WORLD ECONOMIC FORUM

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White Paper

Global Data Access for Solving Rare Disease

A Health Economics Value Framework

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Foreword

The need to reframe our approach and response to rare disease is urgent. Approximately 10% of the global population or 475 million people are affected by a rare condition,[1] with an estimated 15.2 million individuals expected to have clinical genomic testing for a rare condition within the next five years.[2] The number of countries with national initiatives to sequence patients with rare diseases, as well as healthy individuals, is growing. This genomic data, coupled with phenotypic and clinical data, represents a treasure trove of information critical for shortening the diagnostic odyssey faced by rare-disease patients and for powering research and innovation in diagnostics and therapeutics. We believe that federated data systems offer a promising approach, providing researchers and clinicians with access to global rare-disease datasets while allowing local institutions to protect sensitive personal health data and recognize cultural and ethical expectations about data protection and privacy.

The Forum's Breaking Barriers to Health Data pilot project aims to develop and test a proof of concept of how to set up federated data systems, using the case study of accelerating rare-disease research, diagnosis and eventual treatment. Compelling as it is to help rare-disease patients from a moral and ethical point of view, we nonetheless kept receiving requests to justify, from an economics perspective, the investment involved in setting up a federated data system. Thus, we are grateful to the authors of this white paper for elucidating the potential large-scale economic benefits offered by federating data across countries, by improving diagnostic benefit and shortening diagnostic odysseys for patients and their families. The need to share and compile genomic and other health data is crucial and time-sensitive, with millions of people with rare diseases continuing to die each year – often before reaching a diagnosis. Yet we are currently missing a value framework with which to evaluate such an investment. Federated data systems not only help us to do the right thing morally and ethically, they could also enable economic returns in the form of correcting misdiagnoses, shortening the time to a diagnosis, enabling more precise clinical trials and providing curative treatments with long-term economic benefit.

Executive summary

Rare diseases have been an increasing area of focus as three waves have converged in recent years: the continuing innovation stemming from the genomic revolution, the regulatory financial incentives put in place by the US government for rare-disease therapies, and the increasingly mobilized, coordinated and sophisticated patient community. However, the very nature of rare diseases calls for scientific and societal collaboration on an unprecedented scale. Federated data systems are one such example of this scale. A federated data system is 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. The result is a robust and well-annotated dataset that in the case of rare diseases can be contributed to and queried by different countries to enable global and country-specific solutions to diagnosis, treatment, patient trial recruitment, and management. The development and maintenance of federated data systems is one of the many investments countries could make in the name of scientific collaboration – but is it the right one? This paper reviews the “known knowns and known unknowns” of a federated data system solution to the unmet needs of people living with rare diseases. Ultimately, investment will be required to confirm and test the value propositions put forth in this paper. Our aim is to enumerate these value propositions along the lines of diagnostic benefit, clinical benefit, clinical trial benefit and personal benefit to individuals living with a rare disease. This will help collaborating nations to understand whether federated data systems are a best-fit solution to the global challenges inherent in rare-disease diagnosis and treatment plans.

In their own words: people affected by rare disease

Heather Renton, Australia, parent to a daughter with a rare disease, Founder and Chief Executive Officer, Syndromes Without A Name (SWAN) Australia

We waited more than nine years for a diagnosis for our daughter. In that time, I estimate we spent more than $50,000 on therapy, clinical appointments and equipment, not to mention loss of wages as I had to resign from my job to care for my daughter.

We have wonderful genetic services that offer genomic tests, but for many Australians the cost and access to them is prohibited as there is very little government funding to pay for them. Even with the test, the average diagnosis rate is 40–60%. The average time for a diagnosis is nine years. In that time, parents experience high rates of isolation, depression, anxiety, confusion and frustration. The emotional impact of diagnosis is huge and very little research has been done on the cost to parents/carers of managing their mental health or the mental health dollars saved as a result of people receiving a diagnosis.

Then there are the economic savings made by "social precision medicine". Social precision medicine occurs when personal experiences, emotions, coping strategies, medication and therapies are discussed with other people with the same condition – the knowledge derived from their peers is used to influence a diagnosis and treatment plans. There is more to a diagnosis than a name.

Krissa Harris, USA, parent of Hattie, who has a rare disease

The cost of having a child with a rare disease goes far beyond the financial impact. Yes, there are extra costs in having everything adapted (seating, clothing, strollers, toys, beds, showers, schools, homes and cars, to name a few), as well as prescriptions, diapers, doctors' visits, medical procedures and more. These extra expenses will remain for the duration of that person's life, not just 18 years. But what's often not considered is the toll it takes on the caregivers. There is definitely a "cost" to providing care 24/7 for a lifetime. It comes in the form of poor health, depression, divorce, loneliness. My hope going forward would be to treat the medical issues of the person with the rare disorder, but also the caregivers, to ensure a better quality of life for all involved.

Introduction

Rare diseases pose a grave challenge both in their prevalence and in their cost to national healthcare systems. Despite the "rare" in the name, rare diseases, or rare conditions as they are also termed, are anything but rare; rare diseases affect an estimated 10% of the global population, with more than 7,000 identified so far (as improvements in genomics further expand this number) affecting an estimated 475 million people globally.[3] Rare diseases also disproportionately affect children, with 80% of rare diseases caused by genetic or genomic variants.[4,5] The devastating consequences of rare disease in terms of mortality, morbidity and economic burden to the health system are clear, given that one-third of children with a rare disease die before they reach their fifth birthday and one in three hospital beds in paediatric hospitals are occupied by children with a rare disease.[6] The average time to diagnosis is seven years, and the chance of a treatment for a rare disease is less than 5%.[7]

Despite affecting hundreds of millions of people globally, the cost of rare disease, and by corollary the opportunity for savings, continues to increase. The Genetic Alliance UK reported that rare diseases are a "significant economic burden", though there is insufficient evidence available to perform a thorough cost evaluation.[8] Currently, we have comprehensive data on only the 5% of rare diseases with US Food and Drug Administration (FDA)-approved treatments. Of the very few studies looking at the cost of illness, most focus on a *specific* rare disease. One study focused on the costs associated with living with Niemann-Pick disease type C in the UK surveyed patients to estimate an annual cost of $51,095 (£39,168): 46% related to direct medical costs, 24% related to direct non-medical costs and 30% related to indirect costs.[9] For instance, overall, the available studies looking at the costs of living with a rare disease indicate that a significant proportion of costs are shifted to patients, the families of patients and their *non*-medical providers.[10] It is crucial to continue to measure cost as a first step, and also to consider costs from multiple perspectives. The Genetic Alliance UK estimates that the UK's National Health Service (NHS) spent $19.6 billion (£15 billion), or 10% of total NHS spending, on rare diseases categorized as “specialized services” in the year 2016 alone – excluding all primary-care costs, social-care costs and costs to patients and their families.

