED TO FINANCIAL SITUATION 15 (2015), https://www.pewresearch.org/wp-content/uploads/sites/3/2015/12/2015-12-17_parenting-in-america_FINAL.pdf [https://perma.cc/QM4G-MYCD]. Importantly, policymakers frequently rely on a "typical," "middle-class" family when crafting policies and public messaging. *See, e.g.*, Pavithra Mohan, *What Politicians Get Wrong About the Middle*

dren. After the husband develops a rare neurological condition impacting his autonomic nervous system (multiple system atrophy, or "MSA," which presents similarly to Parkinson's Disease but fails to respond to treatment and has an average life expectancy of seven years after the onset of symptoms),[175] the wife begins serving as his caretaker.[176] She is devastated by his diagnosis, but holds out hope that her husband can get treatment.[177] She foregoes her personal and career goals in order to take care of her husband, who has begun to aspirate, or choke, on his saliva during the middle of the night.[178] She is afraid that she can no longer provide suitable care on her own, so she taps into their savings to pay for at-home nursing care.[179] As her husband's condition progresses, she may need to go to grief counseling,[180] make funerary arrangements,[181] and keep herself physically and mentally capable of returning to work to provide for her children.[182] Meanwhile, her ability to do so will decline, leading her to fall back on social safety nets such as Medicaid or Social Security Disability.[183] This draining and debilitating process also affects her children who watch helplessly as their father's health deteriorates.[184] When the husband dies, the wife must support her

Class, FAST CO. (Oct. 7, 2019), https://www.fastcompany.com/90411711/what-politicians-get-wrong-about-the-middle-class [https://perma.cc/24UM-NRL4].

175. G. K. Wenning et al., *What Clinical Features Are Most Useful to Distinguish Definite Multiple System Atrophy From Parkinson's Disease?*, 68 J. NEUROLOGY, NEUROSURGERY & PSYCHIATRY 434, 434, 436 (2000).

176. For a detailed assessment of rare disease caregiver experiences and perspectives, see NAT'L ALL. FOR CAREGIVING, *supra* note 173.

177. Caregivers of rare disease patients with a known condition or a condition that has available treatments more frequently feel that their local hospital can provide care for their loved one. *Id.* at 30.

178. MSA patients often pass away due to aspiration, as their automatic response of swallowing no longer works. Spiridon Papapetropoulos et al., *Causes of Death in Multiple System Atrophy*, 78 J. NEUROLOGY, NEUROSURGERY & PSYCHIATRY 327, 328 (2007).

179. A study by the American Association of Retired Persons on the costs for caregivers found that more than 75% of caregivers spent an average of nearly $7,000 annually on out-of-pocket expenses. *See* Rachel Bluth, *Study: Many Caregivers Spend $7K Annually Out of Pocket*, KAISER HEALTH NEWS (Nov. 14, 2016), https://khn.org/news/study-many-caregivers-spend-7k-annually-out-of-pocket/ [https://perma.cc/3XJR-8DHJ].

180. For a description of depression and grief afflicting bereaved caregivers, see, for example, Richard Schulz et al., *Bereavement After Caregiving*, 63 GERIATRICS 20, 20–22 (2008).

181. For some rare diseases, this can pose a significant challenge. *See, e.g.*, JoNel Aleccia, *Final Fear: Funeral Homes Refuse Victims of Brain Disease*, NBC NEWS (Oct. 2, 2013, 7:56 AM), https://www.nbcnews.com/healthmain/final-fear-funeral-homes-refuse-victims-brain-disease-8C11312131 [https://perma.cc/2MUM-N25A] (describing the difficulty in finding funerary arrangements for family members who have died from Creutzfeldt-Jakob disease, a rare and fatal brain disease, because of unfounded fears of possible disease spread during the cremation or embalming process).

182. For a description of factors caregivers can consider when returning to the workforce, see, for example, Anthony Cirillo, *Returning to the Workforce After Caregiving*, U.S. NEWS & WORLD REP. (Apr. 25, 2019, 6:00 AM), https://health.usnews.com/health-care/for-better/articles/returning-to-the-workforce-after-caregiving [https://perma.cc/D5CY-HBZW].

183. For more information on the U.S. social safety net, see PAMELA LOPREST & DEMETRA NIGHTINGALE, URBAN INST. THE NATURE OF WORK AND THE SOCIAL SAFETY NET 1 (2018), https://www.urban.org/sites/default/files/publication/98812/the_nature_of_work_adn_the_social_safety_net_7.pdf [https://perma.cc/6SFX-Y6XR].

184. Discussing a parent's serious illness with children can be challenging, but resources are available to help guide the discussion. *See, e.g.*, Claire McCarthy, *How to Talk to Children About the Serious Illness of a Loved One*, HARV. HEALTH BLOG (JAN. 14, 2020, 9:47 AM), https://www.health.harvard.edu/blog/how-to-talk-to-children-about-the-serious-illness-of-a-loved-one-2019120218468 [https://perma.cc/S8XG-4MN3]. For tips

children despite the intense grief and suffering.[185] None of this family's experience is captured in basic epidemiology.[186] Nevertheless, this hypothetical case illustrates how the social impact of rare disease affects more than just the patient, demonstrating a strong ripple effect.

These and other social effects can also be seen in children suffering from rare diseases and in their families, who often face especially difficult circumstances.[187] Parents of children with rare conditions may have limited emotional support from others and may have to alter their careers to serve as their child's caretaker.[188] Further, children with rare diseases may have difficulty succeeding in traditional childhood activities such as going to school, playing outside, participating in sports, or making friends.[189] Children born with or who develop rare conditions may be shunned or otherwise face stigmatization,[190] and may face significant hurdles in gaining an education or skills-based training if accommodations are not provided.[191]

Workforce issues are common for those with chronic and rare conditions.[192] Those with rare diseases can have higher rates of absenteeism and lower productivity compared to healthy coworkers[193]—an understandable side effect of their health status. Even if someone with a rare condition is able to work, not

on helping young children with grief, see Sesame Street, *Grief*, SESAME WORKSHOP, https://www.sesamestreet.org/toolkits/grief/ (last visited Nov. 20, 2020) [https://perma.cc/9Z3S-75BH].

185. *See* Sesame Street, *supra* note 184.

186. Epidemiologic methods have been used to study grief severity and persistence, but do not capture the social, economic, emotional, or other effects that a family or individual might experience after the death of a loved one. *See, e.g.*, Jelena Milic et al., *Determinants and Predictors of Grief Severity and Persistence: The Rotterdam Study*, 29 J. AGING & HEALTH 1288, 1299–1303 (2017).

187. *See, e.g.*, Meghan Holohan, *Sophia Weaver, Girl Cyber-Bullied for Facial Deformities, Dies at Age 10*, TODAY (May 24, 2019, 1:12 PM), https://www.today.com/parents/sophia-weaver-girl-bullied-facial-deformities-dies-t154902 [https://perma.cc/MAS6-JR8U].

188. *See* Pelentsov et al., *supra* note 170, at 7–8.

189. A study on the psychological and social impact of Niemann-Pick disease—a rare, chronic, debilitating, and fatal metabolic disorder—found that children faced emotional distress from peers at school. Shelly L. Henderson et al., *Psychological Aspects of Patients with Niemann-Pick Disease, Type B*, 149 AM. J. MED. GENETICS 2430, 2432–34 (2009). Children with chronic conditions—which constitute many rare diseases—also face loneliness and low self-esteem. Marlies Maes et al., *Loneliness in Children and Adolescents with Chronic Physical Conditions: A Meta-Analysis*, 42 J. PEDIATRIC PSYCH. 622, 630 (2017); M. Pinquart, *Self-Esteem of Children and Adolescents with Chronic Illness: A Meta-Analysis*, 39 CHILD 153, 158–60 (2012).

190. *See, e.g.*, Jason Duaine Hahn, *'Destroyed' Dad Pleads with Parents to Educate Their Kids After Bullied Son with Rare Condition Is Called 'Monster'*, PEOPLE (Sept. 19, 2017, 11:24 AM), https://people.com/human-interest/destroyed-dad-pleads-with-parents-to-educate-their-kids-after-bullied-son-with-rare-condition-is-called-monster/ [https://perma.cc/WH3X-H5CB].

191. *See* NEW ENG. GENETICS COLLABORATIVE, ADVOCATING FOR YOUR CHILD WITH A RARE DISEASE AT THEIR SCHOOL 4–5, https://globalgenes.org/wp-content/uploads/2015/08/GG_toolkit_educational-advocacy_web-hyperlinked.pdf (last visited Nov 20, 2020) [https://perma.cc/LR9S-2U62].

192. *See* Garrett R. Beeler Asay et al., *Absenteeism and Employer Costs Associated with Chronic Diseases and Health Risk Factors in the US Workforce*, 13 PREVENTING CHRONIC DISEASE 1, 1 (2016).

193. *See, e.g.*, EUR. ORG. RARE DISEASES, RARE DISEASES: UNDERSTANDING THIS PUBLIC HEALTH PRIORITY 12 (2005) ("Travel costs to specialised centres are high in terms of time off work and financial cost. . . . In the case of an adult rare disease patient who is well enough to be able to work, the work hours must be adapted to allow for medical visits and appropriate care."); *cf.* Rebecca J. Mitchell & Paul Bates, *Measuring Health-Related Productivity Loss*, 14 POP. HEALTH MGMT. 93, 95–98 (2011) (showing that poor health generally can lead to increased absenteeism and decreased work productivity, which lends support to the under-studied problem of absenteeism and presenteeism issues for rare disease patients).

all businesses can or need to provide accommodations.[194] For example, a small family-owned business of five employees would not be required to retrofit their business to allow for wheelchair accessibility.[195] Or, a business may be unable to provide teleworking capabilities to an employee with a rare condition if the setup would be too expensive or if the person's job required "boots on the ground."[196] While employers must provide these accommodations,[197] their effectiveness and implementation is questionable at best and it is unclear whether these accommodations truly support the needs of rare disease patients trying to contribute to the workforce.[198]

Plainly, an individual with a rare disease encounters numerous societal obstacles. Interactions with family, physicians, health insurers, government, lawyers, work, school, and the pharmaceutical industry are complex and intersectional. That is, a rare disease patient may interact with a health insurer to discuss coverage, while that same health insurer works with the patient's physician to work out reimbursement rates using government formulas.[199]

194. For example, an employer would not need to make accommodations that would "impose an undue hardship" on the business. 42 U.S.C. § 12112(b)(5)(A).

195. The Americans with Disabilities Act accommodation requirements only apply to employers with fifteen or more employees. 42 U.S.C. § 12111(5)(A).

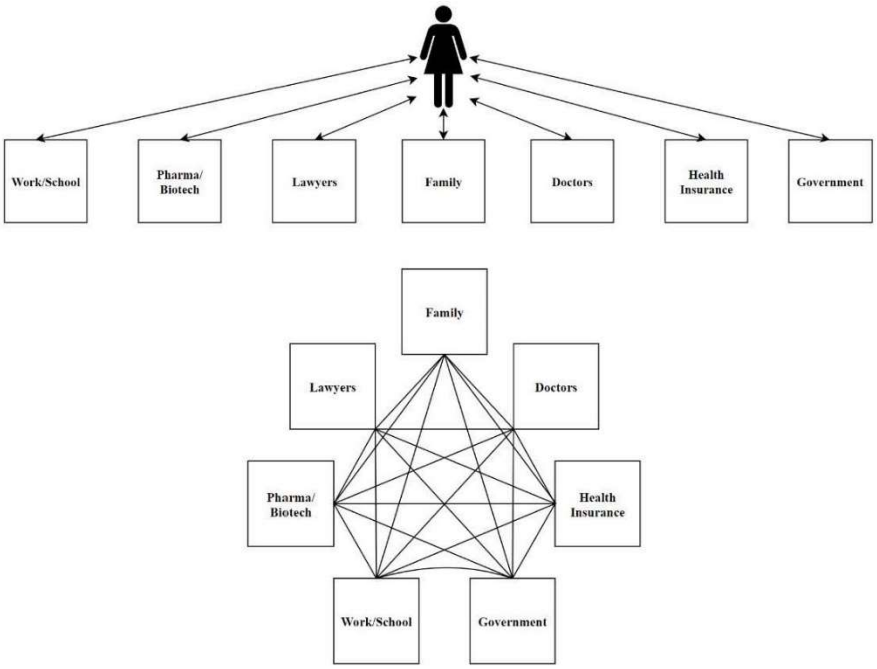
196. 42 U.S.C. § 12112(b)(5)(A) (2018).

