THERAPEUTIC ADVANCES in
Rare Disease

Review

Challenges and opportunities for the use of telehealth in rare disease diagnosis, treatment, research, and education: key opinion leader interviews by the IRDiRC telehealth task force

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***Abstract*:** The International Rare Diseases Research Consortium (IRDiRC) Telehealth (TH) Task Force explored the use of TH for improving diagnosis, care, research, and education for rare diseases (RDs) worldwide. The Task Force members interviewed 23 key opinion leaders (KOLs), providing perspectives from experts in the use of TH for the diagnosis, treatment, and prevention of RDs (10 KOLs); for research and evaluation in RDs (7); and for the continuing education of health care providers (HCPs) in RDs (6). The KOLs represented a broad array of diverse perspectives with regard to both geographic regions, including Europe, United States, Sub-Saharan Africa, and Asia, and professional expertise, including rare disease patients and family members, RD association spokespersons, TH association representatives, physicians, researchers, and regulatory authorities. The Task Force solicited KOL opinions to identify factors that influence TH in improving access to diagnosis, care, prevention, and research experiences for RD patients and providers as well as continuing education and peer mentoring for HCPs. This manuscript represents a synthesis of those interviews and some common themes that emerged, along with identification of evidence and knowledge gaps that will benefit from future research efforts to help advance and expand the use of TH for RD care, research, and education. KOLs agreed on the unique elements of RD medical care that could benefit from TH approaches and recognized the increasing role that remote assessments can play in supporting RD research. They identified models for health care provider education afforded by TH that can enhance care for RD patients and broaden the pool of experts in these conditions. While recognizing that barriers to broad implementation exist, they agreed that TH provides a unique tool to provide greater access to care for RD patients worldwide.

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Plain language summary

Interviews with Experts Reveal the Benefits and Challenges of Using Telehealth for Individuals with Rare Diseases Who Do Not Have Access to Specialty Health Care Providers

What is the issue?

Rare disease patients often have difficulty accessing medical care from experts who understand their condition and can provide timely treatment and care. Telehealth is the use of communication technologies across a distance to provide health care to individuals who otherwise might not have access to those services. It can include diagnosis, treatment, and preventive services, as well as access to research opportunities for patients. Telehealth can also provide education for health care providers to better care for patients with rare diseases.

What was done?

The International Rare Diseases Research Consortium formed in 2011 to bring together multiple stakeholders to improve diagnosis and treatment of rare diseases worldwide. In 2021, this group established the Telehealth Task Force to explore gaps and opportunities in the use of telehealth to improve care, research, and training in rare diseases. The Task Force organized virtual interviews with 23 experts to better understand the use of telehealth to connect individuals with rare diseases to experts in their conditions.

What was learned?

Task Force members learned about the unique role that telehealth can play in providing access to clinical experts for rare disease patients if the technology is available, including broadband internet service. Policies and regulations that encourage telehealth can also promote its use. Research participation also allows collection of digital health data from dispersed patients to improve treatments. Finally, physicians can learn how to treat rare disease patients through established telehealth educational platforms.

Why is this important?

Access to telehealth can improve health outcomes for rare disease patients. Despite challenges in establishing telehealth systems for rare disease patient care, key opinion leaders agreed that the advantages outweighed the disadvantages and supported the use of telehealth for care, research, and training in rare diseases.

Keywords: decentralized clinical trial, eHealth, IRDiRC, key opinion leader, peer mentoring, rare disease, rare disease care, rare disease education, rare disease research, teleconsultation, telehealth, telemedicine

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Introduction

The International Rare Diseases Research Consortium (IRDiRC) is an international collaborative initiative launched in 2011 to advance diagnostics and treatments of rare diseases (RDs) worldwide through research.[1,2] IRDiRC Task Forces (TF) identify gaps and key issues in RD research and develop work products to address these issues. Telehealth (TH) was identified as an emerging topic with untapped potential to revolutionize RD care, research, and health care provider (HCP) training. The IRDiRC TH Task Force, composed of 18 members from 13 countries, was established in October 2021. The goals

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of the TH TF were to identify barriers to and opportunities for the use of TH to improve access to diagnosis, care, prevention, and research experiences for RD patients and providers, as well as continuing education and peer mentoring for HCPs; in addition, to identify evidence gaps for which future recommendations can be developed for introducing and enhancing TH services into RD communities.

The TF first conducted a review of published literature (2017–2023) on existing models of TH, their uptake and usage by the RD community, and barriers to and opportunities for their use, in order to identify the factors that enhance or limit their effectiveness in the RD community.[3] The review found that the use of TH for RD is at an early and rapidly evolving stage of development in many regions of the world. The TF members suggested that additional approaches would be necessary to assess the general direction of the field. This manuscript represents a synthesis of the interviews of 23 KOLs by a team of TF members in an attempt to solicit opinions regarding factors that influence TH initiatives in improving access to diagnosis, care, prevention, and research experiences for RD patients, providers, and researchers, as well as support continuing education and peer mentoring for HCPs.

Methods

The TH TF adopted the World Health Organization (WHO) definition of TH with modification specifically for RDs (in italics): "[The] delivery of health care services, where patients and providers are separated by distance. Telehealth uses ICT [Information and Communication Technologies] for the exchange of information for the diagnosis and treatment of diseases and injuries *of RDs*, research and evaluation, and for the continuing education of health professionals *for RDs*."[4] Based on the WHO TH definition, the TF focused on three key topics or areas in its analysis on TH for both literature review and KOL interviews: (1) TH for Diagnosis, Treatment, and Prevention; (2) TH for Research and Evaluation; and (3) TH for Continuing Education and Peer Mentoring of HCPs. Task Force members established three working groups, based on their expertise and interest, each focusing on one of these topics.