Given the number of rare diseases, the significant time needed to reach a diagnosis and the lack of treatments available, more answers are needed for people with rare diseases from a global, collective approach. Since 80% of rare diseases are genetic, the role genomics plays in diagnosing and treating rare diseases cannot be overestimated. Sharing genomic data has the potential to unlock significant findings within the context of rare diseases. But the nature of genomic information requires generating and interrogating a high volume of data in order to yield the utmost benefit. Data sharing is an opportunity to more efficiently and effectively draw on the datasets we *already have* in isolated data resources to generate new findings that could be applicable to people with rare diseases currently living without answers.

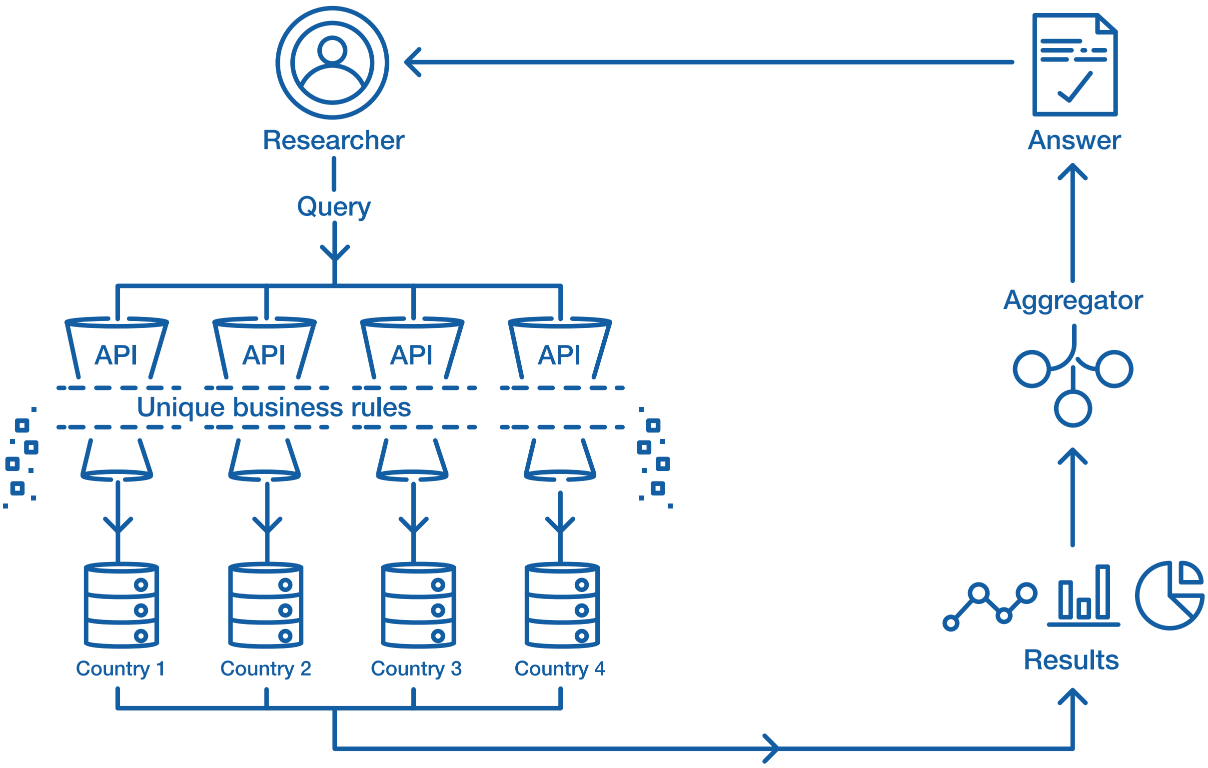
As we enter a new decade, a person with a rare disease in the UK, a person with a rare disease in the US, a person with a rare disease in Australia and a person with a rare disease in Canada could confirm a diagnosis of their disease by comparing similar genomic characteristics, but such an exercise is not easily legally feasible due to the complex data-policy landscape. National, regional and international regulations such as the General Data and Privacy Regulation (GDPR) in Europe and the Health Insurance Portability and Accountability Act (HIPAA) in the US hinder many routes to data sharing that would otherwise unlock the opportunity for people with rare disease – or their clinicians – to share their genomic and clinical data.

While the complex data policy and regulatory landscape across countries makes direct data sharing difficult, federated data systems offer a potential solution.

A federated data system is an approach that allows for both local autonomy and global innovation at scale. A federated data system enables instantaneous, trustworthy access to datasets across countries or institutional locations via a decentralized architecture powered by application programming interfaces (APIs).[11] As outlined in Figure 1 (shown on the next page), APIs provide reliable access to data and ensure interoperability in dataset readability.

Building APIs and negotiating the agreements and frameworks required to address data privacy, security and access in a federated data system is an investment that is under-explored both in terms of the initial cost and in system maintenance for a genomic data use case. General API development – a far simpler use case – is in the range of $15,000–$25,000, with maintenance running at $650–$1,350 per month. However, the cost of building a custom federated data system for genomic data can be hundreds of thousands of dollars if significant restructuring of datasets is required.[12]

Figure 1: Schematic of federated data system elements and features



Source: World Economic Forum, *Federated Data Systems: Balancing Innovation and Trust in the Use of Sensitive Data*

Given that a UK-specific study found that just 258,235 people with rare diseases (out of the UK's total rare-disease population of an estimated 3.5 million people) cost NHS hospitals $4.4 billion (£3.4 billion), or an average of $16,958 (£13,000) per patient, during a 10-year diagnosis period – double the average patient cost over the same 10-year period of $7,709 (£5,910) – an investment in a federation as a way to allow access to genomic and other sensitive health data for rare disease diagnosis and treatment could be economically viable.[13] If federating data saved even a fraction of this cohort from undergoing this same costly 10-year diagnostic odyssey, could such a data system pay for itself? And even if not, could the value of the additional benefits incurred to patients and their families outweigh this investment?

This white paper examines the potential benefits arising from investment in a global federated data system that would unlock access to rare-disease data for the purposes of advancing the diagnosis, treatment and management of rare disease. More specifically, it examines the implications of how federations could positively affect healthcare systems, with a specific focus on the US, the UK, Australia and Canada. In this paper, we identify the potential diagnostic, clinical, clinical trial and personal benefits by globally sharing and allowing access to rare-disease data. Additionally, this paper illuminates the gaps that remain in better understanding the economic landscape of federating data for rare disease.

