European Journal of Medical Genetics 72 (2024) 104977

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

Telehealth for rare disease care, research, and education across the globe: A review of the literature by the IRDiRC telehealth task force

Faye H. Chen [a,*], Adam L. Hartman [b], Mary Catherine V. Letinturier [c], Victoria Antoniadou [d], Gareth Baynam [e], Lara Bloom [f], Marco Crimi [g], Maria G. Della Rocca [h], Giuseppe Didato [i], Sofia Douzgou Houge [j], Anneliene Jonker [k], Martina Kawome [l], Friederike Mueller [m], James O'Brien [n], Ratna Dua Puri [o], Nuala Ryan [p], Meow-Keong Thong [q], Birutė Tumienė [r], Melissa A. Parisi [s,**]

[a] National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH), USA
[b] National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), USA
[c] IRDiRC Scientific Secretariat, French National Institute of Health and Medical Research (Inserm), France
[d] Cyprus Alliance for Rare Disorders, Nicosia, Cyprus
[e] Rare Care Centre, Perth Children's Hospital and Western Australian Register of Developmental Anomalies, King Edward Memorial Hospital, Australia
[f] The Ehlers-Danlos Society, USA
[g] Kaleidos SCS, Scientific Office, Italy
[h] Global Genes, USA
[i] Epilepsy Unit, Sleep Disorders Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Italy
[j] Department of Medical Genetics, Haukeland University Hospital, Bergen, Norway
[k] University of Twente, the Netherlands
[l] Sally Mugabe Central Hospital, Zimbabwe
[m] Department of Child and Youth Psychiatry, Psychosomatics and Psychotherapy, Asklepios Hospital Luebben, Germany
[n] International Prader Willi Syndrome Organisation (IPWSO), United Kingdom
[o] Institute of Medical Genetics and Genomics, Sir Ganga Ram Hospital, New Delhi, India
[p] NCBRS (Nicolaides-Baraitser Syndrome) Worldwide Foundation, United Kingdom
[q] Genetics and Metabolism Unit, Department of Paediatrics, Faculty of Medicine, University of Malaya, Malaysia
[r] Vilnius University, Faculty of Medicine, Institute of Biomedical Sciences, Vilnius University Hospital Santaros Klinikos, Lithuania
[s] Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), USA

ARTICLE INFO

Handling Editor: A. Verloes

Keywords:
Telehealth
Telemedicine
eHealth
Rare disease
IRDiRC
Rare disease care
Rare disease research
Rare disease education
Decentralized clinical trial
Peer mentoring
Remote monitoring

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). The Task Force reviewed related literature published from January 2017 to August 2023, and identified various models and implementation strategies of TH for RD. The Task Force highlighted the reported value and benefits of using TH for RDs, along with the limitations and opportunities. The number of publications sharply increased since 2021, coinciding with the onset of the COVID-19 pandemic, which forced the rapid adoption of TH in many healthcare settings. One of the major benefits of TH for RDs lies in its capacity to surmount geographical barriers, which helps in overcoming the constraints posed by limited numbers and geographical dispersion of specialists. This was evident during the pandemic when TH was used to maintain a level of continued medical care and research when face-to-face visits were severely restricted. TH, through which clinical research can be decentralized, can also facilitate and enhance RD research by decreasing burden, expanding access, and enhancing efficiency. This will be especially beneficial when coupled with the adoption of digital health technologies, such as mobile health (mHealth) and wearable devices for remote monitoring (i.e., surveillance of outpatient data transmitted through devices), along with big data solutions. TH has also been shown to be an effective means for RD education and peer mentoring, enabling local health care providers (HCPs) to care for RD patients, which indirectly ensures that RD patients get the expertise and multidisciplinary care they need. However, limitations and weaknesses

* Corresponding author.
** Corresponding author.
E-mail address: chenf1@mail.nih.gov (F.H. Chen).

https://doi.org/10.1016/j.ejmg.2024.104977
Received 11 March 2024; Received in revised form 28 August 2024; Accepted 5 October 2024
Available online 5 October 2024

associated with using TH for RD care and research were also identified, including the inability to perform physical examinations and build relationships with HCPs. Therefore, TH has been recommended as a complement to, rather than substitute for, face-to-face consultations. There is also a concern that TH may lead to an amplification of health disparities and inequities related to social determinants of health for those with RDs due to lack of access to TH technologies, inadequate digital literacy, and geographical, socio-cultural, and linguistic barriers. Finally, the Task Force also discussed 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.

1. 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) through research (Austin et al., 2018). Gaps and key issues in RD research are identified and tackled by IRDiRC through Task Forces. Telehealth (TH) was identified as an emerging topic with untapped potential to revolutionize care, research, and training for RDs. The IRDiRC TH Task Force was established in October 2021 to explore the use of TH to improve access to diagnosis, care, prevention, and research experiences for RD patients worldwide, as well as provide education and peer mentoring of RD health care providers (HCPs).

The Task Force identified three key objectives: (1) Conduct a review of published literature on existing models of TH, their uptake and usage by the RD community, and their specific value and effectiveness, in order to identify the factors that enhance or limit their adoptability, sustained use, ease of access, and effectiveness in the RD community; (2) 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, including technological, legal, cultural, linguistic, healthcare system, and patient/provider factors; and (3) Identify evidence gaps for which future recommendations can be developed for introducing and enhancing TH services into RD communities.

2. Methods

2.1. Definition of TH

The Task Force adopted the World Health Organization (WHO) 2010 definition of TH with modification specifically for RDs (in italics): "The delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention *of RDs*, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals *with RDs* and their communities."

2.2. The Task Force

The IRDiRC TH Task Force is composed of 18 members from 13 countries, covering Europe, North America, Asia, Africa, and Australia. Members include international opinion leaders representing national funding bodies, RD patients, patient advocates, clinicians, researchers, and a company representative. Based on the WHO TH definition, the group identified three topics, or key areas of focus: (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.

2.3. Literature search

We conducted a scoping review of the literature to identify existing TH models being used and their implementation strategies, specifically related to RDs. Furthermore, we curated data from various publications to perform a comprehensive Strengths, Weaknesses, Opportunities, Threats (SWOT) analysis. Our search covered articles published from January 2017 to August 2023 on PubMed, with additional references from Google Scholar, CORDIS, and relevant national and international TH/digital health guidelines and recommendations identified by Task Force members. For the PubMed search, we employed a combination of two sets of keywords for rare diseases AND telehealth based on task members' suggestions (with an asterisk indicating a wildcard symbol): (rare disease* or rare condition* or rare disorder*) AND (telehealth or telemedicine or tele-health or tele-medicine or "digital health" or "digital medicine" or telecare or tele-care or teledoctor or tele-doctor or "virtual doctor" or "virtual health care" or "virtual healthcare" or "virtual hospital" or "telephone consultation*" or "telephone counseling" or "telenurse" or "tele-nurse" or teleconsultation or tele-consultation or telecounseling or tele-counseling or econsultation or e-consultation or ecounseling or e-counseling or "remote consultation*" or "remote-consultation*" or "remote counseling" or "remote-counseling" or mhealth or "mobile health" or econsult* or e-consult* or eteaching or e-teaching or elearning or e-learning or ehealth or "remote learning" or "remote teaching" or "remote mentoring" or ementoring or e-mentoring or "video consultation*" or "video counseling"). Additional search terms related to Project ECHO with RD generated a few additional papers and were combined with the above search results for review: (teleECHO or tele-ECHO or "project ECHO") AND (rare disease* or rare condition* or rare disorder*). The RD/TH search strategy was also employed in combination with "COVID" to analyze the related use of TH for RDs during the COVID-19 pandemic. Task Force members screened abstracts for relevance related to TH and RDs for further review, while assigning each publication to the three topics. Members in each of the three working groups reviewed the abstracts of the papers assigned to their group for relevance and selected papers of high relevance and strength of evidence for further review and analyses. Discrepancies were discussed at regular working group meetings and task force meetings. Each working group established a writing group to summarize their conclusions and create a SWOT analyses for the working group chairs (FHC, MAP, and ALH) to synthesize into the final manuscript.

