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A Zebra's Trust: How Rare Disease Communities' Participation in Data Trusts' Governance Builds Trust and Drives Research

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ABSTRACT

Data sharing plays an increasingly prominent role in society, but it remains a necessary component of rare disease research. Because rare diseases are—as the name indicates—rare, researchers have only a small number of patients from whom to collect data, and the expense of cross-border data sharing to increase research data is significant. Nevertheless, the rise of artificial intelligence and precision medicine increases the need for usable rare disease data. Current legislation and regulations aimed at addressing rare diseases fall short in addressing these data sharing needs for rare disease research. While the European Union (EU) has invested in rare disease data sharing more than most of the world, its programs are fragmented and limited to the rare disease community.

Simultaneously, data is becoming increasingly viewed as a necessary component of a competitive economy, driving interest in data sharing platforms and initiatives, including the EU's new Trusted Secure Data Sharing Space (TRUSTS) initiative. Perhaps the most promising instrument for data sharing is the data trust, but it suffers from an undefined and uncertain legal structure. This Note suggests that the rare disease community should embrace these broader data sharing initiatives in order to ensure the representation of rare disease data in these data sets and to harness the power of large-scale data sharing. Simultaneously, data trusts should look to rare disease communities for representation in their governance structures in order to establish the patient-centricity and public trust necessary for data trusts to thrive in an uncertain legal environment.

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I. INTRODUCTION

On May 7, 2020, Lisa Cummings listed out the similarities: fear of the unknown, the way people stare, worry, isolation, and hope. With a click, she shared her post on Facebook's "TSC Alliance Tuberous Sclerosis Complex Discussion Group," highlighting the parallels between COVID-19 and her daughter's Tuberous Sclerosis Complex (TSC) diagnosis.[1]

Thirty-one years earlier, Lisa's daughter, Deborah Ann, or as her mother calls her, Dac, began demonstrating the symptoms of TSC at only six months old.[2] TSC, a rare genetic disorder that causes benign tumor growth throughout the body among other symptoms,[3] proved debilitating for Dac, as it does for the majority of the few individuals

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1. Lisa Cummings, TSC Alliance Tuberous Sclerosis Complex Discussion Group, FACEBOOK (May 7, 2020) (private page on file with the author). Dac's story is included with Lisa's permission.

2. Lisa Cummings, TSC Alliance Tuberous Sclerosis Complex Discussion Group, FACEBOOK (May 2, 2013) (private page on file with the author).

3. *See generally About TSC*, TSC ALLIANCE (2021) https://www.tscalliance.org/about-tsc/what-is-tsc/ [https://perma.cc/934M-DF7S] (archived Oct. 28, 2021).

with this diagnosis. Dac grew up suffering from autism and epilepsy and survived multiple surgeries, a brain aneurysm, and a stroke.[4] Now thirty-one, Dac is, as her mother described on Facebook, "forever a toddler locked inside an adult body."[5] While Dac requires full time care from Lisa, Lisa in turn relies on the sense of community she finds in her Facebook "family" of other TSC patients and their communal hope for a cure.[6] This combination of community and hope is often the best that a rare disease patient or their caregiver can expect due to the lack of research and drug development in the rare disease space. However, in the modern age of data-driven medical discoveries, this same community could prove key to turning hope into progress.

When the world was overrun by COVID-19 in 2020, many across the world had their first experience facing the trials of a rare medical condition. As Lisa suggested on Facebook, it was a time to fear the unknown, to have people stare at the signs of illness (whether they be the physical symptoms experienced by a rare disease patient like Dac or the visibility of wearing a mask), to worry, to stay in isolation, and to long for normalcy. For many, it was their first time knowing the frustration of getting mixed information from experts, experiencing a condition about which experts knew little, and facing the fear of unknown treatments that lacked the confidence of withstanding the test of time.[7] However, for the roughly 6–8 percent of the world population that has a rare disease[8]—a population roughly equivalent

4. Cummings, *supra* note 1.

5. *Id.*

6. *Id.*

7. *See generally About Us*, GLOBAL COMMISSION TO END THE DIAGNOSTIC ODYSSEY FOR CHILDREN WITH A RARE DISEASE (last visited OCT. 20, 2021), https://www.globalraredisease commission.com/AboutUs [https://perma.cc/44Q5-J5W8] (archived Oct. 20, 2021).

8. The commonly cited figure is 6–8 percent, but it may be closer to 4 percent. *See, e.g.*, Safiyya Dharssi, Durhane Wong-Rieger, Matthew Harold, & Sharon Terry, *Review of 11 National Policies for Rare Diseases in the Context of Key Patient Needs*, 12 ORPHANET J. RARE DISEASES, 2017, No. 63 (2017) https://doi.org/10.1186/s13023-017-0618-0 [https://perma.cc/VX98-EBCH] (archived Oct. 20, 2021). Studies have reassessed the 6–8 percent estimate to find significantly lower figures (1–2 percent). However, a recent study challenging these estimates concluded that even a conservative estimate fell at 3.5–5.9 percent (263–446 million). This figure excludes certain categories of diseases and conditions, such as rare cancers, and recognizes limitations based upon drawing its data from a European dataset to find that the actual number is likely "considerably higher." *See* Stéphanie Nguengang Wakap, Deborah M. Lambert, Annie Olry, Charlotte Rodwell, Charlotte Gueydan, Valérie Lanneau, Daniel Murphy, Yann Le Cam, & Ana Rath, *Estimating Cumulative Point Prevalence of Rare Diseases: Analysis of the Orphanet Database*, 28 EUR. J. HUM. GENETICS 165, 171 (2020). Most publications continue to use the figure of 6–8 percent.

in size to that of the United States[9]—these experiences remain unextraordinary, even daily, occurrences.

COVID-19's alarming transmission and resulting global impact spurred institutions around the world to share their data.[10] As a result, COVID-19 research teams benefited from international cooperation in data sharing, allowing for rapid developments in care and vaccinations. COVID-19 and the world's responsive demand for data thus serves as a poignant example of how data sharing can drive life-changing and life-saving research and outcomes.

In stark contrast to patients who have experienced COVID-19 and other frequently encountered medical conditions, the rare disease patient population suffers from a "small data" problem; their small numbers hinder the ability to study them and limit the market size from which funders can receive a return on their investment in research.[11] Data sharing is not only a benefit but often a requirement for successful rare disease research. While law and legal scholarship for rare diseases currently prioritize the affordability and marketability of cures and treatments in order to incentivize their development, little attention has been given to how the law can improve data sharing for the rare disease community in order to enlarge the available data sets and expedite research processes. The need to address rare diseases became a national priority in the 1980s and is once again gaining political traction,[12] but these new actions must reach beyond the previous success realized in domestic drug-development incentive programs to expand international cooperation and transnational coordination on data sharing initiatives and overcome rare diseases' small data problem.

Fortunately, data sharing is currently at the forefront of many legal conversations. As the world becomes increasingly data dependent, many countries are beginning to see data as a public good,[13] and government actions to increase the availability of data necessarily

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9. *See U.S. and World Population Clock*, U.S. CENSUS BUREAU, (Mar. 13, 2021) *https://www.census.gov/popclock/* [https://perma.cc/AG9W-J6YA] (archived Oct. 20, 2021) (estimating the U.S. population at over 330 million and the world population at 7.75 billion).

10. *See, e.g.*, Joel G. Ray, Michael J. Schull, Marian J. Vermeulen, & Alison L. Park, *Association Between ABO and Rh Blood Groups and SARS-CoV-2 Infection or Severe COVID-19 Illness*, 174 ANNALS INTERNAL MED. 308 (2020) (associating O and Rh-blood types with a lower risk of severe COVID-19 illness, based upon data provided through Ontario's universal healthcare system); Ensheng Dong, Hongru Du, & Lauren Gardner, *An Interactive Web-Based Dashboard to Track COVID-19 in Real Time*, 20 LANCET 533 (2020) (describing the creation of a dashboard compiling global data on COVID-19 cases).

11. *See infra* Part II.B.3 and accompanying notes.

12. *See* Wakap, Lambert, Olry, Rodwell, Gueydan, Lanneau, Murphy, Cam, & Rath, *supra* note 8, at 171.

13. *See infra* Part III.

affect the rights of data subjects. Government programs like the European Union's (EU's) new data trust initiative, Trusted Secure Data Sharing Space (TRUSTS), aim to commodify data, depicting data sharing as a civic obligation.[14]

Data trusts are a promising instrument for data sharing but remain unsettled in their legal structure. While defined by the obligations between parties, data trusts lack a standard legal form. Even the TRUSTS project has identified a number of prospective legal problems without yet identifying its own legal structure.[15] Nevertheless, current scholarship seems to agree that, as their use increases, data trusts and similar data sharing programs will rely on the interrelated factors of stakeholder participation and trust to be successful.[16] As data trusts determine the nuance of their applicable law and legal structure, they should prioritize how their governance structures meaningfully involve participants to build long-term public trust throughout the data trust's lifespan.

This Note suggests that, rather than focusing on rare-disease-specific data sharing methods, crafting emerging large-scale data sharing programs like TRUSTS with an eye toward rare diseases will benefit both parties. Rare disease communities can harness the power of data trusts to promote cross-border research despite the current shortcomings in rare disease legislation, just as data trusts can welcome these communities' participation as a means to instill public trust in their evolving governance structure. Rare disease populations can benefit from decreasing the costs associated with current rare disease research and drug development—a goal largely beyond the scope of current legislative measures—while ensuring their voice and data are included in data samples intended for cross-sector use. Data trusts can benefit from the community oversight and cooperation of rare disease groups. These groups are regularly comprised of active, social communities uniquely situated to prioritize the success of both data sharing platforms and data protection measures, given their unique vulnerabilities from both constraints on sharing as well as privacy breaches.

Part II will describe rare diseases, the current focus of rare disease legislation, and how precision medicine will benefit from that

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14. *See* Anna Artyushina, *The EU is Launching a Market for personal data. Here's what that means for privacy.*, MIT TECH. R. (Aug. 11, 2020) https://www.technologyreview.com/2020/08/11/1006555/eu-data-trust-trusts-project-privacy-policy-opinion/ (Oct. 20, 2021) [https://perma.cc/BG9B-DC99] (archived Oct. 20, 2021).

15. Charlotte Ducuing, Lidia Dutkiewicz, & Yuliya Miadzvetskaya, *Deliverable 6.2 Legal and Ethical Requirements*, TRUSTS: TRUSTED SECURE DATA SHARING SPACE (Aug. 2020) https://trusts-data.eu/ [https://perma.cc/6LRC-YRP7] (archived on Nov. 10, 2021).

16. *See infra* Part IV.

legislation's structure, potentially exhausting the system to the point of making it ineffective in supporting cross-border research for both rare diseases and precision medicine.[17] Part III will address data sharing initiatives, focusing on the rise of data trusts, their nature, and the legal questions emerging from their structure. Part III will then turn to current data sharing initiatives, beginning with rare disease-oriented initiatives before addressing the EU's shift to broader cross-sector data sharing. Part IV will bring together these two matters to show the mutually beneficial relationship that can be formed through the rare disease population's role in data trust governance. Part V concludes by emphasizing that public trust in data sharing platforms revolves around a sense of personal data security in relationship to the benefits received from that data, and, therefore, any new system of governance requires ongoing monitoring to ensure that trust is well placed.

II. RARE DISEASES

Understanding the impact current and prospective legislative and regulatory schemes may have on rare disease research relies first on understanding what constitutes a rare disease. The challenges present in defining and describing rare diseases indicate both how rare disease populations are disempowered and the unattractive market they present to investors. Their inability to create an attractive market serves as the hindrance to properly addressing rare diseases as the global health crisis that they are. However, these same features make the community strong in its interpersonal connections, its fierce advocacy for its interests, and its eagerness for innovation.

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17. This note is limited in its scope and will not discuss many pertinent issues related to the rare disease community. Specifically, this note is not designed to directly grapple with specifics related to clinicians in diagnosing rare diseases or performing clinical studies. These concepts go hand-in-hand with research. For most rare disease patients, the very process of getting diagnosed is in itself an odyssey involving many years and misdiagnoses. *See generally* GLOBAL COMMISSION TO END THE DIAGNOSTIC ODYSSEY FOR CHILDREN WITH A RARE DISEASE, https://www.globalrarediseasecommission.com/ [https://perma.cc/ZCT8-CU2S] (archived on Nov. 10, 2021) (providing resources to accelerate pediatric rare disease diagnoses). Data sharing is necessary in the diagnostic world, as well, to share information for a patient's individual care and diagnostic tools for clinicians; however, this note focuses on the data sharing hurdles specific to researchers, not care providers. Nevertheless, for a successful approach to rare diseases, further focus should be placed on implementation of programs like the EU's Global Commission to End the Diagnostic Odyssey for Children with Rare Diseases. *Id.* Further research should indicate the possibility of linking data for patients enrolled in clinical and longitudinal studies within the proposed transnational data federation approach suggested here and the associated privacy concerns.

A. *Understanding Rare Diseases*

Defining rare diseases, which are also referred to as zebras[18] or orphan[19] diseases, is a complicated task because of the lack of sufficient data, scientific publications, and databases.[20] Although no universal definition exists, definitions found in legal frameworks, such as those described below, generally rely on prevalence thresholds: rare diseases are those diseases that affect 1 person in 500,000 thousand (0.0002 percent) to 1 in 2,000 (0.05 percent) of a state's population.[21] This reliance on point prevalence serves in large part to recognize the market hurdles facing rare diseases.[22]

An estimated five thousand to eight thousand[23] rare diseases affect an estimated 300 million people. Some rare diseases are recognizable, such as sickle cell disease with its frequent presence in biology textbooks, or amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), which gained attention through celebrity diagnoses and mainstream media.[24] But the majority of rare diseases are suffered

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18. The name "zebra" has been a long-attributed nickname in the rare disease community. Its origins are tied to variations of a medical school adage—"when you hear hoofbeats, you don't look for a zebra"—teaching students to expect routine conditions. *See, e.g.*, Gina M. Cavalier, Note, *Pushing Parentless Pharmaceuticals: Toward an Internationalization Home for "Orphan Drugs" and A Cure for "Zebra" Diseases*, 27 LAW & POL'Y INT'L BUS. 447, 468 (1996) ("'When a hoof beats, you think of horses, not zebras; it's just possible it could be a zebra'") (discussing how the medical community is educated on rare diseases); *see also Rare Diseases in General Practice: Recognizing the Zebras Among the Horses*, 66 BRIT. J. GEN. PRAC. 550, 550 (2016) ("When you hear hoofbeats, don't expect to see a Zebra").

