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The division of rare diseases research innovation at the national center for advancing translational sciences, NIH: mission, history, and current research activities

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Abstract

The mission of the NCATS Division of Rare Diseases Research Innovation (DRDRI), formerly known as the Office of Rare Diseases Research, is to advance rare diseases research to benefit patients. DRDRI is part of the National Center for Advancing Translational Sciences, one of the 27 components of the US National Institutes of Health. DRDRI facilitates and coordinates NIH-wide activities involving rare diseases research, as well as directly supporting rare diseases research activities. These activities include the development and maintenance of a centralized database on rare diseases; collaboration and coordination with organizations focused on orphan products development and rare diseases research across the globe, advising the Office of the NIH Director on matters related to NIH-sponsored research involving rare diseases; and responding to information and policy requests about rare diseases within the NIH. DRDRI also supports various rare diseases research activities, including the Rare Diseases Clinical Research Network, rare disease-related conference grants, and assessment of the costs of untreated rare diseases. In addition, several of the projects DRDRI is supporting are "many diseases at a time" translational approaches for rare diseases, which emphasize leveraging commonalities across multiple rare

diseases. These include the support of "basket trials" based on shared molecular etiologies across multiple rare diseases, as well as therapeutic platforms for the treatment of monogenic diseases, such as gene therapy and genome editing. This Perspective will provide an overview and summary of these various activities, noting where relevant our collaborative partnerships within the U.S. and internationally.

Keywords: Clinical research readiness, genetic disease, diagnostic odyssey, translational research, research funding

DRDRI, A HISTORICAL PERSPECTIVE

Following the completion of the report from the National Commission on Orphan Diseases in 1989, NIH established the rare diseases initiative to implement the recommendations provided by the Commission. In 1993, NIH established the Office of Rare Diseases (ORD) and later changed the name to include Office of Rare Diseases Research (ORDR) to reflect the expansion of activities to focus on research needs and opportunities. Activities included the development of the Genetic and Rare Diseases Information Center (GARD), providing support for the Bench-to-Bedside Awards program at the Clinical Center Hospital with other NIH Research Institutes and Centers, contributions of information to clinical.trials.gov information system provided by NIH's National Library of Medicine, the International Rare Diseases Research Consortium (IRDiRC), the International Collaboration on Rare Diseases and Orphan Products (ICORD), the Rare Diseases Clinical Research Network (RDCRN), and assistance with the development of NIH's Undiagnosed Diseases Program with the expansion to the Undiagnosed Diseases Network (UDN), and the International expansion (UDNI).

On November 6, 2002, the United States enacted Public Law 107-280, the Rare Diseases Act of 2002. This legislative mandate requested NIH to establish and directed ORD to support regional centers of excellence for training and clinical research into rare diseases, and demonstration of prevention, diagnosis, and treatment methods for rare diseases, and to address the needs of rare disease clinical research. The legislation also directed ORD to increase the national investment in the development of treatments and diagnostics for rare disease patients. The legislation suggested a broad range of research and education activities to assist in developing a research agenda for conducting and supporting research on rare diseases. One effective tool used extensively is support for scientific workshops and symposia to identify research opportunities and establish research priorities and a research agenda for rare diseases. ORD established the Genetic and Rare Diseases (GARD) Information Center to provide understandable information about these diseases to the public, medical professionals, and patients and their families.

The National Center for Advancing Translational Sciences (NCATS), one of 27 Institutes and Centers at NIH, was established in 2011 with the goal of transforming the translational process so that new treatments and cures for diseases could be delivered to patients faster. At that time, ORDR was transitioned from within the Office of the NIH Director to become one of the founding programs within the new Center. Finally, in 2022, ORDR became the Division of Rare Diseases Research Innovation (DRDRI), further emphasizing the importance of rare diseases research within NCATS.

DRDRI's portfolio encompasses a broad range of resources [Table 1]. Since becoming part of NCATS, DRDRI has maintained its role in promoting coordination and cooperation among the NIH research institutes and centers that support rare disease research. DRDRI also collaborates with national and international patient organizations, global research investigators, the biopharmaceutical and medical devices industries, and health and scientific organizations with an emphasis on rare diseases. More recently, DRDRI

Table 1. Links to information, resources, and funding opportunities mentioned in the text