How to examine the benefits of rare-disease data federations

A health economics approach is routinely applied to relatively simple decision problems – typically, for instance, to ascertain which of two competing treatment strategies offers the best value for money. However, this conceptual framework is equally applicable to complex, multisystem questions such as those posed by the subject of this white paper. There are critical issues to determine in order to arrive at a meaningful interpretation of "benefits" and "costs" in this context, but these hurdles are certainly surmountable. It will require a complete understanding of: first, the impacts of genomic diagnosis of rare disease; second, the therapeutic implications of this diagnostic strategy; third, the impacts to research and the further development of treatments; and, fourth, the impacts for personal benefit. Each step of this process requires an exploration of both the costs and benefits, with the final analysis requiring an integration of the entire process.

There are evidentiary gaps that make quantification of some of these elements problematic. However, there is nonetheless a significant evidence base to build upon.[14] In the next section, we will consider what is already known, before moving on to identify the nature and extent of the extant gaps, together with an assessment of the research agenda required to arrive at a reliable understanding of the health economic impact of federation in this area of healthcare.

Lynsey Chediak, USA, patient with a rare genetic orthopaedic disease

When people ask me what it is like living with a rare disease, I don't quite know how to answer the question – it's all I have ever known.

Since I was born, I haven't had answers regarding what my disease does to my body, how it makes each joint work "differently" in me than in "normal people", severely limiting my mobility and causing inhibiting pain, or even how it will continue to adversely affect my health and ultimate demise as I age each year. Doctors are fascinated by my disease, but don't know how to help since I'm usually the first one with the disease they've ever seen.

I fought through more than 30 invasive orthopaedic surgeries in less than 30 years – the majority of which failed. I was finally able to stand and walk for the first time at the age of 15 when a surgery "worked". When I stood up for the first time, I should have been elated, and I was – but I was also oddly disappointed. I was shocked at the simple ease with which I could suddenly move through the world. Why had no one helped the tens of thousands (if not more) of people *before me* with the same disease earn this same life-changing freedom? Every other patient I know with my diseases is *still* sitting in a wheelchair – trapped in a world with circumstances no doctor in the entire world can remedy. We simply don't share information nationally – much less globally – even though it could drastically change lives and save money.

Just in the past five years – a quarter of my total number of surgeries over my lifetime – foot surgeries for bone transplants, plates, screws and other hardware, all exploratory in nature, have cost more than $700,000. Just a bone cost me $60,000 in the US – without the cost of the surgery to put it in my body.

All of these costs *exclude* the weeks of work my parents have to miss to take care of me as I recover from surgeries – not to mention their stress and anxiety as I continue to go in and out of operating rooms for hours on end and require full-time care at home for weeks after invasive procedures.

What kind of world is it where my doctors have no choice but to sit and wait for me to ultimately not be able to walk again?

↳

It's incredibly scary to know that my day of not walking again is coming – it's imminent. There are millions of us across the world having to live with a rare disease; and we are ready and waiting for answers.

Sarah and Kane Blackman, Australia, parents of a son with a rare disease called Angelman syndrome

Nothing turns your world upside down like receiving an unexpected, life-altering diagnosis for your precious child. For many, receiving the diagnosis provides answers to the questions posed to numerous doctors over years of searching. For our family, it confirmed our worst fears. For almost two years, our son's delayed milestones were met with responses like "he'll catch up", "boys are slower to develop", "you are an anxious first-time parent" from the medical fraternity, family and friends. We felt failed by a system that patronized rather than diagnosed.

When the news comes, it hits you in an indescribable grief. The joy of parenting becomes marred by trauma – a grief over the unmet expectations of your parenting journey as the normal hopes that you had for your child crumble. These are rewritten piece by piece in a journey that you are now on, that you didn't ask for, and on a path that is yet to be revealed and for which, in the case of rare disease, is a path that is full of unknowns.

On this diagnostic odyssey that rare-disease parents are thrust on without a map, families are also funding and facilitating extensive early intervention therapy. Physiotherapists, speech therapists, occupational therapists, paediatricians, behaviour specialists and general practitioners float in and out, adding a burdensome cost to families.

The possibility of a treatment means more than hope. It means that somewhere in the world, there is a group of people who care about our son and our family enough to dedicate themselves to deliver his best future.

Impact of federated data systems on known benefits

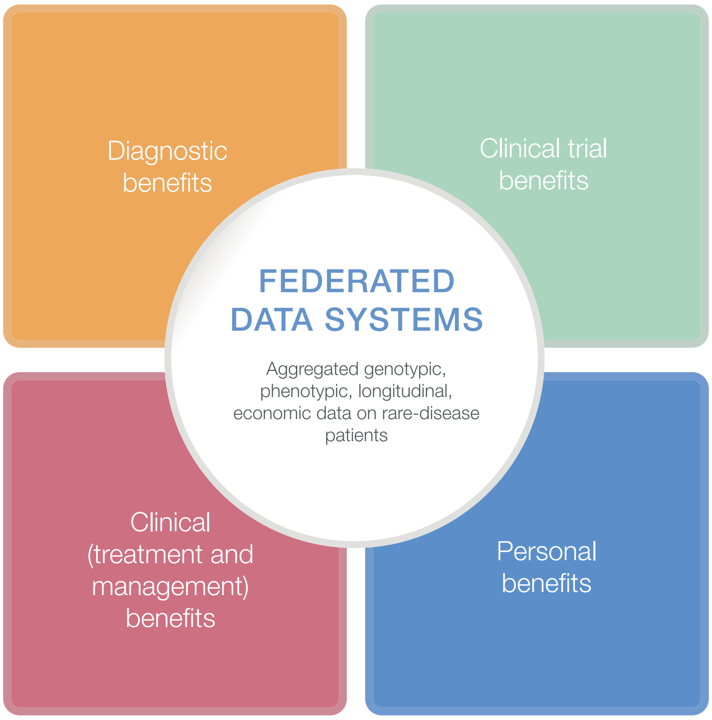
The value propositions of federated data systems as they relate to rare disease can fit into an economic framework characterized by four separate categories of benefit: (1) diagnostic; (2) clinical; (3) clinical trial; and (4) personal benefit.

Definitions of types of benefit

1. **Diagnostic benefit:** The identification of pathogenic or likely pathogenic variants in known disease genes.
2. **Clinical benefit:** Changes in the medical or surgical management of patients as a result of the diagnosis being made. These changes relate to improvements in health outcomes via assignment of therapies (therapeutic benefit) or improvements in the management of patients in the absence of therapy assignment (management benefit).
3. **Clinical trial benefit:** Changes related to the improvement of clinical trial operations.
4. **Personal benefit:** The presence of non-clinical outcomes that are important from a personal point of view to a person with a rare disease or who is affected by a rare disease. These outcomes may relate to the intrinsic value of information, the knowledge about the condition and the opportunity to make plans for the family or the future.

While each of these value propositions and benefits is discussed sequentially, many also overlap. Figure 2 (below) illuminates and categorizes the various value arguments at play.