19. The term "orphan" is primarily used in the pharmaceutical context to describe rare disease treatments as "orphan drugs." *See FAQs About Rare Diseases*, GENETIC AND RARE DISEASE INFORMATION CENTER (last updated Jan. 26, 2021), https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases [https://perma.cc/MU9G-C453] (archived Oct. 20, 2021) ("Rare diseases became known as orphan diseases because drug companies were not interested in adopting them to develop treatments"); *see, e.g.*, Orphan Drug Act, Pub. L. No. 98–551, 99 Stat. 2817.

20. *See* Wakap, Lambert, Olry, Rodwell, Gueydan, Lanneau, Murphy, Cam & Rath, *supra* note 8, at 166.

21. *See id.* at 165; Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 1–2.

22. For information about the use of point prevalence, see generally Wakap, Lambert, Olry, Rodwell, Gueydan, Lanneau, Murphy, Cam, & Rath, *supra* note 8, at 171 (discussing the different applications of point prevalence measures used across the world, that point prevalence allows resource planning to grow with the population, and that a common definition is needed in the global community).

23. Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 1; *see also* Wakap, Lambert, Olry, Rodwell, Gueydan, Lanneau, Murphy, Cam, & Rath, *supra* note 8, at 166, 168 (finding that Orphanet, a European database of rare disease information, contained 6,172 unique rare diseases, even when excluding certain types of disorders).

24. ALS gained public attention with baseball player Lou Gehrig's diagnosis; physicist Stephen Hawking's diagnosis; Hollywood biopic films like the Academy Award-winning *The Theory of Everything*, starring Eddy Redmayne and Felicity Jones; and the social media craze, the Ice Bucket challenge.

in silence with patients feeling alone and forgotten except for their small population of patients and caregivers.

For many people, a medical diagnosis can be stressful and filled with uncertainty for the individual, but for rare disease patients, the stress and uncertainty are multiplied by delayed and mis-diagnoses, limited resources, a lack of information and expertise, and limited or no therapies.[25] Over 90 percent of rare diseases lack an effective treatment.[26] Patients frequently have to self-advocate, educate their own doctors in their disease, and request experimental treatments.[27] Despite "exhibit[ing] considerable diversity," most rare diseases involve pediatric onset, affecting patients throughout their lives with severe physical and mental disabilities, significantly reduced life expectancy, and requiring life-long use of expensive therapeutics, if any exist.[28] Beyond the burden on patients and caregivers, "rare diseases constitute a major economic burden" on countries, regardless of the state's size and demographics.[29]

The limited patient population of rare diseases inhibits research by providing a smaller market from which to reap a worthwhile return-on-investment from that research. Any new drug can cost more than $2.5 billion to develop over a decade, but with rare diseases, fewer individuals are purchasing the end product.[30] In addition to the small market from which to gain revenue, rare disease research also suffers from higher research costs. Rare disease research involves longer time frames for development because base-line information must be gathered first and trial recruitment relies on smaller patient populations, prolonging the recruitment process and, in turn, increasing costs.[31]

B. *Analysis of the Current Legal Frameworks*

In the 1980s, Abbey Myers, a rare disease patient's mother; Henry Waxman, a legislator; and Jack Klugman, an actor, forced rare diseases into the spotlight.[32] Their combined efforts—of Abbey

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25. *See* Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8.

26. Petra Kaufmann, Anne R. Pariser, & Christopher Austin, *From Scientific Discovery to Treatments for Rare Diseases – the View from the National Center for Advancing Translational Sciences – Office of Rare Diseases Research*, 13 ORPHANET J. RARE DISEASES, Nov. 6, 2018, at 1, https://doi.org/10.1186/s13023-018-0936-x [https://perma.cc/NK8R-PR83] (archived Oct. 28, 2021).

27. *See About Us*, *supra* note 7; GLOBAL COMMISSION TO END THE DIAGNOSTIC ODYSSEY FOR CHILDREN WITH A RARE DISEASE, *supra* note 17 (providing information on the "diagnostic odyssey" of one such example of the challenges rare disease patients face).

28. *See* Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 11.

29. *See id.*

30. Kaufmann, Pariser, & Austin, *supra* note 26, at 2.

31. *See id.*

32. *See* Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 17.

Meyers's testimony and advocacy, in hearings called by Representative Waxman, and with scripted references designed into Jack Klugman's popular television show[33]—culminated in 1983 when the Orphan Drug Act was passed in the United States. The Orphan Drug Act's passage and success led to the adoption of rare disease policies in other nations.[34]

Forty years later, rare diseases are once again gaining political traction but now at a more global level.[35] Pledging to "leav[e] no one behind," organizations like the United Nations, World Health Organization, Organization for Economic Co-operation and Development, and Asia-Pacific Economic Cooperation have "move[d] toward adoption of [rare disease] policies and programs."[36] Nevertheless, some countries provide minimal to no support for rare diseases individually or in cooperation with other nations.[37] The legislation in place varies significantly across the world, and while some of those laws and regulations focus on research itself, their most notable provisions focus on incentivizing research through monopoly protections on the back end. The most developed frameworks in areas like the EU, the United States, Japan, and Taiwan focus on these market protections. Trends in medicine, particularly precision medicine, demonstrate the benefits of refocusing legislative action toward data sharing initiatives as an alternative method for promoting

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33. National Organization for Rare Diseases, *Celebrating 30 Years: Empowering the Rare Disease Community!*, NEWS FROM NORD (National Organization for Rare Disorders, Danbury Conn.), Summer 2013, at 1, 4, https://rarediseases.org/wp-content/uploads/2014/12/Newsletter_summer2013.pdf [https://perma.cc/E4ZU-SDUH] (archived Oct. 28, 2021).

34. *See id.*

35. *See* Wakap, Lambert, Olry, Rodwell, Gueydan, Lanneau, Murphy, Cam, & Rath, *supra* note 8, at 21—25.

36. *Id.* at 12.

37. *See, e.g.*, Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 31—33 (discussing eleven national policies and recognizing that Argentina provides relatively less aid to rare disease communities); Gareth S. Baynam, Stephen Groft, Francois H. van der Westhuizen, Safiyya D. Gassman, Kelly du Plessis, Emily P. Coles, Eda Selebatso, Moses Selebatso, Boikobo Gaobinelwe, Tebogo Selebatso, Dipesalema Joel, Virginia A. Llera, Barend C. Vorster, Barbara Wuebbels, Benjamin Djoudalbaye, Christopher P. Austin, Judit Kumuthini, John Forman, Petra Kaufmann, James Chipeta, Désirée Gavhed, Annika Larsson, Maja Stojiljkovic, Ann Nordgren, Emilio J. A. Roldan, Domenica Taruscio, Durhane Wong-Rieger, Kristen Nowak, Gemma A. Bilkey, Simon Easteal, Sarah Bowdin, Juergen K. V. Reichardt, Sergi Beltran, Kenjiro Kosaki, Clara D. M. van Karnebeek, Mengchun Gong, Zhang Shuyang, Ruty Mehrian-Shai, David R. Adams, Ratna D. Puri, Feng Zhang, Nicholas Pachter, Maximilian Muenke, Christoffer Nellaker, William A. Gahl, Helene Cederroth, Stephanie Broley, Maryke Schoonen, Kym M. Boycott, & Manuel Posada, Comment, *A Call for Global Action for Rare Diseases in Africa*, 52 NATURE GENETICS 21 (2019) [hereinafter *A Call for Global Action for Rare Diseases in Africa*] (discussing the need for rare disease initiatives in Africa and connecting them with international collaboration and the launch of the Africa-Rare initiative).

rare disease research and a means of avoiding current legislative pitfalls.

1. Global Legal Landscapes

Many national plans attempt to overcome the market-size obstacle through incentive programs, but these plans resulted in a range of successes and criticisms. An analysis of how these programs around the world work can provide insight into how international efforts might overcome national obstacles in order to foster rare disease research.

a. The United States Leads with the Orphan Drug Act

In the Orphan Drug Act, rare diseases are defined by whether they affect less than two hundred thousand people in the United States,[38] allowing the prevalence rate to vary with population size. The act focuses on reducing the cost of developing drugs for rare diseases and providing financial incentives for their development via research grants, tax credits, and a seven-year period of market exclusivity.[39] Despite leading the prioritization of rare diseases with the Orphan Drug Act, the United States "lacks a formal National Rare Disease Plan, and policy variation across states confounds comparisons with other countries."[40] While the United States also passed the Rare Disease Act to establish the Office of Rare Diseases at the National Institutes of Health and other legislation for specific rare diseases,[41] inadequate funding continues to plague American rare disease research.[42] The United States has attempted to invoke alternative solutions to novel therapies via drug repurposing, and the U.S. Food and Drug Administration's (FDA's) creation of the Rare Disease Repurposing Database "compiles publicly available information not readily available to potential developers," which could prove effective

38. The Orphan Drug act was revised in 1984, so that it currently applies to drugs made for patient populations under two hundred thousand in addition to the original category of drugs that can demonstrate no reasonable belief in profitability. *Compare* Orphan Drug Act, Pub. L. No. 97–414, 96 Stat. 2049 (1983), *with* Health Promotion and Disease Prevention Amendments of 1984, Pub. L. No. 98–551, 99 Stat. 2817 (1984).

39. Brian Su, *Developing Biobanking Policy with an Oliver Twist: Addressing the Needs of Orphan and Neglected Diseases*, 66 LA. L. REV. 771, 786 (2006); *see generally* Orphan Drug Act, Pub. L. No. 97–414.

40. Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 24–25.

41. Neil Khosla & Rodolfo Valdez, *A Compilation of National Plans, Policies and Government Actions for Rare Diseases in 23 Countries*, INTRACTABLE & RARE DISEASES RSCH., Nov. 2018, at 216, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6290840/ [https://perma.cc/9XK2-83QP] (archived Oct. 28, 2021).

42. *See* Su, *supra* note 39, at 787.

in bringing rare disease treatments to market; however, "there is no extra financial incentive to do so."[43]

At first glance, the Orphan Drug Act has been largely successful: according to the FDA "nearly 200 orphan drugs enter development each year and approximately one third of new drugs approved by the FDA are for the treatment of rare diseases."[44] Critics wonder, though, how much pharmaceutical companies are effectively "renewing" their same drugs for rare disease status by resubmitting them for approval under a new therapeutic use in order to maintain their period of market exclusivity and keep prices high for patients.[45] Over seventy therapies currently designated with orphan status and its accompanying protections originally received FDA approval for mass market use, such as Crestor, the cholesterol medication, and Humira, the rheumatoid arthritis drug—and global leader in drug sales.[46] About eighty orphan drugs, such as Botox, have had multiple periods of market exclusivity, reapplying for orphan drug designation under a new use or formulation of the same medication to multiply the seven year monopoly.[47] Meanwhile, the pharmaceutical companies can charge any price while they retain that monopoly protection.[48]

Orphan drugs' price tags represent some of the highest in pharmaceuticals, with some studies indicating that in 2022 they will represent over 21 percent of worldwide brand-name prescription sales.[49] These steep prices are attributable to the combined risk of high development costs and a long timeframe for the return on that investment, as well as factors like pharmaceutical competition, the relative value of the drug compared to the price, and the current legal protections.[50] For the patient, though, the median cost is 5.5 times

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43. Kathryn Brown, Seminar Article, *Repurposing Old Drugs for New Uses*, 28 DEPAUL J. ART, TECH. & INTELL. PROP. L. 1, 11 (2017).

44. Claire Dennis, Note and Comment, *A Comparison of the Pre-Market Orphan Drug Legal Frameworks in the United States and the European Union*, 35 WIS. INT'L L.J. 138, 150 (2017) (citing Shannon Gibson & Barbara von Tigerstrom, *Orphan Drug Incentives in the Pharmacogenomic Context: Policy Responses in the US and Canada*, 2 J.L. & BIOSCIENCES 263, 264 (2015)).

45. *See, e.g.*, Sarah Jane Tribble & Sydney Lupkin, *Drugs For Rare Diseases Have Become Uncommonly Rich Monopolies*, NPR (Jan. 17, 2017), https://www.npr.org/sections/health-shots/2017/01/17/509506836/drugs-for-rare-diseases-have-become-uncommonly-rich-monopolies [https://perma.cc/RY24-JU88] (archived Oct. 28, 2021).

46. Sarah Jane Tribble, *Sen. Grassley Launches Inquiry Into Orphan Drug Law's Effect on Prices*, NPR (Feb. 10, 2017), https://www.npr.org/sections/health-shots/2017/02/10/514373480/sen-grassley-launches-inquiry-into-orphan-drug-laws-effect-on-prices [https://perma.cc/ZT4Z-5GRY] (archived Oct. 26, 2021).

47. *See id.*

48. Tribble & Lupkin, *supra* note 45.

49. Dennis, *supra* note 44, at 149.

50. *See id.*

higher for orphan drugs than non-orphan pharmaceuticals.[51] In the United States, orphan drugs often start at an annual cost for the patient of $50,000 to $500,000, and the top-selling orphan drug exceeded $3.6 billion in sales in 2016.[52] Although the high price tag may allow or even incentivize pharmaceutical companies to enter the research and discovery process, they are burdensome—if not unsustainable—for rare disease patients who often rely on these treatments from childhood through their adult life.

Thus, while the Orphan Drug Act overcomes market obstacles to incentivize research and development, the orphan drugs created via the Orphan Drug Act may not actually serve the rare disease community in meaningful ways or may be too highly priced to be practical medical solutions for a lifetime of care.[53]

While the United States may have led the charge in enacting orphan drug legislation, Europe exemplifies international cooperation for the benefit of rare diseases patients with a slow buildup of an extensive, though fragmented, array of rare disease regulations.

b. Europe's Sweeping Rare Disease Framework

In Europe, both national programs and EU-level regulations work to aid rare disease communities, creating "an integrated, multi-country approach to rare diseases."[54] All states of the EU share a common legal definition of "rare disease" as a medical condition affecting fifty individuals or less for every one hundred thousand people.[55] The EU also provides other support mechanisms including research grants, reduction of marketing fees, and a ten-year period of market exclusivity—adding an additional three years to the American rule.[56]

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51. *See id.*

52. *Id.* at 150. The expense of orphan drugs depends on the national health plans and pharmaceutical regulations of any individual country. For example, on average European prices are 20–40 percent lower.