3. Results and discussion of key findings of the task force

Our PubMed search returned 491 articles published between January 2017 and August 2023. Task Force members screened abstracts for relevance related to TH and RDs and selected 358 publications for further review. The publications were assigned to the topic areas as follows: Topic 1: TH for Diagnosis, Treatment, and Prevention (167), Topic 2: TH for Research and Evaluation (158), or Topic 3: TH for Continuing Education and Peer Mentoring of HCPs (33). Papers were most often published by European (204) and North American (101) authors. A peak of publications beginning in 2021 continued into 2023, which coincided with the onset of the COVID-19 pandemic and the rapid adoption of TH during the pandemic and beyond (Fig. 1).

Many publications identified patients and families as the main beneficiaries of TH. This is evident especially during the COVID-19 pandemic, as TH has been essential in filling the critical gaps in medical access and continuing patient care when in-person visits were severely restricted.

4. TH models and strategies used for RDs

There is a wide array of TH models that can be used as "information and communication technologies" for the "delivery of health care services" that are encompassed within the WHO definition. TH models and implementation strategies that were identified in our literature search included the traditional ones such as email, text message, audio/video conferencing using telephone, web-based video calls, or videoconference on computer or tablet (Hari Eswaran et al., 2022). mHealth technologies and remote patient monitoring have gained significant prominence and have been reported to be used frequently. Wearable devices and smartphone applications have been used to generate large amounts of research data that contribute to outcome measurement. Electronic Health Records (EHR) have also been leveraged to advance RD patient care as well as research objectives. Other models include digitally enabled care systems, established to allow patients to report progress and symptoms from their homes (Wasilewska et al., 2022; Cerdán-de-Las-Heras et al., 2021; Khan et al., 2015). The use of TH for remote monitoring facilitates Real-World Evidence (RWE) for medical products, and has been described as very promising in enhancing patient engagement, improving accessibility, and delivering high-quality medical/clinical services tailored to individual clinical needs (Wasilewska et al., 2022; Khan et al., 2015). Other strategies include websites to disseminate information on treatment guidelines, adverse drug effects, and suggestions for RD patients during the COVID-19 pandemic (Brizola et al., 2020). Chatbots have been tested in triaging RD patients, connecting them with the appropriate experts, providing personalized treatment recommendations, and increasing patient engagement (Li, 2023). Deep learning methods for automation and robotic devices for surgical interventions/procedures were also reported (Wijnen et al., 2017). In a study involving children with Prader-Willi syndrome, a six-week play-based TH intervention was shown to improve cognitive and affective processes for the children. This role play approach modelled social interactions, emotional understanding, and emotional regulation skills. This approach may have potential applications for children with other RDs characterized by developmental delay and/or social-emotional dysregulation (Dimitropoulos et al., 2017).

5. TH for RD diagnosis, treatment, and prevention

There were 167 papers in the literature review that focused on the topic of using TH for RD diagnosis, treatment, and prevention.

6. Diagnosis

TH has been used to diagnose RDs. The European Reference Networks (ERNs) are cross-border networks bringing together European hospital centers of expertise and reference (tertiary care centers) and HCPs across the European Union (EU) to tackle low prevalence (or RDs) and complex diseases and conditions requiring highly specialized healthcare. ERNs use a secure digital platform to facilitate clinical consultations and expertise sharing between referring clinicians and international experts. The ERN for Intellectual Disability, Telehealth, and Congenital Anomalies (ERN-ITHACA), for example, reported using this platform to help with diagnosis in the vast majority (27 out of 28) of its query cases during its first year of operation (Smith et al., 2020).

TH services have been shown to facilitate access to genetic services for patients living in remote locations. To address the global shortage of HCPs specializing in genetics, who are also predominantly concentrated in large academic centers, a partnership model was created in the Dominican Republic between pediatricians and geneticists. This approach mirrors a strategy used in the United States (Kubendran et al., 2017) but operates in a setting of two different countries, healthcare systems, and cultural contexts. Patients were referred if their local HCP suspected a

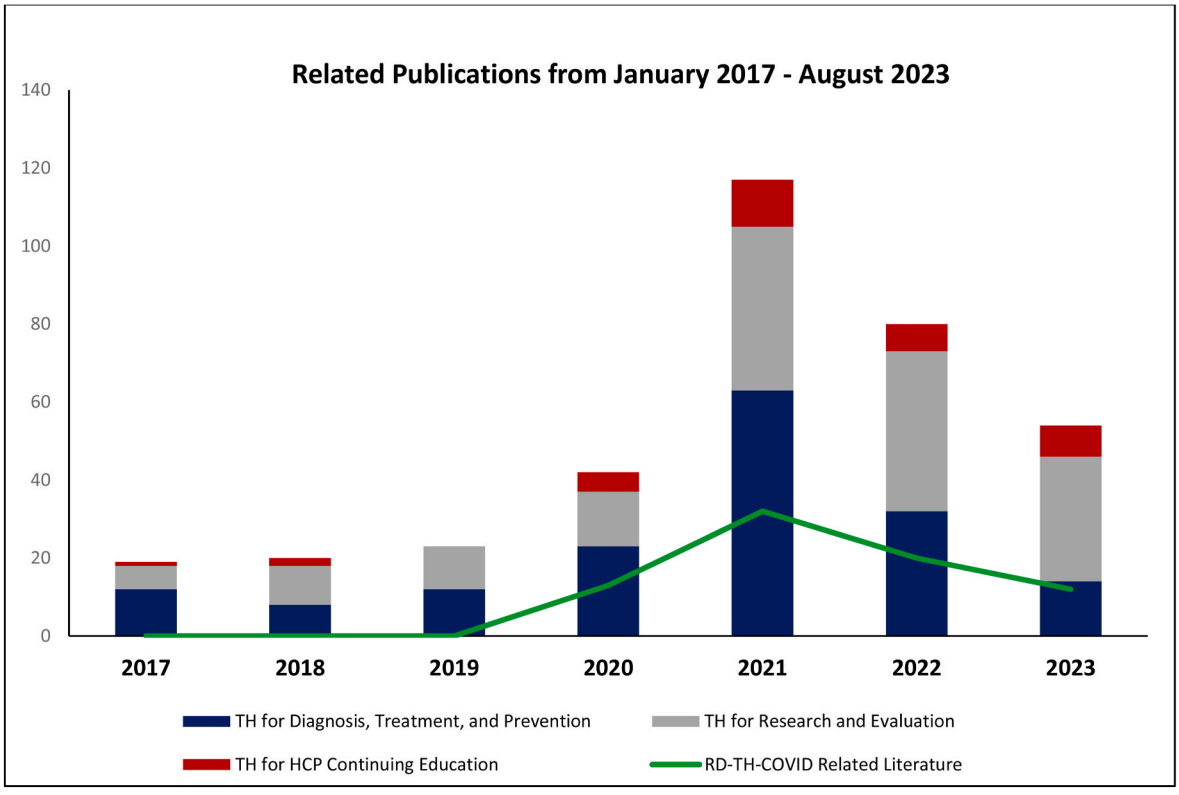

Fig. 1. Numbers of publications related to TH for RDs from 2017 to 2023.
The number of PubMed references related to TH for RDs are shown in bar graph format by publication year, along with their relevance to either the topic of TH for RD diagnosis, treatment, and prevention (blue), for research and evaluation (grey), or for HCP continuing education and peer mentoring (red). The number of publications by year on the topic of TH for RDs related to the COVID-19 pandemic is shown in the line graph (green).

syndromic or genetic etiology. Pediatricians first evaluated patients prior to the TH appointment to review family and medical history. Then, genetic visits were scheduled in collaboration with a TH program at Cincinnati Children's Hospital Medical Center. Over a span of five years, a total of 66 individuals were evaluated, with 57 individuals undergoing genetic studies, resulting in molecular diagnoses for 39 individuals. This approach demonstrated the clinical utility of a partnership between geneticists and pediatricians to provide TH services for RD diagnosis in an international setting (Mena et al., 2020).