Resource	Site	Description
NCATS	https://ncats.nih.gov/about/center/history	This overview covers NCATS history since its inception in 2011. DRDRI is a division of NCATS, which is a center within the National Institutes of Health
Rare diseases act of 2002 (public law 107-280)	https://www.congress.gov/107/plaws/publ280/PLAW-107publ280.pdf	This law established an Office of Rare Diseases and increased the national investment in the development of diagnostics and treatments for patients with rare diseases and disorders
Rare disease day at NIH	https://ncats.nih.gov/rdd https://ncats.nih.gov/events/rdd/past-events	This annual event raises awareness about rare diseases, the people they affect, and NIH collaborations that address scientific challenges and advance research for new treatments
Genetic and rare diseases (GARD) information center	https://rarediseases.info.nih.gov/	GARD is a website and phone line that aims to support people living with a rare disease and their families with free access to reliable, easy-to-understand information
NCATS toolkit for patient-focused therapy development	https://ncats.nih.gov/research/research-resources/ncats-toolkit	This resource repository educates and empowers patient advocacy groups to accelerate research
RePORTER	https://reporter.nih.gov/	This platform has specific information on all NIH-funded research, including DRDRI programs
Rare diseases clinical research network (RDCRN)	https://www.rarediseasesnetwork.org/	The RDCRN is a network of clinical research consortia and a Data Management and Coordinating Center (DMCC), and each consortium actively partners with patient advocacy groups
Impact of rare diseases on patients and healthcare systems (IDeaS) initiative	https://ncats.nih.gov/news-events/news/nih-study-suggests-people-with-rare-diseases-face-significantly-higher-health-care-costs	DRDRI and collaborators quantified the prevalence of rare disease patients and the direct medical costs of 14 representative RD within 4 different healthcare system databases. DRDRI has a contract to inform methods for clinical decision support tools to alert clinicians to possible cases of rare diseases
Clinical Trial readiness (CTR) grants	https://ncats.nih.gov/programs/clinical-trial-readiness	This program supports projects focused on collecting the data needed to move promising rare disease therapies and diagnostics to clinical trials
Diagnostic odyssey grants	https://ncats.nih.gov/programs/diagnostic-odyssey	This two-phase program supports clinical projects that address the critical need for timely identification and accurate diagnosis of rare disease patients
Conference grants	https://ncats.nih.gov/funding/open/conference-grants	This program supports conferences, specifically research opportunities for rare diseases and including patient support groups
Shared molecular Etiologies (SaME)	Mitochondrial disease basket trial https://reporter.nih.gov/search/rP54qWIDQE-L2dHSuxSfow/project-details/10301261 Jak-Stat pathway basket trial https://reporter.nih.gov/search/RTARcTDftU-aPHFm7mZ3Bw/project-details/10476619	These funded projects support basket trials in multiple rare diseases for drugs targeting shared molecular etiologies across multiple different diseases
IRDiRC shared molecular etiologies task force	https://irdirc.org/shared-molecular-etiologies/	This DRDRI-initiated task force extends the basket trial approach in rare diseases internationally
Platform vector gene therapies (PaVe-GT)	https://pave-gt.ncats.nih.gov/ https://pave-gt.ncats.nih.gov/outputs	This program tests the hypothesis that using the same AAV serotype, manufacturing, and production facilities for multiple AAV gene therapies can increase the efficiency of the start-up of AAV gene therapy trials. The second link goes to the Orphan Drug Designation template resources
Accelerating medicines partnership (AMP) program bespoke gene therapy consortium (BGTC)	https://fnih.org/our-programs/accelerating-medicines-partnership-amp/bespoke-gene-therapy-consortium-bgtc/	This Foundation for the NIH public-private partnership is focused on streamlining the regulatory path for AAV gene therapies, with a specific focus on diseases of no current commercial interest
Bespoke gene therapy consortium (BGTC) regulatory playbook version 1.0	https://fnih.org/wp-content/uploads/2024/02/BGTC-Regulatory-Playbook-preliminary-FINAL-FOR-RELEASE_20240205.pdf	The Accelerating Medicines Partnerships® (AMP®) Bespoke Gene Therapy Consortium (BGTC) recognized the need for a comprehensive playbook that would serve as a guiding framework for the development and regulatory submission of adeno-associated virus (AAV) gene therapies for rare diseases. Building out this playbook to support the key processes up to a sponsor's first-in-human (FIH) trial required a collaborative and modular approach. Version 1.0 of the playbook is designed to serve as a one-stop-shop guide and roadmap to investigational new drug (IND) submission for these innovative gene therapies
Somatic cell genome editing (SCGE)	https://commonfund.nih.gov/editing	This NIH Common Fund program is accelerating genome editing technologies into the clinic. Phase 1 focused on technology development, and on better ways to deliver genome editing in different cells and tissues. Phase 2 is more focused on moving into the clinic