53. More research should be conducted into whether the orphan drug designations proportionally match the medical benefits for the rare disease community. While the rare disease community supports the Orphan Drug Act, and it has undeniably benefitted some in the community, in the face of the recent allegations for the inefficacy of the Orphan Drug Act and the loopholes by which pharmaceutical companies are availing themselves, it is possible that the impact has not been significant enough to the benefits awarded pharmaceutical companies. Researchers should investigate whether the benefits to some in the rare disease community and the face value number of orphan drugs created have gained the support of the collective voice of the general rare disease community who hope to see more results for their individual subsegment, while failing to benefit the rare diseases purportedly served in sizable ways.

54. *See* Khosla & Valdez, *supra* note 41.

55. *See* Wakap, Lambert, Olry, Rodwell, Gueydan, Lanneau, Murphy, Cam, & Rath, *supra* note 8, at 165; Khosla & Valdez, *supra* note 41 (legal definition found under the Orphan Medicinal Product Regulation No. 141/2000 (EC)).

56. *See* Su, *supra* note 39, at 787–88.

The EU's programs have extended beyond promoting rare disease treatments to providing more comprehensive aid to the rare disease community.[57] The European Project for Rare Diseases National Plans Development (EUROPLAN) promotes the implementation of national rare disease plans, the sharing of expertise, and the connection of efforts across Europe.[58] These actions include the 2009 "Recommendation on an Action in the Field of Rare Diseases" to encourage member states to adopt their own rare disease strategies and recommending plans that address all aspects of rare-disease patients' needs, from diagnosis and care to public awareness and patient organization empowerment.[59] Moreover, most member states have Compassionate Use Programs that provide "free, short-term access to orphan products."[60] Additionally, the Seventh Framework Program (FP7) funded research, with over €620 million granted to over 120 rare disease research projects[61] These collaborative projects created teams across and beyond European states.[62] Horizon 2020 likewise funds rare disease projects and research.[63]

Across Europe, though, national plans vary widely, with France being a leader in rare disease prioritization. Five years before plans were promoted across the EU, France had enacted its "First National Plan for Rare Diseases," which became the "impetus and model" for other European nations that followed suit in creating rare disease programs.[64] The plan established centers of expertise for diagnosis and care coordination, drafting national protocol, data collection, and clinical trials.[65] More specifically, France is a leader in rare disease research. France funded various research projects and launched a national database and international collaborations, hosting over three hundred clinical research projects in 2017 alone.[66] By contrast, Germany, for example, funds rare disease organizations and research projects, has allocated millions to cross-border research projects, but has no central registry.[67] The United Kingdom collaborates with pharmaceutical companies for patient-centered research and intends to build a rare disease registry.[68] While European rare disease initiatives are positive developments, especially in comparison to other

57. *See* Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 26.
58. *Id.*
59. *See id.*
60. Khosla & Valdez, *supra* note 41, at 217.
61. *Id.*; Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 9.
62. Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 9.
63. *Id.*; *see infra* Part III.B.2 (discussing some of Horizon 2020's rare disease-related data sharing initiatives).
64. Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 2.
65. *Id.*
66. *Id.* at 9.
67. *See id.*
68. *See id.* at 8–9.

places in the world, the overlay of EU-level programs on these distinct national plans has rendered the regulatory and policy landscape incoherent to many researchers.[69]

c. Further Disjunction in Policies across the Globe

Inconsistencies in legal definitions and approaches, like those evident between the United States and the EU, and even among EU member states, extend across the world. For example, Latin American countries exhibit large differences in their rare disease definitions. Countries such as Argentina, Chile, and Mexico adopt the European definition, while other states use their own definitions, such as Brazil's less than 65 in 100,000 individuals or Peru's less than 1 in 100,000.[70]

Despite similar ratios of healthcare spending to GDP as in European countries (like France, Germany, and the United Kingdom), Argentina, Mexico, and Brazil's national rare disease plans "are awaiting development or are very early in implementation."[71] Brazil, the seventh-most populated state in the world,[72] has few legal incentives for research, no long-standing rare disease initiatives, no national registry, only a handful of funded projects, and, as such, the country relies on patient groups for data collection.[73] Likewise, Mexico, with the world's tenth-largest population, [74] has no funded research.[75] Nevertheless, individual pieces of legislation provide assistance in these countries, such as Argentinian legislation giving aid to patients and caregivers of rare diseases or Brazil's "National Policy for Rare Diseases," which aims to increase life-expectancy and quality of life for rare disease patients and calls for treatment centers to provide genetic testing and counseling.[76] While these countries have passed legislation recognizing the public health crisis and individual challenges

69. *See* Su, *supra* note 39, at 788; *cf. infra* Part III.B.2 (discussing how the EU's fragmented approach to rare diseases makes available resources unclear).

70. *See* Khosla & Valdez, *supra* note 41, at 219; Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 2; Supreme Decree No. 004-2019-SA, https://cdn.www.gob.pe/uploads/document/file/297304/Decreto_Supremo_N%C2%BA_004-2019-SA.PDF (Peru) [https://perma.cc/3QAQ-HBZ6] (archived Oct. 28, 2021).

71. Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 3.

72. *U.S. Census Bureau Current Population Statistics*, UNITED STATES CENSUS BUREAU (Mar. 11, 2021), https://www.census.gov/popclock/print.php?component=counter [https://perma.cc/D9TU-ZB7C] (archived Oct. 28, 2021).

73. Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 5.

74. UNITED STATES CENSUS BUREAU, *supra* note 72.

75. Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 3.

76. *See* Khosla & Valdez, *supra* note 41, at 219.

presented by rare diseases, they generally fall short of promoting research or treatment options.[77]

As of January 2022, Canada remains one of the few developed countries without an active national rare disease plan, legislation, or strategy. Nevertheless, the country has made progress in alleviating the price burden of orphan drugs, the Canadian government committed funding for research via the Canadian Institutes for Health Research, and the country has been actively engaging stakeholders in the information gathering necessary for the development of a rare disease plan.[78]

In Asia, some countries like Taiwan and Japan have made significant progress. Japan provides grants, tax reductions, priority placement on examination schedules, and ten years of marketing exclusivity, yet suffers from orphan drug prices that are two to three times greater than US prices.[79] Although China has not implemented a rare disease plan, a 2013 pilot project and the 2016 Rare Disease Clinical Cohort Study have been implemented to create usable guidelines and clinical pathways, establish registries and data repositories, and promote molecular testing.[80]

As of February 2021, Africa and India are both poised to begin new rare disease efforts.[81]

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77. *See* Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 9–10 ("[R]esearch projects in Argentina are often conducted and funded through private initiatives, research grants, or support from patient organizations. Similarly, there is no long-standing initiative to promote research on rare diseases at the national level in Brazil; however, a bill intending to secure funding for rare and neglected disease-related research is currently being reviewed by Congress."). *But see* Khosla & Valdez, *supra* note 41, at 219.

78. *See Canadians Invited to Share Their Views on a National Strategy for High-Cost Drugs for Rare Diseases*, BIOSPACE (Jan. 27, 2021), https://www.biospace.com/article/releases/canadians-invited-to-share-their-views-on-a-national-strategy-for-high-cost-drugs-for-rare-diseases/ [https://perma.cc/S5TC-XRUH] (archived Oct. 28, 2021); *see, e.g.*, *National Strategy for High-Cost Drugs for Rare Diseases Online Engagement*, HEALTH CANADA, (last modified July 26, 2021), https://www.canada.ca/en/health-canada/programs/consultation-national-strategy-high-cost-drugs-rare-diseases-online-engagement.html [https://perma.cc/84ZT-8JAN] (archived Oct. 28, 2021); Khosla & Valdez, *supra* note 41, at 216.

79. *See* Su, *supra* note 39, at 788 (noting that while that Japanese drug prices are much higher, they are also spread across the nation's entire population since prescription drugs are covered by citizen insurance).

80. Khosla & Valdez, *supra* note 41, at 218.

81. *See* Shobita Dhar, *In New Rare Disease Policy, No Cover for Conditions That Cost the Most*, TIMES INDIA (Feb. 18, 2021, 11:15 IST), https://timesofindia.indiatimes.com/india/in-new-rare-disease-policy-no-cover-for-conditions-that-cost-the-most/articleshow/81084272.cms [https://perma.cc/FUA5-YNJD] (archived Oct. 28, 2021); *A Call for Global Action for Rare Diseases in Africa*, *supra* note 37.

2. Critiques of the Current Landscape and the Need to Emphasize Data

Despite their differences throughout the world, current approaches to rare diseases often focus on providing market protection to rare disease drugs to compensate for their small market size, but these approaches do little to decrease the high costs inhibiting the research necessary to bring rare disease drugs to market. As discussed above in regard to the American Orphan Drug Act, pharmaceutical companies may seek rare disease recognition with only minimal aid to the rare disease community,[82] and there are concerns that the system works to the advantage of pharmaceutical companies more than to patients with rare diseases.[83] The problem is not that the rare disease community is not seeing any results but instead whether they are seeing enough and how they can see more.

While grant funding helps, national rare disease plans do not prioritize efforts to decrease the disproportionate costs of rare disease research altogether. Alternatively, research-promoting programs like patient registries and other knowledge-sharing programs largely lack the global focus needed to correct for the limited number of patients that instigates the market failure—in the number of both data subjects and potential consumers.

Current scholarship focuses on the market failures of the current framework, attempting to make available treatments more affordable by balancing the Orphan Drug Act's incentive structure with the actual outcomes of driving up costs to the point of making the products unaffordable to the patient.[84] However, the legal scholarship largely ignores the remaining small data problem inherent to rare diseases. While legislation focused on market exclusivity can guarantee revenue and grant initiatives can offset some costs, less emphasis is placed on directly decreasing the significant costs associated with research—specifically, the costs associated with finding enough patients with a given rare disease, complying with each country's unique regulatory regime for drug research, and spending the time (up to decades) on these prerequisite tasks.[85] Improved data sharing efforts can therefore

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82. *See infra* Part II.A.1. (discussing criticisms of the U.S. Orphan Drug Act and the questionable relationship between orphan drug designations to benefits received by the rare disease community).

83. *See infra* Part II.A.1. (discussing criticisms that the U.S. Orphan Drug Act is being abused by pharmaceutical companies to create price protections for medications with primary non-orphan-designated uses).

84. *See, e.g.*, Cheryl L. Kozdrey, *Robbing the Cradle: The Implications of Depleting Financial Incentives for Orphan Drug Manufacturers and Imposing Stricter Research Guidelines for Rare Pediatric Diseases*, 55 CAL. W.L. REV. 387 (2019) (emphasizing the importance of and criticizing the current structure financial incentives in leading to orphan drug treatments).

85. *See supra* Part II.B. (discussing the challenges facing rare disease research that drive up costs).

decrease costs by drawing on a larger population of potential research participants while also diminishing the "small data" problem that is increasingly exasperated by the rise of black-box technology.[86]

3. Small Data, Precision Medicine, and the Need for Data Sharing

The small numbers of rare disease patients mean international data sharing is essential, as "[n]o single institution, laboratory, or even country is likely to encounter a sufficient number and diversity of patients with a given rare disease to be able to advance research alone."[87] While data-intensive technologies, including black-box technologies and artificial intelligence, are becoming increasingly useful in health-care-related industries and society at large, rare disease populations suffer from "small data."[88] For example, a study on alkaptonuria, a rare autosomal recessive disorder, used data from a 125-patient cohort recruited over almost two decades.[89] This limited sample size was the largest of alkaptonuria patients to date.[90] Thus, the data may not represent the entirety of the patient population and the statistical power of the data available may prove insufficient for use in decision-making.[91] While rare disease data is fragmented into many small datasets, "[m]aking these datasets interoperable for national and international collaborations could greatly speed up

86. In addition to practical benefits, data sharing itself can be seen as a fundamental human right and public good based on the theory that citizens providing their genomes for science have a right to benefit from that data as a fundamental right. Under that theory and with the emergence of the internet, the right expanded to encompass "a data-oriented interpretation" that includes access to scientific information. While "the human rights framework for the governance of science and genomic data has inherent limitations, especially in a transborder context and given the significant contribution to the field by non-state actors," a complimentary global public goods approach is supported by genetic researchers, from comments made in relation to the Human Genome Project in the 90s and early 2000s as well as by the World Medical Association at the 2016 Declaration of Taipei on Ethical Considerations Regarding Health Databases and Biobanks. While the idea of global public goods may not yet be realized and likely will not be realized soon due to the privacy concerns (amongst others), the movement towards making it a public good on a transcontinental scale is possible by creating a public marketplace for data that can be accessed by anyone. *See generally* Rumiana Yotova & Bartha M. Knoppers, *The Right to Benefit from Science and Its Implications for Genomic Data Sharing*, 31 EUR. J. INT'L J. 665 (2020).

87. Adrian Thorogood, *International Data Sharing and Rare Diseases: The Importance of Ethics and Patient Involvement*, INTECHOPEN 1, 3 (2020), http://dx.doi.org/10.5772/intechopen.91237 [https://perma.cc/F862-3M26] (archived Oct. 28, 2021) (discussing the significance of data sharing for rare diseases with examples of the data's use and role in machine-learning tools in rare disease healthcare).

88. *See* Aya A. Mitani & Sebastien Haneuse, *Small Data Challenges of Studying Rare Diseases*, JAMA NETWORK OPEN 1, 1 (2020).