197. All employers in the U.S. must follow the requirements of the Americans with Disabilities Act unless they meet certain exceptions. 42 U.S.C. §§12111, 12113.

198. Requesting workplace accommodations can be challenging. For example, one study found that only 11% of formal workplace accommodation requests mentioning the Americans with Disabilities Act were granted. Shengli Dong et al., *Accommodation Request Strategies Among Employees with Disabilities: Impacts and Associated Factors*, 63 HAMMILL INST. ON DISABILITIES 168, 175 (2020).

199. The resource-based relative value scale, or "RBRVS," is the system used by Medicare and Medicaid to standardize physician payment based on services provided. *See* RVS Update Committee, *RBRVS Overview*, AM. MED. ASS'N, https://www.ama-assn.org/about/rvs-update-committee-ruc/rbrvs-overview (last visited Nov. 20, 2020) [https://perma.cc/HGE2-26XP].

FIGURE 1: INTERACTIONS AND INTERSECTIONS BETWEEN RARE DISEASE PATIENTS AND KEY STAKEHOLDERS



Beyond the impact on the individual, rare diseases have an impact on society broadly. An example can be found in the condition Friedreich's Ataxia ("FDRA"), which is a genetic disorder that results in progressive degradation of the central and peripheral nervous systems.[200] Over 60% of those living with FDRA retrofit their homes to accommodate their health needs, which can be costly.[201] This process can include installing ramps, purchasing an electric bed and specialized mattress, changing home flooring and widening doorways to allow for a wheelchair, and installing an adaptable shower or bath.[202] The costs of making these changes were found in one study to be over €45,000 (nearly $54,000) in Germany and over £33,000 (over $44,000) in the United Kingdom.[203]

200. Paola Giunti et al., *Impact of Friedreich's Ataxia on Health-Care Resource Utilization in the United Kingdom and Germany*, 8 ORPHANET J. RARE DISEASES 1, 1 (2013), https://ojrd.biomedcentral.com/articles/10.1186/1750-1172-8-38#Abs1 [https://perma.cc/DV9Z-8FE9].

201. *Id.* at 6.

202. *Id.*

203. *Id.* at 7–8. Conversion of the Euro and Pound Sterling to U.S. Dollars was performed using XE Currency Converter on November 29, 2020.

There are no empirical studies on the total economic burden of all rare diseases combined, due in part to a lack of reliable information.[204] Rare disease advocates estimate, however, that the costs of not treating rare diseases could be nearly $1 trillion annually in the United States alone.[205] Studies evaluating the economic impact of rare diseases—including data acquisition studies and disease-specific cost-benefit analyses—are ongoing and could provide useful information from which to draw conclusions.[206]

III. ANALYSIS

This Part will investigate the current legal and policy landscape involving rare disease. Specific focus will be given to the allocation of government resources towards rare diseases, the issues surrounding newborn screening for rare diseases, policies promoting the development of novel therapeutics, and the interaction between rare disease patients and the medical malpractice system.

A. Allocation of Government Resources

Federal legislation has allocated significant resources to address rare disease. Primarily, three legislative acts have dramatically increased the amount of resources available to the rare disease community: the Americans with Disabilities Act, the Orphan Drug Act, and the Rare Diseases Act.[207] These three pieces of legislation have changed the landscape of how rare disease patients maneuver within society, how treatments are made, and how research on rare diseases is coordinated nationally.

1. Americans With Disabilities Act

Enacted in 1990, The Americans With Disabilities Act ("ADA") is a civil rights law prohibiting discrimination against "individuals with disabilities in all areas of public life, including jobs, schools, transportation, and all public and private places that are open to the general public."[208] The purpose of the law is to ensure equal rights for people with disabilities, similar to other civil rights laws that protect individuals with on the basis of race, color, sex, national origin,

204. *See* Steve Silvestri, *Please Include $1.5 Million for a Rare Disease Burden Study in the Senate's Fiscal Year 2020 Labor, Health and Human Services, Education Appropriations Bill*, EVERYLIFE FOUND., https://rareadvocates.org/wp-content/uploads/2019/07/Burden-Study-Ask-for-Rare-Across-America-Final.pdf (last visited Nov. 20, 2020) [https://perma.cc/7DTD-S7BC].

205. Telephone Interview with Julia Jenkins, *supra* note 146.

206. *See, e.g.*, JONATHAN BELSEY ET AL., WORLD ECON. F., GLOBAL DATA ACCESS FOR SOLVING RARE DISEASE: A HEALTH ECONOMICS VALUE FRAMEWORK 6 (2020), http://www3.weforum.org/docs/WEF_Global_Data_Access_for_Solving_Rare_Disease_Report_2020.pdf [https://perma.cc/DHW4-2CAY] ("Currently, we have comprehensive data on only the 5% of rare diseases with US Food and Drug Administration (FDA)-approved treatments. Of the very few studies looking at the cost of illness, most focus on a specific rare disease.").

207. *See infra* Sections III.A(i)–(iii).

208. *See, e.g.*, *What Is the Americans with Disabilities Act (ADA)?* ADA NAT'L NETWORK, https://adata.org/learn-about-ada (last visited Nov. 20, 2020) [https://perma.cc/RE2W-M4CA].

age, and religion.[209] The ADA "guarantees equal opportunity for individuals with disabilities in public accommodations, employment, transportation, state and local government services, and telecommunications."[210]

The Americans with Disabilities Act Amendments Act ("ADAAA"), effective January 1, 2009, altered the federal definition of "disability."[211] The changes in the ADAAA resulted in a three-pronged approach in defining "disability," including: (1) "a physical or mental impairment that substantially limits one or more major life activities;"[212] (2) "a record of a physical or mental impairment that substantially limited a major life activity;"[213] or (3) "when a covered entity takes an action prohibited by the ADA because of an actual or perceived impairment that is not both transitory and minor."[214] This definition of "disability" applies to all titles of the ADA, including Title I (employment practices of private employers with fifteen or more employees, state and local governments, employment agencies, labor unions, agents of the employer and joint management labor committees);[215] Title II (programs and activities of state and local government entities);[216] and Title III (private entities that are considered places of public accommodation).[217]

As those with rare diseases have "disabilities" under the definition provided in the ADAAA, they should receive the accommodations provided by the law. One example that illustrates this interaction can be found in Ehlers-Danlos Syndrome, a rare condition that is inherited and results in overly flexible joints, stretchy skin, and fragile skin.[218] A person with Ehlers-Danlos Syndrome is able to work and go to school, albeit not full-time, with accommodations that reduce the level of pain and discomfort they may experience.[219] From a vocational perspective, these accommodations include steps taken by employers to limit specific work activities that cause pain, or otherwise provide services or tools to help the employee integrate into the workplace.[220] In short, if a person has Ehlers-Danlos Syndrome or any other rare disease classifying as a "disability" under the ADAAA, she should receive all available accommodations to assist with their work, school, public transportation, or other activities protected by the law.

209. *Id.*

210. *Id.*

211. *See, e.g.*, *Questions and Answers on the Final Rule Implementing the ADA Amendments Act of 2008*, U.S. EEOC, https://www.eeoc.gov/laws/regulations/ada_qa_final_rule.cfm (last visited Nov. 20, 2020) [https://perma.cc/36XA-EP2A].

212. *Id.*

213. *Id.*

214. *Id.*

215. *Id.*

216. *Id.*

217. *Id.*

218. *Ehlers-Danlos Syndrome*, MAYO CLINIC (Oct. 13, 2017), https://www.mayoclinic.org/diseases-conditions/ehlers-danlos-syndrome/symptoms-causes/syc-20362125 [https://perma.cc/94D2-NQ6E].

219. *See* Brittney Murray et al., *Ehlers–Danlos Syndrome, Hypermobility Type: A Characterization of the Patients' Lived Experience*, 161 AM. J. MED. GENETICS 2981, 2984 (2013).

220. *See* Julie C. Hill, *Zebras in the Workplace: Vocational Rehabilitation Considerations for Individuals with Ehlers-Danlos Syndrome*, 47 J. VOCATIONAL REHAB. 197, 200–01 (2016).

There are several issues with this, however, that can often render the ADAAA useless for rare disease patients. For example, if a rare disease patient wants workplace accommodations, they need to inform their workplace.[221] Disclosing disease status can create several uncomfortable scenarios, including decreased believability and credibility (especially if symptoms fluctuate or are cyclical) and altered professional reputation (especially if the workplace or school stigmatizes the condition).[222] These issues are unlikely to resolve with additional legislation; however, efforts to destigmatize rare diseases may lead to better accommodations for rare disease patients.[223] Treating rare diseases as a public health issue may increase collective understanding and integration of rare disease patients, and thus improve the likelihood of workplaces, schools, and other venues of accommodating rare disease patients.

2. Orphan Drug Act

The Orphan Drug Act ("ODA") was passed in the United States in 1983 to encourage the development of drugs for rare diseases.[224] At that time, drug therapies for such diseases were rare; only thirty-four therapies for rare diseases had been developed.[225] In 2017, over three decades after the ODA was enacted, a total of 487 orphan-designated drugs had entered the U.S. market.[226] In 2018, 58% (thirty-four of fifty-nine) of the newly-approved drugs were for a rare-diseases.[227] Clearly, the ODA has encouraged the development of treatments for rare diseases.[228] Moreover, the ODA has served as a model for other countries, including Australia, Japan, Singapore, and the European Union,[229] in part because of the unique cooperative arrangement between stakeholders that otherwise would be non-existent.[230]

Despite these noteworthy successes, critics argue the ODA has ultimately fallen short of its original goals.[231] The primary incentives outlined in the ODA

221. *Id.* at 200.

222. *Id.*

223. For an example of efforts to destigmatize rare diseases, see Anthony Rimel, *Event Aims to Destigmatize Rare Diseases*, CORVALLIS GAZETTE-TIMES (Aug. 19, 2019), https://www.gazettetimes.com/news/local/event-aims-to-destigmatize-rare-diseases/article_68fae9a0-5a42-5512-b8f3-f2892f53ecbc.html [https://perma.cc/A2LJ-9RDA].

224. Orphan Drug Act, Pub. L. No. 97-414, § 1, 96 Stat. 2049, 2049 (1983).

225. *See* INST. MED., *supra* note 24, at 292 ("[The] 34 drugs . . . approved from 1967 to 1983 would have qualified under the Orphan Drug Act based on their approval for a rare condition.").

226. Ameet Sarpatwari & Aaron S. Kesselheim, *Reforming the Orphan Drug Act for the 21st Century*, 381 NEW ENG. J. MED. 106, 106 (2019).

227. *Id.*

228. *See* Koichi Mikami, *Orphans in the Market: The History of Orphan Drug Policy*, 32 SOC. HIST. MED. 609, 610 (2019).

