ENDING THE DIAGNOSTIC ODYSSEY

FOR CHILDREN WITH A RARE DISEASE

Global Commission Year One Report

It takes an average of 5 years to diagnose a child with a rare disease.

This needs to change.

We brought the rare disease and technology communities together to help solve this problem.

Here are our recommendations.

GLOBAL COMMISSION | to End the Diagnostic Odyssey for Children with a Rare Disease

TABLE OF CONTENTS

In 2018, Shire (now Takeda), Microsoft, and EURORDIS-Rare Diseases Europe joined forces to launch the Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease. The Global Commission is a multidisciplinary group of experts from around the world who have brought their creativity, technological expertise, and passion to accelerate the time to diagnosis.

GLOBAL COMMISSION MEMBERS

SIMON KOS
MICROSOFT

YANN LE CAM
EURORDIS-RARE DISEASES EUROPE

WOLFRAM NOTHAFT
TAKEDA

MOEEN ALSAYED
KING FAISAL SPECIALIST HOSPITAL

KYM BOYCOTT
CHILDREN'S HOSPITAL FOR EASTERN ONTARIO

PAMELA K. GAVIN
NATIONAL ORGANIZATION FOR RARE DISORDERS (NORD)

ROBERTO GIUGLIANI
FEDERAL UNIVERSITY OF RIO GRANDE DO SUL (UFRG)

KEVIN HUANG
CHINESE ORGANIZATION FOR RARE DISORDERS (CORD)

DERRALYNN HUGHES
ROYAL FREE LONDON NHS

ANNE O'DONNELL-LURIA
BROAD INSTITUTE OF MIT AND HARVARD, BOSTON CHILDREN'S HOSPITAL

MARYAM MOHD. FATIMA MATAR
UAE GENETIC DISEASES ASSOCIATION

DAU-MING NIU
TAIPEI VETERANS GENERAL HOSPITAL

MIKE PORATH
THE MIGHTY

ARNDT ROLFS
CENTOGENE

RICHARD SCOTT
GENOMICS ENGLAND

MARSHALL SUMMAR
RARE DISEASE INSTITUTE, CHILDREN'S NATIONAL MEDICAL CENTER

DURHANE WONG-RIEGER
CANADIAN ORGANIZATION FOR RARE DISORDERS AND RARE DISEASES INTERNATIONAL

Special thanks to the team that supported the Global Commission's work over the past year and helped develop this year one report, especially: Linn Parrish, Gabriele Ricci, Hartmann Wellhoefer, MD, Uzma Atif, PhD, and Mladen Bozic (Takeda); Clifford Goldsmith, MD (Microsoft); Simone Boselli (EURORDIS – Rare Diseases Europe); Andrea Caron Nouss and Maria Schneider (Rabin Martin).

Letter from the co-chairs

Parents know when something is wrong with their child. But when it comes to a child with a rare disease, the search for an answer can turn into an odyssey. Today, it can take an average of five years to get an accurate diagnosis, even in countries with sophisticated health systems. Too many families around the world bounce between physicians and specialists only to receive multiple misdiagnoses. The consequences can be devastating: delays in treatment that could save a child's life or, when there is no treatment or cure, robbing families of peace of mind and the ability to plan for their child's future. These challenges are affecting patients, their families, and the many healthcare professionals entrusted with patients' care and wellbeing.

In 2018, Shire (now Takeda), Microsoft, and EURORDIS-Rare Diseases Europe joined forces to launch the Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease. The Global Commission is a multidisciplinary group of experts from around the world who have brought their creativity, technological expertise, and passion to accelerate the time to diagnosis.

We believe that technology provides an unheralded opportunity to help overcome the barrier of "rare" and the unfortunate fact that today, "rare" often equals "off the radar." Many of our recommendations address distinct challenges within rare disease that technology is uniquely equipped to solve. We have launched ambitious pilot projects to explore what's possible – using tools such as blockchain and facial recognition – and outlined policy recommendations to ensure patient privacy is protected while encouraging the sharing of data for analysis and decision making.

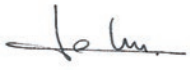
The Global Commission has developed a roadmap – actionable recommendations – to help end the multi-year diagnostic odyssey for a child with a rare disease.

Our goal is to inspire concerted action and mobilize diverse actors – within and outside the health field – to work collaboratively toward a shared ambition.

As champions for people living with a rare disease, we hope you will join us in advocating for families to receive life altering information as quickly as possible, transforming the lives of millions of children and their families around the world.

Sincerely,

SIMON KOS
CHIEF MEDICAL OFFICER
MICROSOFT



YANN LE CAM
CHIEF EXECUTIVE OFFICER
EURORDIS-RARE DISEASES EUROPE

WOLFRAM NOTHAFT
CHIEF MEDICAL OFFICER
TAKEDA

THE CHALLENGE

When it comes to a child with a rare disease, the search for a diagnosis can turn into an odyssey. Too many families around the world are bounced around from physician to specialist and back again only to receive multiple misdiagnoses.

RECOMMENDED SOLUTIONS

We have developed actionable recommendations to help accelerate the time it takes to diagnose a rare disease. Many of our recommendations address distinct challenges that technology is uniquely equipped to solve.

TRACK 1

Empowering Patients and Families

TRACK 2

Equipping Frontline Providers with Tools for Diagnosis and Referral

TRACK 3

Reimagining the Genetic Consultation

Track 1

Empowering Patients and Families

Objective: Develop tools that empower families and caregivers to become more proactive in getting a diagnosis as quickly as possible.

Background

Although individual rare diseases are "rare," it is estimated that 350 million people globally suffer from a rare disease[1]. The term "rare" has led to a common misconception that it is highly unusual to encounter someone with a rare disease. As a result, patients, caregivers, and frontline providers – even those struggling with a difficult case – often do not suspect that a patient may be suffering from a rare disease, thus extending the diagnostic journey.

Greater public awareness of rare diseases and their prevalence is the first step on the path to a quicker diagnosis. Rare disease organizations such as NORD, EURORDIS-Rare Diseases Europe, and the Canadian Organization for Rare Disorders (CORD) have recognized the need to counter the perception of "rare," and have advocated strongly with physician groups to consider rare diseases when pursuing a diagnosis. Some advocates use the phrase "think zebra" to refer to the traditional guidance taught in medical schools, "when you hear hoofbeats, think horses, not zebras," which encourages physicians to look for the most likely diagnosis. Instead, these advocates are urging physicians to "think zebra" and consider a rare disease as a possible diagnosis when a common one does not fit.

When it comes to children who have not yet received a diagnosis, parents and day-to-day caregivers are the critical source of patient information for the physician. They are most familiar with the child's medical symptoms, behavioral patterns, responses to earlier treatment, family history, and previous reports from their physicians and specialists. They are also the child's biggest champion and advocate. Equipping families and caregivers with the tools they need to ask physicians probing questions, connect seemingly unrelated symptoms, or inquire about additional testing is both empowering and an effective route to achieve a correct diagnosis.

350
million people globally
have a rare disease

Online communities have an important role to play in educating and providing support for parents searching for a diagnosis and encouraging them to take greater initiative during physician visits. Likewise, patient ownership of health records is essential in helping families advocate successfully for their child in the doctor's office. When parents have access to their child's complex medical history and can communicate about it in a clear and succinct way, physicians are able to make more informed and quicker decisions about next steps on the diagnostic journey.