89. *Id.*

90. *Id.*

91. *Id.*

progress towards a treatment for more rare diseases" by creating larger, more comprehensive data sets.[92]

Data sharing is of enhanced significance in the fields of genomics and genetics since genetic data provides sensitive and singularly identifiable information.[93] That significance is shared with rare diseases, as most rare diseases are genetic.[94] Since gene-based therapies have gained recent traction and prove promising for future uses, it is important to "find ways to reduce the time, costs, and risks associated with rare disease therapy development; only then will effective treatments be more likely to reach all patients in need."[95] Data sharing powers data-intensive medicine, like genomics, and has "long been a hallmark of genomic research," with funders and journals frequently requiring researchers to share data.[96] Various countries such as the United Kingdom, Australia, and France have implemented national genome projects, and the EU and international organizations have begun facilitating cross-border access to genomic and health data for the benefit of medical discovery.[97]

The emergence of precision medicine—a field powered by genomics and data-intensive medicine—may further complicate the current jurisprudential approach of market protections. Before addressing these complications, its important to first acknowledge that precision medicine is a promising field for rare diseases,[98] as its methods, such as DNA sequencing, provide personalized care that could help diagnose or treat individuals:

> The principles of "precision medicine" are those of rare disease medicine, and each has much to learn from the other. Both depend on effective multi-site networks that allow the study of patient cohorts that are geographically distributed, yet phenotyped, genotyped, and treated under harmonized procedures and data standards. Such networks require innovative ways of

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92. Kaufmann, Pariser, & Austin, *supra* note 26, at 6. Interoperability is a problem throughout medical research; however, it is often exasperated in rare disease research given the low numbers in any given data set makes interoperability a prerequisite or hurdle for research.

93. Thorogood, *surpa* note 87, at 1–2 (2020) ("Data sharing practice and policy has long been a hallmark of genomic research. Many health research funders and journals now require researchers to deposit sequence data in repositories or otherwise make data available to the broader research community.").

94. *See* Wakap, Lambert, Olry, Rodwell, Gueydan, Lanneau, Murphy, Cam, & Rath, *supra* note 8, at 168 (finding 71.9% of the rare diseases in the Orphanet Database to be genetic).

95. Kaufmann, Pariser, & Austin, *supra* note 26, at 3.

96. Thorogood, *surpa* note 87, at 1–2 (2020).

97. Yotova & Knoppers, *supra* note 86, at 667.

98. *See generally* Alex Garner, *Machine Learning in Rare Disease: Is the Future Here?*, PHARMALIVE (last visited Nov. 11, 2021), https://www.pharmalive.com/machine-learning-in-rare-disease-is-the-future-here/ [https://perma.cc/4RLM-XH6U] (archived Oct. 28, 2021) (discussing how machine-learning technologies can assist rare disease populations and the healthcare industry's focus on niche patient groups generally).

> accessing and sharing data across institutions, companies, and systems. They require innovative processes that avoid delays and waste due to bureaucratic redundancies, such as duplicative contract negotiations and IRB [institutional review board] reviews.[99]

Precision medicine is part of a larger trend in medicine towards personalized care, where providers craft and tailor treatments for each patient.[100] This trend has itself developed from the emergence of new technologies and the growing use of "black-box medicine"[101] as a manner of individualized decision-making and treatment in health care. While the rise of precision medicine shares similarities with rare disease research, the stakes remain higher for rare diseases for two reasons. First, other conditions may benefit from more effective treatments with precision medicine, while rare disease patients hope the same technology can discover *a* treatment. Second, precision medicine's use of black-box algorithms relies on large data sets from which patterns can be detected; if patients are not represented in the training data used to teach machine-learning technologies, the unrepresented patients can experience less accurate predictions and treatments from those technologies.[102]

Precision medicine also risks effecting the benefits of current rare disease initiatives. It will arguably change what qualifies as a rare

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99. Kaufmann, Pariser, & Austin, *supra* note 26, at 7.

100. Some clinicians would argue that they have always provided personalized care.

101. Brown, *supra* note 43, at 19–21. The label of "black-box" is taken from the terms used for artificial intelligence and machine learning technologies. Machine-learning methods have been implemented in AI research to recognize patterns in either supervised or unsupervised methods. Supervised algorithms use collections of data ("training" cases) to learn patterns between inputs and the resulting outputs so that the algorithm "learns" to create an output for the inputs of new cases. Alternatively, unsupervised algorithms find patterns in data sets; these algorithms are data intensive, requiring vast quantities of data previously unavailable with medical data. These machine-learning algorithms exist in varying degrees of opaqueness, sometimes being specifically designed by programmers to be "unknowable" by including factors in the final decision that the programmer did not specifically select. As these programs integrate both their own outputs and new data in learn-and-apply processes, the results become exponentially unknowable. For a concise description, see generally Glenn Cohen, *Informed Consent and Medical Artificial Intelligence: What to Tell the Patient?* 108 Geo. L.J. 1425 (2020).

102. *See* Raquel Dias & Ali Torkamani, *Artificial Intelligence in Clinical and Genomic Data*, 11 Genome Med. No. 70, at 9 (2019) http://doi.org/10.1186/s13073-019-0689-8 [https://perma.cc/JCC3-HUVP] (archived Oct. 29, 2021) ("Genetic risk prediction is also prone to unequal performance in different population groups because of underrepresentation in the training data.") (providing the example of DeepGestalt, which demonstrated notable differences accuracy for identifying the rare disorder Down syndrome in African vs. European ancestry individuals).

disease under the current legislative framework[103] since more common conditions could be subdivided into smaller categories and become legally classified as "rare." These conditions could then assume the financial benefits of orphan drug legislation, diluting the efficacy of current legislation.[104] Thus, rare diseases for which there are no therapies may not be able to rely on grant programs or intellectual property protections to make rare disease research feasible, when the current programs could be dedicated to or congested by precision measures aimed at perfecting the use of existing therapies for more common conditions. Because precision medicine trends are otherwise beneficial for both rare and common diseases, legislation should focus on advancing the trend through improving the available data necessary for precision initiatives. This improvement can be achieved through data sharing, but given that precision medicine may ride on the legislative framework of rare diseases, this sharing should be conducted purposefully to ensure rare disease participation and rare disease outcomes.

Data sharing is already presenting itself as a priority and a solution in the rare disease community, as discussed below.[105] New methods of data sharing that have emerged have already proven transformational in diagnosing rare diseases.[106] However, individual

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103. *Cf.* Lori Knowles, Westerly Luth, & Tania Bubela, *Paving the Road to Personalized Medicine: Recommendations on Regulatory, Intellectual Property and Reimbursement Challenges*, 4 J.L. & BIOSCIENCES 453, 496 (2017) (discussing differing views from how the Orphan Drug Act could inform and benefit precision medicine's entry into the market to how doing so could misappropriate the act's incentives).

104. *Cf.* Shannon Gibson & Barbara von Tigerstrom, *Orphan Drug Incentives in the Pharmacogenomic Context: Policy Responses in the Us and Canada*, 2 J.L. & BIOSCIENCES 263, 266 (2015) (supporting the need to reevaluate the Orphan Drug Act in light of the rise of pharmagenomics by noting the Obama administration's investment in precision medicine, a related trend); *see* Margaret Foster Riley, *An Unfulfilled Promise: Changes Needed to the Drug Approval Process to Make Personalized Medicine A Reality*, 70 FOOD & DRUG L.J. 289, 304–306 (2015) (discussing how the values of personalized medicine compare to of orphan drug legislation).

105. *See infra* Part III.B.

106. *See, e.g.*, Birte Zurek, Kornelia Ellwanger, Lisenka E. L. M. Vissers, Rebecca Schüle, Matthis Synofzik, Ana Töpf, Richarda M. de Voer, Steven Laurie, Leslie Matalonga, Christian Gilissen, Stephan Ossowski, Peter A. C. 't Hoen, Antonio Vitobello, Julia M. Schulze-Hentrich, Olaf Riess, Han G. Brunner, Anthony J. Brookes, Ana Rath, Gisèle Bonne, Gulcin Gumus, Alain Verloes, Nicoline Hoogerbrugge, Teresinha Evangelista, Tina Harmuth, Morris Swertz, Dylan Spalding, Alexander Hoischen, Sergi Beltran, Holm Graessner, & Solve-RD consortium, *Solve-RD: Systematic Pan-European Data Sharing and Collaborative Analysis to Solve Rare Diseases*, 29 EUR. J. HUM. GENETICS 1325 (2021); *see also International Data Sharing Project Aims to Improve Rare Disease Diagnostics*, CLINICALOMICS (June 1, 2021), https://www.clinicalomics.com/topics/molecular-dx-topic/genetic-disease-testing/international-data-sharing-project-aims-to-improve-rare-disease-diagnostics/ [https://perma.cc/2TZK-4WS7] (archived October 20, 2021) (reporting on the Solve-RD's first published results and describing its promise for data sharing in the rare disease space).

rare disease initiatives are fragmented and, though aimed at creating coherence, still silo rare disease research to itself rather than weaving it into the broader data sharing environments for large-scale medical research and society-wide machine-learning technologies. Rare diseases need to be represented in these more extensive data sharing programs to ensure they benefit from these new data sharing initiatives and have their data represented in widely-used data sets. Doing so will improve the data available for research and the representation of rare diseases in AI-based outcomes.

III. DATA TRUSTS

In order to create a tenable data sharing environment, international and transnational legal frameworks must recognize that national regulations inhibit data sharing to protect national values. Many countries disallow foreign researchers to recruit their citizens, especially if done without a domestic ethics committee's approval, and for these governments "compliance with research laws and regulations is non-negotiable and non-waivable by individual research participants."[107] Countries assert "economic and dignitary interests" in controlling their research and their population's genetic legacy, and history is marred with notorious incidents of international researchers' misconduct by which these states can justify their positions.[108]

Until states harmonize their standards, researchers are left in the untenable situation of trying to comply with every state's unique requirements.[109] These differences have typically led rare disease researchers to undertake a multi-site approach where each country in which a patient-recruit is located has its own independent collaborator(s) to meet that country's standards and ascertain a local research and ethics approval.[110] Consequently, compliance and ethics reviews for individual states "reach[] a point of diminishing returns and infeasibility."[111] In some instances where laws are silent, it is unclear whether the laws and regulations of the researcher's country or the participant's country apply, adding to the difficulty.[112] Because the rationales for national laws may involve "attempting to protect the

107. Mark A. Rothstein, Ma'n H. Zawati, & Bartha Maria Knoppers, *Regulatory Landscape of International Direct-to-Participant (DTP) Genomic Research: Time to Untie the Gordian Knot?*, 47 J.L. MED. & ETHICS 336, 337 (2019).

108. *Id.* at 337–38.

109. *Id.*

110. *Id.*

111. Mark A. Rothstein, Ma'n H. Zawati, Laura M. Beskow, Kathleen M. Brelsford, Kyle B. Brothers, Catherine M. Hammack-Aviran, James W. Hazel, Yann Joly, Michael Lang, Dimitri Patrinos, Andrea Saltzman, & Bartha Maria Knoppers, *Legal and Ethical Challenges of International Direct-toParticipant Genomic Research: Conclusions and Recommendations*, 47 J.L. MED & ETHICS 705, 717 (2019).

112. *See id.* at 338–40.

country's unique genetic resources from exploitation, to secure intellectual property rights or other benefits for the country of origin, or to safeguard the rights of sample donors, including privacy, once the samples leave the jurisdiction" conflicts in national approaches may be difficult to overcome.[113]

An increasingly popular method of data sharing is the data trust.[114] Data trusts have the benefit of allowing individual parties to retain control over the data they contribute to the trust, helping to alleviate the concerns of international data sharing. However, data trusts are a novel technical and legal instrument, and their legal implications and structure remain uncertain.

A. *Defining Data Trusts*

Like other forms of trusts that have been historically used to steward assets like land, data trusts serve a similar function for data.[115] Fiduciary trusts generally involve "contracts that give a trustee, or a group of trustees, authority to make decisions about how an asset—say, data—can be used on behalf of a group of people."[116] Data trusts are one method of establishing stewardship and governance over data based on a system of fiduciary duties.[117]

Data trusts can take on a variety of forms and purposes,[118] and their value stems from their flexibility to create a unique governance structure. Despite the flexibility, the governance framework is critical to their success as "[t]he way in which a data trust makes decisions is crucial to its legitimacy."[119] To balance interests and achieve trust among stakeholders, data trusts must design its governance structure to focus on shared objectives.[120] A successful governance structure will

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113. *Id.* at 340.

114. *See, e.g.*, Richard Milne, Annie Sorbie, & Mary Dixon-Woods, *What Can Data Trusts for Health Research Learn From Participatory Governance in Biobanks?*, J. MED. ETHICS, 2021, at 1, https://jme.bmj.com/content/early/2021/03/19/medethics-2020-107020 [https://perma.cc/H6AK-5VH6] (archived October 20, 2021) ("[T]he *data trust* model, which has become increasingly prominent in discussion about data governance for research" (emphasis added)).

115. Jack Hardinges, *What is a Data Trust?*, OPEN DATA INSTITUTE (July 10, 2018), https://theodi.org/article/what-is-a-data-trust/ [https://perma.cc/M8G5-3VU2] (archived October 19, 2021).

116. Bianca Wylie & Sean McDonald, *What is a Data Trust?*, CENTRE FOR INT'L GOVERNANCE INNOVATION (Oct. 9, 2018), https://www.cigionline.org/articles/what-data-trust/ [https://perma.cc/UP69-DL2K] (archived October 19, 2021); *see also* Milne, Sorbie, & Dixon-Woods, *supra* note 114, at 2.

117. Hardinges, *supra* note 115.

118. Artyushina, *supra* note 14 (providing examples of different data trusts already implemented).

119. QUEEN MARY UNIV. OF LONDON, PINSENT MASONS & BPE SOLICITORS, DATA TRUSTS: LEGAL AND GOVERNANCE CONSIDERATIONS 42 (Apr. 2019).