SCGE toolkit	https://scge.mcw.edu/toolkit/	The Somatic Cell Genome Editing (SCGE) toolkit serves as the hub to promote the novel strategies and technologies that are funded by NIH Common Fund's SCGE program
TARGETTED challenge	https://www.freelancer.com/nih/targeted-challenge	A prize competition to identify better technologies to either: target genome editors to specific cells and tissues, or non-viral technologies to deliver genome editors across the blood-brain barrier
Therapeutics for rare and neglected diseases (TRND)	https://ncats.nih.gov/research/research-activities/TRND	The TRND program supports the preclinical development of therapeutic candidates intended to treat rare or neglected disorders, with the goal of enabling an Investigational New Drug (IND) application
Ultra-rare Gene-based therapy (URGenT) network	https://www.ninds.nih.gov/current-research/research-funded-ninds/translational-research/ultra-rare-gene-based-therapy-urgent-network	The goals of the URGenT program are to: Accelerate the advancement of discoveries into the clinic Provide resources and expertise not currently available to applicants Deliver therapeutics to patients with ultra-rare neurological diseases Standardize and harmonize best practices and protocols for the development of gene-based therapies for ultra-rare diseases

has directly supported research activities, with a greater emphasis on clinical trial designs that leverage commonalities across different rare diseases, as well as on accelerating therapeutic platforms to treat monogenic diseases, such as gene therapy and genome editing. In the sections below, we highlight some of the main activities supported by DRDRI. Before outlining our current research activities, we first provide an update on the magnitude of the current challenge posed by Rare Diseases.

The scope of the problem

Our understanding of the scope of the challenge posed by Rare Diseases, as well as research and therapeutic strategies, has changed dramatically from the early days of ORDR. Specifically, based on the most current genetic and informatics analyses, there are at least 10,000 rare diseases. Collectively, rare diseases impact approximately 30 million people in the U.S.[1,2]. In addition, multiple economic analyses[3], including work from DRDRI[4,5], have estimated that, in the US, the direct medical costs of rare diseases are around $400 billion/year. Note that these are only direct costs, and do not include indirect/non-medical costs, estimated to be nearly $550 billion[3] in the US. These numbers provide context for the ongoing DRDRI activities highlighted below.

OUTREACH AND INFORMATION RESOURCES

Rare disease day at NIH

Since 2011, DRDRI has hosted an annual Rare Disease Day at NIH event to raise awareness about rare diseases, people living with rare diseases, and NIH collaborations that advance translational rare diseases. The goals of Rare Disease Day at NIH are to: (1) Demonstrate the NIH's commitment to rare disease research; (2) Highlight NIH-supported translational rare diseases research; (3) Facilitate dialogue among the rare diseases community, including patients, caregivers, patient advocates, healthcare providers, researchers, trainees, students, members of industry, and government staff; (4) Exchange the latest rare diseases research information with stakeholders; and (5) Spotlight stories told by people living with a rare disease and their families, and communities. This is an opportunity to work with other NIH Institutes and Centers also interested in rare diseases research and with patient advocacy groups in developing the event agenda each year. In addition to panel discussions and rare diseases stories, there is an opportunity for exhibits, scientific posters, artwork, and networking. Rare Disease Day at NIH is typically a hybrid meeting, so those who cannot travel to the NIH Main Campus in Bethesda, MD, can attend the free event virtually. The event is also archived for anyone to rewatch at their own pace afterward.

The genetic and rare diseases information center

The Genetic and Rare Diseases (GARD) Information Center is a public health resource that aims to support people living with a rare disease and their families with free access to reliable, easy-to-understand

information. The existence of the GARD website is in response to the Rare Diseases Act of 2002. The Act requires "…the establishment of a centralized clearinghouse for rare and genetic disease information that will provide understandable information about these diseases to the public, medical professionals, patients and families". The public can also submit inquiries to GARD.

Patients, family members, and caregivers may contact GARD by using our online contact form or by phone. GARD Information Specialists provide personalized responses that are free of charge, understandable, and confidential.

Because the scientific understanding of individual rare diseases increases every day, it is challenging to stay up to date on each disease. To address this public health challenge, GARD aims to continually provide updated understandable information by modernizing different approaches to this website.

Over the past three years, the GARD website has been undergoing a major redevelopment effort in terms of technology, content, and user experience. A soft launch of the new site was released in the Fall of 2021, and NCATS has been routinely releasing new versions since then.

The goals of the redevelopment include:

• Enhancing user experience.

• Modernizing website design and architecture.

• Expanding the number of diseases covered.

• Expanding the content available for each disease.

• Assisting patients and caregivers in traversing the diagnostic odyssey.

• Providing patients and caregivers with calls to actions.

A key focus of ongoing and future development of GARD will include harmonizing data received from ontology providers such as Orphanet, MONDO (mondo.monarchinitiative.org), and Online Mendelian Inheritance in Man (OMIM).