1. FAQs About Rare Diseases. Retrieved from https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases

The VanHoutan Family, Chicago, Illinois, US

TRACK 1 SOLUTION 1

Empowering patients to ask their doctor to *think differently*

VISION

Equip families with the tools they need to work collaboratively with their doctor to expedite diagnosis.

A set of simple questions and a systematic approach to collecting information can help parents and caregivers engage with their doctor to consider whether their child has a rare disease.

Current Situation

Although they have first-hand knowledge of their child's symptoms, families may experience many challenges to engaging their doctor to pursue a diagnosis of a rare disease. Repeated visits to emergency room, consultations with various specialists, trial-and-error with treatments, and searches through the Internet are "dead-end" paths common to many families along the diagnostic journey.

How it would work

When a child is diagnosed with a rare disease, the parent and physician are often able to look back and, in hindsight, connect the dots between what at the time seemed to be unrelated symptoms and test results. Families that are empowered to ask their doctor the right questions, based on expert knowledge of their child, will be able to work collaboratively with physicians to connect those dots earlier in the diagnostic odyssey. Knowledge of early indicators can help.

The Global Commission recommends a campaign with three goals:

1. Increase public awareness of the prevalence of rare diseases
2. Provide parents and caregivers with the right questions to ask their pediatrician or primary care physician to help determine whether they should consider the possibility of a rare disease
3. Encourage parents and caregivers to systematically document symptoms and interventions

The campaign would feature common signs, or "triggers," that may indicate the need to explore whether a child has a rare disease.

If any of these boxes are checked, the campaign then provides parents with a digital journal to help them carefully track symptoms, consultations, physician recommendations, and treatment successes and failures. With this information in hand, parents are able to have more informed discussions with physicians and should be empowered to ask the doctor to think differently and consider a rare disease.

When to consider if your child may have a rare disease*

- ☐ Your child has been to the pediatrician or emergency room more than 6 times in the past 6 months to deal with similar recurring symptoms.
- ☐ Your child's symptoms do not clearly fit within any common diagnosis.
- ☐ Your child has been referred to two or more specialists.
- ☐ Your child tried several recommended treatments (including surgeries) that have not worked as predicted.
- ☐ There are other family members with similar uncommon symptoms.
- ☐ Your child has stopped growing or developing as expected.
- ☐ Your child "just does not feel right."

** The exact recommendations to be included in the campaign would need to be established following wider consultation with families, patient support groups and professionals*

Discussion questions for families and physicians

What are common diagnoses that might explain my child's symptoms and responses? How well does my child fit those profiles?

Are there additional specialists we should consult?

Should we consider a rare disease? Should we get a genetic test?

Where can we access more information about conditions that might explain these symptoms?

The campaign would provide links to a range of patient advocacy groups for support services. And thanks to technological innovation, online resources are rapidly expanding parents' ability to search for particular symptoms and receive a list of potential disorders which they could discuss with their pediatrician.

Why this is promising

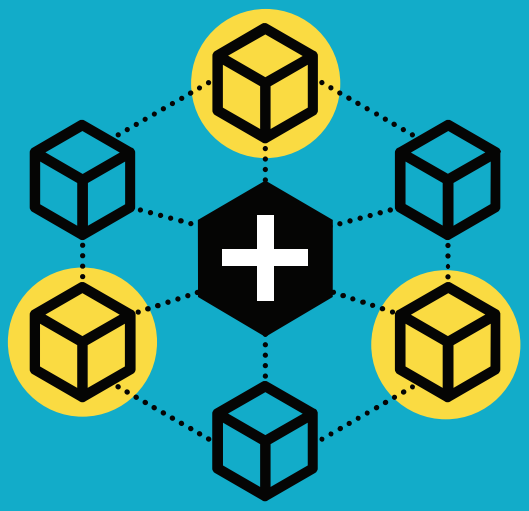
Mobilizing parents is a strong lever for action because they are the biggest champions for their child's health. Raising awareness among parents and providing them with useful information and tools will enable them to work more collaboratively with their child's physician to problem solve. Together, they can chart a path toward testing and specialists who will hopefully be able to help explain the symptoms, rule out conditions, and potentially provide a diagnosis.

Considerations

It will be important to frame the campaign as an effort to help parents and physicians work collaboratively to find a diagnosis. Parents should understand that a rare disease may not be the answer, but it is equally important that physicians listen to families and consider the potential of a rare disease. Not every journey will lead to a rare disease, but these collaborative pathways are important even if a clear diagnosis is not attained because it will help provide a holistic understanding of what the child is experiencing and the best care options.

TRACK 1 SOLUTION 2

Utilizing Secure Technology for Portable Health Records



VISION

Enable patients and their caregivers to securely share detailed medical records with multiple physicians and specialists quickly and efficiently.

A secure, patient-owned data aggregation system eliminates the difficulties of information sharing among frontline providers, geneticists, patients, and caregivers.

How it would work

A secure technology would help aggregate all patient data from physicians and parents, which can be substantial after multiple physician and specialist visits and countless tests. The technology would ensure privacy, give patients full control over their data, and only be accessed by the patient (or his/her parents/caregivers in the case of a minor or guardianship).

Electronic health records, notes from multiple physicians, and other key pieces of information – including patient-entered data – would be in one place and parents would manage the information. Ideally, the parent or caregiver could easily see and transport the comprehensive summary of information through a personal "passport." Parents would bring this passport – or share it beforehand – to each new physician, lab, or specialist visit, ensuring that the entire care team has all relevant patient information at their disposal to make the best decision on next steps.

Why this is promising

Disparate data is a key barrier to improved coordination across specialists, leading to inefficiencies and delays in diagnosis, care, and treatment.

Considerations

Aggregating data across multiple health systems and practices raises several potential challenges, including interoperability with various health record systems, privacy concerns, and lack of trust in the concept of data sharing. Additionally, in some countries such as the United States and Malaysia, patients do not own their own health data. Where this is the case, national policy around health data ownership should be considered in implementing this recommendation.

Blockchain technology: An option for secure patient data

The word "blockchain" combines the two key elements of its technology: A "block" is a record of a transaction or an interaction, secured using cryptography (similar to the code-based encryptions common in medical practice). This block might be the record of a doctor's office visit. The block is linked to all prior transactions or visits, thus forming a "chain."