120. *Id.* at 8.

represent stakeholders in its management and have the oversight and assurance to ensure compliance with the trust's operating rules and the shifting regulatory environment.[121] All of this serves the governance structure's chief aim: trustworthiness.[122]

Data trusts, like other governance models, "seek to respond to the emerging challenges and vulnerabilities posed by rapid evolution in data technologies that extend (and often reimagine) what can be done with data, the appetite for data from different stakeholders, the twin problems of misuse and underuse of data, and the need to secure trustworthiness."[123] In doing so, they aim for data control to protect individuals while simultaneously widening the data available for research.[124]

A data trust's governance determines who has access to data and the terms of that access.[125] Most data is provided through open licenses or similarly permissive relationships.[126] Thus, the challenge of creating a data trust is in getting parties to reach agreement on the necessarily specific parameters of the parties' obligations and expectations, from the data trust's purpose to its structure.[127] While challenging, the act of creating the data trust can help researchers, governments, and other parties with varying interests to openly negotiate terms.[128] Efficient and meaningful ways of interest balancing are a priority with the increasing aggregation of sensitive personal data.[129] Data subjects, with vested civil rights in their data, gain collective bargaining power and leverage in a data trust framework.[130] Data trusts provide a "plural governance tool" to meet the "plurality of interests [affected] by data governance."[131] In doing so, they effectively navigate between the market's failure to impose good data practices on the one hand and countries' often overreaching attempts to govern the internet on the other.[132]

Data trusts can uniquely promote the public interest because they are built on a combination of independent stewardship and flexibility

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121. *Id.*
122. *Id.*
123. Milne, Sorbie, & Dixon-Woods, *supra* note 114, at 1.
124. *Id.*
125. Wylie & McDonald, *supra* note 116.
126. *Id.*
127. *Id.*
128. *See id.*
129. *See id.*
130. *Id.* ("Beyond providing the structure of fiduciary governance, data trusts can act as a way for data rights holders to aggregate and build leverage toward collectively bargaining for more balanced, publicly beneficial data relationships.").
131. *Id.*
132. *Id.*

in order to respect multiple interests;[133] however, the use of a trust does not itself provide security.[134] The choice to create a data trust "doesn't inherently create good governance . . . They are one piece of a larger governance puzzle, one that necessarily includes laws, policies, standards, rights and much more."[135] Part of the challenge of governing a data trust is the inconsistency and uncertainty surrounding the legal framework, structure, and obligation of trusts.

Keith Porcaro describes how the term "data trust" has "metastasized to become a catch-all brand for new data relationships, which may or may not implicate trust law or even trust-like relationships."[136] Untethered from the legal implication of its name,

> [d]ata trusts are used to describe data-sharing contract standards, to keep owners of a data analysis platform at arm's length, to encourage data sharing, to create friction in data sharing, to describe any fiduciary relationship that relates to data, to facilitate intra-institutional data sharing, to represent pooled interests in personal data, to provide alternate data processors, and so on. [137]

Despite the appeal of the term "data trust,"[138] Porcaro cautions use of the "'data trust' brand," for two reasons. Because data trusts do not yet have a "coherent underlying body of law," using the term "could lead users to expect a fiduciary relationship of a data trust where none is present, a set of rights that may not be available, or protections that may not be possible."[139] Additionally, legal trusts, as currently understood in the law, may not adequately support data protection since the ramifications of decision-making on how to use the data will likely extend beyond the data subjects within the trust.[140] Both of these faults in the legal terminology can damage the relationship with data subjects when subjects falsely expect duties owed to them and then cannot invoke those duties when their data is not properly protected. This legal uncertainty could lead to a rapid deterioration in public trust when a subject's data becomes vulnerable, at which point it is likely too late to revive that trust. Better mechanisms, such as those

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133. Milne, Sorbie, & Dixon-Woods, *supra* note 114, at 1–2 (referencing the UK government report, *Growing the Artificial Intelligence Industry in the UK* (Oct. 15, 2017), https://assets.
publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/652097/Growing_the_artificial_intelligence_industry_in_the_UK.pdf [https://perma.cc/9C4N-UDV4] (archived November 12, 2021)).

134. Wylie & McDonald, *supra* note 116.

135. *Id.*

136. Keith Porcaro, *In Trust, Data*, 105 MINN. L. REV. HEADNOTES 332, 333 (2021).

137. *Id.*

138. *Id.* at 334 ("The 'data trust' branding and logic have a simple appeal: to solve irresponsible uses of data, entrust data to someone who is legally required to be responsible for it. To build trust, use a trust.").

139. *Id.* at 334, 342–43.

140. *Id.* at 334.

discussed in Part IV below, are needed to communicate the legal relationships upfront and secure trust with data subjects.

Despite Porcaro's and other experts' warnings against the growing use of the term "data trust" in defining these legal relationships and growing consensus that "trust law is not an appropriate legal structure for data trusts,"[141] the term has grown in use with the predicted uncertainty in its application. For example, the same notions of stewardship and oversight have been achieved through designing contractual[142] or corporate[143] structures despite retaining the name "data trust."[144] Accordingly, data trusts cannot be currently understood as a single legal concept.[145]

Complicating this picture further, and perhaps in response to expert warnings about the term "data trust," are the use of related and overlapping terms to describe the current frameworks and their governance. Different sources label programs, technical structures, legal entities, and governance structures as data "trusts," "consortiums," and "federated"[146] systems. For example, the TRUSTS

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141. QUEEN MARY UNIV. OF LONDON, PINSENT MASONS & BPE SOLICITORS, *supra* note 119, at 8.

142. *Id.* at 14, 20 (based upon obligations in a written data-sharing agreement).

143. *Id.* at 15, 20 (where data is licensed or similarly provided to a separate corporate entity or partnership to manage).

144. *Id.* at 8.

145. Milne, Sorbie, & Dixon-Woods, *supra* note 114, at 2 ("The data trust model is not one thing, nor is it a single, rigid structure. For instance, in the UK, some envisage data trusts as operating within the legal framework of English trust law . . . Others have explored how different areas of law (eg, contract, commercial or charity law) might facilitate the aims of a data trust model or tended instead to 'take inspiration' from the model of beneficiaries . . . to formulate a code of governance that may establish a trust's social licence to operate. Further, a multiplicity of data trusts might exist, allowing data subjects to select the one that most closely aligns with their own goals.").

146. Data federations are "a type of meta-database made up of constituent databases that are transparently interconnected, but not merged–an important point for security and privacy concerns," allowing the original source and owner to continue to house and access it. WORLD ECON. FORUM, *White Paper, Global Data Access for Solving Rare Disease: A Health Economics Value Framework*, 5 (2020); Xplore Rare-X, *Wolrd Economic Forum Proof of Concept for Sharing Rare IDsease Data Across* Borders, RARE-X (Sep. 14, 2020), https://rare-x.org/blog/2020/09/14/wef-proof-of-concept-for-sharing-rare-disease-data-across-borders/ [https://perma.cc/WD2L-WG9R] (archived October 20, 2021). The created datasets are then usable by both domestic and foreign parties often through a consortium of partners and allow these parties to query across distributed data sets without requiring the movement of that data. *Breaking Barriers to Health Data Project*, WORLD ECON. FORUM (last visited Nov. 12, 2021), https://www.weforum.org/projects/breaking-barriers-to-health-data-project [https://perma.cc/AR3E-VS9W] (archived October 20, 2021). Many countries are prevented from sharing data despite a desire to do so because of concerns such as patient privacy, but federated data systems mitigate these concerns. Amanda Russo, *Proof of Concept for Sharing Rare Disease Data Across Borders is Crucial Step for Diagnoses*, WORLD ECON. FORUM (Jul. 30, 2020), https://www.weforum.org/press/2020/07/proof-of-concept-for-sharing-rare-disease-data-across-borders-crucial-step-for-

project (described below) identifies itself as a data "consortium" involving a "federated data ecosystem," but has been described by others, and perhaps can be inferred from the name, as a data trust.[147] Although used interchangeably, these terms vary in their meanings but largely work together to develop a successful data sharing framework: the legal entity of a data trust can be shaped to fiduciary relationships between the constituents within a data federation model, who may be joined as a consortium of partners.

B. *Case Studies of Data Sharing Initiatives*

A number of different data sharing programs have emerged in the past several years, implementing the use of data trust and federation models. While several of these have been specifically designed around data sharing for rare disease patients, the TRUSTS initiative in Europe is far broader and extends beyond health data alone. Each depicts a potential for data sharing, but as the data economy promotes the universal benefits of data sharing, rare diseases can harness the power of broader, emerging data sharing initiatives rather than relying on the current disjointed nature of rare disease programs alone.

1. Breaking Barriers to Health Data

Breaking Barriers to Health Data is a pilot health data consortium developed through the partnership of the World Economic Forum (WEF) and institutions in the United Kingdom, United States, Canada, and Australia. The framework aims "to support the effective and responsible use of federated data systems to advance rare disease diagnostic and treatment-related research"[148] by creating "a scalable governance framework."[149] The project's initial case study aims to share genomic data across borders.[150] The team produced a proof of concept that outlines how countries can come together, use preexisting

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diagnoses/#:~:text=The%20Breaking%20Barriers%20to%20Health%20Data%20project%20aims%20to%20craft,Forum's%20Health%20and%20Healthcare%20platform [https://perma.cc/8SQJ-6S7Y] (archived October 20, 2021). While they are being implemented in different sectors, they are particularly promising for accessing health and genomic data. *See, e.g.*, *Use Cases*, TRUSTS (Dec. 18, 2020), https://www.trusts-data.eu/use-cases/ [https://perma.cc/96U5-C9W7] (archived October 20, 2021) (describing how the test cases will focus on the financial sector).

147. *Compare* Artyushina, *supra* note 14, *with Operator Business Model Options in a Federated TRUSTS Data Ecosystem*, TRUSTS (Feb. 4, 2021), https://www.trusts-data.eu/operator-business-model-options-in-a-federated-trusts-data-ecosystem/ [https://perma.cc/D76N-SRAN] (archived October 20, 2021).

148. *Breaking Barriers to Health Data Project*, *supra* note 146.

149. Xplore Rare-X, *supra* note 146.

150. *Id.*

datasets of coded and de-identified patient information, and access other datasets across country borders with similar data types. Their report outlines the technological framework making the sharing possible while protecting the legal rights of the individuals involved, demonstrating that this level of data sharing is possible under a federation model.[151] Australia and Canada reached an agreement on how to deploy this proof of concept,[152] and the project lead at the WEF, Lynsey Chediak, said this project was a testament to the ability to overcome the "larger challenge" of forming the "necessary relationships between institutions that enable trust and transparency and sustained, predictable operations."[153]

The project first aims to enable all four countries to access each other's rare disease genomic data and will expand to other data types and jurisdictions.[154] It will also test whether federated systems can both overcome barriers to data sharing and support precision medicine by "reduc[ing] friction" amongst different types of institutions, sectors, and stakeholders, when sharing and transferring health data internationally.[155]

The project will produce three core outputs[156]: an economic analysis, a governance framework ("that enables cross-border queries between institutions in a federated system, while respecting and navigating key policies and regulations"), and a proof of concept on the functionality needed to run a federated data system.[157] The project has already published two papers on its lessons learned in building trust in a federated system[158] and an eight-step guide on sharing data in a federated data consortium model.[159] This guide counsels that data trusts must be designed with a consortium framework in order to build a governance system with the necessary relationships for trust as

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151. *Id.*
152. Russo, *supra* note 146.
153. *Id.*
154. *Breaking Barriers to Health Data Project*, *supra* note 146.
155. *Id.*
156. *Id.*
157. *Id.*
158. *See generally* WORLD ECON. FORUM, FEDERATED DATA SYSTEMS: BALANCING INNOVATION AND TRUST IN THE USE OF SENSITIVE DATA (2019), https://www3.weforum.org/docs/WEF_Federated_Data_Systems_2019.pdf [https://perma.cc/45FL-AHFH] (archived Oct. 19, 2021); WORLD ECON. FORUM, GLOBAL DATA ACCESS FOR SOLVING RARE DISEASE: A HEALTH ECONOMICS VALUE FRAMEWORK (2020), https://www3.weforum.org/docs/WEF_Global_Data_Access_for_Solving_Rare_Disease_Report_2020.pdf [https://perma.cc/L2MS-RX6G] (archived Oct. 19, 2021).
159. WORLD ECON. FORUM, Sharing Sensitive Health Data in a Federated Data Consortium Model: An Eight-Step Guide, Insight Report 23 (2020) [hereinafter *Sharing Sensitive Health Data*] http://www3.weforum.org/docs/WEF_Sharing_Sensitive_Health_Data_2020.pdf [https://perma.cc/9B4V-73S5] (archived Oct. 19, 2021).

discussed in Part IV. While the model is new, the reports' focus on providing future guidance indicates an expectation of similar projects. In the United States, the new nonprofit RARE-X is adopting a similar approach.[160]

The Breaking Barriers project will prove critical to determining the success of these governance models and data sharing systems in a cross-border program, but it remains constrained to the genomic data of rare disease patients at participating institutions alone.

2. Other Rare Disease Data Sharing Initiatives

When the EU undertook Horizon 2020 to fund initiatives to keep Europe innovative and competitive on the global stage, they initiated a variety of rare disease and data sharing initiatives.[161] One example of a Horizon 2020 initiative is Share4Rare, a European project with a mission to "[b]oost research in rare diseases through new knowledge generated from connecting patients, carers and researchers."[162] The Share4Rare platforms aims to overcome the low numbers and geographic barriers by promoting global patient involvement in advancing research.[163]

Horizon 2020 also created the European Joint Programme on Rare Diseases (EJP RD) that launched in January 2019.[164] With an over €100 million budget "to make sure that new treatments and diagnostic tools reach those who need them the most," EJP RD emphasizes "maximiz[ing] the potential of already funded tools and programmes by supporting them further, scaling up, linking, and adapting them to the needs of end-users through implementation tests in real

160. *See generally About Us*, RARE-X, (last visited Oct. 19, 2021), https://rare-x.org/about/ [https://perma.cc/M3MC-FPCH] (archived Oct. 19, 2021).

161. *See What is Horizon 2020?*, EUR. COMM'N (last visited Oct. 19, 2021), https://ec.europa.eu/programmes/horizon2020/en/what-horizon-2020 [https://perma.cc/MT4W-2ETG] (archived Oct. 19, 2021); *Rare diseases*, EUR. COMM'N (last visited Oct. 19, 2021), https://ec.europa.eu/health/non_communicable_diseases/rare_diseases_en [https://perma.cc/T4V8-HZTY] (archived Oct. 19, 2021).

162. *Our Story*, SHARE4RARE, (last updated Oct. 19, 2021, 9:25 AM), https://www.share4rare.org/our-story [https://perma.cc/7VJ6-THDM] (archived Oct. 19, 2021).

