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REVIEW

Future of Rare Diseases Research 2017–2027: An IRDiRC Perspective

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The International Rare Diseases Research Consortium (IRDiRC) was founded in 2011 with the conviction that rare diseases research had reached a critical juncture. Proof of principle existed that rare diseases could be diagnosed, new treatments successfully developed and approved, and improvements in quality and quantity of life achieved. Government research funders, companies, scientists, and patient advocacy groups had all demonstrated their commitment and effectiveness in contributing to progress in rare diseases research. However, the work was largely atomized, with each organization, each country, and the champions of each disease pursuing independent, often duplicative solutions. The scale of the "rare disease problem"—thousands of rare diseases, the vast preponderance of them with no approved treatment, and decades-long diagnostic odysseys for many patients—led to the realization that the time had arrived for global cooperation and collaboration among the many stakeholders active in rare diseases research, to capitalize on these proofs of principle, and maximize the output of rare diseases research efforts around the world. IRDiRC's initial aims were to aid in the achievement of two overarching objectives: to contribute to the development of 200 new therapies and the means to diagnose most rare diseases by the year 2020.[1] For more detailed information on the history, governance, and nascent stages of the Consortium, please refer to the accompanying piece on the first 6 years of IRDiRC.[2]

Due to the remarkable global surge in activity in rare diseases research over the last 6 years, including contributions by IRDiRC, the Consortium's 2020 goal for 200 new therapies was achieved in early 2017—3 years ahead of schedule—and the goal for diagnostics—the ability to diagnose most rare diseases by 2020—is within reach; these accomplishments were celebrated at the 3rd IRDiRC Conference in Paris in February 2017.[3] The 6 years preceding this 2017 conference have been truly extraordinary for the rare diseases research community and for rare disease patients. Major public-sector research initiatives focused in this area have emerged or expanded in many countries, most notably from the US National Institutes of Health (NIH), the European Commission (EC), and the newly formed Japan Agency for Medical Research and Development (AMED). Engagement and partnering among public funders, scientists, industry, and people living with rare diseases have gone from being the exception to commonplace. IRDiRC has been a major positive factor in raising public awareness about rare diseases, the need for more research to address them, and for collaborative tools which allow ethical data sharing for and with patients. It has also clearly led to increased investment of public- and private-sector research funds for rare diseases, in addition to the research funding raised by patients and patient organizations. IRDiRC has helped to catalyze several important initiatives that are improving collaboration among researchers and enhancing the ability of patients to engage as constructive partners in research.[2,4]

As gratifying as these developments are, those who lead much of the global rare diseases research community are well aware of the enormous challenges that lie ahead for all patients living with rare diseases to receive an accurate and timely diagnosis, to have approved treatments available, to get access to those treatments, and to realize improvements in their quality and quantity of life; in short, to be able to live the best life possible. Although the means to diagnose most rare diseases that are caused by mutations in the coding genome is on track to be achieved either via genotype–phenotype correlation or novel gene discovery, in practice most patients with rare diseases spend years in the

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healthcare system before an accurate diagnosis is made. For rare diseases that have yet to be defined, next-generation genomics and improved data sharing have resulted in faster discovery of disease gene and consequent development of new diagnostics, although there are signs that the rate of disease gene discovery is now slowing, as the remaining unsolved diseases are likely more complex.[5] To respond to this subsequent level of complexity, novel approaches, particularly ones that better address the nonprotein coding regions of the genome, will need to be developed. There is some cause for confidence with regard to new therapies as the rate of rare disease therapeutic development has been increasing. However, it remains the case that 94% of rare diseases lack an approved treatment,[6,7] that the number of currently untreatable rare diseases that have a first treatment approved each year remains low, and that serious inequities remain with regard to patient access to effective treatments even when they are available. Additionally, the present model for recovering drug development costs from market sales has not been proven in its application to rare diseases with worldwide populations of hundreds or less. To address these therapeutic discovery issues, new approaches including data-mining and repurposing, in addition to new models for funding drug discovery and covering treatment costs, will be necessary for the comprehensive treatment of rare diseases worldwide.