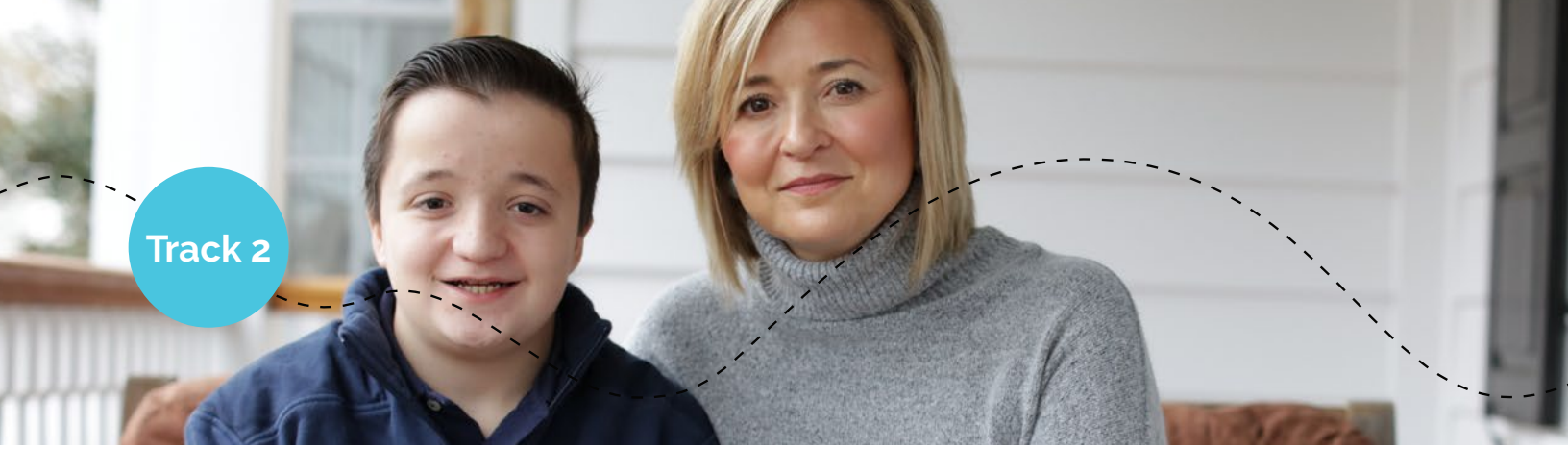
A single, national blockchain-based approach would allow patients to become the owners of their data. It would allow the information to travel with them – to every new emergency department, physician's office and hospital – both safely and securely. It could be updated as soon as new data are entered, anywhere in the country. And it could connect all medical information for the rest of patients lives.

Source: Pearl, R. (2018) Blockchain, Bitcoin, And The Electronic Health Record. Forbes. Retrieved from: https://www.forbes.com/sites/robertpearl/2018/04/10/blockchain-bitcoin-ehr/#25ca86479e77

Patient Benefit
Parents are empowered to share crucial medical and other relevant information without requiring a deep understanding of the medical records.

Physician Benefit
Physicians have a comprehensive summary of all patient data and can make more informed decisions.

Health System Benefit
The health system saves staff time tracking records and saves costs by reducing unnecessary repeat testing.



Track 2

Equipping Frontline Providers with Tools for Diagnosis and Referral

Objective: Equip frontline providers with the knowledge and tools to quickly and effectively identify patients who may have a rare disease and take appropriate action.

Background

Half of all rare diseases begin in childhood[2]. Therefore, frontline providers (i.e. pediatricians, primary care physicians) are generally the initial point of contact for parents of patients with abnormal clinical findings. These physicians play a critical role as both the healthcare provider and the medical gatekeeper. But when it comes to a child who could have a rare disease, these physicians may lack the awareness to consider a rare disease and, if alerted, may not be equipped with the knowledge, tools, and time required to make the best decision about what to do next.

A frontline provider may never encounter a patient with a specific rare disease during his/her medical career. To date, more than 6,000 rare diseases have been described and new diseases are regularly reported in medical literature[3]. While an individual disease might be labeled as "rare," the number of people suffering from a rare disease is estimated at 350 million[4]. In Europe, more than 30 million people have a rare disease, roughly 6-8% of the EU population[5].

There is a very high likelihood that physicians will see many patients with a rare disease in their routine practice, including some whose symptoms have been attributed erroneously to a common condition. Considering rare diseases as part of the differential diagnosis pathway is essential. However, even if a physician suspects that a patient has a rare disease, pre-diagnosis is difficult because many rare diseases do not have standard pathways to an accurate diagnosis.

6 to 8%
of the EU population
has a rare disease[2]

Without the knowledge and tools for following up on a suspected rare disease or condition, frontline providers may delay making a referral to a specialist – extending the diagnostic odyssey.

Frontline providers might not feel confident that they are seeing something out of the ordinary or may not know what kind of specialist the patient should see because the patient has a cluster of seemingly unrelated symptoms or does not resemble the "textbook case" of someone with the same disease.

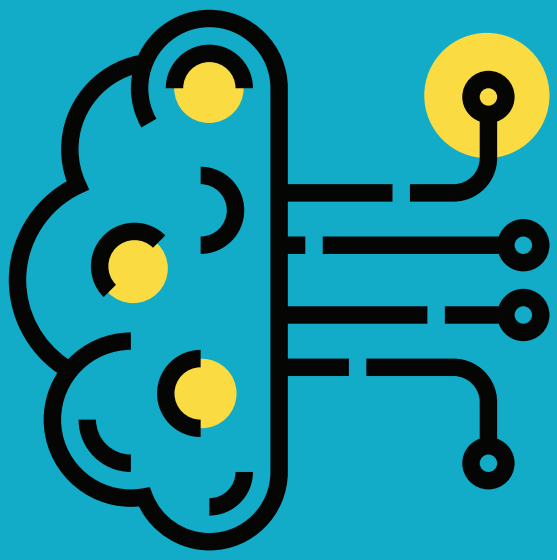
For all these reasons, patients may be referred for evaluation to a variety of specialists – sometimes across different centers, hospitals, or regions of the country and with little communication between institutions. The result is a frustrating process of referrals from one specialist to the next, delaying diagnosis and increasing the risk of misdiagnosis and potential mistreatment.

2. Rode, J. (2005). Rare Diseases: Understanding the Public Health Priority. EURORDIS.
3. About Rare Diseases. (2012) Orphanet.
4. Posada De La Paz, M. et al. (2017) Rare Diseases Epidemiology: Update and Overview. Advances in Experimental Medicine and Biology. Volume 1031:589-604.
5. Rode, J. (2005). Rare Diseases: Understanding the Public Health Priority. EURORDIS.

Deborah Fowler (Sittig) and Cannon Sittig, Morristown, New Jersey, US

TRACK 2 SOLUTION 1

Use Artificial Intelligence to Identify Rare Diseases



VISION

Support frontline physicians to identify patients with a suspected rare disease.

Artificial intelligence, such as machine learning and deep neural network technology, at global scale has the potential to overcome the primary barrier to early and efficient recognition of a patient with a rare disease.

How it would work

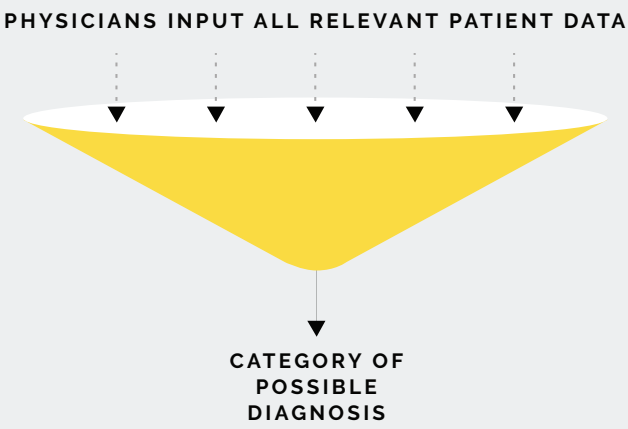
The Global Commission proposes a technology that first "learns" from medical literature based on identified symptoms for each rare disease using natural language processing (NLP) techniques. Then, the technology scans patient health records, highlighting symptoms and matching those symptoms to diseases. It ranks the likelihood that the "matched diseases" are the proper diagnoses for the specific patient. Patient information stored in the cloud would be aggregated globally from all rare disease patients, providing the high volume of data needed to train the technology to detect rare diseases.