Figure 2: Framework for value of federated data systems



Value proposition 1: Improving diagnostic benefit

By sharing genomic data and more rapidly disseminating knowledge, we could better understand the causes of rare diseases and guide clinical care. The rare-disease environment is hindered by a complex data policy and regulatory landscape that perpetuates an average time to diagnosis of seven years (commonly referred to as the "diagnostic odyssey") and the inability to directly share clinical data. A global federated data system is expected to accelerate disease diagnosis by facilitating the identification of pathogenic (disease-causing), or likely pathogenic, variants in known disease genes and the reclassification of variants of unknown significance.

The diagnostic value of global data federation will translate to important economic benefits. A study by Dragojlovic et al. (2019)[15] in Canada estimated that diagnostic testing and specialist consultations during the first year of a patient's diagnostic odyssey cost approximately $2,190 (CAN $2,890). For every additional year that a patient remained undiagnosed, a further $592 (CAN $845) was incurred. Annual travel costs and caregiver productivity loss associated with attending diagnosis-related physician appointments for undiagnosed patients were estimated at $1,449 (CAN $1,907) per family. These are substantial costs that can be saved with a timely diagnosis. Even untracked costs, related, for instance, to the loss of productivity over the lifespan of a person with a rare disease, are at stake. If your disease prevents you from ever being able to go to elementary school or beyond, a more timely diagnosis can prevent your entire exclusion from the job market.

Anonymous, USA, parent of a child with a rare disease

While attending the Global Genes Rare Disease Summit this past September, I couldn't help but feel envy towards the families sharing their ultra-rare diagnoses. Not having a condition to fight is the hardest part of being undiagnosed. We have been searching for 17 years, travelling the country, and seen more than 60 doctors without an answer. Meanwhile, my daughter Cayla continues to battle for her life against "secondary" conditions such as pulmonary and portal hypertension and failing bloodlines that doctors say can improve only if the "underlying" condition is treated.

Recently, after an analysis of her whole exome sequencing, UCLA thought they had found the cause of her illness, a rare n=1 mutation on her T-cell. Last week, we found out this was not the case and again my dream of a diagnosis and ultimately a cure was dashed.

Our next step: whole genome sequencing that was not covered by insurance. We have spent tens of thousands of dollars to provide the best care and search for a diagnosis for Cayla, but I would give my life for hers without question if I knew she could be cured.

Durhane Wong-Rieger, Canada, parent of two children with rare diseases, Founder and Chief Executive Officer, Canadian Organization for Rare Disorders (CORD)

I have two children, both born with rare conditions, one with a diagnosis and one without. What a world of difference a diagnosis makes. With my daughter, who was born with a number of physical and cognitive challenges, she was labelled a "flopsy" baby, but no other diagnosis could be found. So we had no idea as to the prognosis and no roadmap for care and treatment. We were constantly watching, sometimes worrying, but mostly providing all of the rehab and developmental support services we could find for her and, importantly, following her lead as to what she was capable of and wanting to do.

With my son, who was diagnosed with a heart condition at birth, there was not only a plan of care but also clear milestones we should be watching for or warning signs that could signal other actions needed. Luckily, both children have grown to become amazing adults, and we learned a lot along the way about trusting our instincts and mostly trusting our children. But while we have reasonable assurance as to my son's future with his condition, we still have no real idea as to whether there may be future challenges for my daughter.

Similar evidence is also available from Australia. A study by Tan et al. (2017) in children with suspected monogenic disorders (for which changes in a single gene are implicated in the disease process and which usually exhibit characteristic inheritance patterns) identified an average diagnostic odyssey of six years, with each child having approximately 19 tests and eight specialist consultations.[16] Nearly 60% of the children in the study had gone through invasive investigations requiring general anaesthesia, which could have been avoided with a timely diagnosis. The study concluded that genomic diagnosis could result in a cost saving of $6,838 (AUS $9,020). It is important to further note that diagnoses may also provide important benefits to the wider family. For example, cascade genomic testing in asymptomatic (at-risk) relatives of people with a rare disease may be cost-effective. An Australian study in the context of dilated cardiomyopathy found cascade testing to be highly cost-effective, mainly due to the prevention of sudden cardiac deaths and the stop of clinical surveillance in family members without the pathogenic variant.[17]

Value proposition 2: Improving clinical benefit

An important metric of clinical benefit (in the case of a definitive diagnosis) is the availability of corresponding interventions and the opportunity to enhance the management of medical care. While there is substantial value in obtaining a diagnosis for a person with a rare disease in and of itself, there are several ways in which federated data systems will contribute to improved treatment and provision of medical care. While today only an estimated 8% of rare diseases have a therapy available,[18] the rare-disease drug market is large and growing, and is forecasted to represent 21.4% of worldwide prescriptions, exclusive of generics, by 2022.[19] This increase can come to pass either by using existing therapies where possible via drug repurposing or through the development of novel therapies to treat rare conditions.

Therapeutic benefit

Drug repurposing

Drug repurposing (also known as drug repositioning or drug reprofiling) involves the use of existing drugs for novel therapeutic purposes. The success of drug repurposing to treat rare disease depends on the rate at which the genomic targets of rare disease can be uncovered. This rate can increase with the development of federated data systems that aggregate genomic sequencing and phenotypic data from disparate populations of people with rare diseases. Furthermore, as drug repurposing bypasses many of the costly, risky and time-consuming aspects of the traditional "research and development" (R&D) drug process, it is a cost-effective approach to increase the number of people with rare diseases who can be treated with a therapy. Drug repurposing efforts see success in ~30% of the drugs in which repurposing is attempted, while a traditional R&D approach yields a successful drug less than 10% of the time.[20] While the cost of developing a therapy using the traditional R&D approach can be up to $1.5 billion and can take 10–14 years, a drug repurposing strategy can cost around $250,000 and take 18–36 months.[21]

Based on the US FDA Rare Disease Drug Repurposing Database,[22] 22% of the 2,300 orphan drug designations available in 2010 were the result of drug repurposing. (Broadly speaking, orphan drugs are produced as treatments for diseases that are relatively rare in the general population, so many pharmaceutical companies are reluctant to develop them without additional perceived or apparent incentives.) As the body of knowledge describing the genomic underpinnings of rare conditions grows, the pathogenic pathways identified will increasingly overlap with those being targeted in common disorders. The number of genes linked to rare conditions increased by more than 140% in 2007–2017.[23] Of the 4,747 orphan drug designations currently approved by the FDA, 51% of them have occurred since 2010. The percentage of orphan drug designations available as a result of repurposing has increased from 22% to more than 47%.[24] Drug repurposing is a time- and cost-efficient strategy for obtaining therapeutics for rare conditions, and the data that fuels this process can be directly improved and affected by federated data systems.