Mobile applications and software can also help in RD diagnosis, follow-up, and treatment. For instance, the ERN on Rare Multisystemic Vascular Diseases developed a mobile app equipped with features enabling users to locate expert centers and patient organizations specializing in rare multisystemic vascular diseases across Europe. It also developed resources for training and education via digital platforms (eLearning) (Paglialonga et al., 2021). Similarly, three dimensional (3D) facial analysis, using free and open access software, has been deployed for remote diagnosis and treatment monitoring, offering support in Western Australia (Cliniface).

7. Remote monitoring

Another reported significant application of TH for RD care is remote monitoring. The Internet of Things (IoT) – connected devices that are wearable, such as smart watches and biosensors – has provided new mechanisms to help patients stay connected with HCPs through remote monitoring and data collection (Huhn et al., 2022)· (Servais et al., 2021)· (Donald et al., 2019)· (Petracca et al., 2021)· This approach enables the collection of real-time data, including patient-reported outcomes; in addition, it fosters patient engagement as an integral part of real-world information gathering (including aspects of self-care), education, and multidisciplinary care. One study conducted stakeholder interviews of payers and policymakers in four countries (United Kingdom, Germany, Italy, and Spain), and evaluated their policies, insurance reimbursement, and quality indicators for various chronic diseases that employed remote disease monitoring. The findings indicated a moderate-to-high value of remote assessment, particularly benefiting patients who had been recently discharged from hospitals, those living in remote areas, and those with serious and/or complicated diseases (Rojahn et al., 2016). Although derived from common chronic diseases, these conclusions are also applicable to RDs, especially considering that many RDs require continuous lifelong outpatient care.

In addition to reduced patient burden, remote assessments can provide valuable clinical outcome data and may provide a more robust understanding and characterization of disease impact on RD patients, as exemplified by the case of neuromuscular diseases (Montes et al., 2022). Remote assessments can also facilitate better adherence and can serve as a viable alternative to in-clinic assessments (Tjeertes et al., 2023; Davies et al., 2020), though a combination of in-clinic and at-home clinical outcome assessments may be preferred whenever possible.

In the field of neuro-oncology, a study explored caregivers' satisfaction with the current supportive care provision for their loved ones with rare primary brain tumours in two different countries. The study also collected caregivers' thoughts on monitoring their care issues with both paper-based and digital instruments. Results showed that caregivers preferred a brief and easy-to-use 'blended care' instrument that combined digital monitoring with personal feedback; this was likely not influenced by country- or culture-specific differences (Boele et al., 2017).

In addition to qualitative measures of the benefit of TH, some studies also showed quantitative evidence of the benefits of TH as compared to standard face-to-face care. Some studies have shown that TH can deliver effective patient care for disease progression monitoring for some RDs. For example, for Spino-Bulbar Muscular Atrophy (SBMA) patients, two clinical scales have been used to assess disease progression: Adult Myopathy Assessment Tool (AMAT) and SBMA-Functional Rating Scale (SBMA-FRS). During the pandemic, SBMA patients monitored by TH and assessed by remotely administered AMAT and SBMA-FRS showed comparable disease progression as compared to results from in-person visits. This suggests that TH-delivered disease monitoring is a valid tool to monitor patients with SBMA. Thus, AMAT and SBMA-FRS scales delivered by TH can be effectively, reliably, and easily administered remotely (Fenu et al., 2023).

Another study evaluated a three-month program of home electronic spirometry (e-spirometry) monitoring of pulmonary function and respiratory muscle strength in Duchenne Muscular Dystrophy (DMD), as well as patients' benefits from the telemetric program. The study indicated high compliance with the home telemonitoring program, with no significant differences between hospital and at-home spirometry results. Importantly, the study showed that the primary benefit of home e-spirometry for DMD patients was improved breathing, and concluded that remote home spirometry is suitable for daily monitoring of pulmonary function in DMD patients and can support respiratory muscle training (Wasilewska et al., 2022). However, to overcome the observed irregular measurements, patient education and regular reminders are needed to optimize its benefits (Wasilewska et al., 2021).

8. Treatment and prevention

Many of the published papers report on the use of TH for the treatment and management of RD patients. One major advantage of TH is its ability to offer multidisciplinary and specialty care to RD patients. TH has been shown to enable complex multidisciplinary care for RDs, particularly in situations where expertise is limited, especially among underserved populations, in small community hospitals, or at private clinics. Through videoconferencing, individual cases can be discussed, enabling interdisciplinary and even international collaborations and consultations, along with knowledge-sharing and mentorship. This has been beneficial for very rare disorders such as intestinal failure (Winkler et al., 2021). TH can also facilitate building integrative care networks to enable access to multidisciplinary specialized health care workers and supportive services. These networks expand access to experts in specific conditions, reduce unwanted variations in care practice, and streamline care coordination (van de Warrenburg et al., 2021).

In a program developed for Inherited Metabolic Disorders (IMD) patients who were identified by the newborn screening program in Georgia in the U.S., the Georgia Medical Nutrition Therapy for Prevention (MNT4P) program and the Public Health Informatics Institute developed and deployed a digital public health informatics product. The goal of this system was to support lifelong management, deliver personalized nutrition treatment programs, and track long-term health outcomes and needs for these patients. It complies with U.S. privacy regulations, streamlines record-keeping, standardizes data, and harmonizes with the EHR. It allowed the MNT4P staff to transition away from the previous manual processes and expedite the adoption of a TH model during the COVID-19 pandemic. This transition ensured the availability of digital, centralized patient records, ensuring uninterrupted patient care during statewide lockdowns (Singh et al., 2022).

TH also serves as a means to provide specialized medical and hospital care in geographically remote areas with limited expertise, effectively contributing to capacity-building efforts. For example, the care of patients with Prader-Willi syndrome can benefit from multidisciplinary approaches involving collaboration between academic centers, medical homes, industry stakeholders, and parent organizations (Duis et al., 2019). In the case of Hereditary Angioedema (HAE), a TH service operated by trained clinicians has been instrumental in reducing hospital admissions for severe HAE attacks (Riedl et al., 2022). In this way, TH approaches can improve access and delivery of high-quality medical and clinical services, tailored to meet individual clinical needs, thereby providing personalized medicine (Paglialonga et al., 2021). Ultimately, these strategies collectively aim to prevent medical complications in RD patients and improve their long-term quality of life.

TH has also been used to improve the treatment of RDs through patient- and caregiver-targeted educational programs. For instance, the Cure Progressive Supranuclear Palsy Care Guide is an example of a targeted TH nursing intervention designed to provide knowledge, guidance, resources, and local support for individuals and families living with the condition, thereby building a supportive community (Dunlop et al., 2016). A similar model is currently being evaluated in multiple states in Australia (Cannata, 2023). Moreover, electronic and mHealth platforms have been used to engage RD patients and their families to build evolving knowledge about their disease. A report on qualitative data from a pilot study utilizing a mobile device-delivered platform showed its effectiveness in addressing caregiver and individual needs for knowledge, daily management tips and support, and other resources (Lanzola et al., 2014). Another qualitative study found that caregivers of children with Osteogenesis Imperfecta (OI) identified internet-based technologies to be beneficial in supporting their caregiving needs, including daily caregiving activities, seeking OI medical information, and reducing social isolation (Castro et al., 2019).

9. COVID-19 and RD diagnosis, treatment, and prevention

The COVID-19 pandemic highlighted the beneficial role of TH in the treatment and management of RD patients. The COVID-19 pandemic brought on an abrupt and unprecedented disruption of healthcare systems globally, with HCPs often stretched to, or even beyond, their capacity. In addition to the uncertainties of whether the specific RD poses additional risks for contracting COVID-19 or poor prognosis after infection, RD patients encountered additional barriers to accessing care, especially during the early phase of the pandemic when medical resources and HCPs were shifted to prioritize pandemic-related care. RD patients identified reduced healthcare access as the top issue they faced during the pandemic, and reported either cancellations or delays to their appointments, diagnostic tests, and medical therapies (Manzi, 2022; Schwartz et al., 2021; Hughes et al., 2021; Lampe et al., 2020). These disruptions had detrimental effects on the delivery of standard care (Hughes et al., 2021) and led to delays in diagnosing new cases. The extent of the long-term impact of the pandemic on the RD community is yet to be fully understood.