TF members identified KOLs who were considered experts in the use of TH. 23 KOLs (see Table 1) accepted TF invitations for interviews, with 10 KOLs for the topic of diagnosis, treatment, and prevention of RDs, 7 KOLs for research and evaluation in RDs, and 6 KOLs for education and peer mentoring of HCPs in RDs. The KOLs represented a broad array of diverse perspectives with regard to both geographic regions (including Europe, United States (US), Sub-Saharan Africa, and Asia), and professional expertise (including physicians, patient advocacy experts, RD association spokespersons, RD patients and family members, and telemedicine association representatives), as well as regulatory authorities and government officials from Ministries of Health. The structured questions posed to the KOLs, tailored to their areas of expertise, are as follows:

1. What is the model of telehealth (TH) used? What is the uptake of this TH model?
2. What strategies are used for the implementation of this TH model? What are the strengths and weaknesses of the strategies that you used?
3. What are the benefit(s) of TH for the following stakeholders: Patients/families; Health care providers; Private and Public Payers; Regulatory bodies; and Researchers?
4. What are the harms and limitations in the use of TH for the same stakeholders? How would you improve it?
5. What are the opportunities and barriers for the use of TH, for this specific model of TH?

Each KOL was interviewed by three or more TF members via Zoom. Interviewing TF members then summarized each interview and KOL opinions. TF members then established three writing groups, each focusing on one of the three TH topics. The writing groups performed qualitative analysis of all the interviews within the group, and summarized their findings and conclusions. The TF chairs synthesized the final manuscript based on group summaries.

Results

TH models, tools, the extent to which they are used, policies, regulations, and the factors that promote or limit their usage vary for different purposes and across different geographical regions. These are summarized below, for the purpose of (1) diagnosis, treatment, and prevention, (2)

Table 1. Key opinion leaders and affiliations.

KOL role and affiliation	KOL name (if agreed to be named)	Region	Type of stakeholder*	RD stakeholder
Group 1 (10)				
Director of Global Health Telemedicine (GHT)	Michelangelo Bartolo	Europe	Clinical practitioner	No
President, SCImPULSE Foundation	Marco Manca	Europe	Public/private Funder	No
Director, President at Debra (Dystropic Epidermolysis Bullosa Research Association) International	Ritu Jain	Asia	Patient advocate	Yes
Co-founder, Rare Disorders Kenya	Roselyn Kanja-Odero	Africa	Caregiver/parent of RD child	Yes
Head, SingHealth Duke-NUS Genomic Medicine Centre	Tan Ee Shien	Asia	Clinical practitioner	Yes
ERN ITHACA (European Reference Network for Rare Malformation Syndromes, Intellectual and Other Neurodevelopmental Disorders)	Alain Verloes	Europe	Clinical Practitioner	Yes
EURORDIS-Rare Diseases Europe	Jelena Malinina	Europe	Patient advocate	Yes
National Health System Portfolio and Pharmacy (Spain)	César Hernández	Europe	Public/private funder	No
American Telemedicine Association		North America	Non-profit	No
NORD (National Organization for Rare Disorders) Vice President, Policy and Regulatory Affairs	Heidi Ross	North America	Non-profit	Yes
Group 2 (7)				
Digital Health Consulting SRL	Marianna Petrea-Imenokhoeva	Europe	Public/private funder	No
IMI (Innovative Medicines Initiative) Trials@Home and University of Groningen; Professor of Drug Regulatory Science at University Medical Center Groningen	Peter Mol	Europe	Academics	No

(Continued)

Table 1. (Continued)

KOL role and affiliation	KOL name (if agreed to be named)	Region	Type of stakeholder*	RD stakeholder
Chairman at Integrity Healthcare Co; President at Tetsuyu Institute Medical Corporation; Director at International House of Japan; Clinical Professor at Tokyo Medical and Dental University	Shinsuke Muto	Asia	Clinical practitioner	No
Center for Drug Evaluation and Research (CDER)-United States Food and Drug Administration		North America	Public/private funder	Yes
Foundation for Prader-Willi Research, Director of Research Programs	Theresa Strong	North America	Patient/patient advocate	Yes
Digital Health and Innovation, World Health Organization	Salim Azzabi Zouraq	Global	Intergovernmental organization (IGO)	No
Gemelli Digital Medicine & Health SRL, CEO	Alfredo Cesario	Europe	Public/private founder	No
Group 3 (6)				
Director, ECHO Institute/ Project ECHO, University of New Mexico	Sanjeev Arora	North America	Clinical practitioner	No
Medics4RareDisease CEO	Lucy McKay	Europe	Public/private funder	Yes
Research Policy and Initiatives Director, EURORDIS	Roseline Favresse	Europe	Patient/patient advocate	Yes
Rare Disease Education Lead, Senior Director Clinical Strategy, Medscape	S. Christy Rohani-Montez	Europe	Public/private funder	No
University of New South Wales (UNSW), Sydney, Researcher and Clinical Geneticist	Elizabeth Palmer	Australia	Academic and clinical practitioner	No
Mount Sinai Medical Center New York, Director of Adult and Pediatric Intestinal Rehabilitation & Transplantation; Professor of Surgery/Pediatrics at Icahn School of Medicine at Mount Sinai	Kishore Iyer	North America	Clinical practitioner	Yes

*Categories of type of stakeholder include academic researcher, caregiver/parent of RD child, clinical practitioner, intergovernmental organization, non-profit organization, patient or patient advocate, and public or private funder of studies or regulatory activities.

research and evaluation, and (3) continuing education and peer mentoring of HCPs for RDs.