229. *Id.*

230. *See id.*

231. *See, e.g.*, Nicholas Bagley et al., *The Orphan Drug Act at 35: Observations and an Outlook for the Twenty-First Century*, *in* 19 INNOVATION POLICY AND THE ECONOMY 129–33 (Josh Lerner & Scott Stern eds., 2018); *see also* Telephone Interview with Julia Jenkins, *supra* note 146.

include:[232] federal support in the form of grants and contracts to conduct clinical trials of orphan products;[233] a tax credit of 25% of clinical testing costs;[234] and an exclusive right to whoever made an orphan product to market the product for seven years following FDA approval.[235] These incentives have been highly motivating for drug companies,[236] who often promote their drugs by partnering with patient groups during and after clinical trials.[237] Part of this motivation stems from getting an effective monopoly on the resulting therapies due to the seven-year market exclusivity period.[238] In addition, orphan drug manufacturers face significantly less competition with generic drug manufacturers after the market exclusivity period ends compared to non-orphan drug manufacturers.[239]

Despite the success of the ODA, the fact remains that roughly 95% of rare diseases still have no treatment.[240] Moreover, critics of the ODA highlight several noteworthy concerns. For example, because the products being made are for rare diseases, large-scale, randomized clinical trials that are standard for traditional drug development are difficult to perform.[241] Indeed, one analysis found that orphan drug trials were more likely to have smaller numbers of participants and were less likely to be randomized trials compared to non-orphan drug trials.[242]

A second, and arguably more apparent concern is that pharmaceutical companies often charge substantial prices for therapies developed with incentives from the ODAA, in part because the ODA's market exclusivity provision creates a dearth of generic-brand competition and thus leads to high prices and profits.[243] In fact, the top ten orphan therapies sold in 2017 created more than $1 billion in sales for their manufacturers,[244] and the rest of the orphan drug product market generated an estimated $125 billion in sales.[245] Projections indicate that by 2024,

232. Aaron S. Kesselheim, *An Empirical Review of Major Legislation Affecting Drug Development: Past Experiences, Effects, and Unintended Consequences*, 89 MILBANK Q. 450, 465 (2011).

233. *Id.*

234. *Id.*

235. *Id.*

236. *See* Diana Kwon, *How Orphan Drugs Became a Highly Profitable Industry*, SCIENTIST (Apr. 30, 2018), https://www.the-scientist.com/features/how-orphan-drugs-became-a-highly-profitable-industry-64278 [https://perma.cc/XRT4-SDP2] ("Prior to the introduction of [the ODA], 'there was no motivation for industry to invest in treatments for rare conditions' . . . whereas afterwards, firms were driven to create more products.").

237. For a discussion on the interplay between pharmaceutical companies and rare disease advocacy groups, see Brenda Goodman, *When Disease Charities Partner with Drug Companies, Where Does That Leave Patients (and Reporters)?*, ASS'N. HEALTH CARE JOURNALISTS (June 4, 2013), https://healthjournalism.org/blog/2013/06/when-disease-charities-partner-with-drug-companies-where-does-that-leave-patients-and-reporters/ [https://perma.cc/C6E5-3GM3].

238. *See* INST. MED., *supra* note 24, at 301.

239. *Id.* ("The data show that compared to nonorphan drugs, relatively few drugs approved with orphan designations are exposed to generic competition. . . . Among 108 qualifying products with orphan designation approved . . . from 1984 to 1999 that are still available, 49 (45 percent) had A-rated generic alternatives that were manufactured by a competitor.").

240. PHARM. RSCH. & MFRS. AMERICA, *supra* note 34.

241. Shailin Thomas & Arthur Caplan, *The Orphan Drug Act Revisited*, 321 JAMA 833, 834 (2019).

242. *Id.* at 833.

243. *Id.*

244. *Id.*

245. *Id.*

orphan drug sales will amount to $262 billion and comprise 22% of the prescription drug market.[246] In light of these findings, critics of the ODA argue that the incentives create a profitability structure that fails to truly develop rare disease therapies at prices that patients can actually afford.[247]

3. Rare Diseases Act

The Rare Diseases Act of 2002 ("RDA")[248] was enacted to create a centralized research agenda and structure to foster collaborative research and education initiatives for rare diseases.[249] The RDA (1) established and created operating guidelines for the Office of Rare Diseases at the National Institutes of Health;[250] and (2) provided a budget to create rare disease regional centers of excellence.[251] The RDA also defined the duties the Office of Rare Diseases and regional centers of excellence, including research and educational duties.[252] The purpose of the RDA's statutory authorization of the Office of Rare Diseases was primarily to send a "strong signal of the Congress' commitment for both this Office as well as for rare disease research generally."[253] Moreover, the RDA's goal to create regional centers of excellence was rooted in "enabl[ing] the NIH to select sites to concentrate on finding cures and treatment methods for rare diseases."[254]

The RDA text includes a line that continues to resonate today: "Despite the tremendous success of the Orphan Drug Act, rare diseases and disorders deserve greater emphasis in the national biomedical research enterprise."[255] In the nearly two decades since the RDA was enacted, the progress made within rare disease research and therapeutic development has been successful, but falls short of the promise envisioned.[256] For example, the Office of Rare Diseases was established at the NIH in 1993 and was only *statutorily* established in the RDA;[257] the legislation's benefit here was only in codifying what that Office was designed to do. Further, some advocates argue that the regional centers of excellence authorized in the legislation have failed to fully materialize—the funding was authorized, but never appropriated.[258] Instead of the NIH overseeing the designation of all rare disease centers of excellence, the process is piecemeal; patient organizations, individual researchers, academic medical centers, and other consortia have

246. *Id.*
247. *See id.*
248. Rare Diseases Act of 2002, Pub. L. No. 107-280, 116 Stat. 1988.
249. H.R. REP. NO. 107-543, at 4 (2002), *reprinted in* 2003 U.S.C.C.A.N. 1239, 1242.
250. *Id.*
251. *Id.* at 4–5.
252. *Id.* at 5–7.
253. *Id.* at 2.
254. *Id.*
255. Rare Diseases Act of 2002, *supra* note 248, at 1989.
256. *See* Telephone Interview with Julia Jenkins, *supra* note 146.
257. *See* Anne M. Readel, *Finding a Cure: Incentivizing Partnerships Between Disease Advocacy Groups and Academic and Commercial Researchers*, 26 J.L. & HEALTH 285, 304 n.159 (2013).
258. *See* Telephone Interview with Julia Jenkins, *supra* note 146. *But see Rare Diseases Clinical Research Network*, NAT'L CTR. ADVANCING TRANSLATIONAL SCIS. (Oct. 2019), https://ncats.nih.gov/files/RDCRN-factsheet-october-2019.pdf [https://perma.cc/4HL6-DD4A].

deemed their own "centers of excellence."[259] The key shortfall of the RDA and other legislative efforts is that their yield in treating and preventing rare diseases is relatively low—there are still too many patients with undiagnosed diseases or diseases for which there are no treatments.[260]

4. Legislative Progress Since the RDA

At the time of this writing, the footprint of rare disease in national legislative activities has been encouraging but ultimately unsatisfactory. The 116th Congress has put forward one bill, the Elijah E. Cummings Lower Drug Costs Now Act, that would require a study by the U.S. Department of Health and Human Services ("HHS") to identify (1) rare diseases for which there are no FDA approved treatments and (2) "incentives that would lead to the development, approval, and marketing of such treatments."[261] This amendment would also require HHS to report the findings to Congress, as well as recommendations on incentives for treatment development and marketability.[262] While the current form of the Elijah E. Cummings Lower Drug Costs Now Act will not pass (it has passed the House, but is unlikely to pass the Senate and would be vetoed by President Donald Trump regardless of Senate passage),[263] it proves an indicator of where progress on rare disease therapy development has stalled. That is, it is largely unknown how many rare diseases there are, how many of those conditions have treatments, and what it would take to incentivize the private sector to make such treatments.

Other legislative action involving rare disease has been tailored toward declarations and proposed bills. Resolutions creating "Rare Disease Day" have been especially popular, with seventeen resolutions proposed since 2011.[264] Meanwhile, legislation addressing rare diseases has been consistently proposed. The 21st Century Cures Act, a law enacted in 2016 to "accelerate the discovery, development, and delivery of 21st century cures,"[265] specifically addressed the need for further development of drugs for rare diseases. The Act called for facilitation in "the development, review, and approval of genetically targeted drugs and variant protein targeted drugs to address an unmet medical need in one or more patient subgroups, including subgroups of patients . . . [with] rare diseases or conditions that are serious or life-threatening."[266] The Act also created opportunity for drug manufacturers to reuse data from past drug applications to the

259. *See, e.g.*, *Rare KC Summit Introduces Kansas City as Hub for Rare Disease*, BIONEXUS KC (2019), https://bionexuskc.org/vol-1-2019-rare-kc-summit-introduces-kansas-city-as-hub-for-rare-disease/ [https://perma.cc/53LX-AYSV].

260. *See, e.g.*, PHARM. RSCH. & MFRS. AMERICA, *supra* note 34.

261. 165 CONG. REC. H10,210 (daily ed. Dec. 12, 2019).

262. *Id.*

263. 165 CONG. REC. H10,098 (daily ed. Dec. 11, 2019) (Statement of Administration Policy).

264. A search for "Rare Disease Day" on Congress.gov yielded seventeen resolutions introduced in the U.S. Congress since February 17, 2011. These resolutions include, for example, S. Res. 74, 112th Cong. (2011); H. Res. 91, 113th Cong. (2013); and S. Res. 529, 116th Cong. (2020).

265. 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033.

266. *Id.* § 3012.

FDA when developing new drugs for rare diseases.[267] Meanwhile, the FDA Reauthorization Act of 2017 contained several provisions specifically dealing with rare diseases, including the expansion of the FDA Rare Diseases Program; expediting the review process for breakthrough therapies; developing a process to use patient-level evidence; continuing the Patient-Focused Drug Development program; and creating the National Evaluation System for Health Technology.[268]

The effects of this legislation are yet to be realized. Legal epidemiology tracking the effect of rare disease legislation on specific health outcomes has not been conducted.[269] Moreover, studies on the change in patent applications for rare disease therapies use various analysis methods that make it difficult to discern change.[270] In theory, if the legislation touching on rare diseases has been effective, patents and successful FDA application rates would be higher than before the legislation went into effect. Because there is a lack of information in this area, research into the changes in patent applications and drug approval rates would be helpful for interpreting the impact of the laws and crafting future legislation by either tailoring existing laws, or introducing new laws and regulations.

Finally, it should be noted that there are legislators devoted to helping the rare disease community. At the federal level, the Rare Disease Congressional Caucus—a bipartisan and bicameral caucus—has nearly 150 members from the U.S. House of Representatives and twenty-four members from the U.S. Senate.[271] This caucus serves as an important forum for legislators to collaborate on rare disease legislation, as well as to promote awareness of rare diseases through increased media attention and hosting conversations with the medical and rare disease communities.[272] State legislators have also taken an interest in rare diseases. For example, the Rare Disease California Caucus, launched in 2017, has over thirty members.[273] Similar to the Rare Disease Congressional Caucus, the California caucus aims to foster awareness of rare diseases, educate policymakers about rare disease issues, and engage with the rare disease community in the policymaking process.[274] These examples suggest that federal and state legislators are interested in finding solutions to help the rare disease community.

267. *Id.*

268. FDA Reauthorization Act of 2017, Pub. L. No. 115-52, 131 Stat. 1005.

269. A National Library of Medicine PubMed term mapping search of ("legal epidemiology") AND ("rare disease") yielded no results.

270. *See, e.g.*, Bagley et al., *supra* note 231, at 103 (describing how exclusivity periods outlasting patent coverage dropped from 1985 to 2014, but that information on the strength of the patents is unclear).

271. *Rare Disease Congressional Caucus*, RARE DISEASE LEGIS. ADVOCS., https://rareadvocates.org/rare-caucus/ (last visited Nov. 20, 2020) [https://perma.cc/7AUG-CXMR].

272. *Id.*

273. *Rare Disease California Caucus*, CAL RARE, https://www.calrare.org/rare-disease-caucus (last visited Nov. 20, 2020) [https://perma.cc/BJ7M-8PB8].