However, the pandemic also prompted rapid reorganization within healthcare and research systems, leading to the adoption of TH measures and services, even in cases where readiness for implementation was lacking. This shift was necessary in order to minimize the risk of COVID-19 exposure for both patients and providers. While some medical specialties had to swiftly implement TH during the pandemic (Radtke et al., 2021), it is worth noting that TH services already existed for some specialties that treat a number of RDs, such as neurology, rheumatology, and clinical genetics. The pandemic acted as a catalyst, pushing all medical specialties to overcome barriers and accelerate a process already underway. Despite the challenges posed by adopting a new technology and limited evidence of best practices for most RDs, TH offered a level of access and continuity of medical care for RD patients during the pandemic that would have been impossible otherwise. The surge in the adoption and the preference for TH became evident during the pandemic, and its benefits were shown to prevent treatment gaps (Fenu et al., 2023; Radtke et al., 2021; Smyth et al., 2022; Soussand et al., 2022; Pareyson et al., 2021), thereby mitigating the pandemic's impact on RD patients (Radtke et al., 2021). Both patients and some HCPs reported satisfaction with its ease of use (Wasilewska et al., 2021, 2022; Radtke et al., 2021; Walsh and Markus, 2019). TH emerged as a viable alternative to certain face-to-face consultations during the pandemic, effectively bridging geographical gaps and preventing complications by maintaining contact between HCPs and patients virtually.

10. Limitations and weaknesses of using TH strategies for RD diagnosis and treatment

There are several drawbacks and limitations in the use of TH for RD. While TH has been instrumental in providing continuity of patient care during the COVID-19 pandemic despite limited evidence of best practices for most RD specialties, its rapid, widespread use also highlighted its weaknesses and raised concerns about its ubiquitous application without sufficient validation of its appropriate use. One of the most commonly cited concerns is related to the inability to perform physical examinations remotely, which can be crucial for identifying subtle diagnostic clues and monitoring response to treatments (Radtke et al., 2021). TH has also been associated with a higher risk of diagnostic inaccuracies. In one study, patients and clinicians rated telemedicine worse than face-to-face consultations for assessment accuracy even though it was considered more convenient (Sloan et al., 2022). This limitation is particularly relevant for RD patients with neuromuscular disorders and cognitive deficits, or those who did not have a diagnosis. Finally, TH was also associated with an increase in inappropriate genetic testing. Due to the limited in-person evaluations because of TH, more genetic tests may be ordered when they might not be appropriate. This resulted in lower accuracy of the test (and worse pre-test probabilities), higher healthcare expenses and utilization, and less time and resources to test and counsel those patients who would have the greatest benefit.

Other limitations are the challenge of establishing a strong physician-patient relationship and the difficulties faced by some patients who may be uncomfortable with the technical aspects of using an electronic interface. In this regard, TH has been recommended to be used as a complement to, rather than a substitute for, face-to-face consultations (El-Hassar et al., 2023). Overall, it is not clear if some of these negative experiences may have been due to the pandemic or telemedicine specifically. Some authors have concluded that training, personal preference, careful patient selection for TH, and further consultations with clinicians and patients is required to increase TH's acceptability and safety (Sloan et al., 2022).

Many remote measures have not been specifically validated for virtual environments compared to in-person visits, limiting their utility prior to the pandemic. Without many options, clinicians had to adapt protocols for in-person visit monitoring for virtual settings during the pandemic. For example, neuromuscular disease (NMD)-specific clinical outcome assessments (COAs) have been developed through rigorous and iterative processes over many years. They were quickly adapted for remote monitoring during the pandemic. However, it also became clear that existing COAs required modifications for use in a virtual environment, limiting the interpretation of the information gathered remotely when compared to standard, in-person administration (Montes et al., 2022).

HCPs may also experience barriers to the use of TH for RDs, including a lack of awareness about TH capabilities or inadequate training or experience in using these technologies. HCPs and healthcare organizations may also face the challenge of the huge amounts of data generated by TH that can be difficult to manage (Nakshbandi et al., 2021; Bergier et al., 2021). In addition, reimbursement for TH services may be limited or nonexistent, which can discourage providers from offering them to patients. In fact, many insurers are still unequipped to recognize this mode of health delivery and its associated reimbursement policies (Nakshbandi et al., 2021).

A significant concern is that TH may lead to an amplification of health disparities and inequities that may impact future TH policies. Many RD patients have limited access to TH. This can be due to the disease itself that may have affected the cognitive function of the patients, or social drivers of health, such as the availability of the necessary technology and digital literacy, i.e., the "digital divide" (Nadipelli et al.,

2022; Hsieh et al., 2023). Many patients with RDs live in rural or underserved communities, where access to broadband internet and other necessary technology infrastructure may be limited or absent. In addition, some patients may not have the financial resources to pay for necessary technologies for TH or may not have insurance coverage for these services (Rojahn et al., 2016). Finally, privacy and consent challenges may arise if consultations were visible or overheard by unintended parties without the knowledge of the patient, family, and/or HCP.

11. TH for RD research and evaluation

11.1. Application of TH for RD research

Various TH models and methodologies, including digital health, have been used in RD research. These approaches have the potential to not only adjuvate, promote, or accelerate advances in RD diagnosis and treatment, but also to alleviate some of the challenges associated with RD research. Most importantly, TH can enhance the recruitment and retention of RD patients in studies, which often present significant hurdles. Even though many RD patients are engaged and dedicated to research, there are many barriers limiting their participation in traditional research protocols. These barriers include the demanding requirement of traveling to specialized study centers with the appropriate expertise for study enrollment, treatment, and follow-up visits. This is particularly difficult when RD patients are geographically dispersed. One study used remote video conferencing to test a parent-delivered developmental intervention for infants with Tuberous Sclerosis Complex, and found that this TH strategy was effective in addressing challenges in recruitment, yielding a more diverse cohort (Hyde et al., 2020). TH helped increase the number of research participants both in quality and quantity, as wider geographical areas were represented, thereby increasing the research capacity and reach in areas with limited clinical resources. Patients with medical comorbidities that affect mobility could also be recruited, by eliminating or reducing the need for travel. Rapid acceleration in clinical trial enrollment was thus accomplished by a strategy of remote intervention and assessment (Hyde et al., 2020).

The recent explosion of digital health technologies and methodologies has also impacted RD research, including mHealth, wearable technologies, and sophisticated analytical tools used in big data science, such as Artificial Intelligence (AI)/Machine Learning (ML) and EHR (Davies et al., 2020; Bergier et al., 2021; Mohan et al., 2022). For example, a study on Huntington's disease (HD) took advantage of an existing large dataset integrating several observational studies, and applied machine-learning approaches. The results showed that HD clinical phenotypes can be segregated into nine clusters of increasing severity defined by varying combinations of motor, cognition, and function measurements. This provided a more holistic view of disease progression as compared to the previous models and may improve future clinical trial design and participant selection (Mohan et al., 2022).

Digital health technologies also enable large, multi-centre data sets to be examined for rare disorders in a real-world setting. Different studies reported that TH provided a platform for patients to easily provide feedback, thereby enhancing a patient-centred approach to improve research outcomes. Combining patient-reported outcomes with event reporting through wearable device apps in home settings was shown to be more accurate compared to one-time evaluations in a clinical setting (Huhn et al., 2022; Davies et al., 2022). A feasibility study showed that RD patients with late-onset Tay-Sachs and Sandhoff diseases were very enthusiastic and motivated to engage with mHealth and wearables for an observational study, which collected a large amount of real-time symptom data and mobile Patient Reported Outcome Measures (PROMs) to identify the disease impact (Davies et al., 2020).