With this paradox in mind—the desire to celebrate unprecedented progress but recognizing the immense need and opportunities that remain—IRDiRC set about devising new global rare disease goals for the coming decade. Through this year-long collaborative process, IRDiRC aimed to set goals that would achieve all that is scientifically possible in the short term, and aggressively push the limits of what is currently impossible in the longer term, all with the knowledge that patients are waiting, and "Time Equals Lives."[8]

IRDiRC: 2017–2027

Process

To assure input from all stakeholders and arrive at a short list of ambitious but achievable IRDiRC goals for the next decade, a multistep, year-long, objectives-setting process was implemented. Initially, ideas on critical problems in the rare diseases field and solutions to them were solicited broadly from IRDiRC member organizations and nonmembers represented on the IRDiRC Scientific Committees from academia, patient organizations, the biopharmaceutical industry, and regulatory bodies, in each of the three scientific focus areas: diagnostics, foundational/interdisciplinary, and therapies. The hundreds of ideas submitted were grouped and consolidated, debated online and in-person, and then voted on to determine which were of highest priority and need. Based on this process, a series of potential goals were generated, along with activities to advance the goals, and metrics to measure progress. During the internal IRDiRC Meeting in Paris, France in February 2017, the candidate goals, activities, and metrics were further refined by the IRDiRC members. At the open IRDiRC Conference that followed, the goals were presented to the greater rare disease community for feedback, discussion, and questions to further shape the IRDiRC vision and objectives for the next decade. This vigorous, animated, and informed session added broad public input to the goal-setting process and in addition spurred excitement and engagement about IRDiRC's plans to deliver on the promise of science for people living with rare diseases over the next decade. Following the Meeting and Conference, the final IRDiRC Vision and 2017–2027 Goals were formally adopted by vote of the IRDiRC Consortium Assembly.

Framework

Given the unusually broad scope of IRDiRC—in science, constituencies, and geography—the IRDiRC goal-setting process incorporated an unusually broad series of criteria. First, the process utilized the "SMART" criteria—that is, candidate goals needed to be Specific, Measureable, Achievable, Realistic, and Timely. They also needed to be within the scope of IRDiRC's research mission. Lastly, they needed to be easily understood by a wide variety of stakeholders and audiences, while also being bold and transformational. Therefore, it was determined to organize the process on four levels—Vision, Goals, Activities, and Metrics. The Vision is IRDiRC's overarching statement of the end state toward which all its activities drive; the Vision is aspirational and not time-delimited. The Goals state bold but distinct achievements that IRDiRC commits to accomplish over the next 10 years that will advance the realization of the Vision. The Activities are discrete, shorter-term projects IRDiRC will perform to advance each of the Goals; the list of Activities will continually change, depending on successes and failures of previous Activities and evolution of the field. The Metrics will assess and track progress of Activities over time, ensuring accountability and progress toward the Goals.

The new IRDiRC Vision, the IRDiRC Goals for 2017–2027, and exemplar Activities and Metrics, follow.

The IRDiRC Vision

Enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within 1 year of coming to medical attention

IRDiRC is well aware of the aspirational nature of this Vision; IRDiRC is also cognizant that some aspects of the Vision are outside its research mission. However, IRDiRC also believes that the Vision is achievable with all stakeholders' commitment, cooperation, and collaboration. Thus, the challenge inherent in the Vision is intentional, aimed at galvanizing the broad rare disease community, within IRDiRC and outside it, to not only enable universal diagnosis and treatment, but also ensure that these interventions reach people with rare diseases, and have the intended positive impact on their health and well-being.

The IRDiRC Goals for 2017–2027

The three Goals that IRDiRC members have committed to achieving in the next decade to advance the realization of the IRDiRC Vision follow, along with the rationale, challenges, and opportunities of each.