274. *Id.*

B. Newborn Screening

Many diseases can be detected with genetic analyses, blood assays, and other clinical tests.[275] Screening for diseases using these technologies takes place for all newborns across the U.S.,[276] although the diseases that are screened vary by state.[277] Rare genetic diseases, which are often not discernable through a typical physiologic examination, can be identified with newborn screening.[278] According to some advocates, newborn screenings are the best diagnostic tool available to the rare disease community.[279]

The importance of identifying rare diseases in newborns is highlighted in an example from California. In 2003, two boys named Zachary were born with a condition called glutaric acidemia type 1 ("GA1").[280] GA1 is a highly uncommon genetic disease that results in loss of cerebral function and muscle wasting, but can be addressed with vitamin supplements if caught in the first six to nine months of life.[281] One of the boys, Zachary Black, was born in a hospital that required newborn screening; his GA1 was identified, he was given supplements, put on a low-protein diet to treat the condition, and was in "robust" health.[282] Meanwhile, Zachary Wyvill was born in a different hospital that did not perform newborn screening; his GA1 was not identified until after he became severely disabled, unable to eat or even sit up on his own.[283] The "case of two Zacharys" and other stories of undetected but treatable rare diseases present a clear example of how newborn screening can create better outcomes for those with rare diseases. Indeed, these preventable cases have catalyzed actions to create statewide newborn screening programs across the U.S., including in California.[284]

While newborn screening generally falls within state police powers,[285] standards for newborn screening have been adopted at the federal level. The

275. For a description of blood analysis in clinical settings, see Ian D. Watson, *Clinical Analysis: Overview*, *in* ENCYCLOPEDIA OF ANALYTICAL SCIENCE 126, 126–32 (Paul Worsfold, Alan Townshend & Colin Poole eds., 2d ed. 2005). For a detailed description of genetic testing, including its uses in clinical settings and diagnostics, see Kariofyllis Karamperis et al., *Genetic Testing*, *in* APPLIED GENOMICS AND PUBLIC HEALTH 189, 189–207 (George P. Patrinos ed., 2020).

276. *See What Is Newborn Screening?*, GENETICS HOME REFERENCE (Aug. 17, 2020), https://ghr.nlm.nih.gov/primer/newbornscreening/nbs [https://perma.cc/B2E4-P2HM].

277. *See What Disorders Are Included in Newborn Screening?*, GENETICS HOME REFERENCE (Aug. 17, 2020), https://ghr.nlm.nih.gov/primer/newbornscreening/nbsdisorders [https://perma.cc/D5SQ-PUDB].

278. *See, e.g.*, D.C. DEP'T HEALTH & GENETIC ALL., UNDERSTANDING GENETICS: A GUIDE FOR PATIENTS AND HEALTH PROFESSIONALS 21–22 (2010), https://www.ncbi.nlm.nih.gov/books/NBK132149/pdf/Bookshelf_NBK132149.pdf [https://perma.cc/43WS-FT8V].

279. Telephone Interview with Julia Jenkins, *supra* note 146.

280. Michael Waldholz, *A Drop of Blood Saves One Baby; Another Falls Ill*, WALL ST. J. (June 17, 2004, 12:01 AM), https://www.wsj.com/articles/SB108741631056839034 [https://perma.cc/S6JT-DB2Z].

281. *See id.*

282. *Id.*

283. *Id.*

284. *See* April Lynch, *State to Expand Testing of Newborns for Genetic Ills*, MERCURY NEWS, at 1A (Aug. 4, 2004) ("Families of children affected by genetic illness pushed the state to [adopt newborn screening laws].").

285. Public health, including newborn screening, traditionally falls within the police powers granted by the 10th Amendment of the U.S. Constitution. U.S. CONST. amend. X.

"Newborn Screening Saves Lives Act of 2007" was the first such set of standards, codifying the Recommended Universal Screening Panel ("RUSP")—a list of diseases that every newborn should be screened for.[286] For a disease to be included in RUSP, it must (1) "be identified at a time (24–48 hours after birth) at which it would not ordinarily be detected clinically;"[287] (2) have an available test with "appropriate sensitivity and specificity," or accuracy;[288] and (3) have "demonstrated benefits of early detection, timely intervention, and efficacious treatment."[289]

There is continued action to promote and expand state newborn screening programs.[290] The "Newborn Screening Saves Lives Reauthorization Act of 2019,"[291] which has passed the House and is currently under review in the Senate Health, Education, Labor, and Pensions Committee, seeks to reauthorize prior legislation.[292] In addition, the bill "includes reforms to ensure that the activities of [newborn screening regulatory agencies] are transparent," and "requires the [CDC] to standardize data collection and reporting to track and monitor newborn screening in real time."[293] And finally, the bill calls for the National Academy of Medicine to study "the modernization of newborn screening."[294] Rare disease advocates strongly support the House's reauthorization bill,[295] but detractors caution that states harbor blood samples and use those samples for research without first obtaining the parents' consent.[296]

286. *See* Newborn Screening Saves Lives Act of 2007, Pub. L. No. 110-204, § 4, 122 Stat. 705, 707 (2008).

287. Tahra Johnson & Margaret Wile, *State Newborn Health Screening Policies*, NAT'L CONF. ST. LEGISLATURES (Apr. 2017), https://www.ncsl.org/research/health/state-newborn-health-screening-policies.aspx [https://perma.cc/C4JY-8A76].

288. *Id.*

289. *Id.*

290. Telephone Interview with Julia Jenkins, *supra* note 146.

291. Newborn Screening Saves Lives Reauthorization Act of 2019, H.R. 2507, 116th Cong. (2019).

292. H.R. REP. NO. 116-174, at 4 (2019).

293. *Id.*

294. *Id.* at 4–5.

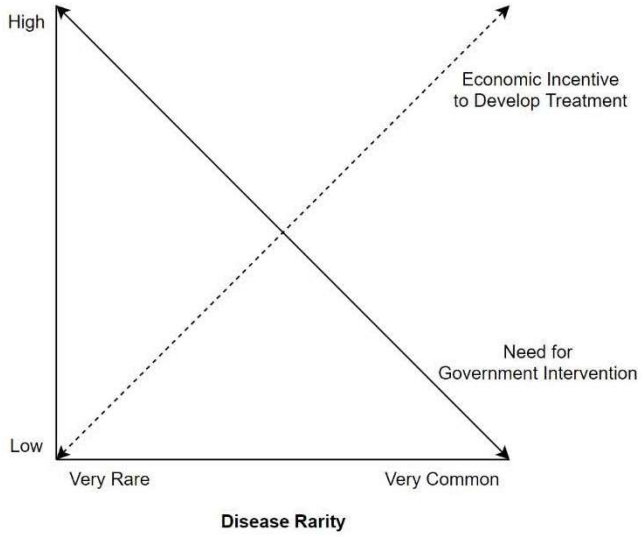
295. *See, e.g.*, R. Rodney Howell, *Newborn Screening Saves Lives. Congress Needs to Reauthorize the Program*, STAT (July 12, 2019), https://www.statnews.com/2019/07/12/newborn-screening-congress-reauthorize/ [https://perma.cc/L3US-7L9C]; *see also* Telephone Interview with Julia Jenkins, *supra* note 146.

296. These concerns were expressed during the initial course of legislation. *See* Alexis Madrigal, *Newborn-Blood Storage Law Stirs Fears of DNA Warehouse*, WIRED (May 21, 2008, 12:00 PM), https://www.wired.com/2008/05/newborn-screening/ [https://perma.cc/J4LY-YABD]. The 2014 reauthorization bill included an informed consent amendment championed by Senator Rand Paul to allay privacy concerns. *See* Daniel James Devine, *Expanded Newborn Screening Raises Privacy Concerns*, WORLD MAG. (Dec. 16, 2014, 8:30 AM), https://world.wng.org/2014/12/expanded_newborn_screening_raises_privacy_concerns [https://perma.cc/4Q2L-QJZ5]. Researchers who use old newborn screening blood samples for research purposes argue that the medical and public health benefits far outweigh the privacy concerns. *See* Wudan Yan, *New Consent Requirements for Newborn Screening Raise Concerns*, 21 NATURE MED. 542, 542 (2015) (according to one researcher, "[i]t's really unfortunate that well-trained physicians like Rand Paul—who introduced much of the [privacy] language in the reauthorization—compromise running good public health programs for rare diseases.").

C. Policies Promoting the Development of Novel Therapeutics

The ODA was the initial stimulus to create new therapeutics for rare disease populations.[297] The ODA defined orphan conditions as those afflicting fewer than 200,000 individuals nationwide or, importantly, conditions for which a drug manufacturer is able to show there would be low likelihood of recovering research and development costs via sales of the product.[298] This definition is broad and underscores the relationship between economic incentives for drug manufacturers and the need for government intervention in the development of new therapies. In short, typical supply and demand economics[299] create market conditions that neglect rare diseases; fewer patients (lower demand) leads to fewer treatments (lower supply). Thus, the need for government intervention to incentivize research and development of novel therapies is dependent on the rarity of the disease.

FIGURE 2: RELATIONSHIP BETWEEN DISEASE RARITY, ECONOMIC INCENTIVES TO DEVELOP TREATMENTS, AND NEED FOR GOVERNMENT INTERVENTION TO DEVELOP TREATMENTS



Federal incentives to create therapies for rare diseases allow manufacturers to target conditions that otherwise might not receive attention. The incentives, however, nudge manufacturers to focus on diseases with higher prevalence but that are still rare enough (or unprofitable enough) for them to reap the benefits.[300]

297. *See* discussion *supra* Section III.A(2).

298. 21 U.S.C. § 360ee(b)(2).

299. *See, e.g.*, *Supply and Demand*, ENCYC. BRITANNICA, https://www.britannica.com/topic/supply-and-demand (last visited Nov. 20, 2020) [https://perma.cc/Q5G6-VQDZ].

300. For an example of the ODA's incentive loopholes and ongoing legislation to address the ODA's flaws, see Aaron L. Josephson, *Closing the Orphan Drug Act Loophole*, NAT'L L. REV (Feb. 18, 2020), https://www.natlawreview.com/article/closing-orphan-drug-act-loophole [https://perma.cc/PZ6D-N9RP].

The ODA's incentives, which include market exclusivity for seven years, tax incentives and grants to cover operational start-up costs for new biotech companies, federal assistance with clinical trial management, and intellectual property protections that are cheaper and easier to acquire than through standard patent protections, are prized by pharmaceutical companies.[301]

Several economic and ethical dilemmas have arisen after the enactment of the ODA. Economically, the incentives are still not enough to encourage research and development—the pipeline for rare disease orphan drugs is minimal, and the majority of rare diseases have no therapeutics in development.[302] Ethically, using resources to direct attention away from more common ailments and toward rare conditions presents a lack of utility—if only a fixed amount of resources exist, shouldn't they be used to tackle the largest problems?[303] From a justice perspective, however, it is vital to ensure that resources are allocated for even the rarest of conditions—no one should be "abandoned," and therapies developed for rare diseases may lead to scientific advances that benefit others.[304] Taking these considerations into account, in addition to the shortfalls of current policies, it is imperative to reframe the discussion of rare disease research in the context of public health, which would satisfy both utilitarian and justice-oriented ethical perspectives. Further, reframing rare diseases as a public health crisis could galvanize efforts to modernize incentives to develop novel therapies.

D. Medical Malpractice and Tort Law

Little is known about whether patients with rare diseases face obstacles when entering medical malpractice litigation.[305] Whether patients with rare conditions find success in other areas of the tort law system is similarly obscure.[306] The limited information on these issues underscores a larger point: patients with rare disease do not fall neatly within traditional medico-legal paradigms.

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301. *See* Sarah Jane Tribble & Sydney Lupkin, *Drugs for Rare Diseases Have Become Uncommonly Rich Monopolies*, NPR: SHOTS (Jan. 17, 2017, 4:59 AM), https://www.npr.org/sections/health-shots/2017/01/17/509506836/drugs-for-rare-diseases-have-become-uncommonly-rich-monopolies [https://perma.cc/8SS2-SSEC].