In addition to supporting GARD, DRDRI staff members also participate in collaborative rare disease informatics research on topics including rare disease epidemiology[6] and artificial intelligence[7].

NCATS toolkit for patient-focused therapy development

The purpose of the NCATS Toolkit for Patient-Focused Therapy Development (NCATS Toolkit) is to educate and empower patient advocacy groups to accelerate research toward effective treatments for their disease by enabling their engagement as research partners. This website was created in response to requests from rare disease patient groups for a repository of resources to help new patient groups become more involved in the development of rare therapies. To coordinate with the larger rare disease community and avoid duplication of efforts, NCATS Toolkit links to existing resources made by and for the patient advocacy group community, especially umbrella rare disease patient advocacy groups. NCATS Toolkit

serves as a key opportunity for strengthened collaborations and working together across different organizations, because patient advocacy groups can submit resources to be evaluated for inclusion in the NCATS Toolkit. NCATS Toolkit puts these resources into context with explanations about how the research process works and how patient advocacy groups can collaborate with researchers in academia, industry, and government agencies. In short, NCATS Toolkit educates patient advocacy groups about translation and empowers them to engage in research.

Currently, the NCATS Toolkit is undergoing a redesign to better serve the needs of the rare disease community. To make information more accessible, it is transitioning from being a standalone site to becoming a part of the NCATS site. As a result, NCATS Toolkit will be positioned as a key NCATS resource for patient advocacy groups. To make information more understandable, relevant, and actionable, the redesign relies on the principles of user experience and scientific communication. Ultimately, NCATS Toolkit seeks to explain translation systematically to early and intermediate patient advocacy group leaders, prepare them to have effective conversations with their research partners, and show them how they can catalyze the therapy development process. NCATS Toolkit illustrates the many ways through which patient advocacy groups can promote research, including maintaining patient registries, which are a key aspect of patient-focused therapy development.

Research projects

Specific information on all NIH-funded research, including the programs listed below, can be found in the NIH RePORTER.

The rare diseases clinical research network

The Rare Diseases Act of 2002 (Public Law 107-280) established the Rare Diseases Clinical Research Network (RDCRN). The National Institutes of Health was directed by this legislation to establish and support Research Centers of Excellence that would facilitate the diagnosis, management, and treatment of rare diseases. The RDCRN consists of multiple clinical research consortia and a Data Management and Coordinating Center (DMCC), and each consortium actively partners with patient advocacy groups. Since its initial funding cycle, the RDCRN has included 33 individual consortia [Table 2], studying over 325 rare diseases. DRDRI NCATS leads this initiative, partnering with multiple other institutes and centers (ICs) across the NIH. (see Home|Rare Diseases Clinical Research Network (rarediseasesnetwork.org) for an up-to-date list). Rare diseases are often multisystemic and do not always fit neatly into the mission of specific NIH ICs. To overcome this challenge, the RDCRN program brings together multiple ICs to collaborate and support different areas of science within a single consortium.

Each consortium focuses on at least three related rare diseases and promotes collaborative and multi-site programs and emphasizes a patient-centric approach focusing on clinical research and translational science. The current cycle emphasizes clinical trial readiness to lessen the risk often faced when a rare disease is targeted in a clinical trial. Actions taken to prepare for trials include conducting natural history studies, identifying biomarkers, developing or modifying existing outcome measures, and establishing cohesive networks of clinicians and patients.

The RDCRN activities are supported by the DMCC. The DMCC provides infrastructure support to individual consortium as well as network-wide activities. Support includes: (1) administrative support to facilitate network operations; (2) clinical research support, including best practices and protocol development; (3) Data management support that builds and maintains a robust and secure data infrastructure; and (4) engagement and dissemination that promotes patient engagement and broad