11.2. Strengths and opportunities for using TH in research

In a landmark decision, the European Medicines Agency (EMA) qualified the first digital endpoint and approved the first wearable-derived digital clinical outcome assessment acceptable for use as a secondary endpoint in clinical trials for DMD (Servais et al., 2021). This constitutes a major breakthrough in the adoption of novel digital endpoints in drug development as it allows functional assessments to be performed in patients' homes with objective, continuous, and sensitive measurements of functional ability during daily life, thus providing high-quality and meaningful efficacy data. This approach has the potential to also reduce the burden on patients and caregivers in clinical trials and can enable more efficient drug development (Servais et al., 2021).

The COVID-19 pandemic disrupted the regular flow of traditional clinical research, acting as a catalyst for immediate and widespread implementation of TH methods and measures. During the pandemic, clinical study protocols were quickly modified to minimize the exposure of researchers and research subjects to the virus. In response, to ensure the safety of trial participants, the U.S. Food and Drug Administration (FDA) issued a guidance on the "Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency" (US Food and Drug Administration, 2023a), allowing trial sponsors to decide whether alternative methods for safety assessments would be feasible and sufficient, such as phone contact, virtual visit, alternative location for assessment including local laboratories or imaging centers. The FDA also issued a draft guideline on Decentralized Clinical Trials (DCTs) (US Food and Drug Administration, 2023b). The FDA states that a "DTC refers to a clinical trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites," and "these trial-related activities may take place at the homes of trial participants or in local healthcare facilities that are convenient for trial participants". The DCT draft guidance also states that "advances in clinical care using electronic communications and information technology to interact with trial participants in different locations (i.e., TH) allow for fewer in-person visits to clinical trial sites and facilitate decentralization. In addition, digital health technologies have expanded the types of trial-related data that can be obtained remotely from trial participants. By enabling remote participation, DCTs may enhance convenience for trial participants, reduce the burden on caregivers, expand access to more diverse patient populations, improve trial efficiency, and facilitate research on RDs and diseases affecting populations with limited mobility" (US Food and Drug Administration, 2023b).

11.3. Limitations for the use of TH in research

Some weaknesses described in the use of TH for research purposes were technology-related, for example, limitations on battery life for wearables and devices, or other technical issues such as synchronisation of the device and app across different mobile platforms (Donald et al., 2019; Davies et al., 2020). Some studies cited the need to train patients, caregivers, or less technologically skilled staff to use the technology or perform remote examinations or interventions (Petracca et al., 2021). This was noted to be important in reducing bias but could also be costly and burdensome (Huhn et al., 2022; Walsh and Markus, 2019; Díez-Juan et al., 2014). Additionally, adherence to TH methods seemed to decline over time, particularly when using wearable devices or burdensome apps or devices (Huhn et al., 2022). Furthermore, some assessments are not well-suited for virtual visits and some lack validation for remote applications. Training AI networks on "real cases" may be challenging and require large datasets, which can often be limited for rare disorders; this is an issue that could be resolved by the engagement of multiple stakeholders in developing algorithms for digital healthcare for RDs.

Cybersecurity is a concern that requires constant vigilance by all stakeholders, although this is not unique to the application of TH to RDs. This includes concerns on digital data security and the potential threat of

hacking. There were also concerns about the potential negative mental and physical health effects of increased screen time for participants, including exposure to cyberbullying and unregulated online content (Castro et al., 2019). Caregivers also sometimes found it challenging and time-consuming to identify and assess accurate and high-quality online information (Castro et al., 2019; Díez-Juan et al., 2014).

Almost all studies reported RD patients and their families as being very receptive to using TH (Wasilewska et al., 2022; Petracca et al., 2021; Castro et al., 2019; Hobson et al., 2019). However, most of the reported studies examining the effect of TH for RD care and research were at the early implementation stage, with only feasibility or acceptability as the outcome measures (Díez-Juan et al., 2014; Hobson et al., 2019; Cummins et al., 2021).

11.4. TH for continuing education and peer mentoring of RD HCPs

One of the key limitations for RD diagnosis, care, and research is the scarcity of a specialized workforce and clinicians with expertise in complex diseases such as RDs. Various measures have been employed to address this issue through continued education and peer mentoring. Several models of TH have been reported to enhance primary care physicians' awareness and knowledge of RDs, fostering an interconnected RD community. These TH models range from direct one-to-one education to successful online and interactive communities of practice, such as Project ECHO® (Extension for Community Healthcare Outcomes) (Project ECHO). The strategies used for implementing TH include videoconferencing-based telementoring, case-based learning for ultra-rare disorders, and other telecommunication means.

In one model, the ERN for Rare Neurological Diseases (ERN-RND) created a website and used several social media platforms to offer up-to-date information, including educational webinars for specific RDs. This serves the purpose of establishing and boosting communication and enabling the flow of knowledge on rare neurological and movement disorders to the medical provider community in hospitals treating patients with these rare and complex conditions (Brunelle Praschberger et al., 2022).

"Telementoring" programs such as Project ECHO have emerged and equipped clinicians working in rural areas to care for RD patients by connecting them with experts from different subspecialties for guidance and consultation. TeleECHO is a collaborative model of medical education and care management that operates on the principle of "moving knowledge, not people," and "demonopolizing medical knowledge" (Arora et al., 2014) while providing patient care. This model leverages scarce specialty expertise to empower local HCPs, enabling them to provide better care to a broader patient population than they traditionally serve, thus effectively multiplying the impact of expert knowledge on patient outcomes. Since its inception in 2003, Project ECHO has been adopted across different medical specialties throughout the U.S. and globally, including programs for several RDs (Project ECHO). In 2019, the Ehlers-Danlos Society launched EDS ECHO – the first ECHO model dedicated to one Rare Disease – the Ehlers-Danlos syndromes (Schubart et al., 2021).

Focusing on another group of RDs, the Bone Health TeleEcho program brought together a broad range of rare bone disease specialists, including geneticists, endocrinologists, and orthopedic surgeons, as well as their support staff. Through the sharing of case studies and experiences via telementoring, participants learned to recognize, diagnose, and care for the more than four hundred currently described skeletal disorders. This increases the number of experts and resources available to treat patients with bone health issues, particularly by providing mentorship to HCPs in rural and underserved communities (Lewiecki et al., 2017, 2019; Tosi et al., 2020). The experiences of the Rare Bone Disease ECHO and EDS ECHO provide insights for other RD groups on how they, too, can extrapolate the ECHO model to meet their needs. The TeleECHO model has been adopted for other RDs, such as intestinal failure and Prader Willi syndrome (Winkler et al., 2021; Schubart et al., 2021)[, 70]. Physicians who participated in the EDS ECHO program reported increased knowledge and confidence in providing care for EDS and hypermobility spectrum disorder patients. They indicated feeling less overwhelmed and frustrated in managing these conditions. Importantly, these physicians also reported increased participation in referral networks (Schubart et al., 2021). In Australia, a RD Project ECHO has been deployed to address common challenges and solutions that crosscut all RDs, focusing on the intersection of primary and specialist care. Initially, the program had a national scope, but it later expanded to participants from the Asia-Pacific Region (Rare Disease Project ECHO®).

New digital platforms and tools have also been developed to facilitate better HCP-patient relationships and engagement of people living with RDs and their caregivers. Growth hormone deficiency (GHD) is an RD that often presents in childhood and requires daily injection of growth hormone. This regimen poses a myriad of challenges, with adherence being a major issue. To address this, a digital ecosystem known as the Easypod™ drug delivery solution has been developed (Assefi et al., 2021). This digital ecosystem includes a platform and reporting system that enables data transmission by patients and caregivers. An accompanying app allows patients and their families to monitor treatment progress, and its patient support program (PSP) enhances their overall experience. The system is also connected with EHR systems, facilitating data exchange and direct input to HCPs. Additionally, an augmented reality (AR) app has been developed to provide training and engagement through avatars and games. This approach has been shown to be effective in engaging and educating patients, particularly young children, as part of their treatment journey (Baños et al., 2023). In this regard, digital health solutions can offer more personalized support to patients and may ameliorate the need for regular contact with HCPs, reducing the need to travel for consultations.