302. The U.S. Food and Drug Administration is working to bolster the rare disease drug development pipeline through its "Rare Disease Cures Accelerator" program, which was started in September of 2019. *Rare Disease Cures Accelerator*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/regulatory-science-research-and-education/rare-disease-cures-accelerator (last visited Nov. 20, 2020) [https://perma.cc/J9D3-YZRK].

303. C.A. Gericke, A. Riesberg, & R. Busse, *Ethical Issues in Funding Orphan Drug Research and Development*, 31 J. MED. ETHICS 164, 165 (2005).

304. *See id.* at 165–66.

305. A search by the author for literature describing how medical malpractice principles are applied in cases of rare disease yielded no results. However, this may be an artifact of inherent problems with medical malpractice not serving the needs of rare disease patients. *See* discussion *infra* Section III.D; *see also* Mark Crane, *When Missing a 'Zebra' Can Land You in Court*, MEDSCAPE (Feb. 20, 2018), https://www.medscape.com/viewarticle/892452_4 [https://perma.cc/EX9T-4K3Z] ("'We just don't get a lot of these claims,' said William S. Kanich, MD, JD . . . 'It isn't usually the rare diseases doctors get sued for. It's the common ones . . . The standard of care in rare disease cases, frankly, is to miss them.'").

306. No resources indicating how rare disease patients use tort law were found by the author. For a discussion on how denial of treatment could breach tort law using the United Kingdom's tort law system, however, see Hanna I. Hyry et al., *The Legal Imperative for Treating Rare Disorders*, 8 ORPHANET J. RARE DISEASES 1, 3–4 (2013).

1. Definition and Requirements of Medical Malpractice

Broadly defined, medical malpractice is "[a] doctor's failure to exercise the degree of care and skill that a physician or surgeon of the same medical specialty would use under similar circumstances,"[307] or similarly an "act or omission by a physician during treatment of a patient that deviates from *accepted norms* of practice in the medical community and causes an injury to the patient" (emphasis added).[308] Medical malpractice falls within the broader subject of tort law associated with professional negligence,[309] and is the most common doctrine under which patients seek recovery from physicians.[310]

In the United States, a patient's claim of medical malpractice can only succeed if four legal elements are satisfied by a preponderance of the evidence: (1) there must be a legal duty on the part of the physician to provide care or treatment to the patient;[311] (2) the physician must have breached this duty in not practicing according to professional guidelines and clinical standards;[312] (3) the breach must have caused injury to the patient;[313] and (4) the injury to the patient must have recourse for which the legal system can provide a remedy.[314]

2. Impact of Medical Malpractice on Healthcare Providers

Medical malpractice has a large impact on the medical profession.[315] Illustrating this point, a study of over 4,000 physicians across more than twenty-five practice specialties found that over half of all physicians have been subject to a medical malpractice lawsuit.[316] That study also found that specialists were more likely to be named in a malpractice suit than general practitioners.[317] Significantly, of those physicians who have been sued, more than half have been sued multiple times.[318] Often, medical malpractice lawsuits come as a surprise, with 87% of physicians reporting being "somewhat" or "very" surprised at being named as a defendant.[319]

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307. *Malpractice*, BLACK'S LAW DICTIONARY (11th ed. 2019).

308. B. Sonny Bal, *An Introduction to Medical Malpractice in the United States*, 467 CLINICAL ORTHOPAEDICS & RELATED RSCH. 339, 340 (2009).

309. *Id.*

310. Jack W. Shaw, Jr., Annotation, *Recovery Against Physician on Basis of Breach of Contract to Achieve Particular Result or Cure*, 43 A.L.R. 3d 1221 § 2(a) (1972) ("The most common theory under which a patient seeks recovery against a physician is that of malpractice; it has been stated that this action is tortious in nature, growing out of the breach of duty which is incident to a consensual relationship, but that some courts emphasize the contract elements, rather than the tort elements, as a basis for the action. The gist of the action, regardless of the elements emphasized, is the physician's wrongful act.").

311. *See* Bal, *supra* note 308, at 342.

312. *Id.*

313. *Id.*

314. *Id.*

315. *See* Sandra Levy & Leslie Kane, *Medscape Malpractice Report 2017*, MEDSCAPE (Nov. 15, 2017), https://www.medscape.com/slideshow/2017-malpractice-report-6009206].

316. *Id.*

317. *Id.*

318. *Id.*

319. *Id.*

Critically, that study yielded information on why the physicians were sued for malpractice.[320] Common reasons were failure to diagnose and delayed diagnosis.[321] Although this study was not specific to medical malpractice stemming from the treatment of rare disease patients (no such study exists),[322] the frequency of rare disease patients either receiving a delayed diagnosis or being left without a diagnosis due to their physician's failure[323] is suggestive that this patient group would, or at least could, make regular use of medical malpractice claims to seek legal remedies.[324] Indeed, rare disease patients are often misdiagnosed with two to three other conditions before being correctly diagnosed.[325] If the misdiagnoses were to lead to inappropriate treatment or lack of appropriate treatment, as is likely in many instances, the causal element of malpractice may be met.[326]

Nevertheless, the other three medical malpractice elements must also be met for a successful claim.[327] The second element—that the patient must prove that the physician breached her duty by not following professional guidelines and clinical standards[328]—is problematic because it may be impossible to meet for many rare conditions. If a disease is so rare that no clinical guidelines have been adopted to treat the condition, how can a patient prove the physician deviated from standard clinical practice? Typical medical malpractice cases involve a comparison of the doctor's actions and course of treatment to the typical "standard of care."[329] This generally involves looking at professional practice guidelines by practice type, region, and other classifying factors.[330] Successful cases for the patient plaintiff require proof that the physician did not act according to these guidelines, or how a reasonable practitioner would have acted in the given circumstance.[331] For rare diseases, however, there are rarely practice guidelines for physicians to follow, and physicians often do not have "reasonable" courses

320. *Id.*

321. *Id.* ("Primary care physicians were most likely to be sued for failure to diagnose/delayed diagnosis (43%) compared with 28% of specialists.").

322. A National Library of Medicine PubMed "MESH" term search of (("Malpractice"[Mesh]) AND "Rare Diseases"[Mesh])) yielded no results.

323. The average rare disease patient sees seven physicians and waits five years before receiving a diagnosis. SHIRE, THE GLOBAL CHALLENGE OF RARE DISEASE DIAGNOSIS: THE BENEFITS OF AN IMPROVED DIAGNOSIS JOURNEY FOR PATIENTS (2016), https://www.shire.com/-/media/shire/shireglobal/shirecom/pdffiles/patient/shire-diagnosis-initiative-pag-leaflet.pdf [https://perma.cc/Z8XD-A5NQ].

324. For examples of clinical guidelines that could be used to support medical malpractice claims, see *Clinical Practice Guidelines*, *supra* note 3.

325. Judy Stone, *Have Pain? Are You Crazy? Rare Diseases Pt. 2*, SCI. AM.: MOLECULES TO MED (Feb. 18, 2014), https://blogs.scientificamerican.com/molecules-to-medicine/have-pain-are-you-crazy-rare-diseases-pt-2/ [https://perma.cc/J53C-LX5W].

326. *See* Bal, *supra* note 308, at 342.

327. *Id.*

328. *Id.*

329. *Id.*

330. *Id.*

331. *E.g.*, Aiken v. Clary, 396 S.W.2d 668, 674 (Mo. 1965) ("'Juries should not be thus turned loose and privileged to say, perchance, the method of treating an injury . . . [or an illness] was negligent notwithstanding, for instance, the uncontradicted competent testimony establish[ing] that the uniformly adopted practice of the most skillful surgeons [or physicians] had been followed.'") (quoting Pedigo v. Roseberry, 102 S.W.2d 600, 607 (Mo. 1937))).

of treatment for these conditions given their rarity.[332] How, then, can a patient with a rare disease seek recourse for physicians who make serious mistakes in their course of treatment?

3. How Rare Diseases are Examined in the Courts

Courts have been uncommon venues for discussing rare diseases, whether in cases of medical malpractice or in other legal matters.[333] The questions arising in these cases are diverse, ranging from issues of Supplemental Security Income coverage[334] to whether a rare disease would make the death penalty unconstitutional by inflicting "cruel and unusual" amounts of pain.[335] Aside from these cases, rare diseases are uncommonly encountered or examined in the courts.

Information as to the extent to which rare disease patients sue physicians for medical malpractice is scant at best, with individual cases being the primary source of information.[336] One is *Zuchowicz v. United States*, in which a patient, Patricia Zuchowicz, developed a rare disease called primary pulmonary hypertension—a fatal condition with no cure[337]—after being prescribed an overdose of the drug Danocrine and brought a medical malpractice suit against her physician.[338] The case centered on the issue of causation.[339] One form of treatment for primary pulmonary hypertension is to perform a lung transplant, so Zuchowicz was put on a transplant waiting list.[340] When Zuchowicz became pregnant while on the waiting list, however, she was no longer eligible for the transplant and died one month after giving birth.[341]

332. INST. MED., *supra* note 24, at 42 ("For the rarest conditions, the literature may consist of a single published report describing a few individuals with a previously unidentified genetic syndrome. For other conditions, including a number of the relatively more common conditions . . . publicly and privately sponsored research has generated a knowledge base that may encompass . . . evidence-based guidelines for clinical services.").

333. A June 20, 2020 search on Westlaw for ["rare disease*" OR "rare condition*"] yielded 1,256 cases, of which 231 mentioned the term "malpractice." Of the total cases, 582 were federal cases (there were five case results for the Supreme Court, 105 in the Appellate Courts, 472 in District Courts, two in Bankruptcy Courts, ninety in Federal Claims Courts, two in Military Courts, three in Tax Courts, and five in Veterans Claims Appellate Courts) and 571 were state cases (Nevada, South Dakota, and Vermont were the only states without a case appearing in the search results).

334. Sullivan v. Zebley, 493 U.S. 521, 536 n.17 (1990) (describing how children with rare diseases would be denied benefits if their impairment(s) do not match the list of impairments set by the Secretary of the U.S. Department of Health and Human Services).

335. Bucklew v. Precythe, 139 S. Ct. 1112, 1137–38 (2019) (Breyer, J., dissenting) (explaining how an inmate with a rare disease, "cavernous hemangioma," would face extreme pain from a lethal injection via airway collapse, asphyxiation on blood, and "visible hemorrhaging.").

336. *See* Crane, *supra* note 305.

337. *Primary Pulmonary Hypertension*, JOHNS HOPKINS MED., https://www.hopkinsmedicine.org/health/conditions-and-diseases/primary-pulmonary-hypertension (last visited Nov. 20, 2020) [https://perma.cc/GF5R-3LC8].

338. Zuchowicz v. United States, 140 F.3d 381, 383 (2d Cir. 1998).

339. *Id.*

340. *Id.* at 384.