Table 2. Funded rare diseases clinical research network consortia 2003-2024

Consortium name	RDCRN1 2003-2008	RDCRN2 2009-2013	RDCRN3 2014-2018	RDCRN4 2019-2024
Genetic disorders of mucociliary clearance consortium (GDMCC)	X	X	X	X
Urea cycle disorders consortium (UCDC)	X	X	X	X
Vasculitis clinical research consortium (VCRC)	X	X	X	X
Porphyrias consortium (PC)		X	X	X
North American mitochondrial disease consortium (NAMDC)		X	X	X
Dystonia coalition (DC)		X	X	X
Brain vascular malformation consortium (BVMC)		X	X	X
Nephrotic syndrome study network (NEPTUNE)		X	X	X
Primary immune deficiency treatment consortium (PIDTC)		X	X	X
Inherited neuropathy consortium (INC)		X	X	X
Lysosomal disease network (LDN)		X	X	X
Clinical research in ALS and related disorders for therapeutic development (CReATe)			X	X
Brittle bone disorders consortium (BBDC)			X	X
Consortium of eosinophilic gastrointestinal disease researchers (CEGIR)			X	X
Developmental synaptopathies consortium (DSC)			X	X
Phenylalanine families and researchers exploring evidence (PHEFREE)				X
Myasthenia gravis rare disease network (MGNet)				X
Congenital and perinatal infections consortium (CPIC)				X
Frontiers in congenital disorders of glycosylation (FCDGC)				X
Global leukodystrophy initiative clinical trials network (GLIA-CTN)				X
Rett syndrome, MECP2 duplications, and rett-related disorders consortium (RTT)	X	X	X	
Rare kidney stone consortium (RKSC)		X	X	
Sterol and isoprenoid diseases consortium (STAIR)		X	X	
Autonomic disorders consortium (ADC)		X	X	
Rare lung diseases consortium (RLDC)	X		X	
Advancing research and treatment for frontotemporal lobar degeneration consortium (ARTFL)			X	
Clinical investigation of neurologic channelopathies (CINCH)	X	X		
Salivary gland carcinomas consortium (SGCC)		X		
Chronic graft *vs.* host disease consortium (cGVHD)		X		
Bone marrow failure consortium (BMFC)	X			
Rare genetic steroid disorders consortium (RGSDC)	X			
Rare thrombotic diseases consortium (RTDC)	X			
Cholestatic liver disease consortium (CLiC)	X			
Data management and coordinating center - DMCC-CCHMC				X
Data management and coordinating center - DMCC- USF	X	X	X	

dissemination of research. The current model for the DMCC provides centralized support and tools that are shared across the network.

The current network consists of 20 consortia with 358 active clinical sites, with an average of 19 sites per consortium. Each consortium currently investigates an average of nine different disorders.

The RDCRN as a network has been highly productive, producing 2,763 publications in 644 journals from 2004 to 2020 with well over 100,000 citations[8]. Their work has directly or indirectly led to the development of ten FDA-approved therapeutics. As one recent example, a publication from the Inherited Neuropathy Consortium (INC) explored gene variants related to Charcot-Marie-Tooth disease. The INC research team

found that specific variants in the *SORD* gene resulted in the loss of function of the enzyme sorbitol dehydrogenase (SORD), resulting in intracellular sorbitol accumulation. The result is a disorder that presents in a manner similar to Charcot-Marie-Tooth disease. In fact, the individuals identified with the variant had previously been diagnosed with Charcot-Marie-Tooth disease (CMT2)[9]. The SORD variants were previously not identified, as they were obscured by a "pseudogene" called SORDP2 that was not picked up by software commonly used for analysis.

Building upon this finding, the INC team initiated a pilot study with AT-007 (NCT05397665), an aldose reductase inhibitor, in patients with the specific variant in the SORD gene. The study demonstrated the ability to reduce sorbitol levels by a mean of 66%[10]. This promising finding led to Applied Therapeutics initiating a registrational phase III study of AT-007. This occurred within three years of the initial discovery of the variant.

The preliminary results from the 12-month Interim Analysis of Govorestat (AT-007) in the Ongoing INSPIRE Phase 3 Trial in Sorbitol Dehydrogenase (SORD) Deficiency have been very encouraging. The results demonstrate that: (1) Interim primary endpoints have been met; (2) Sustained, significant reduction in sorbitol in govorestat-treated patients compared to placebo control; and (3) highly statistically significant effects on a patient-reported outcome measure, the CMT Health Index (CMT-HI), with a particular benefit of govorestat on measures of lower limb function, fatigue, pain, mobility, sensory function, and upper limb function[11].

• Opportunities for strengthened collaborations and working together across different organizations and regions.

The RDCRN emphasizes the FAIR principles of research. These include data that are (1) Findable - rich metadata; (2) Accessible - can be easily downloaded with standard protocols; (3) Interoperable - Metadata that uses an accessible protocol; and (4) Reusable - data that are well described and provide clear usage information. To achieve this goal, the RDCRN reaches out to other data gathering and data standards organizations (e.g., C-Path, C-Disc) and confirms that the data from the RDCRN will be interoperable with other systems.

• Global involvement to identify additional individuals with rare diseases.

Many of the consortia within the RDCRN collaborate with clinical sites around the world. The RDCRN has collaborators in eleven countries including Australia, Belgium, Canada, England, Germany, India, Ireland, Italy, The Netherlands, South Africa, and Switzerland.

• Collaboration with international organizations on data standards and operability.