Efforts have also been made to improve digital health literacy of HCPs managing GHD patients. Massive Open Online Courses (MOOCs), an online platform offering unlimited participation and open access courses via the internet, was first introduced in 2008 as part of a distance learning and education system (Massive Open Online Courses). Using a multimodal eLearning model, the MOOC entitled "Telemedicine: Tools to Support Growth Disorders in a Post-COVID Era" was launched in 2021. Learners' knowledge was assessed using pre- and post-course surveys. Results showed improved digital capabilities and confidence of HCPs and users in managing growth disorders. This suggested that MOOCs such as this for GHD hold potential as a scalable solution for training health care professionals, especially in resource-limited settings (Dimitri et al., 2023).

Application of TH should also take local health care system, socioeconomics, culture, and language into consideration. The international Prader–Willi Syndrome Organization's ECHO program showed that different countries and regions are at different stages of development and had different needs and priorities that were specific to the local health care system or local culture. This meant that a successful model used in one country may need to be adapted for another country. This is especially true when implementing TH models in low- and middle-income countries, since they are usually developed by more mature organizations in high-income countries (Rujeedawa et al., 2022).

To help address health inequity and support more culturally safe and responsive care, "Lyfe Languages" was developed to deliver Indigenous language translation of medical terms, common words, and common phrases, which are presented in text, images, and audio. Additionally, community narratives are used to explain RD concepts using animations (Lyfe Languages).

TH approaches are believed to hold great promise for RD education and peer mentoring by effectively increasing access to the available expertise, which indirectly ensures that RD patients get more accurate and timely diagnosis and appropriate treatment. TH strategies can serve as inexpensive and efficient ways to educate HCPs and staff about RDs that they may encounter infrequently. However, the outcomes and true

impact of treating RDs by clinicians trained through TH, such as Tele-ECHO, in comparison to traditional in-person specialist care are yet to be fully understood.

12. Conclusions and discussion of evidence gaps

Based on evidence from the literature review, TH has been found to address some of the critical issues facing RD diagnosis, care, research, and education, but there are also limitations to its use in these settings. This is summarized by the SWOT analysis (Fig. 2).

Traditionally, one of the most critical barriers for RD care and research has been the limited numbers and availabilities of specialists for RD patients, many of whom reside in areas far from expert care for their specific RD. TH can bridge these gaps by enhancing access to RD care, breaking down barriers imposed by distance, time, and lack of expertise. Therefore, the IRDiRC TH Task Force adapted the WHO definition of TH for RDs, but noted, based on its experience and literature review, that TH not only overcomes limitations where distance is a critical factor, but also limitations due to time constraints, and more importantly, limitations due to scarcity of specialists, particularly for RDs where access to multidisciplinary specialty care is often required. While there are common elements related to the use of TH for common diseases and RDs, the Task Force members recognized the crucial role of TH in improving access to expert care for RD patients, which is one of the most acutely felt barriers for RD patients as compared to patients suffering from more common diseases.

Important advances in TH in the RD context likely will be critical in improving RD patient management and research in the future. One key approach relates to remote patient monitoring. This has provided new mechanisms to help patients stay connected with HCPs to provide real-world evidence of their condition, and to enable better understanding and management of RDs. There is also an emerging trend in the development of portable, low-cost, and easy-to-use disease diagnostic and monitoring platforms. These digital health technologies have the potential to improve early diagnosis, facilitate drug treatments, and enhance personalized medical care. For RD research, the adoption of decentralized clinical trials incorporating TH methodologies can overcome several key limitations of the traditional trial design and facilitate research on RDs. This combination has the potential to expand the access to research by an increasingly diverse pool of RD patients who are geographically dispersed. Digital solutions and wearable devices, coupled with EHR data, can prove to be immensely helpful in powering research, especially in light of the limited real-world clinical research data available for most RDs.

Our review of the literature also identified several evidence and knowledge gaps as well as areas that need further improvement before TH can be universally applied for RD care, research and education. Some of these are not specific to RD or different from the usage of TH for more common diseases. In fact, RDs can benefit from adopting TH experiences based on common diseases while adapting to specific RD requirements. For example, while AI/ML has the potential to transform health research by analysing, synthesizing, and deriving new and innovative insights from the vast amount of data generated, it is still in the early stages of development. To address this, the FDA issued an "Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan" (US Food & Drug Administration, 2021) which applies to both common and rare diseases. While real-time and continuous data from wearable technologies may provide real-world evidence and aid in understanding disease pathology and determining endpoints during interventions, these technology platforms also produce vast amounts of data. This data deluge can be overwhelming, and it may not be validated or calibrated. Innovative advanced data management systems are needed to handle this potential data overload.

The usefulness of TH for initial engagement and enrolment of RD patients remains to be shown, as the inability to physically examine patients was identified as a significant limitation for TH. Based on the

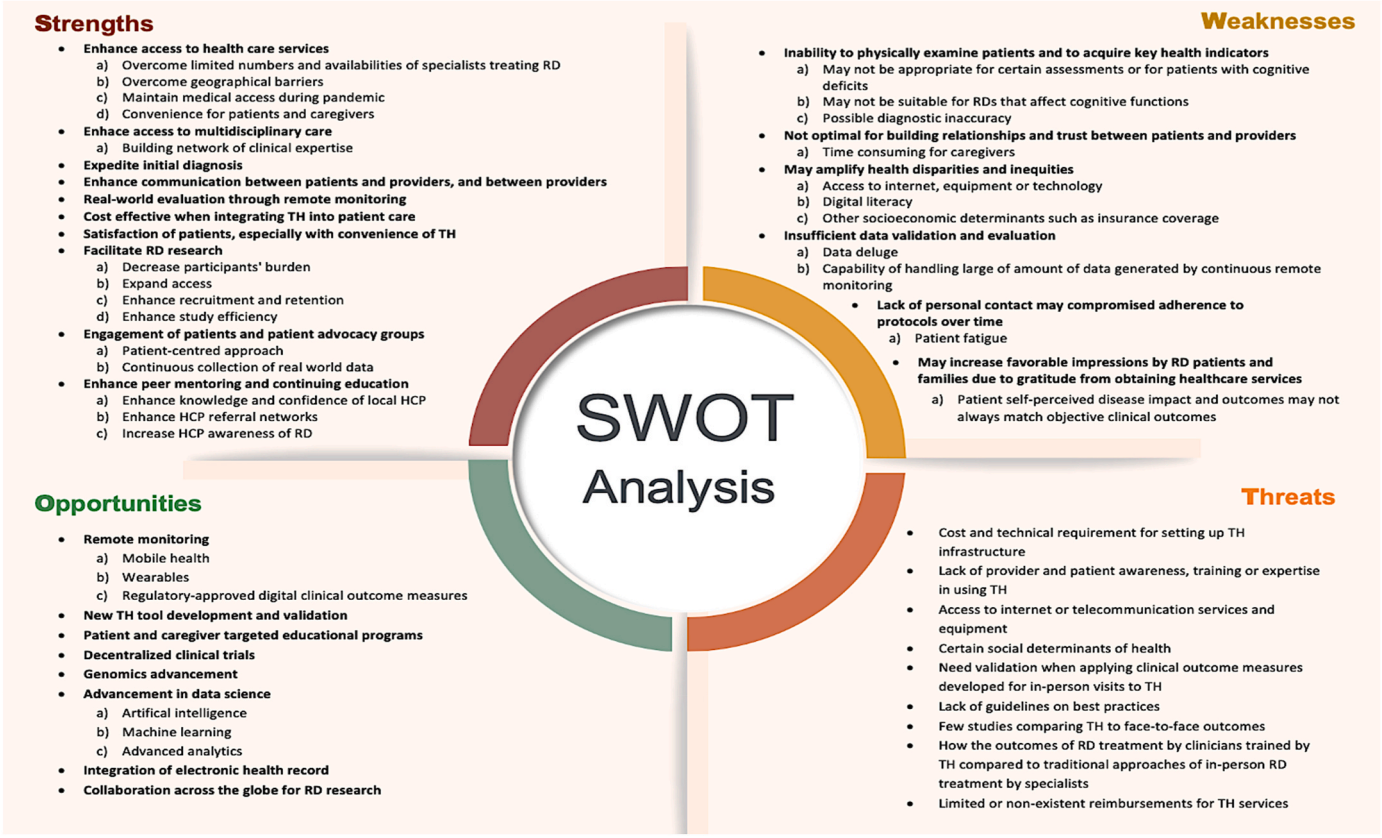

Fig. 2. Summary of reported Strengths/benefits (S), Weaknesses (W), Opportunities (O), and Threats (T)/barriers of TH for RDs.