341. *Id.*

The rarity of primary pulmonary hypertension hampered the plaintiff's ability to prove causation in the trial,[342] but the jury ultimately decided that the Danocrine overdose was the but-for cause of Zuchowicz's development of primary pulmonary hypertension and eventual death.[343] The key takeaway from this example, in regard to how medical malpractice suits are conducted in cases of rare disease, is that traditional medical malpractice methods remain in play. That is, rare disease cases like *Zuchowicz* still encompass determining duty, breach of duty, injury, and causation, and also continue to rely on expert testimony to validate or invalidate medical decision making.[344]

Another case illustrating rare disease and medical malpractice is *Deasy v. United States*.[345] In this case, John Deasy—a permanently disabled veteran—filed a medical malpractice claim against three Veterans Affairs hospitals.[346] Deasy suffered from many conditions, but his diagnosis of Ormond's Disease was particularly troublesome for his medical care.[347] Because the condition is medically complex and Deasy's experience with it was atypical,[348] his diagnosis was difficult to reach.[349] The alleged malpractice was Deasy's physicians failure to listen to him.[350] According to the opinion,

> Mr. Deasy has been living with his psychiatric and physical illnesses for thirty-five years. His detailed testimony demonstrates that he is extremely knowledgeable about his illnesses. He knows what medical texts say about his ailments and he has tremendous insight into how his case differs from most. He is a well-educated, intelligent man who did everything he could to alert the [Veterans Affairs] doctors of his need for treatment directed to his physical symptoms. Yet with a paternalism reminiscent of bygone medical practice, his doctors assumed that he, a mere layman, could not shed light on his medical condition. He was not accorded the simple, humane consideration and respect to which every patient is entitled whether inside or outside the [Veterans Affairs] system. *Had his doctors merely listened to him and given reasonable weight to what he knew of his own bodily condition*, they would not today be involved in a malpractice case.[351]

342. *Id.* at 385 ("The rarity of PPH, combined with the fact that so few human beings have ever received such a high dose of Danocrine, obviously impacted on the manner in which the plaintiff could prove causation.").

343. *Id.* at 386–87, 390.

344. *Id.* at 389–90.

345. Deasy v. United States, No. 91-C-1082, 1995 U.S. Dist. LEXIS 22519 (D. Colo. May 2, 1995).

346. *Id.* at *1.

347. *Id.* at *2–14.

348. *Id.* at *2 n.1 ("Ormond's Disease causes scar tissue to form in the peritoneal cavity, usually encasing tubular organs or tubular structures between organs, such as veins and arteries. Its course tends to be cyclical, with alternating periods of activity and remission.").

349. *Id.* at *3–4 n.2 ("The correct diagnosis of Ormond's Disease was difficult to reach because it is a relatively rare disease. Further, Mr. Deasy's experiences with it have been atypical from the beginning. While it generally appears for the first time in the fifth or sixth decade of a patient's life, Mr. Deasy's symptoms appeared when he was only twenty-five years old. Additionally, his disease has had a more widespread presentation than usual.").

350. *Id.* at *26–27.

351. *Id.* at *27 (emphasis added).

This case, in which the jury ruled in favor of Deasy and awarded him over $4.5 million,[352] highlights a common issue faced by rare disease patients: they must be their own advocate and become experts in their own health.[353] Moreover, both *Zuchowicz* and *Deasy* illustrate how difficult it may be for rare disease patients to leverage common legal arguments. For example, the doctrine of *res ipsa loquitur* ("the thing speaks for itself")[354] is unlikely to ever apply in malpractice cases involving rare diseases.[355] They also demonstrate how medical malpractice cases centered on rare diseases proceed through litigation.

Publicly available information on cases involving settlements is limited, but some settlement reports in legal databases and journals provide a glimpse into how rare disease patients and their families pursue legal action. For example, a 2005 case involving a twenty-four-day-old girl with propionic acidemia (a metabolic disorder that can lead to brain damage and death) was settled for $3.5 million.[356] The girl's parents argued their daughter's eventual brain damage could have been prevented had her doctors made a quicker diagnosis and ordered the appropriate tests; the defendants countered by saying propionic acidemia is rare and hard to detect.[357] With modern newborn screening, propionic acidemia is now tested for at birth.[358]

Another case involved a fifteen-year-old girl with Takayasu arteritis (a condition that can lead to the narrowing of blood vessels and, in this case, stroke).[359] The outcome was in favor of the defendant physician.[360] The result was due, in part, to Takayasu arteritis being a rare disease, as well as the plaintiff's failure to partake in prescribed physical therapy;[361] detailed analysis on the plaintiff's and defendant's arguments, as well as the jury's deliberation, however, are not available.

The general lack of information on medical malpractice cases and settlements involving rare diseases makes it indeterminable whether those avenues of the law are helpful to rare disease patients who have faced malpractice.[362] It is

352. *Id.* at *35.

353. Von der Lippe et al., *supra* note 170, at 766.

354. *Res Ipsa Loquitur*, BLACK'S LAW DICTIONARY (11th ed. 2019) ("The principle does not normally apply unless (1) the occurrence resulting in injury was such as does not ordinarily happen if those in charge use due care; (2) the instrumentalities were under the management and control of the defendant; and (3) the defendant possessed superior knowledge or means of information about the cause of the occurrence.").

355. *See, e.g.*, Meraz-Camacho v. United States, 2010 WL 605376, at *4 (W.D. Wis.) (rejecting application of *res ipsa loquitur* doctrine as "Plaintiff's condition was rare and not easily diagnosed and beyond the common experience of his treating doctors, let alone a layperson. In other words, a layperson could not have concluded that the [Plaintiff's] symptoms . . . required immediate hospitalization.").

356. Chau Lam, *Settlement Nets $3.5 Million for Couple,* NEWSDAY (Jan. 11, 2005), https://www.ndlaw.com/article/settlement_nets_couple.pdf [https://perma.cc/7TB6-EVFY].

357. *Id.*

358. Advisory Committee on Heritable Disorders in Newborns and Children, *Recommended Uniform Screening Panel*, U.S. HEALTH RES. & SERVS. ADMIN. (Feb. 2020), https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html [https://perma.cc/2VB9-4ZY6].

359. Jury Verdict, Doyle v. Alario, 1285-CV-02118 (Mass. Super. Ct. June 29, 2018).

360. *Id.*

361. *Id.*

362. For several examples of patients not having recourse through medical malpractice claims, see Marshall Allen & Olga Pierce, *Ten Patient Stories: When Attorneys Refused My Medical Malpractice Case*, PROPUBLICA

also unknown as to what extent malpractice claims are dropped,[363] or how malpractice suits alter the care that rare disease patients receive.[364] As there are limited cases of rare disease medical malpractice and limited information on settlement proceedings or impact on care delivery, more research on this subject is warranted.

IV. RECOMMENDATION

The issues impacting the rare disease community are clearly significant, multifaceted, and involve a variety of parties with unique interests. Addressing these issues through a public health approach (or at least conceptualizing rare diseases in aggregate) could greatly benefit both rare disease populations and the public. Treating rare diseases as a public health problem could lead to faster development of therapies benefitting rare disease patients, efficient allocation of resources that reduce financial burdens on society and individual patients, and more just legal protections for vulnerable citizens. This Part will describe these solutions in greater detail, first by describing the need for better information on rare disease epidemiology.

A. Population Health Modeling

The bedrock of public health practice is basic epidemiology.[365] Responding to disease is largely ineffective without first understanding the morbidity, mortality, and other measures of disease impact.[366] Further, finding diseases requires testing and diagnostics, which must be valid and reliable in order to effectively identify disease.[367] The natural progression of the disease must be known in order to determine the prognosis of the condition,[368] and clinical trials must be performed to develop prevention measures and therapeutic interventions.[369]

Basic epidemiology requires tracking diagnoses, disease progression, and ultimate health outcomes.[370] By understanding who has a particular disease, assessments can be made to determine who is at risk for developing or acquiring

(Jan. 9, 2014, 11:57 AM), https://www.propublica.org/article/ten-patient-stories-when-attorneys-refused-my-medical-malpractice-case [https://perma.cc/RH4B-S2QB].

363. *See* Dwight Golann, *Dropped Medical Malpractice Claims: Their Surprising Frequency, Apparent Causes, and Potential Remedies*, 30 HEALTH AFFAIRS 1343, 1348–49 (2011).

364. *See, e.g.*, Lee Black, *Effects of Malpractice Law on the Practice of Medicine*, 9 AM. MED. ASS'N J. ETHICS 437, 439 (2007).

365. *See* Epidemic Intelligence Service, *Epidemiology Training & Resources*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/eis/request-services/epiresources.html (last visited Nov. 20, 2020) [https://perma.cc/FH68-D27E].

366. *See* LEON GORDIS, EPIDEMIOLOGY 2 (David D. Celentano & Moyses Szklo, eds., 6th ed. 2018).

367. *See id.* at 106.

368. *Id.* at 197.

369. *Id.* at 216.

370. *See Principles of Epidemiology in Public Health Practice*, CTRS. FOR DISEASE CONTROL & PREVENTION 1-49 (2012), https://www.cdc.gov/csels/dsepd/ss1978/ss1978.pdf?fbclid=IwAR0T430uxNjeuq_vc8EiRAwXZ1JsQ090LwfE7xdTclZQoaixOcwPIxZmako [https://perma.cc/2RVP-9UQM].

the condition and who would most benefit from prevention and treatment efforts.[371] Having epidemiologic data on hand allows for primary, secondary, and tertiary prevention measures.[372] Primary prevention—preventing the initial development of a disease—can be essential to stem certain rare conditions.[373] Vaccines for rare infections, for example, may be useful for populations at risk of exposure (e.g. an Ebola vaccine).[374] Secondary prevention, or the early detection of an existing condition to mitigate severity and complications, is also based off of epidemiologic data.[375] For example, genetic screening may indicate a rare condition that develops later in life, which can then give the patient time to prepare.[376] Finally, tertiary prevention—reducing the impact of the disease—is similarly based off of epidemiologic data, specifically prognostic data.[377] An example may be daily regimens of physical therapy for those with musculoskeletal disorders.[378]

Treating rare diseases as individual conditions under a traditional medical approach weakens the ability to allow for aggregation of disease data that is essential for epidemiology, and ultimately prevention activities. Thus, treating rare diseases in aggregate form as a public health problem opens the door for better data acquisition and analysis, as well as prevention.

B. Policy Interventions

Although the first tool of public health is epidemiology, "[t]he second public health tool might well be the law."[379] Once the scope and impact of rare diseases are determined using epidemiologic and other population health measures and interventions, evidence-based public and private policy interventions can take shape. Public policy—that of governments at the national, state, and local levels—stands to have great impact. For example, public policy can increase the allocation of research dollars to study rare diseases, incentivize private actors to take action in developing orphan drugs or medical devices for rare disease patients, and incorporate rare diseases into the defined characteristics needed to qualify for public programs such as Medicare or Social Security.[380]

371. *See id.*at 1-49 to 1-50.

372. *See, e.g.*, *Prevention*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/pictureofamerica/pdfs/picture_of_america_prevention.pdf (last visited Nov. 20, 2020) [https://perma.cc/4XHV-VNRM].

373. INST. MED., *supra* note 24, at 56.

374. *See* CTRS. FOR DISEASE CONTROL & PREVENTION, *supra* note 372.

375. *See id.*

376. *See id.*

377. *See id.*

378. *See id.*

379. William H. Foege, *Redefining Public Health*, 32 J.L. MED. & ETHICS 23, 23 (2004).

380. *See, e.g.*, INST. MED., *supra* note 24, at 179–203 (describing federal social program incentives and disincentives for orphan drug coverage and reimbursement).

1. Increased Government Support

Legislative efforts to address rare diseases have been highly beneficial, providing accommodations to rare disease patients, increased development of therapies, and promotion of rare disease research.[381] These admirable successes are paralleled, however, by unattained goals—the vast majority of rare disease patients still have no treatments for their disease, economic incentives to create novel therapies have been exploited for common conditions, and research networks have been confined to a handful of institutions and makeshift alliances.[382]

While these initiatives have fallen short of reaching their stated goals, a public health approach could help fill the gaps. Several factors suggest that renewed legislative efforts could be successful. First, legislative support already exists in the form of the Rare Disease Congressional Caucus.[383] With nearly a quarter of U.S. House Representatives and U.S. Senators serving as Caucus members,[384] there is no shortage of potential sponsors for rare disease legislation. Second, Congress is highly tuned to public health in the wake of COVID-19, evident in the more than $2 trillion coronavirus relief bill passed in March 2020.[385] Finally, public health-focused groups have routinely advocated for bolstered public health systems.[386] With public health systems still facing budgetary cuts even with the ongoing COVID-19 crisis,[387] legislators have begun calling for increased support for public health.[388] Thus, a window of opportunity to fold rare diseases into the public health paradigm has opened.