Role of TH in diagnosis, treatment, and prevention of RDs

KOLs noted that an important usage of TH widely applied in both developing countries and western countries is teleconsultation, or remote medical consultation. Some clinical contexts are more amenable to TH than others, such as follow-up clinical visits that are less dependent on an in-person examination, and consultation for return of test results such as genetics/genomics evaluations. TH also facilitates peer discussions between doctors on medically complex and RD cases with challenging symptoms. The models of TH discussed for RD diagnosis and treatment vary according to the KOL members' backgrounds and expertise, mostly reflecting the geographical regions and the healthcare systems they represent. For example, in Kenya, mobile phones, given their ubiquity, have been the major tool used. Laptops and other electronic platforms are also in service in developing countries. In many developing countries, chat program such as WhatsApp and chat groups have also been used to deliver TH services, such as sharing images and videos for diagnosis, physician recommendations, providing support such as emotional support, and for disseminating information and common suggestions. More advanced platforms and TH models, including asynchronous ones, with data federation and security controls for confidential information, are being developed and used in high-income countries. Scotland's national telehealth and telecare organization NHS 24[5] was cited as an example that aims to provide continuous medical care for patients outside of regular hours. While WhatsApp has been reported to be widely used in Singapore, many European Union (EU) HCPs do not use this platform because it is noncompliant with the EU General Data Protection Regulation (GDPR)[6]; instead, EU providers use fully encrypted services. European Reference Networks (ERNs)[7] play a critical function in providing RD care and research including TH in Europe. Twenty-four cross-border ERNs bring together close to 1000 specialty healthcare units from more than 300 hospitals in 26 European countries to provide highly specialized care for RDs and other low-prevalence and complex diseases. The European Cross-Border Healthcare Directive[8] states that every person residing in the EU has the right to seek healthcare in another EU country and be reimbursed. An information network involving ERNs called "Únicas"[9] works with hospitals regionally in order to provide research, early diagnosis, and clinical facilities to children and adolescents with RDs.

TH has enabled patient access to HCPs, facilitated provider-to-provider virtual advice and consultation, brought patients together, and created communities to share information between patients and physicians. Regardless of where TH is applied, the most mentioned benefit of TH for clinical care and diagnosis lies in its ability to break down geographic barriers, and to provide care to patients when in-person visits are not possible or are difficult. TH could also limit the risk of infection for certain patient groups, for example, immunocompromised patients. The KOLs mentioned the option offered by TH for alternating in-person and remote visits, whenever possible. Because many patients live in small towns, primary care is their initial point of contact. In this setting, TH can help with integrating patients into a central referral system to reach experts, including research, clinical, and non-health specialists such as social services. TH also helps build communities among RD individuals with shared diagnoses. In this way, TH provides an opportunity to access services across health systems without limiting the best services to those living in more populated or developed regions. A KOL cited as an example a government-led digital ophthalmology initiative known as the Scottish Eyecare Integration Project that established a centralized electronic referral system in Scotland. This system enables electronic image exchange and has revolutionized ophthalmic disease screening, referrals, and shared care between community and specialty clinicians. This initiative has been shown to decrease false-positive referral rates and has reduced average referral time to treatment from 6–9 months to 6–12 weeks. Remote diagnosis and integration of community eye care also resulted in less travel time for patients.[10] In addition, as a result of the accumulation of a large amount of data and clinical information, a virtual learning platform for ophthalmology was established, and a master's degree in Primary Care Ophthalmology was created to enhance community eye care.

Across the globe, governments have realized the benefits of TH, and some have either established policies to promote its use or are heavily investing in TH. In Kenya, a national e-Health policy helps to establish TH, with 20 hospitals approved to provide digital health services. EU Member States have budgeted €12 billion for investments in digital health, and the EU Commission will provide over €810 million to support the European Health Data Space regulation (EHDS[11]). Based on feedback from the KOLs, more support is needed to enable HCPs to participate in using TH for care and realize its full benefits. Some HCPs are skeptical of the use of TH services and may have technological limitations, necessitating training to encourage widespread adoption. In addition, some KOLs considered reimbursement for HCP TH service to be a barrier for wider implementation of TH.[12,13] They mentioned that some doctors, especially from developing countries, simply deliver TH services for free, motivated by altruism, collegiality, respect, and kindness. For these physicians, financial incentives are inadequate to drive their use of TH with their patients.

KOLs consider technical issues to be one of the major barriers for TH implementation. Aside from the availability of technology and infrastructure for TH, digital health literacy has been cited as an important limitation in using TH. Therefore, KOLs considered it vitally important to enhance telehealth competency training for health care professional within medical provider training curricula. Furthermore, the complexity of some RDs might limit the utilization of new digital health tools. The ability to accurately explain the health problems of the specific RD patient depends on their health literacy, as well as the digital expertise of the patients, their caregivers, or even the HCPs. In addition, standardization of electronic health records data to ensure interoperability and data quality is critical for data exchanges to facilitate TH. Language may become an important barrier in this regard, and KOLs emphasized the need to ensure that no meaning is lost due to language differences, especially in electronic health records. One example is the use of International Classification of Diseases (ICD) codes for diseases and medical conditions. While ICD-11[14] is preferred, as it is considered more comprehensive and inclusive of more RDs, there can be enormous costs to implement the newest ICD codes. KOLs considered proper training and education of RD HCPs and patients in TH health literacy, as well as enhanced TH information dissemination, to be critical opportunities for the future. Some KOLs mentioned that in some settings, patients and providers are not aware of the resources available including TH as an option. In the EU, in spite of the provisions for reimbursable RD medical care within the Cross-Border Healthcare Directive,[8] patients may not be aware of this resource.