Gene therapies

There is a category of novel therapies that lend themselves particularly well to rare-disease populations and whose development, pricing approaches and commercialization will particularly benefit from accessing genomic and other health data via federated data systems. Approximately 80% of the 7,000 rare diseases defined today stem from a gene defect, making rare diseases a promising field of targets for gene therapies. Gene therapies involve correcting or replacing dysfunctional genes via the introduction of a viral vector into the patient that "infects" the patient's cells as viruses do, but which then deposits the functional DNA, enabling appropriate protein production and healing.

Healthcare payers have been carefully tracking the progress of gene therapies in rare disease. The US approved a gene therapy for the first time only in 2017, but the pace of development and submission to the US FDA has rapidly expanded. Twenty gene therapy products have been approved worldwide, and more than 2,000 gene-therapy clinical trials have been reported.[25] Given the volume of gene therapies in Phase 3 clinical trials, it is estimated that by 2030 there will be 50–60 total approvals in this category.[26] However, the immediate impact upon taxpayers of all nations will be notable, regardless of their long-term curative impact.

Gene therapies are expensive to develop, test and manufacture – leading to costs of up to $2.1 million for therapies on the market today. However, the efficacy of gene therapies can greatly depend on the time in a patient's disease progression in which they are administered, which in turns affects the level of impact on annual federal and local budgets. An example from the US debate on gene therapy cost in sickle-cell disease illustrates this point. A sickle-cell gene therapy priced at $1 million would be a justifiable price for the almost $1 million worth of healthcare services that could be saved by the US healthcare system per sickle-cell patient by age 45. With approximately 70,000 US sickle-cell patients, that $70 billion expense would be borne out over two to three years, with the intent to cure patients as soon as possible. Such a sum would immediately squeeze local healthcare funds, necessitating the use of federal emergency funds.[27] However, the impact of this therapy on a newborn sickle-cell patient and a 45-year-old patient could be vastly different.[28] Information on the efficacy of the gene therapy as a function of the patient's disease progression would allow for the maximally effective release of funds. So, when do we treat which patients with gene therapies, and at what cost? Federated data systems are crucial in answering these questions, as they allow for both earlier overall administration via the location of patient candidates, and analysis as to the value (and, perhaps, cost) of each therapy as a function of the efficacy it shows in at various disease stages.

The intersection of the high cost of gene therapies and the data capacities of federated data systems position federated data systems as a leading solution in ensuring that national and private payers have the right real-world and cost-effectiveness data to cover and provide access to these treatments. Treatment cost is a vital consideration for all decision-makers regardless of geography or presence/absence of a nationalized health system. In order to fully analyse the cost-effectiveness of gene therapies, the full benefit of their curative nature needs to be assessed.

The existing literature comments on both the US and the European Union's[29] weaknesses in: (1) recognizing savings in the social care budget and evaluating healthcare cost solely out of the healthcare budget; and (2) analysing over a time horizon longer than one to two years. Federated data systems can enable enhanced data gathering in both of these areas, which is critical to fully evaluate the benefits of gene therapies to societies.

Furthermore, federated data systems can help nations overcome inherent weaknesses in their own decentralized systems by assigning each gene therapy patient a universal identification number, enabling longitudinal tracking and contribution to the total gene therapy cost by the various healthcare payers that pay for that patient throughout the course of their lives. As federated data systems identify and aggregate patient candidates for gene therapies, it would become easier for healthcare payers to stage payments for these therapies, and peg payment to efficacy or response milestones. Federated data systems would further enable pharmaceutical companies to more accurately predict their market, execute clinical trials and develop endpoints that are both cost-effective and patient-centric, prompting higher evaluation by payers. If the goal of gene therapies is widespread patient access, the goal of federated data systems as it relates to gene therapies should be as an efficacy evaluation and payment support tool.

Care management improvements

As fewer than 10% of rare diseases are currently associated with treatment pathways, care management has a separate clinical benefit and value for people with rare diseases for whom no treatment is available. The longitudinal phenotypic data that will be contained in the federated data system may enable clinicians and researchers to promptly identify rare-disease types through the presentation of symptoms, and construct clinical-care pathways based on symptom alleviation, which can then be tested and optimized from a clinical and health economics perspective. Federated data systems could substantially improve clinical care by avoiding unnecessary, and often invasive, investigations and ineffective treatments, while allowing for specialized care and comprehensive monitoring of symptoms. This is a patient-centric model of care management that is largely lacking today due to the dearth of large-scale datasets that aggregate patient symptoms and enable analysis and testing based on their alleviation.

Value proposition 3: Clinical trial benefit

Improving clinical trial operations for all novel therapies

The size and length of trials, as well as the robustness of trial conclusions, contribute substantially to the evidence base upon which therapeutic approvals rest. As many as 30% of people with a given rare disease can participate in a clinical trial, as compared to 1–3% of patients in a non-rare-disease trial.[30] The small sample of people with rare diseases in clinical trials has led to a unique set of challenges that can be ameliorated with the ability of federated data systems to quickly elucidate larger numbers of qualifying patients from various countries and speed their recruitment. A 2017 study found that the average sample size of a rare-disease clinical trial in the European Economic Area (EEA) is 335.8 patients, while a non-rare-disease clinical trial in the same region enrolls on average 1,406.3 patients.[31] A comprehensive, six-year review of 133,128 clinical trials registered with ClinicalTrials.gov paints a comprehensive picture of the challenges in rare-disease trial design and execution. Of the 24,088 trials able to be appropriately categorized, 11.5% were classified as rare-disease trials while 88.5% related to non-rare conditions. Rare-disease trials enrolled fewer participants, were more likely to be single arm (63.0% vs. 29.6%), non-randomized (64.5% vs. 36.1%) and open label (78.7% vs. 52.2%). A higher proportion of rare-disease trials were terminated early (13.7% vs. 6.3%) and proportionally fewer rare-disease studies were actively pursuing, or waiting to commence, enrolment (15.9% vs. 38.5%).[32]

Federated data systems can aggregate the geographically dispersed people with rare diseases sufficiently to enable a clinical trial and study the natural progression of a higher number of patients in order to better determine clinical trial endpoints and outcome assessments. The geographic information in federated data systems can further optimize the location of clinical trial sites (particularly for gene therapy, which pose a challenge because the clinical organizations that may have sufficient experience with gene therapies may not be close to the patients who would become trial participants). To overcome this issue in gene therapy trials in particular, for example, a "centralized dosing" approach has been suggested,[33] whereby patients would be screened and experience follow-up in a local site close to their homes but would receive dosing in the centralized site experienced in that aspect of treatment. Federated data systems could quickly become a tool to enable this large-scale coordination, which would involve different health systems, geographic locations and perhaps nations, and the medical records, tasks and data exchange inherent in the trial. Furthermore, advocacy groups and educational organizations could use federated data systems to provide the widespread information and recruitment activities needed to educate patients on the safety, efficacy and developing success of trials.