Goal 1: All patients coming to medical attention with a suspected rare disease will be diagnosed within 1 year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline

Recent data indicate that approximately half of the individuals with a suspected rare disease are undiagnosed, while those who have received a diagnosis wait on average 5–6 years,[9,10] and diagnostic delays of several decades have been observed. The clinical introduction of new diagnostic methods such as next-generation sequencing has allowed the laboratory turnaround time to be as short as several weeks to diagnose some of the rare diseases with a known molecular basis. Each undiagnosed rare disease represents an opportunity to open up a new area of biological insight, and it follows that, as the number of novel genes and pathogenic variants identified increases, so does the diagnostic yield. The time has come for researchers, clinicians, and patients worldwide to collectively understand the etiology of the vast number of rare diseases, make the final push to enable the diagnosis of all rare diseases, and facilitate access to an efficient diagnosis for patients. Within the next decade, IRDiRC will work together to implement a system whereby patients with a suspected rare disease of known molecular basis will be diagnosed within 1 year of initial presentation to a medical professional instead of confronting a years-long diagnostic odyssey. The challenges in achieving this part of Goal 1 are principally operational, involving public and physician awareness, efficient referral within the medical system, and the requirement for radically more efficient sharing of diagnostic expertise and data among practitioners and researchers worldwide.

Rare disease mechanism discovery

The number of unsolved patients following whole exomes sequencing argues that more disease genes and variants await discovery, thus the discovery effort must be expedited. So far, most of the known disease variants fall in coding regions of the genome, but much less is known, for example, about the role of noncoding region variants and structural variants in disease.[5] This calls for approaches that are complementary to whole exome sequencing (WES) such as whole genome sequencing (WGS), long read technologies, and transcriptome sequencing that can more effectively target noncoding regions and/or structural variants. Moreover, variant interpretation still needs improvement through developments in bioinformatics, analysis algorithms, and data sharing. Wide acceptance of data standards and ontologies (e.g., Human Phenotype Ontology (HPO)[11] and Orphanet Rare Disease Ontology (ORDO)),[12] and automated exchange of phenotypic and genomic information via shared platforms and tools (e.g., Matchmaker Exchange[13] and RD-Connect[14]) should be required to transform sequence information into diagnostic knowledge. Functional analyses at scale will need to be developed to facilitate variant interpretation in conjunction with data sharing.

Patient access to diagnosis

After initial presentation to a medical professional, patients with a rare disease often spend a long time trying to find a specialist with appropriate expertise to recognize the syndrome or perform the correct diagnostic test. Comprehensive and easily accessible information about subspecialty medical professionals and diagnostic laboratories can help shorten this time. In conjunction, sequencing and analysis costs will need to continue to drop to improve affordability. Finally, robust data should be collected and analyzed on diagnostic utility, clinical utility, and cost-effectiveness to facilitate reimbursement of sequencing-based diagnosis by more health insurance companies.

International network for undiagnosed patients

It has been shown that undiagnosed patients have an increased chance for their diagnostic challenge to be "solved" in a research setting where more comprehensive sequencing, analysis, and data sharing can be performed. It is time to establish global networks of clinical and research laboratories to collectively tackle undiagnosed diseases. Ideally, appropriate consents including the provision for research and data sharing should be obtained from the outset of the clinical testing process. Samples for further research using sequencing and other genomic methods should be collected and stored in appropriate biorepositories. However, there is only so much that can be done without cooperation and coordination on a larger scale. If a diagnosis is not made after initial sequencing, then the data should be immediately transferred to a global network of appropriate expertise that can accept it for further study and immediate feedback of the result. The Undiagnosed Diseases Network International (UDNI)[15]—modeled after the US NIH's Undiagnosed Diseases Program (UDP)—is an example of a program established to aid in this effort. Collaboration with the UDNI as well as UDP will bring crucial attention to complex cases, where collective expertise will lead to a higher chance of providing a much-needed diagnosis in order to identify the best course of treatment for each patient. IRDiRC also encourages collaboration with national programs, such as the Japanese Initiative on Rare and Undiagnosed Diseases (IRUD),[16] to capitalize on additional knowledge and data sharing with the aim of bringing diagnoses to rare diseases patients.

Education of physicians and engagement of patients

To take advantage of fast-evolving technologies, established networks, and available tools, it is necessary to educate physicians and engage patients and families. For example, education can be provided via courses on rare diseases and new diagnostic methods and targeted to various end-users, including physicians and patients, with different levels of knowledge at the outset. Patient engagement in research and clinical networks should continue to be facilitated.