In agreement with our literature review,[3] KOLs attributed the COVID pandemic as the event responsible for the explosion of TH use in healthcare, including for RD. Some regions did not use TH until the pandemic, when RD patients experienced long waits for in-person medical appointments. For RD patients, 60%–80% experienced cancelled or postponed medical appointments and treatment during the pandemic, and when offered a TH appointment, 88% accepted,[15] with over 90% reporting a positive experience.[15,16] RD communities have come to expect and rely on TH, with the majority of patients expressing the desire for a telemedicine option for medical appointments. In the US, federal regulations prior to the pandemic restricted the ability of HCPs to practice medicine across state borders without a license; as a result, physicians' ability to provide TH outside their jurisdictions was limited. These geographic restrictions were waived during the pandemic, and insurance policies were also updated to cover TH.[17] However, globally, TH usage has declined post-pandemic. KOLs attributed this decline to several possible reasons, such as restrictive laws and regulations that affect the integration of TH in medical care. In the US, some KOLs consider post-pandemic reinstitution of state medical licensure requirements a critical barrier. Although an Interstate Medical Licensure Compact (https://imlcc.com/) exists in the US, and is designed to streamline license requirements to allow physicians to practice in multiple states,[18] it may not meet the needs of individual RD patients who require multidisciplinary care that may not be licensed in their state even with this mechanism in place. There seems to be better mutual recognition of medical licenses within the EU between countries for the sake of virtual and physical appointments; however, this also depends on the specialties and different laws on consent and privacy protections among member states. KOLs emphasized the need for ensuring

proper training around consent and privacy protections for those partaking in TH and the technology used to conduct the TH appointments in order to comply with all the necessary laws and guidelines. Therefore, there is the view that TH should be treated with the same standards as in-person care and should not have its own specific regulations.

KOLs discussed other policy and regulatory issues that are not specific for RDs but are critically important to the future of TH for RD. These include data security and confidentiality, and how to harmonize and handle the data. Approaches vary with the different regions and health care systems. The GDPR regulates information privacy, covering individual health data in the EU and the European Economic Area. While GDPR has established strict laws governing data privacy, it also provides flexibility for individual member states to modify some of its provisions, so different EU countries may be more liberal or more conservative in their GDPR requirements. This has introduced complexity in practice. A new EU regulation that will have a significant impact is the European Health Data Space regulation (EHDS).[11] EHDS intends to create an EU health data sharing framework for "establishing clear rules, common standards and practices, digital infrastructures and a governance framework for the use of electronic health data by patients and for research, innovation, policy making, patient safety, statistics or regulatory purposes." This will allow patients better control of their health data. With improved interoperability, HCPs will be able to access a patient's medical history across borders within the EU for the primary purpose of making decisions on treatment and diagnosis. EHDS will also establish a framework to regulate secondary use of health data such as for research purposes.

As each country has a specific context of using TH, KOLs held the opinion that there is a need to provide overall global direction, incorporating the varied local approaches. TH as such is also part of the WHO's global digital health strategy,[19] developed in collaboration with global and regional partners. One of the main priorities of this strategy is to develop a regulatory framework that can be applied across multiple countries.

Role of TH for RD research and evaluation

All seven KOLs interviewed on the use of TH for RD research shared the view that its use for research is at a pivotal point, and the field is expected to move forward rapidly. The application of TH in research can be different from or complement traditional methods of research. Various TH models have been utilized for RD research, including asynchronous, synchronous, remote patient monitoring, and "mHealth," a tool that uses mobile phones or other wireless technologies to improve health care. KOLs agreed that the TH models should be adapted to the setting and fit-for-purpose, considering the type of research (e.g., natural history, clinical trial, post-clinical, or implementation), the context (e.g., type of patients, age of patients), the types of activities (e.g., outcome measurements, data gathering), and the setting (country, region). Most of the KOLs did not specifically focus on RDs only. However, they acknowledged that RD research should be a good test case for TH, given the critical barriers for RD patients to access care and research as well as their motivation and willingness to participate in knowledge development. In addition, regulations and guidelines concerning the use of TH in research need to incorporate the needs of RD patients.

- Several KOLs commented on the remarkable progress in digital health development and its resulting tools in changing the way clinical studies are conducted. KOLs posited that TH offers many opportunities to conduct innovative research, particularly in places where there is a high unmet need with few treatments or drugs available, and when the classical clinical trial design is not feasible. This is particularly true for RD research, where the historical model of requiring research subjects to live in close proximity to the study center is no longer critical. For example, digital health methodologies have been used for the collection of physiological data and study outcomes through remote patient visits rather than having the RD patients travel to the clinical trial center.[20] Health outcome data can be collected directly from the patient's home in some cases. Examples include wearable devices measuring different clinical parameters, such as mobility, electronic documentation of patient-reported outcome measures, monitoring of drug efficacy in post-marketing studies, and follow-up of adverse effects.[21] In doing so, TH research has the potential to be more inclusive of

varied experiences of subjects. In addition, TH may also add value to the study by providing objective measurements remotely in a real-world setting. An example is using home-based mobility tests, rather than the Duchenne Muscular Dystrophy 6-minute walk test, that many see as flawed and unable to capture the range of phenotypes and outcomes.[22] Home-based testing could provide more reliable data, as it provides functional outcomes during daily life in a real-world setting. Other examples of measurements that can provide benefit over traditional standard trial measurements include environmental sensors for movement and sleep, medical devices for vital parameters acquisition, or artificial intelligence (AI)-analyzed measured inputs on speech, cough, or movement.[23]

For research, additional advantages of TH tool use include the optimization of work processes and the fact that digital connectivity allows measurements to be entered directly into the researcher's database or registry.[24] Digitally collected data using TH tools have the potential to be shared more readily and could be annotated more easily, with the possibility of comparing data from global sources. TH methodologies can collect data from dispersed RD patients, followed by centralized data analysis, using new data science technologies such as AI. Thus, the application of TH has the potential to streamline research and shorten the time in bringing new treatments to market.