163. *Id.*

164. *Commission establishes €100 million partnership to boost research into rare diseases*, EUR. COMM'N, https://ec.europa.eu/info/news/commission-establishes-eu100-million-partnership-boost-research-rare-diseases-2018-dec-06_en (last updated Nov. 30, 2020) [https://perma.cc/59NT-LPJZ] (archived Oct. 19, 2021).

settings."[165] The program extends between 130 institutions in twenty-seven EU member states and eight other countries.[166]

One of its two objectives is "[t]o improve the integration, the efficacy, the production and the social impact of research on [rare diseases] through the development, demonstration and promotion of Europe/world-wide sharing of research and clinical data, materials, processes, knowledge and know-how."[167] By creating a "[c]ommon virtual platform for discoverable data and resources for [rare disease] research," EJP RD aims to tackle the fragmentation among the various methods and resources storing data.[168] It will accomplish this through extensive and compliant platforms (that can be queried through a central access point) and by researchers having the ability to deposit, share, and analyze data "in a harmonised, standardised manner."[169] As such, this platform will build and scale up current resources in a way that makes them more usable.[170] In the plans for its data ecosystem, users are set to play active roles in leadership and decision-making.[171]

The EU also has the EU RD platform "to provide interoperability for [rare disease] data collection and data sharing"[172] and to likewise overcome "the enormous fragmentation of rare disease (RD) patients[']' data contained in hundreds of registries across Europe."[173] The platform allows researchers to search rare disease registries to

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165. *Id.* (additionally noting that €55 million of the funding comes from Horizon 2020); Eur. Joint Program on Rare Diseases, *Periodic Reporting for Period 1 - EJP RD*, EUR. COMM'N (last updated Sept. 24, 2020), https://cordis.europa.eu/project/id/825575/reporting [https://perma.cc/L5G3-2H7F] (archived Oct. 19, 2021).

166. Thorogood, *supra* note 87, at 3 (other countries include Canada, Armenia, Georgia, Israel, Norway, Serbia, Switzerland and Turkey).

167. The second objective is "[t]o implement and further develop an efficient model of financial support for all types of research on RD (fundamental, clinical, epidemiological, social, economic, health service) coupled with accelerated exploitation of research results for benefit of patients." *About EJP RD*, EUR. JOINT PROGRAMME RARE DISEASES (last visited Oct. 19, 2021), https://www.ejprarediseases.org/index.php/about/ [https://perma.cc/825U-W24P] (archived Oct. 19, 2021) (emphasis removed). EJP RD is organized into five pillars: "Transversal and Communication," "Fundings and Calls," "Coordinated Access to Data and Services," "Training and Empowerment," and "Innovation and Clinical Trials Support."

168. ORPHANET, DEL 10.1 FIRST ANNUAL STRATEGIC REPORT AND ACTION PLAN FOR PILLAR 2 14 (2019), https://www.ejprarediseases.org/wp-content/uploads/2020/12/EJPRD_D10.1_First-Annual-Strategic-Report-Action-Plan-Pillar2_VF.pdf [https://perma.cc/QX46-DMKB] (archived Oct. 19, 2021).

169. *Id.*

170. *Id.* at 14.

171. *Id.* at 7.

172. EUROPEAN JOINT PROGRAMME RARE DISEASES, DEL 10.5 REPORT ON THE STATE OF THE ART OF EXISTING RESOURCES IN EUROPE 11 (2019).

173. Eur. Platform on Rare Disease Rsch., *Aim of the Platform*, EUR. COMM'N (last visited Oct. 19, 2021), https://eu-rd-platform.jrc.ec.europa.eu/aim-of-the-platform_en [https://perma.cc/8PTU-VKHC] (archived Oct. 19, 2021).

exponentially increase the use of registries' data.[174] In addition to supporting and creating current registries, the platform will create and require EU-level standards for data collection and exchange within the platform and make recommendations for data collection and sharing.[175]

The existence of the EU RD platform emphasizes the many efforts Europe has undergone to support rare disease communities, but it also emphasizes how disjointed, fragmented, and confusing these combinations of policies and resources have become even just within the European community. Thus, it stands to emphasize the need to have an operable system that consolidates resources and makes resources easily available and usable by researchers.[176]

Rare disease-specific genomic projects like Breaking Barriers and the Horizon 2020 programs, though, are limited to the rare disease populations providing data. With the rise of AI and black-box technologies, medical research can benefit from broader comparative metrics. Current disease-based programs are not enough since "[m]any valuable lines of research do not map to a constituency that can be organized around a single disease."[177] For example, individuals

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174. *Id.*

175. *See id.*; ORPHANET, *supra* note 168, at 4.

176. Some actions similarly aimed at connecting research and data across the world are occurring in the private sector without data federations, as with AllStripes (previously known as RDMD). AllStripes "aims to generate a rich, regulatory-grade biobank, database, and registry of patients with rare disease from across the United States (US) and internationally." To accomplish this, AllStripes "leverages the rights of patients in the US and in other countries to request access to their health records and biospecimens for onward transfer to [AllStripes]." AllStripes then enters partners "with pharmaceutical companies to accelerate their research into rare disease therapies." Thorogood, *supra* note 87, at 4. Their website lists 30 rare disease for which they are currently promoting research, as well as the option for individuals to "[j]umpstart [their] condition." ALLSTRIPES (last visited Oct. 19, 2021) https://www.allstripes.com/ [https://perma.cc/6L5N-N3EL] (archived Oct. 19, 2021). In February 2021, the company expanded from the U.S. and Canada to the U.K., allowing them to collect data from U.K. citizens and provide data for U.K. research. *AllStripes Announces Rare Disease Research Expansion into the United Kingdom*, BUS, WIRE (Feb. 20, 2021) https://www.businesswire.com/news/home/20210210005187/en/AllStripes-Announces-Rare-Disease-Research-Expansion-into-the-United-Kingdom [https://perma.cc/6EBU-H3XX] (archived Oct. 19, 2021). Similar models are used by other groups, including those in the voluntary sector, such as the Tuberous Sclerosis Alliance's Biosample Repository, which collects data from patients and grants use to approved research projects. *Biosample Repository*, TUBEROUS SCLEROSIS ALL. (last visited Oct. 19, 2021), https://www.tsalliance.
org/researchers/biosample-repository/ [https://perma.cc/8KC4-NZVS] (archived Oct. 19, 2021). The Tuberous Sclerosis Alliance is looking to expand this program with their international affiliates. Video interview with Gabrielle Rushing, Associate Director, Research, Tuberous Sclerosis Alliance (Mar. 12, 2021) (on file with author).

177. Amy L. McGuire, Mary A. Majumder, Angela G. Villanueva, Jessica Bardill, Juli M. Bollinger, Eric Boerwinkle, Tania Bubela, Patricia A. Deverka, Barbara J. Evans,

unaffected by a genomic variant typically attributed to a specific disease can nevertheless provide insight into that disease.[178] This has spurred large-scale genomic projects, but larger-scale cross-sector projects like TRUSTS also intend to interact with the same type of data.[179] As such, rare disease communities have an interest in broad data collection to harness the power of large-scale initiatives while promoting the distribution of data essential to researching their conditions.

Moreover, broader data sharing initiatives will make rare disease-specific initiatives less necessary. This effectively takes an inverted approach to the current problem; the data captured from an enlarged pool could power research into specific rare diseases. Currently health data is too narrow to capture a large enough population in any given rare disease for adequate research into that disease, so individual rare disease communities collect their own data for research in smaller, independent pools. Instead, broader data collecting initiatives enlarge the pool of data for all areas—necessarily capturing more rare disease patients as the entirety of the data pool enlarges—while also capturing the comparative data of other participants. This benefit allows rare disease groups to (a) benefit from comparison to and research on these larger samples outside of their community and (b) more effectively use their energy in bolstering data sharing initiatives, as they can promote initiatives that already exist for a broader audience within their community rather than having to create, maintain, and bolster simultaneously. And, by promoting the use of these programs for rare disease patients, specifically rare disease groups can (c) ensure that their interests and data are represented in cross-sectional studies.

3. The EU's Move toward Broad Data Trusts and Usable Data

In February 2020, the EU published a series of documents, indicating a transition into a new era of data usage: "European strategy for data" (Data Strategy), "Report on the safety and liability implications of Artificial Intelligence, the Internet of Things and robotics," and "White Paper on Artificial Intelligence—A European

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Nanibaa' A. Garrison, David Glazer, Melissa M. Goldstein, Henry T. Greely, Scott D. Kahn, Bartha M. Knoppers, Barbara A. Koenig, J. Mark Lambright, John E. Mattison, Christopher O'Donnell, Arti K. Rai, Laura L. Rodriguez, Tania Simoncelli, Sharon F. Terry, Adrian M. Thorogood, Michael S. Watson, John T. Wilbanks, & Robert Cook-Deegan, *Importance of Participant-Centricity and Trust for a Sustainable Medical Information Commons*, 47 J.L., MED. & ETHICS 15, 14 (2019).

178. *Id.* at 14–15.

179. *Id.* at 15.

approach to excellence and trust."[180] The Data Strategy discussed the purposes and strategy of a new framework adopted in August 2020.[181] While acknowledging that the EU has the technology, knowledge, and workforce to find success in the "data-agile economy," the European Commission noted that the United States and China's quick innovation is "projecting their concepts of data access and use around the globe."[182] The EU proposed its own vision to take a competitive place in the world, while both protecting individuals and benefitting from their data.

The EU aims to create a single European data market that can securely accommodate global data inputs of both personal and non-personal natures.[183] Users would then "have easy access to an almost infinite amount of high-quality industrial data, boosting growth and creating value."[184] With the General Data Protection Regulation (GDPR), Europe became a world leader in comprehensive data privacy legislation, taking a privacy-friendly approach based in the practice of balancing out risks with appropriate precautions.[185] This new data strategy thus heralds in a new era of data commodification to embrace the benefits of big data and AI and creates an international competitive advantage.[186] The data market would be subject to and require effective enforcement of EU laws and norms, including the GDPR; in turn, trust should increase, leading to more data stored and processed in the EU market.[187]

Identifying benefits to particular sectors of the EU's economy, the Commission acknowledged that for health data the GDPR failed to resolve fragmentation amongst member states.[188] The new strategy aims to "link and use, through secure, federated repositories, specific

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180. Eur. Comm'n, *White Paper On Artificial Intelligence - A European Approach to Excellence and Trust,* COM (2020) 65 final, Feb. 19, 2020, at 1; *Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions Concerning a European Strategy for Data,* COM (2020) 66 final, Feb. 19, 2020, at 1, 4; *Report from the Commission to the European Parliament, the Council, and the European Economic and Social Committee on the Safety and Liability Implications of Artificial Intelligence, the Internet of Things and Robotics,* COM (2020) 64 final, Feb. 19, 2020, at 1.

181. *Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions Concerning a European Strategy for Data,* COM (2020) 66 final, Feb. 19, 2020, at 1,4.

182. *Id.* at 3.

183. *Id.* at 4–5.

184. *Id.*

185. *See* Elizabeth Pike, *Defending Data: Toward Ethical Protections and Comprehensive Data Governance,* 69 EMORY L.J. 687, 716 (2020); Deliverable 6.2, TRUSTS (2020).

186. *See Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions Concerning a European Strategy for Data, supra* note 181, at 5.

187. *Id.* at 4–5.

188. *Id.* at 29.

kinds of health information, such as [electronic health records], genomic information (for at least 10 million people by 2025), and digital health images, in compliance with the GDPR."[189]

To achieve the EU's Data Strategy and situate the EU in a position to securely enable AI to process big data, the EU requires a trusted mechanism by which to share data across borders.[190] Currently, different national projects are working towards the Digital Single Market (discussed below), but these projects vary in scope (both in terms of their technology and their industries of focus).[191] Additionally, continental projects fail to address integration and interoperability of the national platforms.[192] Commercial data markets operated by private parties are generally not scalable.[193] Moreover, as more of these initiatives emerge, the diverging levels of technicality and quality as well as the different legal regimes that they prompt could decrease trust in data markets.[194]

Trusted Secure Data Sharing Space (TRUSTS) sets out to solve these problems and establish trust by developing a single European Data Market, as part of the European Digital Single Market (DSM strategy) adopted in May 2015. The DSM strategy is founded on the values of better digital access in Europe, fostering an equitable and nurturing environment for digital networks and innovation, and maximizing the digital economy's growth potential.[195] Despite the current focus on financial and corporate data, TRUSTS, if successful, will eventually operate for all data. When the EU initiated this project, they did so with an expectation that it would involve health data and be implemented in the health sector;[196] accordingly, this model may provide valuable insight into how to effectively build data trusts that can act as stewards of the legal and ethical obligations of databases.

The TRUSTS project's Deliverable 6, which lays out the legal and ethical implications of the project, emphasizes the legal uncertainty of the project. Despite approval and steps towards implementation, Deliverable 6 states that the project is still too abstract in its development "to determine data protection responsibilities in the data market ecosystem."[197] As discussed above, a data trust itself does not

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189. *Id.* at 30.

190. *Motivation & Objectives*, TRUSTS (Dec. 18, 2020), https://www.trusts-data.eu/motivation-objectives/ [https://perma.cc/RTH7-5QKD] (last visited Oct. 19, 2020).

191. *Id.*

192. *Id.*

193. *Id.*

194. *Id.*

195. *Id.*

196. *See generally Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions Concerning a European Strategy for Data*, *supra* note 181.

197. Ducuing, Dutkiewicz, & Miadzvetskaya, *supra* note 15, at 26.

have a clear legal structure but an interrelated network of duties and responsibilities owed between parties. Thus, the project, like any data trust, faces uncertainty in the legal ecosystem it will inhabit and the legal form it will take.[198] The guidance further acknowledged the complexities caused by the overlapping intersection of privacy (GDPR),[199] contract, financial and blockchain, and competition law and regulation present in widespread data collection, sharing, and use.[200]

TRUSTS and Breaking Barriers together demonstrate the global movement toward data federations, yet Horizon 2020's approach to rare diseases suggests that these data federations are not being sufficiently considered as a solution to the obstacles to rare disease research. Moreover, if these data federations evolve without considering their use or implication on rare disease populations, the norms that are established could result in research conditions that comparatively harm rare disease research. Instead, a data trust should be established with consideration of rare diseases that can both serve to benefit the rare disease community and help establish norms of inclusivity and trustworthiness moving forward.

IV. PROMOTING RESEARCH AND BUILDING TRUST

While there are no rigid legal structures surrounding the creation and use of data trusts, a fundamental agreement to adhere to fiduciary duties underlies all data trusts. Thus, no matter how data trusts develop within the law, their governance structure—from which these duties extend—will be key to adapting to their legal landscape. As governance structures are charged with crafting systems of adherence to the legal requirements of data sharing operations, the changing atmosphere of data and data trust law will require a responsive governance structure. Fundamental to such a structure's success, though, is the public trust and confidence in the data trust's adherence to data protection measures and individual countries' expectations, laws, and regulations around consent and privacy. Burgeoning data trusts must evoke the public support required for success.