Over time, the technology continues to learn and becomes more accurate in extracting symptoms from health records and matching those symptoms to the appropriate disease. Physicians continuously train the technology by inputting a range of data on their undiagnosed patients, culled from medical records and patient reports. The technology then applies learnings from previous analysis to narrow down possible diagnoses. Rather than providing a definitive diagnosis, this technology would identify a category of likely diseases, giving physicians an evidence-based jumpstart in making the right diagnosis. Ultimately, this technology could be applied preemptively, constantly scanning or "mining" electronic health records to flag patients who may have a rare disease in real time, thereby further reducing the diagnostic journey.

MACHINE LEARNING

"Machine Learning facilitates the analysis of large volumes of data by employing algorithms that iteratively learn from that data."

Source: Microsoft Developer



Why this is promising

The benefit of using machine learning algorithms and global, cloud-based data to increase the accuracy of diagnosis is being proven across many health conditions, including cancer, heart diseases, and Parkinson's disease. Its globally applicability is demonstrated in diabetes care in the U.S. and India. Furthermore, it is unrealistic to expect that one physician could identify symptoms for thousands of rare diseases to accurately diagnose every rare disease patient. These types of tools, and other innovative uses of technology advancements, are needed to help frontline providers navigate the complexity of a rare disease diagnosis with speed and precision.

Considerations

A key challenge to implementing this technology globally is the interoperability of the machine learning technology with existing electronic health systems and physician workflows. The technology should be integrated seamlessly with existing systems, platforms, and workflows to encourage physicians to adopt it as standard practice and ensure that no additional training or system changes are required.

Patient Benefit
Patients have the data to validate often dismissed symptoms. Diagnosis will not be dependent on a chance meeting with a physician who happens to have the awareness to match their symptoms with a specific condition.

Physician Benefit
Physicians have evidence-informed guidance on diagnosis pathways for patients.

Health System Benefit
Integrating artificial intelligence and electronic health record technologies allows for targeted diagnostics and reduces unnecessary testing and treatments.

TRACK 2 SOLUTION 2

Facilitate and Expand Access to Diagnostic Testing

VISION

Provide greater access to diagnostic testing for patients who would benefit most.

A technology-enabled solution can solicit guidance from geneticists and other experts to inform decision-making about who should receive diagnostic testing.

Current Situation

The field of genetics and genomics is evolving rapidly – holding great promise for diagnosing rare diseases since 80% are genetic in origin. At the same time, the cost of genetic testing, or genome-wide sequencing (GWS), has gone down dramatically and will continue to fall. Nevertheless, there is limited access to GWS, in part because of the assumption that it is costly to the health system and the patient, even though it may lead to savings if patients are diagnosed and treated earlier. Also, many speciality centers have a long waiting list to receive GWS because of the lack of experts qualified to analyze the findings.

How it would work

This platform allows frontline providers to provide patient information – based on medical records and other relevant information, including family history – to a panel of experts via an online input system. These experts then work with the physician to make informed decisions about whether genetic testing is warranted and, if so, which test to order. Ideally – keeping in mind variance by healthcare system and availability of genetic counselors – the primary care physician or pediatrician who requested the consult will be able to order the test. Equipping physicians with this information will enable them to order the appropriate genetic test based on each patient's set of symptoms, reducing unnecessary testing and better pinpointing the right test. The results are faster and more accurate diagnosis and savings to the healthcare system.

Why this is promising

An easily accessible tool that frontline providers and insurers trust to provide the best available guidance on testing would reduce costs and speed up diagnosis time for patients.

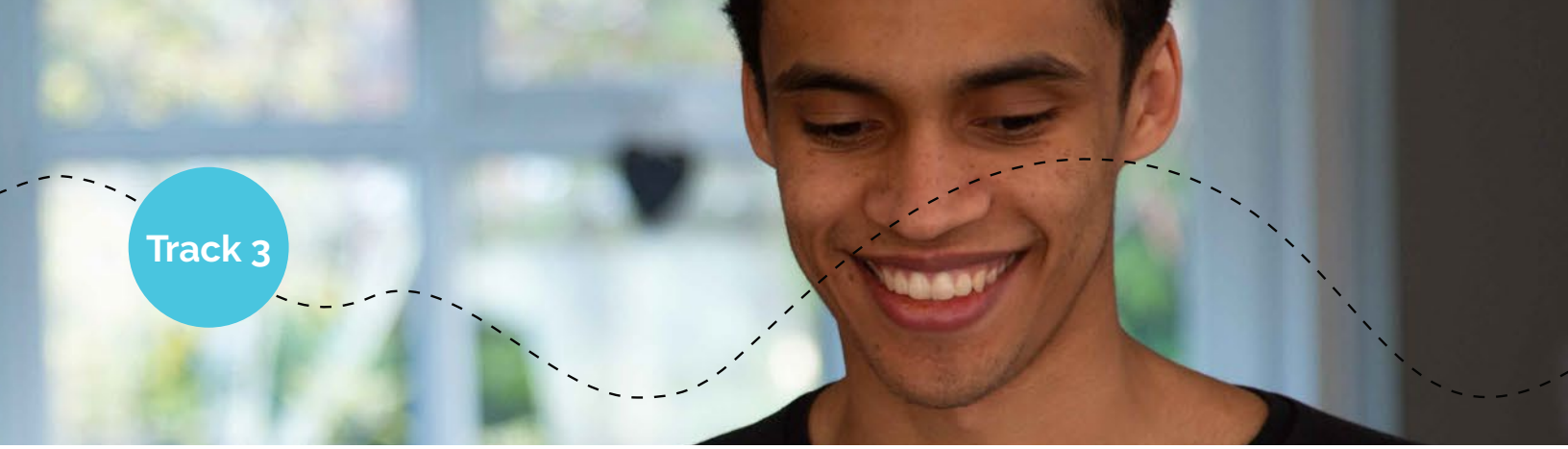
Considerations

With the current rate of advancements in technology and diagnostics, a traditional triage solution may become obsolete over the next 5-10 years. As prices for GWS decrease, more is known about how to interpret genetic data, and more experts are trained to analyze complex genomic data, it is likely that GWS will become the standard of care for many people in many countries. Mirroring this anticipated demand for testing will be an increase in demand for genetic counselors and the need for optimizing their time and resources so they can best serve patients. Furthermore, understanding of sequencing data continues to evolve and improve (i.e. variants of currently unknown significance). This knowledge would need to be incorporated on an ongoing basis. In the interim, evidence of efficacy will be required to support reimbursement for this approach.

Patient Benefit
More timely diagnosis with fewer tests and, as a result, reduced burden on the patient and lower costs.

Physician Benefit
Quick and easy access to genetics experts and genetic testing to determine best options for patient.