Metrics

Online Mendelian Inheritance in Man (OMIM)[17] and Orphanet[18] will continue to be reliable resources for monitoring newly reported diseases and disease genes. The time it takes for a patient to be diagnosed could come from surveys of specialty physicians, clinical labs, and patient

organizations, or more targeted sampling via rare disease networks.

Goal 2: 1000 new therapies for rare diseases will be approved, the majority of which will focus on diseases without approved options

Although the rate of therapy development for rare diseases has been increasing, the fact remains that most rare diseases—well over 90%—lack an approved treatment and the number of currently untreatable rare diseases to receive a first treatment each year remains low. The introduction of regulations, policies, and incentives dedicated to orphan drug development has spurred significant investment in therapeutic development to the benefit of rare disease patients.[19] Since 2010, IRDiRC has tracked the number of orphan medicinal products (OMPs) receiving first approval for a new indication in the European Union and/or the United States, and has found an increase from 15 in 2010 to more than 40 in 2014 and 2015, with a current average of ~35 approvals per year. Between 2010 and 2016, over 220 OMPs have received first approval for a new indication in the European Union and/or the United States. While significant, this achievement does not negate the fact that patients with one of the thousands of other rare diseases are still waiting for a therapy to be approved for their conditions. Innovative approaches, including clinical trial design, data and specimen collection, clinical end points, repurposing, natural history studies, and engaging the many players involved are necessary for exponentially improving therapy development on a global scale.

Therapeutic development pipeline

Assuming a constant delivery of OMPs from the pipelines of biopharmaceutical industries, in the next 10 years treatments would become available for only ~600 of the 7,000 known rare diseases. Thus, new approaches will be needed, particularly since the current pace may not be sustained. In 2016, only 34 new indications were approved, suggesting a slowing of the development and approval pace. Moreover, developed drugs have often clustered around similar technologies or therapeutic approaches that will soon have maximized their capacity to generate new therapeutic advances. For instance, the systemic manifestations of several lysosomal storage disorders (LSDs) have been quite successfully addressed by treatments based on enzymatic replacement through recombinant proteins containing mannose-6-phospate residues or small molecules through substrate inhibition, but the list of remaining LSDs to be targeted is significantly shrinking and all these drugs leave unaddressed the same manifestations (e.g., the central nervous system involvement). The "lower-hanging fruits" of easily developable indications, addressable by traditional approaches, will likely decrease over time, leaving more complex therapeutic targets and yet unproven technologies.

In addition to challenges specific to rare diseases, the risk-adjusted development costs in the pharmaceutical industry have witnessed an overall increase, and postregulatory approval access challenges have become larger due to budgetary constraints of payers.[20,21] In order to achieve the IRDiRC goal of 1,000 new therapies in the next decade, a significant increase in R&D productivity is needed, with a compounded annual growth rate at or above 10%, thus tripling the current rate. Moreover, the IRDiRC goal is for new orphan drug approvals to be predominantly for diseases currently without approved drugs. Although IRDiRC anticipates that many of the 1,000 new approvals will be new indications for existing agents rather than new molecular entities, scalability and sustainability will be significant challenges, both to the regulatory system, and to healthcare budgets. IRDiRC includes representatives from the world's major pharmaceutical regulatory agencies and is deliberately increasing representation from health technology assessment agencies, in order to anticipate and mitigate these challenges.

Potential advancements in therapeutic development

This important goal can be achieved only through a dramatically more efficient development process driven by a radically new approach utilizing common standards across distinct research fields, sharing of best practices, creating sustainable business models, and redefining the regulatory environment. New methodologies are needed to streamline drug development. These include early stage improvements such as increasing the efficiency of data collection and sharing, improving the understanding of disease progression and phenotypes, improved methods for preclinical assessment of safety and efficacy, and methodologies for small size clinical trials. In addition, later stage advancements including defining end points more universally suitable for measuring patient's benefit, providing medical relevance, generating regulatory benefit/risk evidence, and quantifying a product's economic value for payers, companies, and society at large are essential. The emerging European Reference Networks[22] and the potential collaborations with the US Rare Diseases Clinical Research Network[23] provide an unprecedented opportunity for coordinating global rare diseases research to: improve care standards, increase access to diagnosis and treatment, increase the understanding of phenotypes and natural history, increase enrollment of patients into clinical trials, and more effectively create and manage disease registries.