The RDCRN, via the NCATS program, has been involved in international data standards and operability discussions including the conference organized by the International Rare Diseases Research Consortium (IRDiRC) and the European Joint Programme on Rare Diseases (EJP RD), focusing on rare disease clinical research networks (CRNs). The conference brought together experts from different countries and programs to share experiences and knowledge related to clinical research center structure and activities. Efforts to establish collaboration and ensure interoperability across networks were identified as important goals for the organizations.

As a follow-up, RDCRN, via NCATS, participated in the ERICA 3rd General Assembly. The European Rare Disease Research Coordination and Support Action consortium (ERICA) is an organization in which all 24 European Reference Networks (ERNs) participate. Such meetings provide opportunities to share knowledge with individual ERNs. Through knowledge sharing and engagement with stakeholders in the rare disease domain, the RDCRN and European investigators will continue to have follow-up conversations on topics of common interest.

Medical cost of rare diseases

Our mission of advancing rare diseases research cannot be met without an increased understanding of the patient journey within our healthcare systems (HCS). Due to the large number of individual rare diseases affecting a small patient population, fragmented across different healthcare systems, understanding the medical needs of patients is a difficult task. In 2021, NCATS, along with external collaborators (Eversana™, Oregon Health & Science University (OHSU), Sanford Health (Sanford), a large Midwestern integrated HCS, and a health insurer in Australia), set out to quantify rare disease prevalence and the direct medical costs of 14 representative rare diseases in 4 different HCS databases. This came to be known as the IDeaS (Impact of Rare Diseases on Patients and Healthcare Systems) Initiative[4].

The IDeaS pilot study found that (1) ICD coding makes it difficult to count RD patients, which likely results in inaccurate estimation of their true economic impact; (2) direct medical costs of rare diseases per patient were estimated to be three to five times higher than age-matched controls; and (3) preliminary evidence shows that diagnostic journeys are prolonged, which may result in progressive, irreversible, and costly disease complications. Yearly direct medical costs are estimated to be around $400 billion in the U.S., on par with cancer and heart disease expenditures. The results of this study suggest that RDs have a major impact on patients and our healthcare system.

The legacy of the IDeaS study is the demonstration of the feasibility of gathering valuable information on the prevalence, cost, and natural history of rare diseases. Data science approaches in rare disease research face challenges, such as a general lack of individual diagnostic codes, thus leaving patients invisible to the healthcare system, fragmented care due to a lack of general knowledge about RDs, and individually small patient populations, decreasing statistical power for analyses. The results of this study suggest innovative AI/ML tools that take these challenges into account will be necessary to speed rare disease knowledge, time to diagnosis, and treatment.

Thus, following the publication of the pilot study, NCATS DRDRI has allocated funding through a contract mechanism to further develop this methodology in a differing HCS context and a wider set of rare diseases. This next iteration of the IDeaS initiative intends to use the results of the initial pilot study to inform methods for clinical decision support tools to alert clinicians to possible cases of rare diseases. We hope to identify utilization patterns prior to accurate diagnosis and estimate costs of medical care during the diagnostic odyssey, with the larger goal of using this information to inform the development of approaches to diagnose and identify rare disease patients sooner, while improving overall patient care management.

Clinical trial readiness, diagnostic odyssey, and scientific conference grants

The clinical trial readiness (CTR) grants support projects focused on obtaining the data needed to enable efficient and effective movement of candidate therapeutics or diagnostics toward clinical trials, and to increase their likelihood of success by the development and testing of rigorous biomarkers and clinical outcome measures, or by better delineating the presentation and course of a rare disease to facilitate upcoming clinical trial design. Given that only a small percentage of the thousands of rare diseases have an approved therapy, the intent of this funding opportunity is to focus on projects that would help move more

rare diseases closer to a clinical trial and provide valuable data to increase the likelihood of that clinical trial to succeed. The first CTR grant was awarded in 2019, and the program remains active in funding projects to this day. Through September 2023, there have been 42 awards made to a variety of rare diseases. A full listing of funded research can be found in NIH RePORTER under opportunity numbers PAR-18-952, PAR-18-953, PAR-22-100, PAR-22-101, PAR-23-159, and PAR-23-160.

The diagnostic odyssey funding opportunity is intended to support clinical projects to accelerate the identification and accurate diagnosis of rare disease patients. The focus is on diagnostic approaches that combine machine-assisted analysis, genomic sequencing, and clinical evaluation. Importantly, successful strategies must be suitable for implementation at the primary or secondary care facilities by front-line healthcare providers, and readily integrated into their standard clinical care workflow.

These diagnostic odyssey awards come in two phases. In the first phase, researchers develop a strategy for using their proposed approach to make faster diagnoses and test that strategy in a real-world setting. If that milestone is achieved, researchers will get access to a second phase of funding to test their approach in a different healthcare setting which presents novel challenges or obstacles. The program awarded three research projects in 2022, each of which is exploring a different approach to speed up the timeline for a correct rare disease diagnosis. A listing of this program's funded research can be found in NIH RePORTER under opportunity number RFA-TR-21-008.