Health System Benefit
Fewer tests per patient and more definitive tests leading to reduced overall costs; quicker diagnosis alleviates pressures on over-burdened health systems.



Track 3

Reimagining the Genetic Consultation

Objective: Develop innovative ways to enable medical geneticists to see priority patients more quickly – especially given the growing shortage of geneticists.

Background

An estimated 80% of rare diseases are genetic in origin, which means that undiagnosed patients are largely dependent on medical geneticists to facilitate diagnosis. However, even in the United States, it takes a patient on average between three and nine months to be seen by a geneticist[6], assuming one is even available.

Across the world, the situation is even more dire. The demand for geneticists' services vastly exceeds the supply, and this trend will undoubtedly continue. The significant shortage of geneticists leads to high workloads that further impede these specialists' ability to see patients, significantly delaying diagnosis of a rare genetic disease. The situation is much worse for patients living outside of urban areas or far from academic medical centers. Additionally, the way that geneticists have practiced historically may not be optimal in terms of efficiency, further contributing to wait times and delays in diagnosis. In general, this situation applies to any service that specializes in one of the rare diseases.

80%
of rare diseases are **genetic in origin**

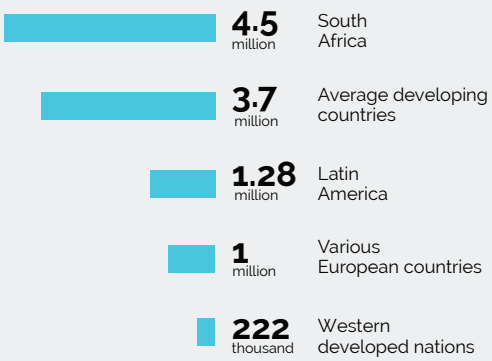
Strategies to shorten the time to receive a genetic consultation – which can be extreme in many countries – are essential to accelerate diagnosis.

Reimagining the diagnostic path and the role of the geneticist can significantly reduce bottlenecks on the patient journey.

6. *Kubendran, S., Sivamurthy, S., & Schaefer, G. B. (2017). A novel approach in pediatric telegenetic services: geneticist, pediatrician and genetic counselor team. Genetics in Medicine, 19(11). 1260-1267.*

Medical Geneticists per Population Size

1 Medical genticist per:



In various European Union countries, there is a range of only one to seven clinical geneticists per million population. Throughout Latin America, it is estimated that there are approximately 500 trained clinical geneticists for more than 640 million people. China, with the largest number of patients with genetic disorders, based on population size, would need to build a workforce of 13,000 medical genetics specialists.

The number of medical geneticists in Africa is unknown, but in South Africa, it is estimated that there is one medical geneticist for 4.5 million people, significantly fewer than the rate of one per 3.7 million in other developing countries and one in 222,000 in Western developed nations.

Sources: Li, P., Zhang, H. Z., Li, M. M., Yu, C., Qi, M., Yu, J., & Wu, B. (2013). Progress and Perspective of Professional Training in Medical Genetics and Genomics: A Report of the Association of Chinese Geneticists in America. North American Journal of Medicine and Science, 6(4),; Kromberg, J., & Krause, A. (2013). Human genetics in Johannesburg, South Africa: Past, present and future. South African Medical Journal, 103(12), 957-961. doi:10.7196/SAMJ.7220

The Webb Family, London, UK

TRACK 3 SOLUTION 1

Establish Pre-Appointment Centers in Genetics Clinics

VISION

Facilitate access to genetic consultations more quickly and efficiently using technology and collaboration.

Prioritizing the needs of patients and shifting select responsibilities from overburdened geneticists to other qualified healthcare professionals has the potential to streamline current processes and get patients in the door faster.

How it would work

As part of making a referral for a genetic consultation, The Global Commission recommends that frontline providers input essential patient data into a digital system that collects data in a standardized way. The physicians also order any additional tests before a child's first genetic consultation to ensure that geneticists have the baseline data needed to make informed decisions during the first appointment. Before the appointment, a genetics team reviews the information to understand the child's symptoms, prior test results, and the reason for the referral.

Because data are collected through a standardized system, these teams can compare data across patients to have a better understanding of potential diagnoses and next steps. The platform collects data from many types of medical record systems and categorizes the information in a consistent format for the reviewer. The team then determines whether a genetic consultation is needed and, if so, which additional tests (i.e. analysis of genome, special biomarkers) should be conducted beforehand and shared with the frontline provider. There is also

EFFECTIVE PRIORITIZATION

A function or department within a genetics clinic that works with the patient and referring physician before the appointment would ensure that patients are seen by the most relevant specialist, the appropriate tests are ordered in advance of a visit, and all test results and patient data are available – saving the patient precious time and ultimately accelerating diagnosis.

the option to conduct any pre-test counseling, if that is relevant to the patient's situation. This type of collaboration results in a more effective and efficient visit with a geneticist, saving valuable time for both the patient and the geneticist.

Ultimately, this technology could be scaled globally, using an artificial intelligence-enabled system to compare larger volumes of data. With sufficient data volume, an automated system could prioritize the most urgent needs of patients with increasing efficiency and accuracy, leading to even more efficient use of geneticists' limited time and a faster diagnosis.

Why this is promising

Similar approaches have been successfully implemented across many types of clinical practice. In a children's hospital in Singapore, a combination of clearing back-logged cases, developing referral guidelines, and establishing a comprehensive triaging system reduced the wait time to see physicians at the hospital from 50 days to approximately 27 days.

Considerations

Creating the system will likely require more staff (case managers, genetic counselors, or similar sub-subspecialties) and development of data systems.

Patient Benefit
Patients see specialists sooner, optimize the time spent with the relevant expert, and avoid unproductive appointments.

Physician Benefit
Appointments are more efficient and productive.

Health System Benefit
Health professionals function at optimal levels, reducing backlogs and increasing employee and patient satisfaction.

TRACK 3 SOLUTION 2

Information Capture and Tele-Consultations for Patients in Rural and Remote Areas

VISION

Ensure that patients in remote areas have access to the quality and type of diagnosis and care that they need.

Technology-enabled data capture and greater use of tele-consultations improve access to geneticists and reduce the strain on families to travel for clinic visits.

Current Situation

While "telemedicine" is already widely available, it is not being activated on a large scale for a genetic diagnosis and to connect rural patients to rare disease specialists. Patients and caregivers often need to travel far distances and invest significant time and money to attend appointments with pediatricians, primary care physicians, geneticists, and other specialists during the search for a diagnosis. Collecting information remotely and transmitting it to the appropriate physician can reduce the burden on children and families, especially those from rural and remote areas.

How it would work

The parents complete an online form in advance of an initial consultation with a geneticist. This patient-friendly form, designed in collaboration with the end-user, uses simple questions and lay language and encourages parents to fill it out with the help of their primary care or referring physician. Making this information available to a specialist will ensure an informed, productive first visit and may avoid the need for multiple in-person appointments. This will optimize the time and resources of patients, caregivers, and geneticists. The form includes prompts for physician notes and additional information to ensure that appropriate tests or records are sent to the specialty clinic before a virtual consultation takes place as a first appointment to avoid unnecessary travel and time. Only when an in-person visit is deemed essential will the family travel for a physical visit.