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198. The TRUSTS project's Deliverable 6, which lays out the legal and ethical implication of the project, based its reasoning on "Version 1.0" of drafted guidance from the European Data Protection Board. *See id.* at 23, 26. However, there remains two major problems with planning for the legal outcomes of the TRUST. First, while the guidelines "are likely to be decisive in the decision-making practice of data protection authorities, and may also be endorsed (fully or in parts) by Courts," they are still only soft law instruments and thus lead to the inherent uncertainty present in planning a data trust. *Id.* at 23.

199. For example, Deliverable 6 expresses that determining who is a data controller and allocating data protection responsibilities will involve analyzing control of data processing activities and accounting for the evolving case law of the Court of Justice of the European Union. *See id.* at 26.

200. *See id.* at 98–99.

This Note proposes that broad-ranging data trusts like TRUSTS should include rare disease advocates in their governance structure. In an environment of high legal uncertainty, strong governance is essential to maintain compliance with changing laws and guidance as well as to secure the public trust that will legitimize the data trust, drive its use and, therefore, determine its success. Rare disease representation in governance can provide insight into public interest balancing, leading to public buy-in.

Simultaneously, broader acceptance of data sharing generally promotes the data sharing needs of the rare disease community, and the rare disease community should actively support initiatives like TRUSTS that promote cross-border data sharing for a wide range of data types and uses. The emergence of these data sharing systems will address the problems of current legislation. Data sharing, particularly with cross-border foci, decreases the extensive costs of rare disease research, which may be exacerbated when current state-funded grants equally apply to precision medicine. Broad-scale data trust models avoid fragmentation of design in rare disease-specific programs, improve cross-referencing in black-box models, and integrate precision medicine and rare disease insights while ensuring that rare disease groups are represented in the data. In this way, data trusts and rare disease communities provide a solution for one another: rare disease populations benefit from building trust in a project that promotes sharing their data, while the data trust receives essential public confidence.

Public confidence will be determined by how data trusts organize their governance, so they need governance systems that are inclusive of participant and community views and responsive to stakeholders' needs. According to a study of medical information commons, the two features that determined these commons' success were orientation around the data subjects (the intended beneficiaries) and the trustworthiness of the system.[201] A focus on the individuals involved in data sharing and trust are themes repeated throughout the literature, whether specific to medicine or not. To be successful, data trusts will require patient centricity and trust, both of which can be provided through incorporating the voices of the rare disease community. By incorporating their voices, rare disease communities will benefit from ensuring their representation in these large-scale data sets intended to impact greater society, allowing them to influence how their data is accessed and used and verifying that minority groups

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201. Which they "define as networked environments in which diverse sources of data on large populations become broadly available for research use and clinical applications, and which include the collection of many different common pool resources." *See Importance of Participant-Centricity and Trust for a Sustainable Medical Information Commons*, *supra* note 177, at 12.

experience the benefits from the data they provide. Their representation will also guide data trust formation in a trustworthy direction, building systems of data sharing in which rare disease patients feel comfortable participating.

A. *Patient–Participant Centricity*

The patient centricity that guides healthcare data sharing is intended to promote public participation, which will be equally important in the development of trustworthy systems given the legal uncertainty of data trusts. Patient centricity can thus be analogized from the medical literature to provide guidance as to the importance of participant engagement in multi-sector data trusts (participant centricity). Moreover, participating data subjects must continue to be viewed as patients, despite a multi-sector approach, due to the sensitivity of the health data involved; therefore, a patient-centric approach is also necessary to preserve the patient protections.

Like a medical information commons, a data trust's effectiveness can be judged on "its ability to meet the needs of the people it is supposed to serve."[202] The design of the data trust must align not only with needs and functions of academic research institutions, commercial labs, and other parties but also with the best interest of the data subjects.[203] Indeed, as discussed above, the values of participatory governance are part of data trusts' distinctive characteristics.[204]

Patient centricity involves methods of empowering data participants through involvement in the research process with control over their data and engagement "in a reciprocal partnership with researchers."[205] Doing so respects "participants *as* persons with a voluntary, continuous role in decision-making, versus human subjects who are only engaged during the consent process, or sets of data points without interest or concern for how the data are used or analyzed."[206] Stakeholders' voices must be meaningfully included to align their values and investment in the data trust.[207] Patient centricity also involves the recognition and mitigation of risks to participants, the protection of patient privacy, and the respect of patients' sense of community.[208] Thus, "participant-centricity has a robust ethical and

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202. *Id.* at 13.

203. *Cf. Importance of Participant-Centricity and Trust for a Sustainable Medical Information Commons*, *supra* note 177, at 13.

204. *See supra* Part II.A.

205. *See Importance of Participant-Centricity and Trust for a Sustainable Medical Information Commons*, *supra* note 177, at 13.

206. *Id.* at 13–14.

207. *See id.* at 14.

208. *See generally* Thorogood, *surpa* note 87.

pragmatic policy justification and is critical for commons sustainability."[209]

Current systems exhibit a wide range of participation and respect for participants' engagement.[210] Many current systems, though, are outdated, being designed prior to the era of individual control over data or mass privacy breaches.[211] Participant-centric design must not be marginalized but central and visible.[212] A primary method of participant centricity is embedding stakeholders meaningfully in the governance of a common resource.[213] This role should be ongoing and dynamic, include voting rights, and recognize diversity. While patient centricity comes with its share of difficulties, it is both reliant on and essential to trust in the data sharing system and can be achieved through rare disease representation.[214] In a study laying out these values for participant centricity, rare disease groups were among the most active advocates and engaged participants when given the opportunity.[215]

Patient-centricity helps promote a sense of control and, therefore, confidence in the use of data. As a result, it is linked to the other success factor: public trust.

B. *Trustworthiness*

To last, data sharing systems must be trustworthy. In this context, trust can be understood as "the willingness of a trustor to accept the potential risks involved in the sharing and further use of their personal data resulting from both optimism about the trustees' goodwill and interest in the public good."[216] Moreover, it is essential that trust is built into the system upfront as it is difficult to restore once lost.[217]

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209. *Importance of Participant-Centricity and Trust for a Sustainable Medical Information Commons, supra* note 177, at 15.

210. *See id.*

211. *See id.*

212. *See id.*

213. *See id.* at 14.

214. *Cf. Importance of Participant-Centricity and Trust for a Sustainable Medical Information Commons, supra* note 177, at 16–17 ("Perhaps one of the most important things we have learned from our work about participant-centricity is that if the rhetoric of reciprocal relationship (or participant empowerment, partnership, or engagement) is not matched by performance, distrust will result. One or a few instances of misuse of data or exploitation of participants have the potential to create skepticism or outright hostility toward the entire enterprise of building an MIC. For an MIC to be successful, it must be trustworthy.").

215. *Id.* at 14

216. *Importance of Participant-Centricity and Trust for a Sustainable Medical Information Commons, supra* note 177, at 17 (citation omitted).

217. *See id.*

Patient centricity is a first step in building trust.[218] Often, trust is thought of as nothing more than informed consent. It must, however, extend beyond consent to engage participants in the governance of the data sharing system as a demonstration of "respect for the values and priorities of participants" and a means of "emphasiz[ing] the good intentions of other stakeholders involved in building and maintaining" the system.[219]

To be trustworthy, governance must be transparent and accountable.[220] Transparency is widely regarded as both a moral obligation as well as a principle of responsible data sharing.[221] Additionally, transparency improves the recruitment of participants and their willingness to extend access to sensitive data. Transparency can involve open communication but can be improved through "engaged communication that builds relationships and forms collaborations."[222] This communication should cover "how data are being used (or not) and why, how the commons is governed, what security mechanisms are in place, when data breaches occur, and how data breaches are being dealt with."[223]

Accountability requires "[a] more robust system," including "sanctions for misuse."[224] The accountability for data misuse varies across the world. By creating cross-border data trusts that must adhere to the stricter requirements of more protective countries, cross-border trusts can raise the expectation for security across the board by demonstrating the possibility of higher levels of protection and exemplifying protective norms. For data trusts like TRUST, the EU's regulations provide significant, arguably difficult, standards for research adherence on accountability.[225] Data sharing faces significant legal obstacles because personal data may be identifiable to an individual who has a right to privacy and who, by use of the data, may have other fundamental rights infringed upon, such as non-discrimination.[226] Thus, the data trusts must "ensure that data

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218. *See id.*

219. *See id.*

220. QUEEN MARY UNIV. OF LONDON, PINSENT MASONS & BPE SOLICITORS, *supra* note 119, at 42. For MICs, trustworthiness relied on the factors of transparency, data access, security, and accountability. Data access and security are important points of focus for responsible governance but may not be solved through the structure and participants in the governance system itself. For example, data security primarily poses a technical challenge. *Importance of Participant-Centricity and Trust for a Sustainable Medical Information Commons*, *supra* note 177, at 18.

221. *See Importance of Participant-Centricity and Trust for a Sustainable Medical Information Commons*, *supra* note 177, at 17.

222. *Id.*

223. *Id.*

224. *Id.* at 18.

225. *See id.*

226. *See* QUEEN MARY UNIV. OF LONDON, PINSENT MASONS & BPE SOLICITORS, *supra* note 119, at 10.

sharing does not infringe those rights."[227] Usually, data sharing can avoid interfering with these rights with certain protections set in place by the data trust's system of governance.[228] Additionally, EU data protection laws significantly constrain data sharing,[229] and as the governance body is ultimately responsible for creating an entity that conforms to the laws, the body's development of a legal compliance program also goes directly to the protection of individuals' fundamental rights.

The trustworthiness of data trusts is multifaceted: data providers must entrust responsibility with stewards, users must entrust stewards with maintaining the integrity of the data, and the public must trust the parties developing the data trust for it to progress.[230] All of these trust relationships revolve around trustworthy governance.

C. *Building Trust through Good Governance*

Trust can be built through governance structures. Just as data trusts provide the flexibility in governance to create a mechanism for trustworthiness, so too will good governance of that data trust "engender a sense of trustworthiness and therefore has the power to 'make or break' any data trust."[231]

The governance structure does not have to be strictly defined for every data trust nor should it be, as preserving flexibility is key to the success of data trusts and the ability of their various stakeholders to negotiate and unify around common values. The consortium structure provides flexibility in bringing various parties together to "create and encourage a cohesive, symbiotic relationship between institutions with otherwise differing models of consent, operations, security and technology."[232] These relationships of trust between institutions prove both necessary and challenging—but feasible.[233] While creating a consortium can be a laborious process of negotiating to create a clear governance model, a well-functioning end product allows for data access and use maximization.[234] In its guidance on how to create a strong consortium data sharing structure (resulting from the Breaking Barriers Project), the WEF states:

> The first step, and the singular component that appears to make or break a federated data consortium, is establishing trust with identified prospective

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227. *Id.*
228. *See id.*
229. *Id.*
230. *See id.* at 42.
231. *Id.*
232. *Sharing Sensitive Health Data*, *supra* note 159, at 23.
233. *See id.* at 5.
234. *See id.* at 23; *see also* WORLD ECON. FORUM, *supra* note 146, at 23.

> partners entering a data consortium. Establishing trust between partners is also the most time-consuming component in establishing a successful data consortium. . . . [D]espite many technical solutions designed to encourage trustworthy behaviour between data-sharing partners once a consortium is up and running, establishing trust at the beginning of the relationship is nevertheless contingent on our everyday social structures and perceived social relationships.[235]

Including diverse interests from various stakeholders in governance cannot guarantee fair decisions as "data trusts and the principles of participatory governance that inform them are not inherently just" but "require careful design and operationalisation."[236] The nature of participatory governance amongst different data trusts will change as it is crafted to its specific stakeholders and objectives.[237] Nevertheless, participation must be initiated during the planning phase of the trust.[238]

First, upstream deliberative approaches can effectively bring together the shared values of the different stakeholders when setting the terms of the trust.[239] These consultations should occur during the process of establishing the trust "to establish legitimacy and public trust" from the onset.[240] Moreover, as these consultations would set the terms of the trust, they would also determine how patient voices would be incorporated and heard in governance moving forward.

Some trusts have held these as public consultations on features of the trust but have failed to meaningfully involve members on issues they value.[241] However, not formalizing these roles into the governance structure risks their impact on decision-making being lessened or seen as lessened, thereby decreasing the trustworthiness they intend to foster. Consequently, any such panels must have clear roles, an obvious impact on decision-making, and set aside the time and expense that reflects that.[242]

Large-scale data trusts like TRUSTS blur the distinction between participant and community input since these trusts are formed around the idea that most members of the community (or at least a diverse and representative number of community members) will also be participants. Thus, there will be less of a gap between the security interests of participants and the public interest. Nevertheless, data trusts of all fashion must balance these interests and may need to

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235. *Sharing Sensitive Health Data, supra* note 159, at 6.

236. *See* Milne, Sorbie, & Dixon-Woods, *supra* note 114, at 4.

237. *See id.*

238. *See id.* at 1 (extrapolating lesson from the participatory governance of biobanks to the use of data trusts for health research).

239. *See id.* at 3.

240. *Id.* at 2.

241. *See id.* at 2–3.

242. *See id.* at 4–5.

change their representation by issue if they cannot find a group that already significantly values both perspectives.[243] For these broad-reaching programs, the representation of minority perspectives becomes more significant.

Participation relies on representative voices, and for projects like TRUSTS that involve various sectors and countries, representation will need to include individuals with a stake in specific sectors. The health sector must be among these as it involves some of an individual's most sensitive data. The rare disease community already works on the local and global scale, is invested in the success of data sharing, demands security in data sharing, and is a vocal advocate for the individuals it represents.[244] Rare disease advocates represent individually weak minority communities but combine for significant engagement.

D. *The Role for Rare Disease Populations*

Rare diseases are at the heart of the strongest participant-led programs.[245] If rare disease communities can view broad data sharing programs as in their interest, then their high levels of interaction and participation could prove significant in developing strong, active participant engagement in the governance structures of data trusts. Rare disease groups can address the two significant factors of transparency and accountability discussed above. The active communities of rare disease patient and caregivers thrive in communicative and social settings and can harness that communication to improve transparency. Rare disease groups are also zealous advocates and could help prompt legislators to adopt methods of accountability.