Additionally, NCATS participates in NIH support for conferences and scientific meetings. DRDRI specifically has an interest in conferences identifying research opportunities for rare diseases, and those including the active participation of relevant patient support groups in the meeting planning. While all allowable costs are considered, NCATS is particularly interested in supporting trainees, students, fellows, and young investigators to attend conferences, and participate in the meetings via poster presentations or short talks. A focus on ensuring a diverse representation among invited speakers is also an important consideration. There are three due dates per year for grant applications, and requests from intramural NIH investigators are also allowed. These scientific conferences can often make a difference and move a rare disease field forward by bringing together key individuals, such as researchers, clinicians, patients, families, patient advocacy groups, and early-stage investigators, to name a few. The latest developments and research results are shared with a robust exchange of information in multiple directions. These meetings are also a great way to energize the community and inspire those involved to continue helping the patients.

"Many diseases as a time" projects

As noted above, current estimates are that the number of rare diseases with a known molecular basis is estimated to be greater than 10,000[1,2], although this number can vary depending on the extent of lumping *vs*. splitting of different genetic disease subtypes. Regardless, this is a large number, and is likely to increase given the expanded use of whole-genome sequencing for rare disease diagnosis. The sheer number of diseases, as well as the fact that the majority of these diseases have a prevalence of approximately 1/million people[12], present significant practical challenges from a commercial development standpoint (see also[13]). However, based on knowledge of the molecular basis of many rare diseases, it is possible to develop a rational therapeutic strategy for many of them, regardless of prevalence. Given this reality, there is clearly a need for a fundamentally different approach to rare disease clinical trials and therapeutics development.

Shared molecular etiologies basket trials

While there are thousands of different rare diseases, the number of underlying pathogenic mechanisms, or molecular etiologies, is far less. Moreover, many of these are, in principle, therapeutically actionable.

Therefore, one promising strategy to increase the number of rare disease patients in clinical trials is to focus on drugs targeting etiologies that are shared across multiple rare diseases. Such shared molecular etiologies may include biochemical pathways that can be targeted by small molecule drugs. Using this approach, we can create new disease entities based not on traditional clinical phenotypes, but on shared molecular etiologies that are therapeutically actionable. As highlighted in an early publication[14], the rare disease field could adapt the tissue agnostic basket trial approach that has been used successfully in the field of oncology, and led to regulatory approvals in that area[15].

DRDRI has developed funding opportunities that specifically support basket trials in multiple rare diseases for drugs targeting shared molecular etiologies across multiple different diseases, including RFA-TR-20-031 and RFA-TR-21-010. Under TR-20-031, we funded two projects. One project focuses on a clinical trial to treat two rare mitochondrial diseases using an epigenetic modifier. The other project utilizes a Janus kinase (JAK) inhibitor to treat multiple diseases with activating mutations in the JAK-STAT signaling pathway. Importantly, as of the end of 2023, both projects met their key milestones of obtaining INDs (Investigational New Drug) applications for the basket trials from the US FDA.

To raise awareness of the basket trial approach in rare diseases internationally, DRDRI initiated the Shared Molecular Etiologies task force within IRDiRC Shared Molecular Etiologies Underlying Multiple Rare Diseases - IRDiRC. The activity of this task force culminated in a recent publication[16].

Gene-targeted therapies and platforms

An estimated 80% of all rare diseases are monogenic, i.e., they result from mutations in a single gene. Monogenic disease is, therefore, perhaps the most common shared molecular etiology of all rare diseases. As such, these diseases are, in principle, amenable to gene-targeted therapies such as gene therapy, gene editing, and oligonucleotides. Each of these approaches is, in fact, a therapeutic platform that can be readily adapted to different diseases based on knowledge of the sequence of the disease-causing mutation(s). The current approach is to use these therapeutic platforms to develop therapeutics for one disease at a time. Unfortunately, this approach consumes much time and effort in commercially developing treatments for the most common rare diseases, thereby leaving the largest fraction of less common rare diseases behind, even though these less common rare diseases may be good, if not better, candidates for drug development.