Why this is promising

Research suggests that communications technology is effective in improving access to care in remote or rural areas through telemedicine. By making data capture easy for patients and leveraging the expertise of trained healthcare professionals, remote information capture can support patients and caregivers across the continuum of care.

Considerations

It is imperative that patients and their parents are supported by adequately-trained healthcare professionals to assist in filling out these digital forms correctly and completely. Families living long distances from these health professionals must be able to access their expertise remotely, meaning either via telephone or video-based telemedicine consultation, which requires an internet connection.

Patient Benefit
Patients and caregivers are less burdened by travel for a consultation and possible follow-up visits and have access to high-quality care despite their geographic location.

Physician Benefit
Geneticists ensure that appointments are used efficiently and effectively.

Health System Benefit
Data collection is completed before specialty visits, reducing unnecessary or less-productive appointments. More patients are able to access physicians at tertiary care centers.

TECHNOLOGY PILOT PROGRAMS

The rare disease community needs proof-of-concept projects to drive progress in shortening time to diagnosis. The Global Commission members are supporting three pilot projects that both bring to life the solution ideas outlined in the report and lend themselves to near-term scale. These projects are utilizing the expertise of the Members as well as engaging additional like-minded partners that are pushing the boundaries of innovation.

PILOT 1

Multifactorial Machine Learning to Recognize Symptom Patterns

PILOT 2

Enable Collaboration Tools for "Intelligent Triage" and Clinical Geneticist Virtual Panel Consultation

PILOT 3

Explore a Blockchain-based Patient Registry and Rare Disease Passport

Pilot 1

Multifactorial Machine Learning to Recognize Symptom Patterns

Summary

By leveraging the power of machine learning, this pilot is testing algorithms that can identify symptom patterns that a physician may not immediately associate with a rare disease. The concept is that technology may lead to a faster diagnosis by linking together subtle symptoms that may seem unrelated when viewed by physicians who have never seen a patient with the disease.

The technology will help analyze medical records data, patient-reported data, and genomics data. Upon successful completion of the pilot, the goal is to use this proof of concept to encourage integration into hospital EMR systems worldwide so that symptom patterns are flagged, prompting a physician to consider testing for a rare disease.

To learn more or to get involved, please contact Julian Isa Gomez (juliani@microsoft.com).

GEOGRAPHIC LOCATION

Centro de Investigación Biomédica en red de Enfermedades Raras (CIBERER), Madrid, Spain

Hospital La Paz de Madrid in Madrid, Spain

NIMGenetics, Madrid, Spain

Idibell, Barcelona, Spain

TECHNOLOGY UTILIZED

Multifactorial machine learning algorithms

DIAGNOSIS BARRIER TARGETED

Difficulty in linking disparate symptoms to make a rare disease diagnosis

Pilot 2

Enable Collaboration Tools for "Intelligent Triage" and Clinical Geneticist Virtual Panel Consultation

Summary

This pilot will utilize virtual collaboration tools and other health templates to design a reliable, multi-purpose platform that will allow genetic clinics to deliver genetic assessments and counseling remotely to patients and primary care physicians. Technology solutions such as facial recognition, virtual consultations, and a triaging system will be packaged on one uniform platform that will be piloted at Children's National Hospital in Washington, DC. If the pilot is successful, the platform will be available for adoption by clinics around the globe and will help to reduce time to diagnosis by minimizing the burden placed on patients in regard to time and cost spent on in-person consultations.

To learn more or to get involved, please contact Carlos Pelayo (carlos.pelayo@takeda.com).

GEOGRAPHIC LOCATION

Children's National Hospital in Washington, DC, USA

TECHNOLOGY UTILIZED

Asynchronous physician consultation app, telemedicine technology

DIAGNOSIS BARRIER TARGETED

Time and cost incurred by the patient through in-person consultations

Pilot 3

Explore a Blockchain-based patient registry and Rare Disease Passport

Summary

Secure technology will be used to create a platform that will empower patients as advocates by giving them control of their own patient data which could ultimately become part of a global patient registry for rare disease patients. Blockchain technology will be used to assure patient privacy and to manage patient consent. Patients will have their information stored in a manner that can be easily accessed and the data will be owned by them, giving patients the power they need to seek additional opinions and lead the pursuit of a diagnosis.

The first phase of this pilot is exploring a proof of concept using dummy patient data, with plans to expand into a trial phase with a partnering organization. Successful results from this pilot can ideally be leveraged by hospital systems, governments, and databases around the world.

To learn more or to get involved, please contact Rune Wetlesen (rune.wetlesen@takeda.com).

GEOGRAPHIC LOCATION

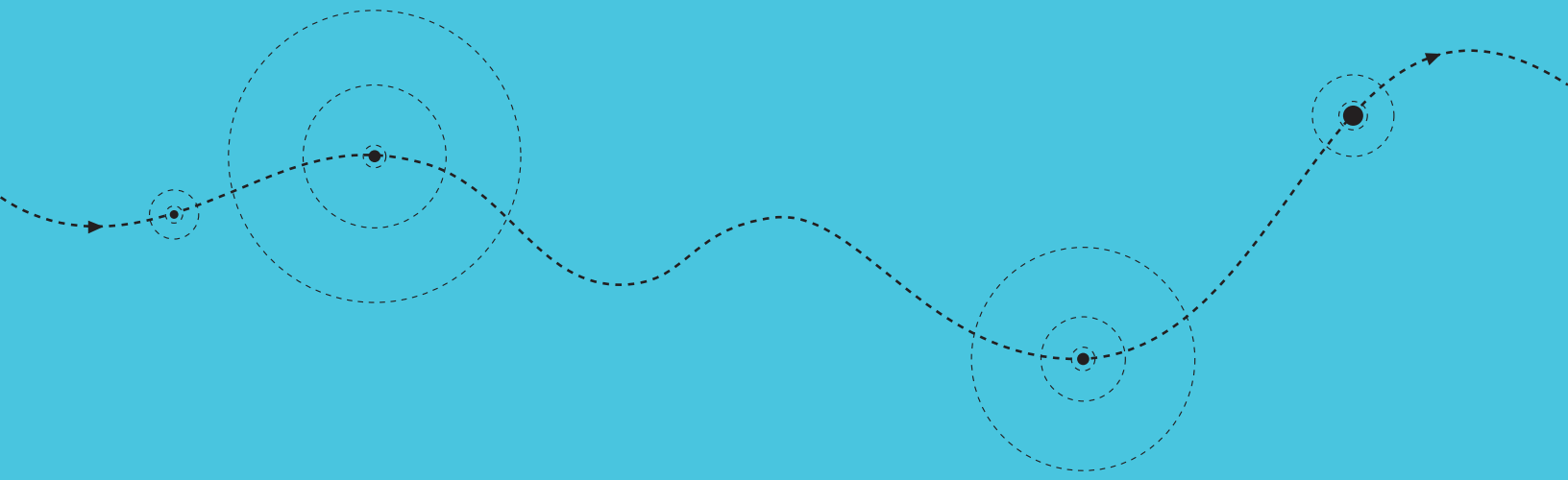
Takeda, Zug, Switzerland

TECHNOLOGY UTILIZED

Blockchain technology to handle identity and consent management

DIAGNOSIS BARRIER TARGETED

A secure way for patient ownership of their health records



GLOBAL POLICY

Introduction to Policy Framework

There has been growing activity at the UN level and different regional/country levels, such as the EU and Asia-Pacific Economic Cooperation (APEC), to develop policy platforms and frameworks to address rare diseases. Examples include: the UN NGO Committee for Rare Diseases; the European Union Commission; the National Plans for Rare Disease in EU Countries; and APEC.