literature review, there is a general agreement on the value of in-person visits for building a patient-physician relationship of trust. Therefore, there seems to be a consensus that TH should be used in conjunction with in-person visits. However, the aspects of medical care that should remain in-person, versus those that can be carried out through TH, or more likely, that comprise the best hybrid model, remain to be determined and may be different for different RDs. Future TH policies and studies also should be implemented to prevent disparities and inequities in access to care and research for RD patients, due to either clinical or social determinants linked to the specific RD or RD patients, and including disparities related to lack of access to TH technologies.

Based on our review, we found very few articles that have directly investigated the quantitative impact of TH on RD clinical outcomes as compared to in-person visits in rigorously conducted trials. Strong evidence is needed based on innovative trial designs with carefully chosen outcome measures that can impact clinical practice. For example, while adapting outcome measures for remote monitoring, it is essential to validate these results against in-person data, while providing opportunities for future modifications.

In the area of continuing education of the RD workforce and HCPs, TeleECHO and other educational programs like MOOCs hold great promise. Some RDs have reported beneficial outcomes with these models, showing improved knowledge and confidence among HCPs in treating RD patients. However, this has not been translated to demonstrate that the quality of care and patient outcomes are better than or equivalent to outcomes from direct patient care. In fact, it is yet to be shown that outcomes for RD patients treated by clinicians trained by the TeleECHO or other TH means are comparable to traditional approaches of RD treatment by specialists, as has been shown in the case of managing complex diseases like Hepatitis C (HCV) infection by primary care clinicians at ECHO sites in rural areas (Arora et al., 2011). This remains a gap where research is needed to demonstrate the ultimate effectiveness of using TH for clinical education and mentoring for the purpose of amplifying the expertise needed to treat all the RDs.

Through the course of this literature review, few publications addressed the policy, regulatory, legal, and/or ethical issues of TH when applied to RDs, nor the health economics of TH for RD care and research. Existing knowledge on facilitating factors and barriers for telemedicine solutions, as published by the WHO for non-RDs ("Telemedicine: opportunities and developments in Member States, a report on the second global survey on eHealth" (World Health Organization, 2010)), may most likely apply to RDs, although different regions with varying resources and technology platforms may require different approaches for using TH for RD patients. Issues related to resources for building TH infrastructure, ensuring access to and familiarity with TH technologies, and concerns about privacy and data security remain a challenge. Varying regulations and laws across countries, particularly regarding insurance coverage and medical licensure requirements for TH, also limit the use of TH for RD patients.

Despite all the challenges, TH will likely continue to expand in use, especially for RD patients with limited access to personalized therapies. The development of the most effective TH model that is "fit for purpose" and adaptable for different RD patients across various regions and countries, each with its unique healthcare landscape and policies, represents a lofty goal that will require a great deal of research before it can be fully realized.

Ethics approval and consent to participate

The study does not involve human data or human tissue. No ethics approval was required.

Consent for publication

The study does not contain any individual person's data.

Competing interests

FHC, MCVL, VA, GB, LB, MC, MDR, GD, AJ, MK, FM, JOB, RDP, NR, MKT, BT, and MAP declare no competing interests.

ALH provides medical consultation services for Teladoc, Inc. ALH serves on the Editorial Board for Neurology.

SDH provides medical consultation services and is a stakeholder at Terra Genetica Ltd. SDH is Editor-In-Chief for Clinical Dysmorphology.

Funding

The IRDiRC Telehealth Task Force was supported by the Scientific Secretariat of IRDiRC, funded by the European Union through the European Joint Programme on Rare Disease (EJP RD) under the European Union's Horizon 2020 Research and Innovation Programme Grant Agreement N°825575. The Scientific Secretariat is hosted at the French National Institute of Health and Medical Research (INSERM) in Paris, France.

CRediT authorship contribution statement

Faye H. Chen: Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Adam L. Hartman:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Mary Catherine V. Letinturier:** Writing – review & editing, Supervision, Project administration. **Victoria Antoniadou:** Writing – review & editing, Writing – original draft. **Gareth Baynam:** Writing – review & editing, Writing – original draft. **Lara Bloom:** Writing – original draft. **Marco Crimi:** Writing – review & editing, Writing – original draft. **Maria G. Della Rocca:** Writing – original draft. **Giuseppe Didato:** Writing – review & editing, Writing – original draft. **Sofia Douzgou Houge:** Writing – review & editing, Writing – original draft. **Anneliene Jonker:** Writing – review & editing, Writing – original draft. **Martina Kawome:** Writing – review & editing, Writing – original draft. **Friederike Mueller:** Writing – review & editing, Writing – original draft. **James O'Brien:** Writing – review & editing, Writing – original draft. **Ratna Dua Puri:** Writing – original draft. **Nuala Ryan:** Writing – original draft. **Meow-Keong Thong:** Writing – original draft. **Birutė Tumienė:** Writing – original draft. **Melissa A. Parisi:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization.

Data availability

No data was used for the research described in the article.

Acknowledgements

This manuscript was prepared by the authors in their personal capacity. The views and opinions expressed here are those of the authors and do not necessarily reflect the views, opinions, or positions of their employers or any subsidiary companies.

Abbreviations

3D	Three Dimensional
AI	Artificial Intelligence
AMAT	Adult Myopathy Assessment Tool
COA	Clinical Outcome Assessments
CORDIS	Community Research and Development Information Service
DCTs	Decentralized Clinical Trials
DMD	Duchenne Muscular Dystrophy
ECHO	Extension for Community Healthcare Outcomes
EDS	Ehlers-Danlos Syndrome
EHR	Electronic Health Records
EMA	European Medicines Agency
ERN	European Reference Network
ERN-ITHACA	ERN on Intellectual Disability, Telehealth, and Congenital Anomalies
ERN-RND	ERN for Rare Neurological Diseases
EU	European Union
FDA	The U.S. Food and Drug Administration
FRS	Functional Rating Scale
GHD	Growth Hormone Deficiency
HAE	Hereditary Angioedema
HCPs	Health Care Providers
HCV	Hepatitis C Virus
HD	Huntington's Disease
IMD	Inherited Metabolic Disorders
IoT	Internet of Things
IRDiRC	International Rare Diseases Research Consortium
MND	Motor Neuron Disease
ML	Machine Learning
MOOCs	Massive Open Online Courses
MNT4P	US Georgia Medical Nutrition Therapy for Prevention
NMD	Neuromuscular Disease
OI	Osteogenesis Imperfecta
PAO	Patient Advocacy Organization
PROMs	Patient Reported Outcome Measures
PSP	Patient Support Program
RD(s)	Rare Disease(s)
RWE	Real-World Evidence
SaMD	Software as a Medical Device
SBMA	Spino-Bulbar Muscular Atrophy
SWOT	Strength, Weakness, Opportunity, Threat
TH	Telehealth
WHO	World Health Organization

References

Arora, S., et al., 2011. Outcomes of treatment for hepatitis C virus infection by primary care providers. N. Engl. J. Med. 364, 2199–2207.

Arora, S., et al., 2014. Demonopolizing medical knowledge. Acad. Med. 89, 30–32.