Multiple solutions to increase support for rare disease patients can be implemented through public health-based legislation. For example, rare diseases could be reported to the CDC for tracking and epidemiologic purposes. The CDC already tracks about 120 conditions through the National Notifiable Diseases Surveillance System ("NNDSS").[389] Adding "rare diseases" to this list would not

381. *See supra* Section III.A.

382. *See supra* Section III.A.

383. *Rare Disease Congressional Caucus, supra* note 271.

384. *Id.*

385. *See* Jacob Pramuk, *Trump Signs $2 Trillion Coronavirus Relief Bill as the US Tries to Prevent Economic Devastation*, CNBC (Mar. 27, 2020, 1:28 PM), https://www.cnbc.com/2020/03/27/house-passes-2-trillion-coronavirus-stimulus-bill-sends-it-to-trump.html [https://perma.cc/D2CU-AQYA]; *see also* Heather Long, *The Federal Reserve Has Pumped $2.3 Trillion Into the U.S. Economy. It's Just Getting Started.*, WASH. POST (Apr. 29, 2020, 5:00 AM), https://www.washingtonpost.com/business/2020/04/29/federal-reserve-has-pumped-23-trillion-into-us-economy-its-just-getting-started/ [https://perma.cc/T7ZD-KE7Q].

386. *See, e.g.*, *Public Health Priorities*, AM. PUB. HEALTH ASS'N, https://www.apha.org/policies-and-advocacy/advocacy-for-public-health/priorities (last visited Nov. 20, 2020) [https://perma.cc/L3ZP-SRGL].

387. *See* Lauren Weber et al., *Hollowed-Out Public Health System Faces More Cuts Amid Virus*, KAISER HEALTH NEWS (July 1, 2020), https://khn.org/news/us-public-health-system-underfunded-under-threat-faces-more-cuts-amid-covid-pandemic/ [https://perma.cc/DG7T-SXLT].

388. *See, e.g.*, Annalisa Merelli, *Senators Want a US "Health Force" to Tackle the Coronavirus Crisis—And More*, QUARTZ (May 9, 2020), https://qz.com/1852061/senators-want-a-us-health-force-to-tackle-coronavirus-and-more/ [https://perma.cc/8AFU-R5SX].

389. *National Notifiable Diseases Surveillance System (NNDSS)*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://wwwn.cdc.gov/nndss/ (last visited Nov. 20, 2020) [https://perma.cc/F3G3-7ZD5].

be easy, nor would current law allow for the CDC to require this reporting.[390] Despite this, one state—Washington—has already begun this tracking.[391] The Washington requirements are broadly tailored towards rare infectious diseases,[392] akin to disease reporting structures generally.[393] Still, the Washington tracking law could be replicated in other states and tailored towards all rare diseases, including chronic diseases diagnosed in clinical settings and genetic conditions diagnosed through newborn screening. The CDC has broad authority to curate the list of notifiable conditions and could partner with the Council of State and Territorial Epidemiologists and other stakeholders to add rare diseases to the NNDSS.

Another solution to support rare disease patients would be funding the creation of rare disease treatment guidelines for general practice, family, and emergency medicine physicians. Without guidelines, rare disease patients can frequently encounter misdiagnoses throughout the "diagnostic odyssey."[394] Congress could allocate resources to the National Academy of Medicine, The Joint Commission, and other stakeholders to create clinical guidelines for physicians to use for patients with an unclear medical problem that could be a rare disease. Such guidelines could then be studied with support from the National Institutes of Health, the Agency for Healthcare Research and Quality, or other federal health agencies, and incorporated into The Joint Commission and other accreditation organizations standards. By standardizing rare disease treatment guidelines, the goal of reducing misdiagnoses and addressing undiagnosed diseases would be met.

The lowest hanging fruit, in terms of government support, is in enacting current legislative proposals. Bills such as the "Creating Hope Reauthorization

390. Generally, states have their own laws governing what conditions must be reported to state health officials; these conditions are then voluntarily reported to the CDC through NNDSS. *Data Collection and Reporting*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://wwwn.cdc.gov/nndss/data-collection.html (last visited Nov. 20, 2020) [https://perma.cc/X9PV-MVR7].

391. *Rare Disease of Public Health Significance*, WASH. STATE DEP'T HEALTH, https://www.doh.wa.gov/ForPublicHealthandHealthcareProviders/NotifiableConditions/RareDiseasesofPublicHealthSignificance (last visited Nov. 20, 2020) [https://perma.cc/7KD5-5EB4].

392. *Id.* ("'Other rare diseases of public health significance' means a disease or condition, of general or international public health concern, which is occasionally or not ordinarily seen in the state of Washington including, but not limited to, spotted fever rickettsiosis, babesiosis, tick paralysis, anaplasmosis, and other tick borne diseases. This also includes public health events of international concern and communicable diseases that would be of general public concern if detected in Washington.").

393. *See National Notifiable Diseases Surveillance System (NNDSS)*, *supra* note 389.

394. *See, e.g.*, MELISSA ADAMS ET AL., PATIENT-CENTERED OUTCOMES RSCH. INST. (PCORI), LANDSCAPE REVIEW ON RARE DISEASE RESEARCH REGISTRIES 6–7 (2015), https://www.pcori.org/sites/default/files/PCORI-Report-Landscape-Review-On-Rare-Disease-May-2015.pdf [https://perma.cc/EM6W-2KMB].

Act,"[395] the "RAREBAct of 2019,"[396] and the "Protecting America's Life Saving Medicines Act of 2019"[397] are examples that illustrate Congress's engagement with rare disease efforts. Other proposals, such as expanding telehealth flexibilities created during the COVID-19 pandemic, could also benefit rare disease patients.[398] These and other proposals would provide much needed government support for the rare disease community.

2. Newborn Screening

As a key diagnostic tool for the rare disease community, broadening the inclusion of rare diseases in newborn screening regulations could be a major boon to preventing and treating rare diseases. One particular component of newborn screening that should be expanded is the use of genomic sequencing, or the testing of DNA for genetic disorders.[399] Genomic sequencing can help identify rare diseases that are outwardly indiscernible or conditions that may express later in life.[400] This early identification can significantly improve quality of life and life expectancy for many rare disease patients and can prevent high cost healthcare expenditures. Indeed, results from California's "Project Baby Bear" study found that genomic sequencing of newborns led to updated treatment plans and over $2 million in cost savings from reduced inpatient time.[401] The study also showed that genomic sequencing could identify diseases that are almost never seen, detecting thirty-five diseases impacting fewer than one out of 1 million babies.[402]

Even though there are substantial benefits to newborn screening, it is also imperative that ethical concerns be continuously addressed to mitigate unintended harms to the rare disease community. For example, genomic sequencing may reveal genetic changes that exist throughout the family, not just the infant.[403]

395. Creating Hope Reauthorization Act, H.R. 4439, 116th Cong. § 2 (2019) (creating a priority review voucher system to "encourage treatments for rare pediatric diseases.").

396. RARE Act of 2019, H.R. 4228, 116th Cong. §§ 2–3 (2019) (appropriating more funds for NIH to designate rare disease centers of excellence and creating CDC surveillance program for rare diseases).

397. Protecting America's Life Saving Medicines Act of 2019, H.R. 5402, 116th Cong. §§2–3 (2019) (allocating resources to study pharmaceutical drugs currently being evaluated by the FDA that are unlikely to be approved but would address an unmet medical need for rare diseases and providing tax incentives for clinical research).

398. *See* Letter from Healthcare, Telehealth, Ins., & Patient Orgs. to Mitch McConnell, Majority Leader, U.S. Senate, Charles Schumer, Minority Leader, U.S. Senate, Nancy Pelosi, Speaker, U.S. House of Reps., and Kevin McCarthy, Minority Leader, U.S. House of Reps. (June 29, 2020), https://everylifefoundation.org/wp-content/uploads/2020/06/Post-COVID-Telehealth-Priorities-Group-Letter-FIN.pdf [https://perma.cc/T99T-VCLS].

399. *See What Is Newborn Genomic Screening?*, GENETICS HOME REFERENCE, https://ghr.nlm.nih.gov/primer/newbornscreening/newborngenomicsequencing (last visited Nov. 20, 2020) [https://perma.cc/7JCB-6FBL].

400. *Id.*

401. *See* Shalina Chatlani, *Study: Genetic Test Diagnoses Babies with Unknown Diseases Quickly, Saves Money*, KPBS (July 1, 2020), https://www.kpbs.org/news/2020/jul/01/study-finds-genetic-test-diagnoses-babies-unknown-/ [https://perma.cc/C7QS-GXXY].

402. *Id.*

403. *What Is Newborn Genomic Screening?*, *supra* note 399.

In addition, interpretation of genomic data may change over time with new science, and genetic counseling may be challenging if the genetic changes only impact the patient later in life.[404] Finally, genetic information that is added to the newborn's medical record could create biases and genetic discrimination in future medical care.[405]

Balancing the benefits of newborn screening against the risks tips in favor of adopting rare disease genomic sequencing. The ethical concerns are largely mitigated through informed consent requirements found in the Newborn Screening Saves Lives Act of 2019,[406] meaning that parents would be able to decline the screening. Moreover, the difficulties involved with genetic counseling should not result in shirking responsibility to diagnose and treat rare diseases; while it is difficult to interpret genomic data, it should still be attempted.

With California showing proof-of-concept,[407] other states should initiate their own studies to adopt rare disease genomic sequencing into their newborn screening requirements. Federal funds allocated to the U.S. Health Resources and Services Administration through the Newborn Screening Saves Lives Act[408] can be reserved to support these state projects.

3. Medical Malpractice

Medical malpractice laws should also change, as the current form fails to accommodate rare disease patients. Within this overarching issue, two conflicting sides must be addressed. First, patients with rare conditions often do not get the answers they need and spend far more time, money, and energy on getting adequate healthcare compared to those with more common conditions. They need to have recourse for when providers do not treat them appropriately or delay their diagnosis or treatment based on neglect. Second, it is unfair for doctors to be on the hook for knowing thousands of rare conditions that they may see only a handful of times in their career, if ever.[409] Further, it is economically inefficient to test extensively for rare conditions[410]—this is a major issue for insurance companies and government sponsored care.

The solution here lies at the intersection of medical self-regulation and a new "standard of care" for patients with rare disease. The "standard of care" for treating rare diseases may not exist, and thus negligent medical decisions may be

404. *Id.*

405. *Id.*

406. Newborn Screening Saves Lives Reauthorization Act of 2014 § 12, Pub. L. No. 113-240, 128 Stat. 2851.

407. Chatlani, *supra* note 401.

408. Newborn Screening Saves Lives Reauthorization Act of 2014, Pub. L. No. 113-240, §§ 10, 12.

409. *See* Lisa Esposito, *5 Rare Diseases You've Never Heard Of (Until Now)*, U.S. NEWS & WORLD REP. (Nov. 28, 2016, 11:51 AM), https://health.usnews.com/wellness/slideshows/5-rare-diseases-youve-never-heard-of-until-now [https://perma.cc/ZX46-9VLU] ("With rare diseases . . . most doctors have never seen a case, so 'patients go from doctor to doctor to doctor.'").

410. Lynsey Chediak, *The Bad Economics of the U.S. Health Care System Shows Up Starkly in Its Approach to Rare Diseases*, TIME (Feb. 29, 2020, 4:09 PM), https://time.com/5793080/rare-disease-health-care-economics/ [https://perma.cc/HW77-FJRZ].

difficult to identify.[411] Although an expert could be retained to describe why the treatment of a rare disease patient was negligent, many rare conditions are so rare that true experts on the condition may be few and far between. In fact, often the patient may be the best "expert" on their own condition.[412] This scenario requires both the patient and provider to work in tandem and revise their expectations of each other. Because guidelines for treating rare diseases are so scarce,[413] it is vital that guidelines be developed and adopted.