Optimizing the clinical trial process for rare diseases will lead to the growth and proliferation of all novel therapies, and integration of trials with federated data systems will increase the therapeutic benefit of establishing a rare-disease diagnosis, as trial identification and enrolment could then occur almost automatically.

Value proposition 4: Improving personal benefit

A further consideration in assessing the value of a data federation is measuring the value of diagnostic testing and receiving a test result for the patients and families with rare diseases beyond that captured with the traditional metrics applied in health economics, which are focused on health outcomes. Personal benefit reflects the value of non-health outcomes and process outcomes. Examples of non-health outcomes include the positive value of information even in the absence of changes in treatment or management (and therefore on health outcomes) or the negative impact of a false positive from a diagnostic test. An example of process outcomes would be the time waiting for test results and the time to a diagnosis – the practical implications of long delays in the diagnostic journey.[34] In principal, guidance on health economic evaluation suggests that all health and non-health effects of interventions should be captured and quantified; but this is not always the case, and it is especially critical in the context of rare diseases. People with rare diseases often experience a prolonged and expensive diagnostic odyssey culminating in a delayed diagnosis or, frequently, no diagnosis at all, with 25–30% of patients waiting 5–30 years for a diagnosis.[35,36] Using preference methods from health economics to estimate the personal benefit of diagnostic testing, it has been shown that the personal benefit associated with testing and obtaining a diagnosis sooner is considerable. For example, specifically in the area of children with developmental disabilities, parents were willing to pay an average $1,523 more for genetic testing than conventional cytogenetic testing.[37]

A more recent study found that parents of children with rare diseases value the time to obtaining an answer from diagnostic testing, even if the results do not provide a diagnosis, and are willing to pay for a reduction in that time. In this study, it was estimated that parents were willing to pay almost $5,000 for exome sequencing compared with operative procedures that might be experienced in the diagnostic odyssey. Furthermore, parents of children with rare diseases were willing to pay approximately $1,710 for every additional percentage point increase in the chance of receiving a diagnosis. Timely access to diagnosis has the potential to reduce both the time to achieve a diagnosis and the costs associated with the diagnostic odyssey in people with rare diseases.[38]

The federated data system, in and of itself, would not necessarily collect and measure these non-health benefits. It is expected that a federated data system would improve these measures (i.e. reduce the time to obtain a test result or to receive a diagnosis). These aspects of value could be measured as part of the performance metrics in evaluating a federated data system.

Figure 3: Potential outcomes of globally federating data for rare disease

Type of benefit	Diagnostic benefit	Clinical benefit	Clinical trial benefit	Personal benefit
Decrease time to disease diagnosis	✓	✓		✓
Decrease time between diagnosis and treatment	✓	✓		✓
Increase identification of pathogenic ("disease-causing") variants	✓	✓		✓
Decrease number of unnecessary diagnostic tests	✓	✓		✓
Increase the number of therapeutics available via drug repurposing (using existing drugs for a new purpose)		✓		
Decrease traditional research and development (R&D) costs		✓	✓	
Increase efficacy of gene therapy treatment plans		✓		
Better construct symptom-based clinical care pathways		✓		✓
Increase pipeline to rare disease-specific clinical trials			✓	
Increase information delivered to people with rare disease				✓
Increase speed in which information about a disease or treatment is delivered to people with rare disease				✓

Gap analysis

For each of the four value propositions identified in the proposed framework, there are unresolved questions that have yet to be explored in the published literature; even where information exists, it may be difficult to generalize beyond the context in which it is generated. In this section, we provide an overview of the current state of relevant evidence in the field, in order to assist in the definition of future research priorities. However, it is important to bear in mind the likely sources of uncertainty when considering the quality and completeness of health economic evidence in this field. The main issues to consider include:

1. The nature of rare diseases is that they are self-evidently rare. This means that data for individual diseases is always likely to be sparse, especially where research is generated by a single centre. This has implications for both the precision of any quantitative cost estimates and their generalizability.

2. Aggregating data from multiple diseases, in order to overcome issue 1, is tempting but may actually obscure critical information. The economic consequences of genomic diagnosis will vary according to the nature, management and consequences of individual diseases. Combined analysis may consequently result in a false perception of cost consequences, depending on the blend of diseases under consideration.

3. Genomics is a rapidly evolving science, with substantial changes in both approaches and conclusions being seen on a regular basis. As new diagnostic and therapeutic technologies emerge, health economic metrics may be expected to undergo significant change, the nature and direction of which is likely to influence the decision-making process.

Value proposition 1: Improving diagnostic benefit

The extended delay between a patient presenting and a rare disease diagnosis being made has been well documented.[39] Equally, published evidence exists to support the premise that delay in diagnosis of rare diseases results in significantly increased costs attributable to recurrent specialist consultation and diagnostic procedures.[40] This is important information and, purely from the standpoint of the pre-diagnostic costs, it seems reasonable to expect that earlier diagnosis will result in a reduction in these diagnostic costs and that the adoption of a federated data system would further enhance this cost reduction by improving the diagnostic yield of the genomic testing. It is important to note, however, that neither of these hypotheses has yet been formally evaluated in the published literature.

In reality, however, any reduction in diagnostic costs must be placed in a broader context of global pathway expenditure, incorporating the downstream healthcare costs attributable to the diagnosis. It is well documented that rare diseases consume a disproportionate amount of healthcare resources relative to their prevalence.[41] Equally, it is clear that improved diagnostic yield within genomic testing will result in an increase in the number of people with a formal diagnosis. What is unclear is whether the net cost impact will be negative – by virtue of a reduction in the requirement for downstream medical interventions – or positive – reflecting the use of specific high-cost therapies once the diagnosis has been made.

As highlighted above, it is likely that the net cost consequences will vary across different rare diseases, and aggregated analyses and more granularity (disease/group of disease-specific models) will be needed to complement each other. While it is unlikely that individual economic models will be available for every disease under consideration, at some level this exercise needs to be undertaken in order to understand the potential range of cost outcomes across an economy, given the range of new rare-disease diagnoses expected. In parallel, we know that 80% of people with rare diseases are affected by one of approximately 350 rare diseases out of the 7,000 currently categorized.[42] A priority exercise to delineate the individual economic models for these 350 rare diseases could be undertaken. Within those 350 rare diseases, the following questions would yield the highest amount of new information. Parallel to this, ensuring granular rare-disease coding (for example, Orphanet codes) in health datasets will be critical; coding systems such as ICD-10 and ICD-11 do not have codes for the majority of these rare diseases.