Where possible, the Global Commission suggests that its policy recommendations be incorporated into existing local/regional frameworks and be considered during the development or review of Rare Diseases Plans, within the working plans of government bodies responsible for rare disease policy implementation, and through innovative frameworks of how the use of AI and technologies can disrupt healthcare delivery. In addition, the recommendations adhere to guidance outlined through the EU General Data Protection Regulation (GDPR).

A CASCADE OF BENEFITS

These policy recommendations aim to support a better environment for rare disease diagnosis by:

Improving Efficiency

- By encouraging the use of disruptive technologies such as genetic sequencing, blockchain, and advanced data sharing, diagnostic innovations have potential to deliver efficiencies throughout the healthcare system
- Implications for capacity and cost savings have to be assessed

Reducing Costs

- Use of technology could offer the opportunity to reduce the cost of diagnosing rare diseases (e.g. by reducing the number of doctors appointments and follow-ups) by establishing a more streamlined diagnosis process
- The speed at which genetic screening technologies are integrated into the healthcare systems will increase when their cost declines

Increasing Patient Access

- As the costs for diagnosis are reduced, this helps expand patient access, particularly across less mature healthcare systems where traditional barriers in rare disease diagnosis are greater and prevent patients accessing diagnosis and treatment

KEY FOCUS AREAS

Centers of Excellence

National healthcare systems should issue guidance on collaboration between primary care centers and centers of excellence to ensure consistent, effective and efficient diagnostic and referral protocols. The guidance should address coordinating care, laboratory resources, and knowledge sharing across country borders.

Data Sharing

To fully leverage the global benefit of cloud-based data storage – of particular value to countries with limited patient data (common in the case of rare disease) – health policies should encourage data sharing across borders to increase the likelihood of a match to determine a diagnosis.

Genetic Screening

As countries develop policies around genetic screening, these should incorporate next generation sequencing given its declining cost and potential to more quickly pinpoint a diagnosis, thus generating savings in unnecessary provider visits and diagnostic tests.

Privacy

In encouraging patients to provide medical and other information about their symptoms to help expedite diagnosis, it's critical that countries implement adequate privacy safeguards.

Track 1 Policy Recommendations

Empowering Patients and Families

- **Government support for platforms for shared action across stakeholders**
  Governments should provide a platform for uniting patients, patient advocacy groups, healthcare professionals and policymakers to increase awareness and understanding of the issues patients face in rare disease diagnosis.

- **Enable cross-country sharing of electronic medical records to improve diagnosis efficiency**
  Governments should find optimal ways for cross-country sharing of electronic medical records to increase diagnosis efficiency, while preserving patient privacy and enabling physicians to adopt these systems.

- **Recognize benefits of cross-country rare disease research networks on best practice sharing**
  National healthcare systems and medical societies should recognize the benefits that cross-country rare disease research networks have on diagnosis and encourage national organizations to exchange knowledge and best practices.

Track 2 Policy Recommendations

Equipping Frontline Providers with Tools for Diagnosis and Referral

- **Standardization of diagnostic and referral protocols between primary care centers and centers of excellence**
  National healthcare systems should issue guidance on the collaboration between primary care centers and centers of excellence to ensure standardization of diagnostic and referral protocols within a common user interface.

- **Development and implementation of a genomic sequencing strategy**
  Genomic sequencing strategy setting out how to screen more patients using sufficiently broad, targeted gene panels should be developed and implemented to support diagnosis of rare diseases with known interventions.

- **Defined pathways that ensure access to diagnostic tools**
  Dedicated access pathways that account for the value of diagnostics should be developed and adequate funding for diagnostic tools should be available so that patients have timely and broader access to these technologies.

- **Infrastructure that supports the development and implementation of next-generation sequencing**
  Forward-looking vision on infrastructure investments, specifically supporting the development of next-generation sequencing infrastructure (i.e. molecular genetics labs), should be developed and implemented.

- **Primary care technical training to incentivize adoption of novel approaches**
  The development of new training programs with technical specifications should be incentivized to increase familiarity with novel diagnostic approaches, 'big data', and artificial intelligence.

Track 3 Policy Recommendations

Reimagining the Genetic Consultation

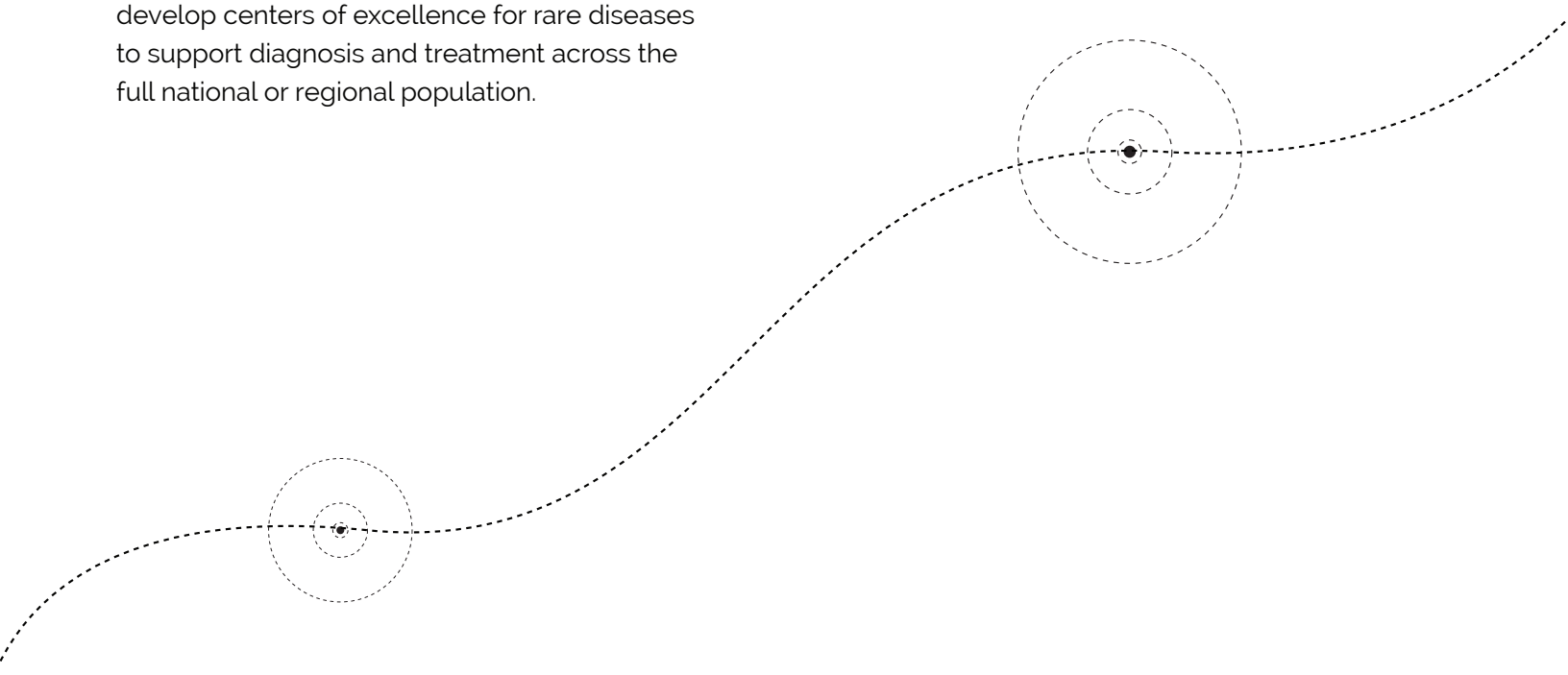
- **Establishing regional centers of excellence and networks to speed up diagnosis**
  International, regional, and national public authorities should engage in activities that encourage and support the establishment of regional centers of excellence and networks that directly facilitate timely diagnosis and act as regional hubs for best practices in the diagnosis of rare diseases.