To address this problem, DRDRI is involved in the leadership of several programs that seek to develop gene-targeted therapies as therapeutic platforms that can be readily adopted for multiple patients and diseases. Two projects focus on gene therapy using adeno-associated virus (AAV) vectors. The Platform Vector Gene Therapies (PaVe-GT) program is testing the hypothesis that using the same AAV serotype, manufacturing, and production facilities for multiple AAV gene therapies can increase the efficiency of the start-up of AAV gene therapy trials. PaVe-GT is a collaborative effort between DRDRI, the Therapeutics Development Branch of NCATS, and NIH clinical investigators from NHGRI and NINDS. One goal of PaVe-GT is to disseminate information about the AAV gene therapy regulatory process to stakeholders, specifically to those patient advocates trying to develop AAV gene therapies for rare diseases of no commercial interest. In addition to an academic publication[17], we released our Orphan Drug Designation for our first drug, AAV9-hPCCA, as well as our approved Rare Pediatric Disease Designation Request. Additionally, we have provided fillable templates for each of these documents that can be used to prepare and submit their own based on our approved documents.

The Bespoke Gene Therapy Consortium is a public-private partnership managed by the Foundation for the NIH. The main goal of the BGTC is streamlining the navigation of the regulatory path for AAV gene

therapies, with a specific focus on diseases of no current commercial interest. The first deliverable of the BGTC is the Bespoke Gene Therapy Consortium (BGTC) Regulatory Playbook Version 1.0. This initial version of the playbook is a comprehensive document outlining the clinical development process of AAV gene therapy. While this version is quite generic, subsequent versions will include learnings from the work of the BGTC, including efforts to develop standardized minimal sets of critical quality attributes for human AAV gene therapies, as well as minimal sets of animal toxicology studies. The common goal of both the BGTC and PaVe-GT efforts is to increase the efficiency of getting AAV gene therapies into first-in-human trials, while protecting patient safety.

In the gene editing space, the NIH Somatic Cell Genome Editing program, supported by funds from the NIH Common Fund, is accelerating genome editing technologies into the clinic. The first phase of the program focused on technology development, with an emphasis on better ways to deliver genome editing in different cells and tissues. The program developed a publicly available resource, called the SCGE Toolkit, to make the data generated available to the public.

Phase 2 of the SCGE program is more focused on moving genome editing into the clinic. Specific initiatives include developing technologies and assays for safety and efficacy studies; supporting genome editing-based therapeutic leads through the IND phase; supporting novel platform genome editing clinical trials for more than one disease; and a translational coordination and dissemination center for SCGE phase 2 projects.

Another initiative of SCGE Phase 2 is a prize competition, called the TARGETTED challenge, to identify better technologies to deliver genome editors. There are two target areas: programmable solutions for targeting genome editors to specific cells and tissues, and non-viral technologies to deliver genome editors across the blood-brain barrier. The winners of the first phase of the challenge were announced in December of 2023 (National Institutes of Health Announces Phase 1 Winners of the $6M TARGETED Challenge| Freelancer), along with the opening of Phase 2 National Institutes of Health Announces Launch of Phase 2 of the $6M TARGETED Challenge|Freelancer .

Policy implications of gene-targeted therapy platforms

The rapid expansion and development of gene-targeted therapy platforms such as gene therapy, gene editing, and other modalities stands in contrast to the traditional "one disease at a time" approach to rare disease drug development. The implementation of such platforms represents an opportunity to bring gene-targeted therapies to large numbers of patients with monogenic disease. However, such implementation comes with substantial policy and economic challenges impacting the broader biomedical science, regulatory, and healthcare enterprise. In 2021, DRDRI organized a series of meetings to discuss the practical, financial, ethical, and regulatory issues posed by the broad implementation of gene-targeted therapy platforms. The results of that meeting series were published in a Special Issue of *American Journal of Medical Genetics*[18]. Individual publications included discussion of readiness for gene-targeted therapies[19], ethical and social implications[20], newborn screening[21], and economic implications[22].

CONCLUDING COMMENTS

In this article, we have highlighted some of the major rare diseases research activities supported by DRDRI. While we have focused on DRDRI activities, we would like to emphasize that support of rare diseases research at NCATS and NIH is not limited to DRDRI. Many of the other Divisions within NCATS support some rare diseases research efforts. Notably, the NCATS Therapeutic Development Branch supports the Therapeutics for Rare and Neglected Diseases program, which provides access to contract services to accelerate rare disease translational science. Across NIH more broadly, many other Institutes and Centers at

NIH support rare disease research portfolios. One example is the recently developed Ultra-rare Gene-based Therapy (URGenT) Network, supported by the National Institute of Neurological Disorders and Stroke (NINDS). Indeed, as we noted above, nearly all DRDRI programs and activities listed here are collaborative efforts that involve working with other divisions of NCATS, other NIH Institutes and Centers, and external partners both within the U.S. and internationally. We believe that such a collaborative approach is essential to effectively advancing and navigating a global rare disease community.

DECLARATIONS

Authors' contributions

Made final edits: Brooks PJ

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All authors declared that there are no conflicts of interest.

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Not applicable.

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