In discussing factors that negatively impact TH use in RD research, KOLs held the opinion that inadequate infrastructure often impedes the use of TH. Many current trial structures are not set up to specifically utilize TH. Technical issues such as connectivity and internet speed or even the TH platform can be limiting factors. The willingness and readiness of HCPs to work with TH can also sometimes be an issue; this includes concerns for privacy and lack of trust in tools for data collection using digital health devices. In addition, the cost of TH tools can be a limiting factor. Some TH solutions are based on technology that the patients or caregivers already have, such as data collection using smartphones or web-based portals via a computer. However, some technology solutions can also be quite expensive to establish. Utilizing both expensive and inexpensive technologies thereby enables different types of research to be undertaken by both well-funded and underfunded researchers. KOLs also pointed out the importance of developing TH systems taking into consideration design principles of accessibility for people with rare diseases and disabilities to enable them to fully participate in TH. RD patients, similar to people with intellectual disabilities, may face additional challenges in utilizing TH services, not only because of a digital divide (e.g., lack of access to good internet and compatible technologies) but also by the fact that TH may make it harder to build authentic rapport and provide mental health support for those with verbal or cognitive impairments who may need accessible communication modalities, such as multimodal aids and Easy Read resources.[25] Finally, language can be a limiting factor. Most physicians living in the patient's community speak their mother tongue, while TH and the tools it uses are not necessarily available in that particular language, limiting the full participation of the patient, the caregiver, and the HCPs.

TH is a field with a lot of innovation that may challenge and revolutionize the current centralized models for clinical studies. KOLs commented that TH solutions to be used in clinical research need to have demonstrated safety and performance. This is one of the current limitations for TH research but also an opportunity: the need for adequate data to prove that TH tools for research are superior, or at least equivalent to, current tools, in terms of reliability and reproducibility. In addition, there are limited digital data derived from TH approaches in RD clinical trials for definitive evaluation against standard clinical measures.

The experience using TH for RD research is still limited in spite of dramatic increases in recent years. KOLs emphasized that using TH in research brings an extra dimension to the relationship between the patient, the family, the HCP, and the researcher, and allows for novel types of research to be conducted. With these new developments, several organizations have issued guidelines for the development, use, and implementation of different types of TH to help shape the field, and have provided both regulation and support for its use in different aspects of research, such as natural history, registry development, clinical trials, and post-marketing clinical studies. For conducting clinical studies, the US Food and Drug Administration (FDA)[26,27] has

established guidelines in using digital health technologies. The European Medicines Agency (EMA) provides opinions on pathways for new methodology qualification, including digital outcomes and remote patient monitoring.[28] The KOLs from regulatory agencies expressed openness to the use of TH in clinical studies and the possibilities to discuss these instruments within the regulatory frameworks established within the EU and the US. As a matter of fact, the EMA, in conjunction with the European Commission (EC) and the Heads of Medicines Agencies (HMA), has published a recommendation paper,[29] and the FDA finalized its guidance in 2024 on conducting decentralized clinical trials.[30] As one example, the Trials@Home project, funded by a large public-private partnership between the EU and the pharmaceutical industry, is testing the use of TH and digital technologies in conducting remote decentralized clinical trials in comparison to conventional clinical trials, and will assess differences in patient satisfaction, data quality, ethical compliance, and other parameters between the approaches.[31]

Role of TH for RD medical provider education

The use of TH to deliver health information services, including patient and provider education, is increasingly gaining traction as these platforms are mostly free, or available at relatively low cost, and are a flexible, location-independent way to easily spread knowledge to large audiences across geographical regions. Based on the WHO definition of TH, the task force members and KOLs considered online medical education as part of, or at least, an extension and complementary use of TH service for the purpose of medical provider education. The initiatives KOLs discussed generally fell into two large categories: some focus on individual RDs or groups of RDs, while others adopt a general approach to RD education, or address systems-level challenges in healthcare delivery for RD patients, particularly in primary care settings. By raising clinicians' awareness of RDs while seeing patients, the latter form of TH may shorten the diagnostic odyssey for RD patients,[32,33] enabling faster diagnosis and improved management. The educational models include: (1) short e-courses given by experts involving text-based information as well as simulation and case-based discussion for providers to earn continuing education credits (e.g., Medscape)[34]; (2) free web-based distance learning programs offering asynchronous education to large numbers of geographically dispersed audiences (e.g., Massive Open Online Courses, or MOOC[35]); (3) virtual mentoring and training programs using videoconferencing to build virtual communities of practice, to enable clinicians without specialty training or in remote areas to treat and manage complex health conditions, as exemplified by the Project ECHO (Extension for Community Healthcare Outcomes) Program[36]; (4) training and capacity building programs or hybrid "communities of learning practice" used by multiple stakeholders, that is, RD associations and clinicians that share knowledge and resources and overcome challenges collectively[37]; and (5) lessons and modules covering various aspects of RDs such as research, clinical trials, early access programs, and mental health, that provide a basic level of knowledge and then encourage further training in specific rare diseases or disease areas.[38]

The uptake of TH models for medical education varies. Important factors are the extent to which the model addresses topics of local, regional, or international interest, dissemination carried out by the creators of the model, whether it is available in widely spoken languages or local languages, and the degree to which TH models are integrated into mainstream medical practice and/or university curricula. The latter is considered to be a key factor for successful uptake, contextualizing the educational program and turning it from informal voluntary training based on individual interests to formal university or medical training. Examples include MOOC and Medics 4 Rare Diseases (M4RD),[38] which aim to promote education about RDs to medical trainees and physicians.