- **Healthcare systems to improve coordination and standardization of clinical practice**
  National healthcare systems should aim to increase operational efficiencies in routine practice through better coordination and national standardization between healthcare professionals, geneticists, and specialists.

- **Governments to issue plans to establish centers of excellences in support of diagnosis**
  Governments should issue clear plans to develop centers of excellence for rare diseases to support diagnosis and treatment across the full national or regional population.

- **Ensure interoperability across established centers of excellences to optimize data sharing**
  National healthcare systems should not only ensure the availability of novel technologies, but also seek to address system interoperability across the healthcare system, particularly between centers of excellences for rare diseases.

- **Support investment in data network and connectivity to ensure uniform adoption of technologies**
  Governments should support investment in immature data networks and connectivity to support adoption of novel healthcare technologies.



THE PATH FORWARD

The Global Commission's work will continue beyond the publication of this report. As rare disease champions, Global Commission members are committed to making sure our recommendations to end the diagnostic odyssey spark global change across the rare disease field to improve the lives of children. Over the coming year, we will focus on three areas:

1 Implementing technology-based pilot projects

Developing a proof-of-concept for the technology solutions we have proposed is a top priority. By starting in a few defined geographies, we will learn important lessons that will guide how to scale these innovations and bring them to other countries.

2 Leveraging technology to overcome barriers in lower-income countries

Families searching for a diagnosis in developing countries often confront the challenges of weak health systems, lack of specialists and limited access to care, especially if they live in remote communities – factors which make it extremely difficult to identify rare diseases. By helping countries harness technology, we hope they will be able to bypass these common barriers so that frontline providers can offer much needed diagnostic tools and resources.

3 Measuring our progress

Our goal is that this report will become a roadmap for the rare disease community and that our recommendations to end the diagnostic odyssey will be implemented by patients and their families, frontline providers, specialists, hospital systems, and policy makers. We are developing a framework to track actions taken following this report and look forward to sharing progress in 2020.

REFERENCES

About Rare Diseases. (2012) Orphanet. Retrieved from https://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php?lng=EN

Asia-Pacific Economic Cooperation. (n.d.). Retrieved from https://www.apec.org/rarediseases

Charles, B. L. (2000, April). Telemedicine can lower costs and improve access. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10915354

CORD is Canada's national network for organizations representing all those with rare disorders. (n.d.). Retrieved from https://www.raredisorders.ca/

Dinu A.J., Ganesan R., Felix J., Balaji V. (2017). A study on Deep Machine Learning Algorithms for diagnosis of diseases. International Journal of Applied Engineering Research. ISSN 0973-4562 Volume 12, Number 17, pp. 6338-6346. https://www.ripublication.com/ijaer17/ijaerv12n17_03.pdf

Does Your Rare Disease Have a Code? (n.d.). Retrieved from https://www.eurordis.org/news/does-your-rare-disease-have-code

EUROPLAN: European Project for Rare Disease National Plans Development. (n.d.). Retrieved from http://www.europlanproject.eu/NationalPlans?idMap=1

FAQs About Rare Diseases. (n.d.). Retrieved from https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases

Genetic and Rare Diseases Information Center (GARD) – an NCATS Program. (n.d.). Retrieved from https://rarediseases.info.nih.gov/

Guideline of the Malaysian Medical Council. (2006). Medical Records and Medical Reports. http://www.mmc.gov.my/images/contents/ethical/Medical-RecordsMedical-Reports.pdf

Gulshan V, Peng L, Coram M, et al. Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs. JAMA.2016;316(22):2402–2410. doi:10.1001/jama.2016.17216

Hunis, B., Alencar, A. J., Castrellon, A. B., Raez, L. E., & Guerrier, V. (2016). Making steps to decrease emergency room visits in patients with cancer: Our experience after participating in the ASCO Quality Training Program. Journal of Clinical Oncology, 34(7_suppl), 51-51. doi:10.1200/jco.2016.34.7_suppl.51

Li, P., Zhang, H. Z., Li, M. M., Yu, C., Qi, M., Yu, J., & Wu, B. (2013). Progress and Perspective of Professional Training in Medical Genetics and Genomics: A Report of the Association of Chinese Geneticists in America. North American Journal of Medicine and Science, 6(4).

Klimova, B., Storek, M., Valis, M., & Kuca, K. (n.d.). Global View on Rare Diseases: A Mini Review. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28494745

Kromberg, J., & Krause, A. (2013). Human genetics in Johannesburg, South Africa: Past, present and future. South African Medical Journal, 103(12), 957-961. doi:10.7196/SAMJ.7220

Kubendran, S., Sivamurthy, S., & Schaefer, G. B. (2017). A novel approach in pediatric telegenetic services: geneticist, pediatrician and genetic counselor team. Genetics in Medicine, 19(11). 1260-1267.

National Organization for Rare Disorders (NORD) Policy Issues. (n.d.). Retrieved from https://rarediseases.org/advocate/policy-priorities/issues/

NGO Committee for Rare Diseases. (n.d.). Retrieved from https://www.ngocommitteerarediseases.org/

Posada De La Paz, M. et al. (2017) Rare Diseases Epidemiology: Update and Overview. Advances in Experimental Medicine and Biology. Volume 1031:589-604.

Rare diseases - Public Health - European Commission. (2018, December 13). Retrieved from https://ec.europa.eu/health/non_communicable_diseases/rare_diseases_en

Rode, J. (2005). Rare Diseases: Understanding the Public Health Priority. EURORDIS.

The EU General Data Protection Regulation (GDPR) is the most important change in data privacy regulation in 20 years. (n.d.). Retrieved from https://eugdpr.org/

Tiong Tan, J. H., Rajendra, B., Shahdadpuri, R., Loke, C. Y., Ng, S. S.-L., Jaafar, N., … Arkachaisri, T. (2017). A quality improvement project to reduce waiting time for pediatric outpatient referral clinics in Singapore. Proceedings of Singapore Healthcare, 26(4), 224–229. https://doi.org/10.1177/2010105817695294