Specific evidential gaps for clarification:
a) Does the use of genomic testing result in the anticipated reduction in pre-diagnostic expenditure?
b) Does the amalgamation of diagnostic information by federating data result in an incremental saving?
c) Across a range of different rare diseases, what is the net cost impact of earlier diagnosis on total care pathway costs (including costs to people affected by rare disease: e.g. the patient, their families and communities)?

Value proposition 2: Improving therapeutic benefit

This area is probably the most important potential driver of expenditure in the rare-disease field. Currently, <10% of rare diseases are associated with a specific therapy, although this is changing rapidly. The arrival of new and potentially high-cost therapies on the market is consequently inevitable, and the value of federated

Jillian Hastings Ward, United Kingdom, parent of a son with a rare disease, Board Chairwoman of the Genomics England Participant Panel

Our son seemed perfect when he was born. We were so happy that our family was now complete; his big sister is only two years older and we expected them to be very alike. Unfortunately, by the time he was three months old we realized he couldn't see and, as my maternity leave progressed, it became apparent that he was not meeting any developmental milestones. On his first birthday, we were told that a degenerative disorder couldn't be ruled out. My employers were very understanding and allowed me to extend my leave for a further year, but he developed increasingly complex needs and I had to give up my professional career completely to look after him. By his second birthday, he'd been diagnosed with epilepsy after a series of increasingly frightening and unexplained seizures, culminating in one that required him to be put in an induced coma for 24 hours.

We moved across the country to be closer to family, and bought a house that we hoped would be more suitable for him, but we still had no diagnosis. We were able to access an excellent range of health services and special-needs support groups, but they could treat only the symptoms and not an underlying cause. He had multiple medical appointments, and securing the help he needed was a full-time job. We found it impossible to plan for our longer-term future at all.

The turning point came when he was diagnosed with an ultra-rare genetic variant, thanks to the 100,000 Genomes Project in England. There is no recognized treatment, but suddenly we have a means of finding other families like ours. Most of them live thousands of miles away, but at least we are now able to find out more about what may lie ahead.

Christina Hartman, USA, parent of Charlotte, who has a rare disease

We live a couple of blocks from the US National Institutes of Health in an area teeming with expert scientists and clinicians. As a result, our diagnostic odyssey lasted only a year. Charlotte's relatively quick diagnosis (via whole exome sequencing) gave us the knowledge about what to expect and meant we were able to find and engage her disease community and access the resources she databases in this context will be in enabling nations to best evaluate the market impact, effectiveness and willingness to pay of/for these therapies.

In many health economies, decisions on the availability of diagnostic and therapeutic technologies are made on the basis of a cost-effectiveness analysis, typically based on economic models derived from the results of controlled clinical trials and real-world studies. While concessions may be made for rare diseases and/or orphan drugs in terms of acceptable input sources and output thresholds, the fundamental structure of the health technology assessment (HTA) process – which assesses the properties, effects and impacts of health technology – remains essentially constant.

As highlighted in the previous section, there is minimal published evidence for the costs associated with post-diagnostic management of rare diseases using the current treatment options. If the incremental benefits and costs of new therapies are to be meaningfully assessed, understanding these baseline care pathways will become doubly important.

Specific evidential gaps for clarification:
a) What are the cost and benefit drivers associated with the top 350 most prevalent rare diseases and how are these potentially altered by the availability of a greater number of specific therapies?
b) How do we define the ways in which federated genomics data systems can help identify, characterize and prioritize important genomic targets where intervention is likely to be justified on clinical, health economic and overall quality of life grounds?
c) At what cost and level of patient access would a novel, repurposed or gene therapy provide cost savings in the patient population as compared to current costs of care?

Value proposition 3: Clinical trial benefit
The operational weaknesses of clinical trials today lend themselves to being improved through a host of varied mechanisms, including federated data systems. We propose in this document that a federated data system will facilitate the recruitment and evaluation process to support this undertaking.[43] This is a reasonable assumption, based on existing experience with single rare-disease registries (e.g. ACCELERATE Registry: NCT02817997). However, it has yet to be proven in the broader genomics field.

Specific evidential gaps for clarification:
a) How do we devise and initiate a clinical trial, using a federated genomics data system as the recruitment source, to demonstrate proof of principle?
b) How do we compare the cost of executing such a trial with an estimated status quo scenario?
c) How do we determine the extent to which any differences in clinical trial cost would be reflected in the final price of the therapy offered?

Value proposition 4: Improving personal benefit

Personal benefit is an important value component in the diagnosis of rare diseases. While the importance of personal benefit is increasingly recognized, clinical and policy decision-making is predominantly based only on diagnostic and clinical information. The evidence presented in this paper highlights the relevance of parental preferences for the outcomes resulting from access to genomic information.[44] Using stated-preference methods, these studies were able to quantify valuable elements of personal benefit in a relevant way to inform healthcare priorities. Both studies stated that there is substantial intrinsic value to genetic information and knowledge. This method can be used to capture additional value components derived from testing and definitive diagnosis. Even though there is still a long way to go to understand the performance of traditional health economics outcome measures in the context of genetics, tools exist to allow for informed clinical and policy decisions when increased data access is achieved.

Specific evidential gaps for clarification:
a) What is the relevance of current traditional patient-reported outcome measures in capturing personal benefits?
b) What is the relative importance of health, non-health and process outcomes associated with a diagnosis?
c) What preferences do people with rare disease have about data sharing and associated risk-benefit trade-offs?
d) What preferences and values do people have for genomic testing across clinical contexts?

needed. The early and intense therapeutic intervention she received set her on her best possible path: It gave her brain the knowledge needed to allow her to walk. It is our hope that with continued intervention, she will continue to progress physically and may even eventually learn how to speak.

The overall costs of having a child with a rare genetic disorder as compared with a typical child are astronomically different. Our typical child has an infinite number of options and opportunities. Charlotte was dismissed from daycare at two years old and the full-time nanny we were forced to employ ended up costing more than our mortgage. The stress to our family has been astronomical and we fear for the future, though we focus for today and the fact that we currently have the capabilities to get through it. Everything we need is a fight with the insurance company – the helmet she needs to wear due to frequent falls, the special-needs bed so she can sleep safely, and even the whole exome sequencing that gave us her diagnosis.

Sonja Durinck, Canada, patient with a rare disease

Although quantitative and qualitative costs of delayed or no diagnosis for rare disease vary with symptoms and circumstances, everyone who faces this situation experiences financial, physical and emotional effects. The longer the delay, the more significant these effects become, particularly if there is no medical insurance or health benefits or an available circle of support. Left without a diagnosis – dealing with symptoms that can't yet be treated while trying to be your own advocate – you are completely vulnerable and quickly become isolated. With no diagnosis, a significant source of personal support from others who may have the same condition is lost.