Scalability is a crucial advantage identified by KOLs when discussing TH in comparison to traditional face-to-face education. By utilizing mobile technology, TH platforms can reach a broader audience and accommodate the busy schedules of HCPs, facilitating widespread adoption and outreach of TH for educational purposes. By doing so, TH also helps to bridge the critical bottleneck of RD care: the shortage of expertise and the limited access to experts due to geographical barriers. TH educational systems, such as Project ECHO,[36] enhance self-efficacy and knowledge for the clinicians; telementoring also helps to disseminate best practices to decrease disparities in outcomes. TH models appear

unique for spreading specialized information to underserved populations. This decentralization of specialist knowledge, achieved by harnessing the power of technology, has the potential to bring better and wider coverage to global RD patient healthcare.

In addition to serving as a gateway to a large breadth of information, TH education provides clinicians with tools to quickly access resources and supports for patients, connecting them with appropriate specialists or centers of expertise, as well as other patients. For example, the European Reference Networks provide a framework for accessing European centers for RDs, and in this sense, TH helps to build a network and community of RD care, with clinicians working in teams. This also reduces work isolation. Physicians and other HCPs can obtain online links to diagnostic testing information, expert and referral centers, professional medical societies, patient advocacy groups, and guidelines. Furthermore, many TH models include the perspectives of multiple HCPs, providing a comprehensive understanding of the challenges and opportunities in managing RDs from a multidisciplinary perspective, thus enriching the educational experience.

KOLs also emphasized the value of patient-centered approaches, particularly for medical professional education. Many of these TH initiatives are often initially established by strong RD advocates, individuals, organizations, or patient groups, who are well-aware of the related to a critical shortage of qualified RD HCPs. Therefore, these models are informed by the expressed needs of patients and healthcare professionals and designed collaboratively. This ensures that RD patients' voices and their lived experiences are well integrated. As a result, patients are treated as experts in their own diseases. Case presentations of real patients provide realistic views of the challenges they face. This helps to create empathy and understanding among HCPs, making these educational projects more relatable and impactful. Co-leadership with patient organizations further ensures active involvement, expertise, and accountability of the educational programs.

The KOLs attributed the success and credibility of some TH projects to factors such as the support of the government, alignment with local priorities, and the establishment of partnerships with other stakeholders from multiple fields. For example, in 2016, the US ECHO Act, Public Law 114-270 was signed into law,[39] requiring studies and reports to examine the use of technology-enabled collaborative learning and capacity building models, such as Project ECHO and ECHO-like programs. The RArEST Project has been funded by the Australian government to address priorities outlined in the Australian National Strategic Action Plan for Rare Diseases.[37] Collaborating with established organizations like Mental Health First Aid Australia and Project ECHO has enhanced the credibility of educational projects in RDs and allowed for the adaptation of expertise and resources to the specific RD context.

KOLs emphasized the importance of evaluation and measurement of impact to ensure that the TH models responded to and addressed the needs of the RD communities. Measurements of impact normally include statistics on the number of participants by region, as well as more qualitatively oriented measurements for achieving learning objectives, such as improvement in terms of knowledge, competence, and performance, and participants' confidence levels in managing different tasks pre- and post-learning. Consistent with our literature review, very few studies have translated these positive short-term qualitative measures to improved patient care or clinical outcomes.[3]

KOLs recognized that TH educational efforts still have a long way to go. For example, Project ECHO is recognized and widely adopted internationally. However, fewer than ten ECHO programs focus on RDs. In addition, the projects that can be used to educate medical students (e.g., the MOOC model used by M4RD) are currently not embedded in a specific medical school curriculum or compensated with medical school credits. Furthermore, it is critical to ensure inclusivity and cultural sensitivity. For example, the experience of the RArEST program demonstrated that emphasizing cultural appropriateness and accessibility by all populations, including indigenous communities, is essential. Here, incorporating language programs and addressing translation needs can play a vital role in improving access and outcomes. KOLs noted that securing sufficient funding for TH initiatives remains a significant challenge. Sustainable funding is vital for long-term project success. Exploring additional funding opportunities, such as partnering with patient

organizations and companies, and demonstrating the value and benefits of the program, can help garner financial support for its sustainability.

Overall, TH offers promising avenues for continuing medical education in RDs, but financial support, evaluation metrics, and alignment with patient-centered care remain current challenges.

Discussion

KOLs recognized that there is no single TH initiative or model that can cover the needs of the 10,000+ RDs.[40] Rather, the TH model and tools should be specific for the objectives and should be "fit for purpose." The implementation of a TH model depends on the infrastructure, the capacities, the policy and regulations, and the particularities/preferences of the patients, caregivers, and HCPs. See Table 2 for a summary of key themes articulated by each group of KOLs, along with a summary of their responses across all three groups.

In agreement with our previous literature review, the greatest advantage and benefit of TH is that it affords RD patients access to health care and research that are otherwise not possible or readily available. TH can arguably revolutionize the concept of time and space in accessing quality, expert, and multi-disciplinary care for RD patients. This is further enhanced by using TH for continuing education that decentralizes specialized knowledge and further expands availability and access to experts. It has advantages for broadening accessibility, either because it reaches over distances, improves access, and allows patients to interact more directly, or allows better physiological, meaningful outcomes to be obtained to develop safer and more effective treatments. However, TH can exacerbate disparities because of its heavy reliance on technology and established infrastructure, in addition to the required health literacy and digital literacy of the patients, caregivers, and HCPs. Therefore, the reliance on digital solutions may inadvertently disadvantage RD patients who lack access to necessary resources and cannot engage online effectively. There is a need to address the potential limitations related to technology-centric approaches. The invisibility of RD patients and their access to TH is a risk that must be addressed in the planning, implementation, and funding of TH projects.

In addition to providing RD patients access to the expert care they need, TH also allows more RD patients to participate in research and may also add value to studies by providing objective measurements in a real-world setting. Patient-centered approaches such as incorporating patient voices, collaboration, and community engagement in research and education also help to accelerate RD research through achieving meaningful outcomes for RD patients.