Several methods exist for developing clinical practice guidelines. First, internal hospital guidelines may be used. These guidelines would inform practitioners within an individual healthcare setting on what steps are required to take place when consulting with a rare disease patient. Some rare conditions—namely, infectious diseases—have such protocols in place. Should a rare infection present at a hospital, the hospital will likely initiate protocols for quarantines, testing, clinical rounds, and internal review of clinical care. These protocols should be expanded for treating any rare condition.

A second method to develop clinical practice guidelines is through professional societies. The Infectious Diseases Society of America, for example, has created practice guidelines to treat common (e.g. pneumonia) and rare (e.g. cholera) infections alike.[414] Professional societies such as NORD or Genetic Alliance may be uniquely situated to create clinical practice guidelines. Physician guides written by physician specialists on several rare diseases have already been produced by NORD, but only cover sixteen rare conditions.[415] Both NORD and Genetic Alliance could follow other professional societies by offering more robust clinical practice guidelines focused on patient interactions, testing checklists, pharmacology resources, and "for the patient" information that can be given to the patient after a clinical consultation.[416] Partnering with provider-centric services such as UpToDate would increase the visibility of the guidelines.[417] Moreover, clinical fellowships in rare disease may also increase exposure to rare disease clinical guidelines—infectious disease, pediatrics, geriatrics, clinical

411. *See, e.g.*, Sabina Gainotti et al., *Meeting Patients' Right to the Correct Diagnosis: Ongoing International Initiatives on Undiagnosed Rare Diseases and Ethical and Social Issues*, 15 INT'L J. ENV'T RSCH. & PUB. HEALTH 1, 2 (2018) ("In both primary and specialized care, diagnostic delays and/or errors may occur [because] the physician may lack knowledge regarding the specific manifestations of the condition or may not have performed the necessary and appropriate diagnostics tests.").

412. Budych et al., *supra* note 163, at 156.

413. Joshua P. Metlay et al., *Diagnosis and Treatment of Adults with Community-Acquired Pneumonia*, 200 AM. J. RESPIRATORY & CRITICAL CARE MED. e45, e46 (2019); Andi L. Shane et al., *2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea*, 65 CLINICAL INFECTIOUS DISEASES e45, e66, tbl.6 (2017].

414. Shane et al., *supra* note 413.

415. *Physician Guides*, NAT'L ORG. RARE DISORDERS, https://rarediseases.org/for-patients-and-families/information-resources/physician-guides/ (last visited Nov. 20, 2020) [https://perma.cc/NU8F-2LUG].

416. *See, e.g.*, *NCCN Guidelines for Patients*, NAT'L COMPREHENSIVE CANCER NETWORK, https://www.nccn.org/patients/guidelines/cancers.aspx (last visited Nov. 20, 2020) [https://perma.cc/48AZ-KG3L].

417. UpToDate is widely considered "the most widely used and universally respected educational resource for clinicians around the world." Martin Pollack et al., *Remembering UpToDate Creator Burton (Bud) Rose, the 'Steve Jobs of Medicine'*, STAT (Apr. 25, 2020), https://www.statnews.com/2020/04/25/remembering-uptodate-creator-burton-bud-rose/ [https://perma.cc/Y72P-MXQF].

education, and other specialties give member physicians professional designators (e.g. "FACP" for "Fellow of the American College of Physicians"),[418] and this could be replicated for rare diseases (e.g. "FNORD" for "Fellow of the National Organization for Rare Diseases").

A third way to create clinical practice guidelines for rare disease is to involve private accreditation and hospital review boards. The Joint Commission, the National Committee for Quality Assurance, the Leapfrog Group, and other hospital accreditation and review agencies frequently evaluate hospitals by how care is delivered.[419] These agencies can create safety and quality metrics specifically oriented toward rare disease treatment. A recent standard adopted by The Joint Commission on antimicrobial stewardship (i.e. ensuring that antimicrobials are prescribed and delivered appropriately so that antimicrobial resistance does not develop) serves as a useful comparison.[420] That standard requires any health care organization that regularly prescribes antimicrobial medications to (1) identify an antimicrobial stewardship leader; (2) establish an annual antimicrobial stewardship goal; (3) implement evidence-based practice guidelines related to the antimicrobial stewardship goal; (4) provide clinical staff with educational resources related to the antimicrobial stewardship goal; and (5) collect, analyze, and report data related to the antimicrobial stewardship goal.[421] The Joint Commission could adopt similar requirements for rare conditions and require hospitals to meet certain benchmarks in order to gain accreditation. For example, a rare disease treatment leader could be required of hospitals, as could the implementation of generic rare disease clinical practice guidelines and the incorporation of education on rare diseases for clinical staff.

Taken together, these solutions would create a more robust sense of rare disease treatment and clinical care. Not only would this benefit the patients struggling with their rare conditions, but it would also serve as guidance for providers who are similarly frustrated about not being able to give their patients the help they need. Moreover, a stronger semblance of clinical care pathways for rare disease would enable stronger medical malpractice claims and defenses.

418. *ACP Fellowship*, AM. COLL. PHYSICIANS, https://www.acponline.org/membership/physician-membership/acp-fellowship (last visited Nov. 20, 2020) [https://perma.cc/E9U5-LEU3].

419. *See, e.g.*, Christoph Pross et al., *Measuring, Reporting, and Rewarding Quality of Care in 5 Nations: 5 Policy Levers to Enhance Hospital Quality Accountability*, 95 MILBANK Q. 136, 154 (2017).

420. THE JOINT COMMISSION, ANTIMICROBIAL STEWARDSHIP IN AMBULATORY HEALTH CARE, R3 REPORT (2019), https://www.jointcommission.org/assets/1/18/R3_23_Antimicrobial_Stewardship_AMB_6_14_19_FINAL2.pdf [https://perma.cc/3PBA-HQVK].

421. *Id.*

C. Novel Therapeutic Development

An economic truth is that developing new drugs, biologics, and medical devices is expensive. The average cost to develop a new drug is estimated at between $2 to $3 billion.[422] Given these research and development costs, there is limited ability for the producing company to recoup those costs if only a small number of patients will ever use the product. Even with incentives under the Orphan Drug Act, only about 600 drugs and biologics have been brought to market, which pales in comparison to the over 7,000 known rare diseases.[423] Thus, even though legislation was enacted to stimulate and incentivize industry to create therapeutics for patients with rare diseases, a massive shortfall in treatment options persists.

There are two major policy initiatives that must be brought in order to stimulate the development of therapeutics for rare diseases. First, federal policy must increase incentives for orphan drug development and the creation of medical devices for rare diseases. These incentives take two shapes: upstream financial incentives and downstream financial incentives. Upstream incentives reduce financial risks frequently faced by pharmaceutical and medical device companies during initial research and development phases, one of the costliest parts of creating a new therapeutic.[424] Downstream incentives promote economic rewards for therapeutics that gain FDA approval and hit the market.[425]

Current incentives have failed to accomplish the goal of providing treatments to the majority of rare disease patients.[426] Thus, new incentives utilizing upstream and downstream factors are needed. The goal with both upstream and downstream incentives should be to kickstart companies to research and develop products for rare diseases, as well as to reward companies that make the products while limiting the egregious pricing that can occur.

One such upstream strategy is to synthesize research findings and data. An example of this is found in the Cystic Fibrosis Foundation.[427] Their research pipeline has resulted in several new therapies that have led to better health outcomes for Cystic Fibrosis patients.[428] Specifically, they created a "Therapeutics Laboratory" which "identifies and tests potential groundbreaking therapies for [Cystic Fibrosis], readying them for further development."[429] Additionally, they

422. News Release, *Cost of Clinical Trials for New Drug FDA Approval Are Fraction of Total Tab*, JOHNS HOPKINS BLOOMBERG SCH. PUB. HEALTH (Sept. 24, 2018), https://www.jhsph.edu/news/news-releases/2018/cost-of-clinical-trials-for-new-drug-FDA-approval-are-fraction-of-total-tab.html [https://perma.cc/HJ67-T8HN].

423. *Developing Products for Rare Diseases & Conditions*, U.S. FOOD & DRUG ADMIN. (Dec. 20, 2018), https://www.fda.gov/industry/developing-products-rare-diseases-conditions [https://perma.cc/D28B-P8G4].

424. "Upstream" and "downstream" are terms used by the author to broadly categorize where incentives may impact the research and development process. For more on pharmaceutical development incentives, see Paul Grootendorst et al., *New Approaches to Rewarding Pharmaceutical Innovation*, 183 CAN. MED. ASS'N J. 681, 683–84 (2011).

425. *Id.*

426. *See, e.g.*, Bronstein et al., *supra* note 164.

427. CYSTIC FIBROSIS FOUND., *supra* note 85.

428. *Id.*

429. *Id.*

created a "Therapeutics Development Network," which is a global clinical trials network providing "resources and support for studies that are leading to important new therapies and better treatments" for Cystic Fibrosis.[430] Finally, they created "research centers" at "top universities and medical schools across North America, where scientists from many disciplines are brought together to combine their expertise to find a cure" for Cystic Fibrosis.[431]

This example could be employed across the rare disease spectrum. Similarly, the combination of rare diseases could have therapeutics laboratories, therapeutics development networks, and research centers. Indeed, this exists in piecemeal. Rare Disease Reference Networks in Europe provide for "virtual centers of excellence," and involve providers across Europe to "tackle complex or rare diseases and conditions that require highly specialized treatment and concentration of knowledge and resources."[432] A system like this could work well in the U.S., where centers of excellence—such as those in the Rare Disease Clinical Research Network[433]—are spread out and could benefit from a virtual network of experts to reach patients regardless of geographical setting.

V. CONCLUSION

Rare diseases are a common problem.[434] Estimates suggest that about a tenth of the population have a rare disease.[435] Despite this fact, the public health response has been limited at best, in part because rare diseases are often treated individually. However, when considering rare diseases as a whole, it is clear that more needs to be done to address this public health problem. First, greater epidemiologic evidence is desperately needed to get a handle on the scope and impact of rare diseases. Moreover, the social impact of rare diseases is expansive and warrants renewed attention. Second, rare disease patients have questionable recourse via medical malpractice for negligent treatment, as there is rarely a "standard of care" for rare disease treatment that can be referred to in a malpractice suit.[436] And, because there is limited data on rare disease medical malpractice cases—either those that went to trial or those that settled out of court—more research is needed to understand this particular interaction between rare disease patients and the law. Third, government resources and policies addressing rare disease need to be refreshed and modernized. While legislation has helped to advance the landscape of rare disease patient rights and protections, as well as the development of therapies and research, much more needs to be done to find treatments for the 95% of rare disease patients facing uncertain futures. By rein-

430. *Id.*
431. *Id.*
432. Dirk Moritz, *Rare Disease Centers of Excellence*, BLUE MATTER (June 13, 2018), https://bluematter-consulting.com/rare-disease-centers-of-excellence/ [https://perma.cc/Y89H-N52G].
433. *Rare Diseases Clinical Research Network*, *supra* note 258.
434. Stoller, *supra* note 20, at 1309.
435. *Id.*
436. Crane, *supra* note 305.

vigorating economic incentives for developing treatments for hyper-rare conditions, as well as providing research and development databanks to spur innovation, a greater proportion of rare diseases can have treatments developed in the future.

Too often, the law faces a dilemma of prioritization—the squeaky wheel gets the grease. Individually, rare diseases hardly "squeak." They are found in individuals who have nobody to relate to, in families that mistakenly think their poor health is shared by everyone else, and in groups that struggle to make their voices heard. By accounting for all rare diseases, a new framework utilizing public health and the law can provide better therapies, better research, and ultimately better recognition and representation for people suffering from rare disease.