Engaging patients and regulators

Placing patients at the center of clinical research, drug development, and evaluation is increasingly recognized as paramount to fully understanding a disease and to identifying meaningful end points. Their knowledge, contribution, empowerment, and participation are crucial to increasing the efficiency of such efforts. Close cooperative actions with regulators will also be indispensable, particularly via early dialog with regulators and product development with protocol assistance to ensure regulations are adhered to at every step, thus maximizing the potential outcome of a marketing authorization. To cope with an increased volume of applications and requests of protocol assistance, a number of changes will be necessary: streamlining the approval process, creating collaborative review processes between regulators from different jurisdictions, increasing human resource and training programs, and potentially updating regulations to assist in accelerating therapy development. Efforts are already under way to streamline and align regulatory processes across jurisdictions[24]; IRDiRC aims to aid and foster

such efforts, as they will ultimately contribute to the development of new rare disease therapies. In addition to coordinating research efforts, data sharing, and patient engagement, it is also vital to promote changes to the drug development landscape such as new models of risk and incentive sharing between public and private partners, systematic repurposing of existing agents, and developing a more flexible regulatory framework. IRDiRC is committed to work as a key enabler of this quantum change as reflected in the vision. IRDiRC promotes the development and sharing of new tools, best practices, and recommendations to inform research policies and strategies worldwide. IRDiRC also will foster new methods to enable dialog between private and public research funders and regulators with the goal of bringing about this quantum change needed to reach the ambitious goal of developing 1,000 new therapies within the next decade.

Metrics

The number of new indications treated with medicinal products for rare diseases receiving marketing authorization in the European Union, the United States, and Japan will be the main indicator of progress toward the 1,000 therapies goal, based on information from the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). A number of secondary metrics will also be developed to monitor the quality of evolution of the field, e.g., the number of medicinal products for rare diseases with marketing authorization but without orphan designation, and the number of RDs that are addressed by these medicinal products.

Goal 3: Methodologies will be developed to assess the impact of diagnoses and therapies on rare disease patients

While faster diagnosis and increased development of new therapies are essential, their impact on people living with rare diseases cannot be assumed; for example, patients can benefit only to the degree that they have access to the interventions, and access may or may not lead to the intended improvement in quantity and/or quality of life. Although IRDiRC members, representing funders, companies, patient advocacy groups, scientists, and other stakeholders agreed on this truism, they varied in their view of IRDiRC's role, as a research organization, in addressing the impact issue. While patient advocacy group members tended to support inclusion of impact assessment as critical IRDiRC research, many scientific and funder members felt that this was more the mandate of health technology assessment authorities. A rich and important debate, including with numerous stakeholders participating in the IRDiRC Conference in February 2017, concluded with the realization that no matter what organization is charged with impact assessment, the methods to do that assessment are currently woefully inadequate, and that IRDiRC therefore could and should focus on the development of improved methodologies and tools for performing such impact assessments.

Appropriate access to diagnosis and treatment depends on a multitude of factors, including clinical guidelines and recommendations; regulatory policies; pricing; insurance, coverage, formulary, and reimbursement; and even the awareness of healthcare providers. The efficiency and extent of translation of diagnostic and treatment developments into tangible outcomes and practice are currently hampered by limited assessment of their impact on patients. Development of robust methods to measure access, effectiveness in real-world settings, and impact on patient outcomes will therefore be a focus of the IRDiRC over the next decade. Such research needs to particularly involve underdeveloped areas worldwide, which starts by expanding our global footprint into more underrepresented regions and the inclusion of such members in all activities. Equally important, as a global health issue, IRDiRC members are committed to implement these advances equitably to reduce existing and potential health disparities. Such disparities include those between Indigenous and non-Indigenous peoples, which, at its core, requires indigenous-specific reference genetic data sets to improve clinical diagnosis and optimize therapies.[25–28] We anticipate that this research will not only benefit rare disease patients worldwide, but also have impacts in the wider context of personalized medicine.