KOLs identified several common elements critical for the successful implementation of TH initiatives, including funding support and conducive policies and regulations. KOLs consider streamlining licensure requirements and insurance coverage of TH to be critical issues for TH in the US. Although these seem to be less of an issue in the EU, KOLs acknowledge that data security and confidentiality policies can be better harmonized across countries and regions. When different EU countries adopt different provisions for GDPR, this introduces complexity in practice, especially for research. The KOLs expect that EHDS may alleviate some of these bottlenecks with improved interoperability for treatment and research, but large-scale implementation has not yet been accomplished.

The experience using TH for RD research is still limited, but it has increased dramatically in recent years. KOLs emphasized that using TH in research, enabling decentralized clinical research, will accelerate RD medical discoveries. However, the reliability and reproducibility of the resulting data need to be demonstrated. As there is currently not a large body of data in RD research, validation of digital outcome measures such as those from consumer digital health products has not been widely shown, and this remains a current gap in evidence. However, the ongoing Trials@Home project may provide the critical evidence base to demonstrate the utility and feasibility of remote digital assessments for decentralized clinical trials.[31]

TH is empirically beneficial in shortening the RD diagnostic odyssey and improving management outcomes, through addressing various major medical needs and critical barriers to access to care. A fundamental issue for RD, based on a large survey, is that physicians, especially pediatricians and primary care physicians, often dramatically underestimate the prevalence of RDs.[41]

Table 2. Key themes from structured interview questions posed to KOLs organized by group, along with a summary of responses across all three groups.

Question	Key themes—group 1: TH for diagnosis, treatment, and prevention of RDs	Key themes—group 2: TH for research and evaluation in RDs	Key themes—group 3: TH for continuing education of HCPs in RDs	Summary of responses across all three groups
1. What is the model of telehealth (TH) used? What is the uptake of this TH model?	Teleconsultation/remote medical consultation is the most common. Modalities ranged from mobile phones to secure electronic platforms. Referral to ERNs for RD care and research across EU. Developing countries may use mobile phones, WhatsApp, and chat groups; high-income countries may use TH models with security controls compliant with data protection regulations.	Many modalities used: asynchronous, synchronous, remote patient monitoring, and mHealth (mobile phones or wireless devices). Should be "fit for purpose" based on type of research, patient characteristics, goals of research, and setting. Wearable devices can be used to gather data remotely and in real-world settings.	Education of HCPs in RD diagnosis and management use different models: short e-courses; web-based distance learning (asynchronous); virtual mentoring and training programs; communities of learning practice programs; lessons and modules to cover general RD education with training options for specific RDs available.	Provision of remote medical care, education, and training for RDs was used broadly across countries and regions but modality of provision varied widely depending on resources available, country and regional policies and regulations, and purpose of use (medical care, research, or provider education).
2. What strategies are used for implementation of this TH model? What are the strengths (S) and weaknesses (W) of the strategies that you used?	Provision of diagnosis and care when in-person care is not available due to geographic barriers. S: Primary care HCPs can refer to centralized specialty providers. W: Less ideal for some clinical contexts such as initial visits or those requiring in-person exams.	TH can increase sample size for RD research, for example, via decentralized trials. S: Allows novel data collection and study design; can collect digital data worldwide that can be more readily collated across sources. W: Inadequate infrastructure to support research applications; cost of TH tools and technologies.	TH and telementoring can expand the number of HCPs with knowledge of RDs. S: Dissemination of critical knowledge to decrease disparities in patient outcomes. W: Lack of options for training in all RDs a provider may encounter.	Patients with RDs can access specialty services and research opportunities more readily using TH and digital data collection tools. For provider education, remote options can fill needed gaps and improve patient outcomes. There is a need for demonstrated metrics to ensure safety, reliability, and performance for use in clinical settings, research, and health care provider (HCP) education.
3. What are the benefits of TH for the following stakeholders:				
Patients/families	Access to specialty care faster and without need for travel or time off work, including for fragile patients. Access to expert care even during COVID pandemic.	Research participation speeds treatment development and ultimately improves patient care.	The best models include partnerships with patients and organizations through case presentations. Increase knowledge of HCPs to improve patient care.	TH can build virtual communities of RD patients, researchers, providers, and advocacy groups to improve care and treatment and ultimately, speed development of new treatments.
Health care providers	Facilitates primary care referrals to RD specialists. Reduce diagnostic odyssey.	May provide access to novel treatments not typically available to patients and HCPs.	Empowers HCPs to gain knowledge about RD care and management.	TH provision of RD training and research opportunities for RD patients can enhance HCP knowledge and care for these patients.
Private and public payers	Relaxation of licensure requirements allowed cross-border care provision during COVID.		Some legislation encourages studies of collaborative learning models for RDs.	The COVID pandemic significantly increased access to TH services for patients and provided flexibility for medical providers and researchers in many regions.

(Continued)

Table 2. (Continued)