1. Being Heard

Whatever manner or method participation takes, it must be meaningful and should not devolve into "a tokenistic quick fix that neither enables genuine deliberation nor facilitates genuine involvement."[246] Because the rare disease community has limited resources, is familiar with having to self-advocate to be heard, and

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243. *Id.* Furthermore, ongoing evaluation is necessary in any participation method.

244. *See id.* at 3 (noting that "it is important to consider who should be included at this stage—particularly in a context where people may have roles as patients, citizens consumers or advocates—and how this may influence discussions and outcomes.").

245. *Importance of Participant-Centricity and Trust for a Sustainable Medical Information Commons*, *supra* note 177, at 14 ("To date, most of the strongest participant-driven projects focus on cancer or rare, often inherited, diseases.").

246. *See* Milne, Sorbie, & Dixon-Woods, *supra* note 114, at 3.

because it has made progress in advancing rare-disease specific initiatives, it is less likely it would continue to lend support to an initiative if its needs were going unanswered and voices were going unheard.

2. Hesitancy toward Data Sharing

The hesitancy toward data sharing will inevitably decrease trust from the outset. The literature on global data sharing, particularly in the context of public health, frequently ignores popular attitudes toward international data sharing. However, the public resistance to cross-border data sharing could upend international collaborations.[247] A review of public attitudes toward sharing genomic data suggests that further research is needed to determine the source of this reluctance, though potential factors include nationalism and economic competitiveness.[248] Additionally, concerns about the use or exploitation of data may also lead to resistance, particularly for poorer countries or those with indigenous populations or populations who fear they will not reap the benefits of providing their data.[249]

To solve this public reluctance, governance models must promote the system's trustworthiness through patient centricity. Doing so will require representatives that have the necessary buy-in to fight for the data sharing project's success despite the general hesitancy. The rare disease population provides a group that both equally needs the success of data sharing measures and faces significant harm from these public concerns about data sharing. But rare disease patients, while recognizing and sharing the public's same fears, embrace data sharing initiatives.

Rare disease populations find that "the hope and promises associated with developments in technologies have often been slow to translate into clinical outcomes, and that while there might be scientific merit, patient communities have often not experienced any benefit," with some in the rare disease population even feeling exploited.[250] Engagement comes at the further risk of

247. Mary A. Majumder, Robert Cook-Deegan, & Amy L. McGuire, *Beyond Our Borders? Public Resistance to Global Genomic Data Sharing*, 14 PLOS BIO., no. 11, 2016, at 1.

248. While "investment in biomedical research is often promoted as an engine of national economic growth and competitive advantage," cooperation can be equally if not more so significant in creating a competitive edge. *Id.* at 5.

249. *Id.*

250. *See* Sandra Courbier, Rebecca Dimond, & Virginie Bros-Facer, *Share and Protect our Health Data: An Evidence Based Approach to Rare Disease Patients' Pespectives on Data Sharing and Data Protection—Quantitative Survey and Recommendations*, 14 ORPHANET J. RARE DISEASES, no. 175, Jul. 12, 2019, at 2, https://ojrd.biomedcentral.com/track/pdf/10.1186/s13023-019-1123-4.pdf [https://perma.cc/6P3F-4UZA] (archived Oct. 13, 2021).

reidentification,[251] a higher risk for people whose condition inherently makes them part of a small group. Rare disease patients remain concerned about data security and misuse, as well as "their vulnerability associated with having a rare disease and that knowledge generated through genomic developments and data sharing could lead to their discrimination."[252]

Nevertheless, compared with the general public, rare disease patients and representatives are more willing to share data, regardless of their disease severity, demographic, their perceived sensitivity of the data, and the potential for international data sharing.[253] Rare disease patients are increasingly engaged in data sharing to generate knowledge in hopes of progressing research toward diagnoses or treatments, but they do so with an expectation of transparent and ongoing communication.[254] In a recent study, rare disease patients "widely support data sharing if done in the interest of rare disease patients."[255] The study demonstrated that this willingness extends to sharing data beyond the medical field.[256]

However, this willingness comes with expectations of control over how and why the data is shared, transparency, communication, and the minimization of risks. [257] These requirements run parallel to the same values of strong governance. Moreover, rare disease patients' trust in data sharing depends on the organization that handles the information. Seventy-seven percent of patients have high confidence in their patient organizations.[258] Because patient representatives would likely be identified for governance involvement from these already-established patient advocacy groups, they already engender trust in the rare disease community. Since patient trust in other groups is low (such as the private pharmaceutical industry receiving 50 percent opposition to data sharing and insurance companies receiving 80 percent opposition), broad sharing initiatives would need these positive representations of trust to offset the loss of trust from others' access.[259] Thus, rare disease patients will promote the success of the data trust as members of its governance structure while also requiring that it

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251. Reidentification refers to the process of using data to trace back to the individual to whom the data applies. It is usually used in a negative context for the insufficiencies of anonymized data that is actually identifiable and the risks posed by that identification and linking that specific data to the individual.

252. Courbier, Dimond & Bros-Facer, *supra* note 250, at 4.

253. *Id.* at 11.

254. *Id.* at 2, 13.

255. *Id.* at 6.

256. *Id.* at 6. Notably, though, "respondents from countries belonging to the European Union are less favourable (50% compared to 60% outside the EU) to share data for non-medical purposes."

257. *Id.* at 4.

258. *Id.* at 9.

259. *See id.* at 9.

meets the obligations to users that will instill trust and patient centricity.

3. Active and Engaged Participation

Mere interest in data sharing is not enough. Governance requires formal investment and an advocacy role for the interests of the data subjects. These are both hallmarks of the rare disease community. Rare disease populations are more than just patient groups; they are active, social communities. From the active patient community that successfully pushed for the Orphan Drug Act to engaged rare disease Facebook groups today, rare disease communities are their own strongest asset and should be better leveraged to further research. Rare disease advocacy, affinity, and support groups and organizations support rare disease patients and caregivers with fundraising for research and development, educational programs and resources, and patient recruitment for clinical trials.[260] Recently, these advocacy groups have shifted toward partnering with private sector companies in the name of research.[261] In doing so, they have taken a step toward active participation in not only fundraising, advocacy, and educational initiatives, but also in research and drug development.[262]

Patient communities are critical to "elevating the patient voice and partnering in the development of programs to address the needs of patients with rare diseases."[263] What the rare disease community lacks in population size, it supplements with active participation. Not only would this social community allow for easy communication about data federations, which can build both early political support and adoption, but it will help to build the much-needed public trust that data federations rely upon for long-term participation and success.[264]

The active social media presence of rare disease communities can be harnessed to help data federations communicate with the power of direct-to-consumer initiatives that have expedited recruitment in rare disease research.[265] One study on two rare diseases (Fontan-associated PLE and PB) "resulted in the largest reported contemporary cohort of Fontan patients and patients who have PLE and PB" in only one year

260. Brown, *supra* note 43, at 19.

261. *Id.*

262. *See id.*

263. Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 2.

264. *See generally Importance of Participant-Centricity and Trust for a Sustainable Medical Information Commons*, *supra* note 177, at 12–13 (discussing how a focus on patients and trust can be implemented in and benefit a medical data commons).

265. *See* Kurt R. Schumacher, Kathleen A. Stringer, Janet E. Donohue, Sunkyung Yu, Ashley Shaver, Regine L. Caruthers, Brian J. Zikmund-Fisher, Carlen Fifer, Caren Goldberg, & Mark W. Russell, *Social Media Methods for Studying Rare Diseases*, 133 PEDIATRICS 1345, 1350–52 (2014).

and with minimal expense.[266] That study found that "[p]atient-run, disease-specific communities were a major asset in recruiting" by sharing their participation throughout the patient community and allowing the study recruitment to "[go] viral" within their rare disease cohort.[267] It did so without the usual regard for geographic boundaries.[268] Additionally, younger rare disease community members are more open to receiving feedback on data sharing on a mobile app, indicating a potential future in less formal feedback structures for data sharing platforms that could harness the energy of rare disease social media networks. Thus, global participation in data trusts can and will follow through the natural and trusted communication platforms of rare disease communities.

4. Advocates of Needed Legal Structure

Part of the difficulty in forming a data trust is the legal uncertainty. Rare disease groups are active lobbyists and are well-positioned to support measures to make international trusts more effective from within participating countries by pushing for the legislative and regulatory guidance needed for effective data trust planning and use.

Patient advocacy groups already play important roles around the world in driving political action for rare diseases, and in countries with or without budding rare disease legislation, they may be the sole mover in the rare disease space.[269] For example, in Argentina, the Pituitary Diseases Association educates professionals, traveling throughout the country to provide trainings and medical updates.[270] Similarly, the China Alliance for Rare Disease Prevention and Treatment created "the first ever national research program of prevention and treatment for rare diseases."[271] These examples demonstrate how "patient advocacy organizations can drive successful implementation of programs that can help support the key needs of rare disease patients" regardless of national policies or support.[272] In some countries like Mexico, these groups already actively work with their national health

266. *Id.* at 1352.
267. *Id.* at 1351
268. *See id.*
269. Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 11 (These groups "[provide] leadership in addressing gaps and implementing programs to support key needs within the community."); Courbier, Dimond, & Bros-Facer, *supra* note 250, at 2 ("The role of patient communities has been well documented in raising awareness of little known medical conditions and campaigning for access to research funding and healthcare resources.").
270. *See* Dharssi, Wong-Rieger, Harold, & Terry, *supra* note 8, at 11.
271. *Id.*
272. *See id.*

commissions.[273] Additionally, patient communities are integral to the implementation and adoption of national rare disease plans and their programs.[274] For example, the Canadian Organization for Rare Disorders was instrumental in the strategic development and implementation of the Canadian NRDP, and the EUROPLAN actively incorporates patient input into their work.[275] Based upon the success of EUROPLAN, other countries have in turn included a patient-oriented consultation process.[276]

As the law begins to reform in response to the emerging data economy, rare disease groups invested in data sharing can act as advocates for the interests of data trusts to drive meaningful legislative and regulatory change. Reform of trust law to appropriately govern data trusts would be difficult and is likely unnecessary because of contract, corporate, and other forms of law that can work together to create data trusts in other structures.[277] Nevertheless, the uncertainty of sharing personal data under different consent structures could be reduced with regulatory guidance on how current data protection laws apply to data trusts. In turn, confidence will grow in data trusts that more clearly meet the expected requirements of the law for the protection of individuals' data.[278]

To make the meaningful difference in rare disease research, countries involved in international data trusts must extend beyond the European nations already embracing data trusts. Extending beyond the EU creates immediate tensions. As noted by the EU's Data Strategy, other states like the United States and China have very different views on data governance, and as evidenced by the current problems in rare disease research, a wide variance of standards for recruitment, privacy, and consent exist around the world. Nevertheless, these discrepancies are necessary points of negotiation for any data sharing and particularly to achieve the population size necessary for rare disease research.

While compromises would need to be made for a transnational data federation model, this approach need not replace nations' domestic rare disease frameworks and, instead, will make them more effective. Indeed, in addition to pushing for further guidance on current laws, rare disease groups can and should petition for shared standards to be adopted into countries' orphan drug legislation. Because one of the primary legal flaws is the infeasibility and cost of getting approval for research in every country where one might find a willing research

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273. *See id.*
274. *See generally id.*
275. *Id.*
276. *Id.*
277. *See* QUEEN MARY UNIV. OF LONDON, PINSENT MASONS & BPE SOLICITORS, *supra* note 119, at 58.
278. *Id.* at 8.

participant, transnational efforts are required to bring the legal requirements of independent countries into accord. As data federations are shared government structures, they are thus optimal for rare disease research since they can meet multiple countries' regulations and norms through multinational cooperation on standards used in the data federation. When data trusts are responsibly used and governed with rare disease representation, countries should allow the agreed-upon consent standards to be woven into the research and drug approval processes of the cooperating nations (such as through their orphan drug legislation). In doing so, they ensure that researchers need only meet one set of compliance standards and that the benefits (in the forms of therapies) are returned to the patients who provided their information for research. This is not to say every country will have to change the way they approach drug regulation. Instead, it will recognize that rare disease populations require flexibility in treatments beyond that of other pharmaceuticals—a fact that rare disease legislation inherently already acknowledges.

V. CONCLUSION

Data trusts are evolving and are going to require constant monitoring and reevaluation, particularly of their governance models. However, that evaluation should come in some part from the individual data subjects, who ideally double as the end beneficiaries of data sharing.

As emerging technologies change the landscape of medicine, current legislative approaches, where they exist, will prove insufficient in addressing the needs of the rare disease community. Precision medicine's reliance on big data will force nations to increasingly recognize and build platforms geared at harnessing the power of big health data. The EU's move to create the TRUSTS project has heralded in a new age of data usage, sharing, and, in turn, governance. International data sharing may become the future of research, but it is already essential to progress in the field of rare diseases. Data federations and other sharing platforms must ensure that they do not leave behind small data communities like the rare disease population that arguably stand to benefit the most from these technological developments.

In order to maintain public trust in the use of this data, the formation of these projects must consider vulnerable and minority populations in the community. The rare disease community's active population presents one such group that will not only benefit from the making of these data sharing mechanisms but will actively participate in their creation and success. In order to maintain trust in these programs, interaction with the public is a necessity, and the rare disease community provides an ideal test group for communication, as

a group that is familiar with new endeavors and stands to benefit most from these projects.

With public cooperation through patient groups establishing public trust, nations must also commit to adopting the standards of the data federation into their rare disease legislation in order to allow for researchers to benefit from the data federation initiative without the legal hurdles currently inhibiting research. Concurrently, the data trust can thrive off rare diseases' social communities and active representation of the health sector and minority interests, their simultaneous demand for data sharing and that the sharing be conducted responsibly, and their willingness to advocate for the necessary legal change in the name of research.

Rare disease patients have longed for recognition and have demanded that recognition through banding together in political activism. No more can health research or data sharing only listen for the hoofbeats of horses when up to 8 percent of the world's population is a zebra. Data sharing initiatives should heed this lesson of seeing the individuals among the masses by recognizing the individual data subjects represented in their data sets. Ultimately, public trust will rely on the individual's sense of security in his or her personal data's use in relationship to the benefits received from that data.

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