Your doctor and others may begin to question your veracity, privately labelling you as a chronic complainer or hypochondriac, and not deal with the symptoms collectively.

Medical expenses, including medication, counselling fees, alternative treatments, travel and accommodation costs (out-of-province and out-of-country) for medical advice or medical therapy, or even court costs for a wrongful dismissal, can be exorbitant, straining personal relationships and potentially jeopardizing the ability to live independently. Quality of life is affected at every level: physical, emotional, financial, personal and professional. The emotional burdens that can accompany a chronic undiagnosed illness, from missing a daughter's wedding to failed relationships and, for some, even suicide, are incalculable. Without a diagnosis, there is no resolution, no path to potential wellness. This journey is long and lonely.

Naka King, USA, parent of Rylan, with rare disease dup15q syndrome

Our daughter was around three months old when we started seeking answers to some of her symptoms. When our local doctors couldn't provide a diagnosis, we were forced to travel to a bigger city. We bounced around three major hospitals, hours from home, visiting doctor after doctor, each with no explanation for her symptoms. Finally, three long years later, after a gauntlet of expensive and invasive tests, one drop of blood for a genetic test gave us an answer: a piece of extra 15th chromosome resulting in a condition known as dup15q Syndrome, and finally all her symptoms fit.

Ian Stedman, Canada, patient with a rare disease

My diagnostic odyssey lasted 32 years. I visited my family doctor more than 180 times in my first 18 years of life. I also saw dozens of specialists, went to walk-in clinics and waited my turn at more hospital emergency rooms than I can remember. I eventually gave up searching for answers when I turned 18. I decided that I would instead try to live my life the best I could despite my many debilitating symptoms. I was 32 when I was finally diagnosed as having Muckle Wells syndrome and given life-changing treatment. Everything changed overnight – I no longer felt the burden of having a genetic disorder that could potentially take my life. It has been night and day for me, and I am grateful beyond words for what my diagnosis and treatment have given me.

Conclusion

When federated data systems operate to unlock rare-disease data across country borders as collective, coordinated efforts, it will be possible to deliver economic benefits through the ensuing diagnostic, clinical, clinical trials and personal benefits. Amid the evidence base supporting the varying utilities and overall value of allowing access to rare-disease data across borders for the purpose of diagnosis and treatment, significant gaps remain in our understanding of specifically *how* such global data sharing will deliver new value.

The number of people living with a definitively diagnosed rare diseases and, similarly, the costs associated with caring for people who do not have clear diagnostic and treatment options, are only going to increase. The diagnostic benefit of providing a diagnosis to the 40% of people with rare diseases experiencing a misdiagnosis or no diagnosis at all is expected to provide savings to healthcare systems and positively affect people's health, well-being and quality of life. A diagnosis, however, is most valuable with clinical benefit – meaning that it is possible to influence how a clinical team manages a person with rare disease to positively influence their livelihood, whether in symptom mitigation or, in some cases, by providing a cure for a rare disease. Additionally, while there are many rate-limiting steps inherent in making a therapy (novel or otherwise) newly available to patients with a certain rare disease, being able to access disparate datasets of health and genomic data via federated data systems can in principle improve the speed, efficiency, scope and cost of performing a range of steps, from target discovery to post-market safety and cost-effectiveness studies. What will be paramount to measuring the efficacy and cost-effectiveness of federated data systems is structuring discrete trials for repurposed, novel and ultra-novel gene therapies using insights gleaned from federated data systems to study the effects the trial medium has on the development, launch and access of the therapy. Lastly, federated data systems could help overcome the limits of collecting and measuring the additional non-health benefits that come from the peace of mind of receiving an accurate diagnosis. Having a diagnosis for a rare disease carries a psychological value in and of itself beyond what is currently recorded and tracked as data points and metrics in standard economic value.

Ultimately, the volume of rare-disease data at a global scale is rapidly growing, and the need to take a global, collective approach to improve the lives of people with rare diseases necessitates a federated data approach to sharing data to move forward. The economic viability of a federated data system can be determined by its ability to facilitate the identification of specific rare diseases, changes in medical treatment plans for people living with a given rare disease, improvement in health outcomes and provision of non-health outcomes such as peace of mind. However, we also need to implement specific metrics to *measure* how much of these benefits and values are actualizing. A coordinated, purposeful and global effort focused on consistency will be vital to realizing the economic viability of federated data systems.

If a consortium pursuing a federation sets specific outcomes, agrees to common terms of reference and common terms of research, and establishes metrics to track their group performance, people with rare diseases, and health systems, could experience cost savings. As more and more tranches of isolated data emerge at the national and subnational level that contain rare-disease data, it is crucial that we move forward with a federated approach to reduce the diagnostic odyssey, suffering and morbidity; reduce the mental health burden; generate personal, familial and health system efficiencies and savings; and deliver insights into new therapies, other innovations and economic opportunities. Hundreds of millions of lives – and the qualities of those lives – are likely to be improved by federating rare-disease data across country borders.

Sabrina Millson, Canada, parent of a child with a rare disease

The process of finding answers on our child's condition was extremely frustrating and disappointing: the many years of countless appointments, time off work, test after test, retelling the painful details to every provider, all in hopes of confirming a diagnosis to help open doors for support; attempts by well-meaning physicians to guide you in the best possible direction, to act now and start early intervention at home due to long wait times through a publicly funded system, thus resulting in the spending of copious amounts of money out of pocket for private therapy. It's only when the unthinkable happens, when you rush your child to the emergency department, that they offer the most powerful diagnostic tools, scans and genetic testing, tools which, if they were offered first, could have improved outcomes and saved massive amounts of time, stress, pain and money.

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Endnotes

1. There is disagreement about how many people are living with a rare disease globally – especially given that these populations are not systemically tracked or logged. The BLACKSWAN Foundation estimates there are more than 475 million people globally with rare disease, while the United States Center for Disease Control estimates there are about 400 million people globally. Until we start to track rare disease in the clinic and beyond, it is impossible to know the exact figure; see Introducing the Rare Diseases Genomics and Precision Health Knowledge Base, CDC, 4 April 2019: https://blogs.cdc.gov/genomics/2019/04/04/introducing-the-rare-diseases/ (link as of 26/2/20).
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5. Conservative estimates based on the limited information we have in the Orphanet database on rare disease estimates the population prevalence at 3.5–5.9%, which is 243–446 million people globally at any point in time – and this information represents only 67.6% of the prevalent rare diseases. Source: Nguengang Wakap, S., Lambert, D.M., Olry, A. et al., 2020. Estimating Cumulative Point Prevalence of Rare Diseases: Analysis of the Orphanet Database. *European Journal of Human Genetics*, 28, 165–173. doi:10.1038/s41431-019-0508-0.
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