Question	Key themes—group 1: TH for diagnosis, treatment, and prevention of RDs	Key themes—group 2: TH for research and evaluation in RDs	Key themes—group 3: TH for continuing education of HCPs in RDs	Summary of responses across all three groups
Regulatory bodies		EMA and FDA have established guidelines for use of TH in clinical research.	Establishment of certificate programs and incorporation into training curricula enhances uptake.	The willingness of regulatory bodies to establish guidelines for the use of TH in research and incorporation of these approaches in medical education have increased uptake.
Researchers		Access to RD patients that are geographically dispersed; allow development of novel drugs and treatments for RD patients when larger sample sizes available.	Improved HCP education increases diagnosis of RDs and facilitates participation in research.	TH can facilitate establishment of "communities of practice" between HCPs and RD researchers and enhance recruitment of RD patients across larger geographic areas to increase sample size and power in research studies.
4. What are the harms and limitations in the use of TH for the following stakeholders:				
Patients/families	Technical barriers/access to broadband services; inadequate privacy protections. Language barriers. Can exacerbate disparities in access to care.	Technical barriers—need for accessible devices for those with disabilities; language barriers.	Lack of cultural sensitivity may impair effectiveness of provider education. Few TH training programs specifically for RDs.	Potential limitations for RD patients to take advantage of TH services include privacy issues, language barriers, and lack of digital and technical accessibility; harms may include lack of cultural sensitivity and appropriateness.
Health care providers	Licensure requirements and lack of reimbursement for TH care provision; skepticism of quality of remotely delivered care (initial visits in-person may be a priority for many HCPs).	HCPs may not want to work with researchers using digital tools to collect data or have concerns about privacy.	Lack of digital health literacy and access to digital resources by HCPs in underserved regions of the world; language barriers.	Regulatory burdens, lack of access to TH resources, and skepticism of its utility by HCPs may negatively impact their enthusiasm to embrace TH for RD care, research, and education. Many have concerns about inadequate reimbursement for TH services.
Private and Public Payers	Lack of standardization of diagnosis codes and EHR systems; lack of coverage and reimbursement for TH services. Regulations restrict access to some TH services post-pandemic.		Lack of data that demonstrate HCP education and RD training programs improve clinical care and patient outcomes. Lack of payment for training activities and programs.	Private and public payers may have concerns about lack of standardization of diagnosis codes and EHR systems used in TH for RD care. The lack of established metrics for quality of care and provider education results in restrictions on payments for care reimbursement and training programs.

(Continued)

Table 2. (Continued)

Question	Key themes—group 1: TH for diagnosis, treatment, and prevention of RDs	Key themes—group 2: TH for research and evaluation in RDs	Key themes—group 3: TH for continuing education of HCPs in RDs	Summary of responses across all three groups
Regulatory bodies	Lack of interoperability of EHRs; lack of health data security protections.	Reliability and reproducibility of research results when collected remotely.		Regulatory bodies have concerns about health data security across digital platforms and EHR interoperability used for RDs. Reliability and reproducibility of remote data collection also impact uptake of TH for RD research.
Researchers		Not all research can be conducted via TH; fidelity and cost of data collected remotely can be issues.	Limited number of TH educational programs and RDs covered impact research recruitment.	There are limitations of the use of TH to remotely monitor patients in RD clinical research studies, and costs can be prohibitive, along with ensuring fidelity of data.
5. What are the opportunities (O) and barriers (B) for the use of TH, for this specific model of TH?	O: TH creates options for improved global care delivery for RD patients. B: Lack of adequate resources and reimbursement for TH as well as consistent regulations can limit access to TH for all RD pts.	O: Treatment development is enhanced when adequate numbers of RD patients are enrolled in TH-enabled research studies. B: Data fidelity and cost of digital tools can be prohibitive.	O: TH can address a major barrier to RD care, which is shortage of qualified HCPs worldwide. B: Lack of reimbursement and support for HCP training in RDs limits its uptake.	O: TH can break down geographic barriers and build connections among RD communities, including patients, HCPs, and researchers. B: There is a lack of consistent, harmonized resources, policies, and regulations across countries and regions to enhance worldwide access to TH for RD patients and providers.

EHR, electronic health records; EMA, European Medicines Agency; ERNs, European Reference Networks; EU, European Union; FDA, Food and Drug Administration; HCPs, health care professionals; KOL, Key Opinion Leader; RD(s), Rare Disease(s); TH, Telehealth.

Enhanced education about RDs raises clinicians' awareness of patients with RD in their practice, by recognizing and identifying "red flags" that suggest the possibility of a RD. KOLs suggested that the impact could be higher if this awareness was instilled earlier in medical students when they start their training.

Developing effective evaluation metrics is a major challenge and opportunity identified by several KOLs, particularly for evaluating the impact of using TH for educational and peer mentoring purposes. Although short-term impacts are commonly observed and reported through positive feedback from course participants using the various TH models, objective clinical outcome measures and impact assessments on parameters such as diagnostic accuracy, time to diagnosis, and disease outcomes would be preferable for evaluating the impact of these programs. This remains challenging, requiring further research with proper study design.

The limitations of this review include the potential for restricted experiences of the KOLs selected and the internal biases of the interviewers, such that not all viewpoints and perspectives were recognized or evaluated, an intrinsic shortcoming of any subjective survey such as this one. In addition, the regional backgrounds of the KOLs may reflect biases in that there was limited representation from Africa, as well as no perspectives from South America, suggesting a paucity of opinions from many low- and middle-income countries. The focus on perspectives from the EU and US may skew the findings toward those of countries with more resources and fewer barriers to implementation of TH programs, particularly for health

care and research. Conversely, the preponderance of KOLs from these wealthier countries may over-emphasize the increased policy considerations, regulatory burdens, and licensure requirements that exist for TH usage in RDs in these settings.

Conclusion

In conclusion, KOLs agreed that the promise of TH for diagnosis, research, and medical education for RDs remains a tantalizing possibility, with many early successes, particularly in the domains of patient diagnosis, care, and ongoing clinical management. The use of TH and mobile health-acquired data to track RD patients participating in clinical studies has the potential to accelerate novel discoveries and treatments. Finally, TH affords many opportunities to advance training and education of medical providers caring for RD patients to optimize patient-centered outcomes and provide precision therapeutics. It remains to be seen if the technical and health literacy demands, as well as regulatory and privacy concerns, can be consistently overcome to make TH truly a tool for all of those with RDs across the digitally interconnected world.

Declarations

Ethics approval and consent to participate

Ethics approval was not required for this survey of opinions from experts in the field. No consent to participate was required.

Consent for publication

KOL interviewees gave consent to be listed in the acknowledgment section of this manuscript.

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