Measurement of impact

Assessing the impact of diagnosis remains a complex issue. Counting the number of diagnostic tests might be relatively simple given the various worldwide, country-specific, and company-specific listings but is nonspecific and indirect, speaking only to availability and not access. Quantifying the number of people who have received a diagnosis, the length of the diagnostic odyssey, and the impediments to diagnosis is, however, not straightforward. This quest goes beyond the mandate of a single clinical or research team. Aggregating this information requires a multidisciplinary and multistakeholder approach that must navigate the continuum from clinical research to healthcare services in multiple systems and cultures. Thus, measuring the impact of diagnosis may include such items as quantitative and statistical analysis, assessment of quality of life, and/or economic dissection of repercussions on medical care.

Assessing the impact of treatment is also largely limited to regulated therapies, since these are easier to count. It has been suggested that other types of treatments or interventions, such as nonpharmaceutical approaches, physical and behavioral therapies, and/or devices may be as valuable to patients as "drugs," but these are generally neglected when considering impact. Similarly, research into healthcare system optimization and the implementation of recommendations to improve its functions may have an important impact on patients' outcomes and health.

The use of existing tools and platforms, e.g., the NIH Genetic Testing Registry,[29] and RARE-Bestpractices,[30] that help develop rigorous process and qualitative markers for the evaluation of the diagnostic and modes of care should be factored into any methodology development. The funders should engage in identification and financial support of research projects that will tackle the complexities around the measurement of health outcomes. Research in health systems, economics, and ethical frameworks should also be promoted. Furthermore, IRDiRC may consider how to engage appropriate stakeholders in healthcare systems to

ensure that any methods developed could be recognized rapidly, and applied at both the national and international levels.

CONCLUSION

The members of IRDiRC and, more important, their organizations, have committed themselves to an ambitious set of 10-year goals that will advance the realization of the IRDiRC vision of prompt and accurate diagnosis, effective treatment, and amelioration of illness for all people living with rare diseases. In an ambitious and multifaceted project like IRDiRC's, coordination and monitoring of progress will be essential; these will be performed by the IRDiRC Committees and Scientific Secretariat. The Committees and their Task Forces will promote activities to advance the goals, and metrics will be applied to monitor progress toward the goals. Some may question whether the costs of IRDiRC's vision can be justified, given the low prevalence of these disorders. We, the leadership of IRDiRC, believe that, to the contrary, the global community cannot afford *not* to achieve these goals, and the resources the member organizations are committing to rare diseases research to realize the IRDiRC vision testify to this conviction. On a purely financial level, the cost to health systems of caring for people whose rare diseases are undiagnosed or untreatable are disproportionate and growing. On a human level, we believe that every person with an illness, whether rare or common, has the same right to a diagnosis and treatment, and that the contributions to humanity of rare disease patients are well beyond our imagining. We are all familiar with how people living with HIV/AIDS, once an undiagnosable, untreatable rare disease, are continuing to enrich the human family in innumerable ways, and how much the work to diagnose and treat HIV/AIDS taught us about human biology and other diseases. This is our vision for the millions of people living with the thousands of other rare diseases.

As leaders of the global rare diseases community in the public and private sectors, we are under no illusions about the challenges to achieving our new goals by 2027. However, we are equally aware of the epochal advances in rare diseases science and medicine over the last decades, the evolution of a culture of collaboration, teamwork, and common cause that now unites the rare disease community, and the reality that the pace of progress is positioned to accelerate. These are goals that can only be achieved with fundamental changes in the conduct and sharing of science, and application of that science as rapidly as possible to advance the care of rare disease patients—changes IRDiRC members have committed to catalyze. We believe that these goals are eminently achievable over the next decade—but only with continued commitment to scientific excellence, rapid and ubiquitous sharing of approaches and data and resources, and continued monitoring of progress and constant reevaluation of direction based on new data. IRDiRC's is a rigorous, noble—and achievable—vision, which we believe will bring out the best in science, in medicine, and in ourselves. We welcome new members, who share our vision and commitment to action, to join us. And we look forward to updating the community on our progress.

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