Assefi, A.R., Roca, F., Rubstein, A., Chareca, C., 2021. Positive impact of targeted educational intervention in children with low adherence to growth hormone treatment identified by use of the Easypod™ electronic auto-injector device. Front Med Technol 3, 609878.

Austin, C.P., et al., 2018. Future of rare diseases research 2017-2027: an IRDiRC perspective. Clin Transl Sci 11, 21–27.

Baños, R.M., Peltonen, L.-M., Martin, B., Koledova, E., 2023. An augmented reality mobile app (Easypod AR) as a complementary tool in the nurse-led integrated support of patients receiving recombinant human growth hormone: usability and validation study. JMIR Nurs 6, e44355.

Bergier, H., et al., 2021. Digital health, big data and smart technologies for the care of patients with systemic autoimmune diseases: where do we stand? Autoimmun. Rev. 20, 102864.

Boele, F.W., et al., 2017. Neuro-oncology family caregivers' view on keeping track of care issues using eHealth systems: it's a question of time. J. Neuro Oncol. 134, 157–167.

Brizola, E., et al., 2020. Providing high-quality care remotely to patients with rare bone diseases during COVID-19 pandemic. Orphanet J. Rare Dis. 15, 228.

Brunelle Praschberger, A., Post, A.E.M., Hermanns, S., Graessner, H., 2022. Establishing and boosting communication in the European Reference Network for Rare Neurological Diseases (ERN-RND): the impact of offering free educational webinars. Orphanet J. Rare Dis. 17, 89.

Cannata, S., 2023. Grant update: rare and complex disease telehealth nurse program. Rare Voices Australia. https://rarevoices.org.au/grant-update-rare-and-complex-disease-telehealth-nurse-program/.

Castro, A.R., Chougui, K., Bilodeau, C., Tsimicalis, A., 2019. Exploring the views of osteogenesis imperfecta caregivers on internet-based technologies: qualitative descriptive study. J. Med. Internet Res. 21, e15924.

Cerdán-de-Las-Heras, J., et al., 2021. Tele-rehabilitation program in idiopathic pulmonary fibrosis-A single-center randomized trial. Int. J. Environ. Res. Publ. Health 18, 10016.

Cliniface. *Cliniface* https://cliniface.org.

Cummins, K.M., et al., 2021. Acceptability, validity, and engagement with a mobile app for frequent, continuous multiyear assessment of youth health behaviors (mNCANDA): mixed methods study. JMIR Mhealth Uhealth 9, e24472.

Davies, E.H., Johnston, J., Toro, C., Tifft, C.J., 2020. A feasibility study of mHealth and wearable technology in late onset GM2 gangliosidosis (Tay-Sachs and Sandhoff Disease). Orphanet J. Rare Dis. 15, 199.

Davies, E.H., Matthews, C., Merlet, A., Zimmermann, M., 2022. Time to see the difference: video capture for patient-centered clinical trials. Patient 15, 389–397.

Díez-Juan, M., et al., 2014. Parent-delivered touchscreen intervention for children with fragile X syndrome. Intractable Rare Dis Res 3, 166–177.

Dimitri, P., Fernandez-Luque, L., Koledova, E., Malwade, S., Syed-Abdul, S., 2023. Accelerating digital health literacy for the treatment of growth disorders: the impact of a massive open online course. Front. Public Health 11, 1043584.

Dimitropoulos, A., Zyga, O., Russ, S., 2017. Evaluating the feasibility of a play-based telehealth intervention program for children with prader-willi syndrome. J. Autism Dev. Disord. 47, 2814–2825.

Donald, A., et al., 2019. Measuring disease activity and patient experience remotely using wearable technology and a mobile phone app: outcomes from a pilot study in Gaucher disease. Orphanet J. Rare Dis. 14, 212.

Duis, J., et al., 2019. A multidisciplinary approach to the clinical management of Prader-Willi syndrome. Mol Genet Genomic Med 7, e514.

Dunlop, S.R., Kent, V.P., Lashley, M., Caruana, T., 2016. The cure PSP care Guide: a telephonic nursing intervention for individuals and families living with progressive supranuclear Palsy. J. Neurosci. Nurs. 48, 105–106.

El-Hassar, L., et al., 2023. Telemedicine in neuromuscular diseases during covid-19 pandemic: ERN-NMD European survey. J. Neuromuscul. Dis. 10, 173–184.

Eswaran, H., et al., 2022. Telehealth: Current Definitions. Rural Telehealth Evaluation. Center, University of Arkansas for Medical Sciences. https://idhi.uams.edu/rtec/wp-content/uploads/sites/4/2022/05/Telehealth-Definitions-Paper-06MAY2022-1.pdf.

Fenu, S., Tramacere, I., De Giorgi, F., Pareyson, D., 2023. Reliable virtual clinical assessment in spino-bulbar muscular atrophy (SBMA). J. Neurol. Neurosurg. Psychiatry 94, 161.
Hobson, E.V., et al., 2019. Using telehealth in motor neuron disease to increase access to specialist multidisciplinary care: a UK-based pilot and feasibility study. BMJ Open 9, e028525.
Hsieh, E., et al., 2023. Global perspective on the impact of the COVID-19 pandemic on rheumatology and health equity. Arthritis Care Res. https://doi.org/10.1002/acr.25169.
Hughes, M., Pauling, J.D., Moore, A., Jones, J., 2021. Impact of Covid-19 on clinical care and lived experience of systemic sclerosis: an international survey from EURORDIS-Rare Diseases Europe. J Scleroderma Relat Disord 6, 133–138.
Huhn, S., et al., 2022. The impact of wearable technologies in health research: scoping review. JMIR Mhealth Uhealth 10, e34384.
Hyde, C., et al., 2020. A telehealth approach to improving clinical trial access for infants with tuberous sclerosis complex. J. Neurodev. Disord. 12, 3.
Khan, F., Amatya, B., Kesselring, J., Galea, M.P., 2015. Telerehabilitation for persons with multiple sclerosis. A Cochrane review. Eur. J. Phys. Rehabil. Med. 51, 311–325.
Kubendran, S., Sivamurthy, S., Schaefer, G.B., 2017. A novel approach in pediatric telegenetic services: geneticist, pediatrician and genetic counselor team. Genet. Med. 19, 1260–1267.
Lampe, C., et al., 2020. The impact of COVID-19 on rare metabolic patients and healthcare providers: results from two MetabERN surveys. Orphanet J. Rare Dis. 15, 341.
Lanzola, G., Ginardi, G., Russo, P., Quaglini, S., 2014. G-quest: a single platform for delivering questionnaires, educational material, and checklists on mobile devices. Stud. Health Technol. Inf. 205, 408–412.
Lewiecki, E.M., et al., 2017. Leveraging scarce resources with bone health TeleECHO to improve the care of osteoporosis. J Endocr Soc 1, 1428–1434.
Lewiecki, E.M., et al., 2019. Bone health TeleECHO: a force multiplier to improve the care of skeletal diseases in underserved communities. Curr. Osteoporos. Rep. 17, 474–482.
Li, L., 2023. Role of chatbots on gastroenterology: let's chat about the future. Gastroenterol. Endosc. 1, 144–149.
US Food & Drug Administration, 2021. Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan.
Lyfe Languages. https://lyfelanguages.com/.
Massive Open Online Courses (MOOC). MOOC.org. https://www.mooc.org.
Manzi, G., et al., 2022. Telehealth: a winning weapon to face the COVID-19 outbreak for patients with pulmonary arterial hypertension. Vascul Pharmacol 145, 107024.
Mena, R., et al., 2020. An international telemedicine program for diagnosis of genetic disorders: partnership of pediatrician and geneticist. Am J Med Genet C Semin Med Genet 184, 996–1008.
Mohan, A., et al., 2022. A machine-learning derived Huntington's disease progression model: insights for clinical trial design. Mov. Disord. 37, 553–562.
Montes, J., Eichinger, K.J., Pasternak, A., Yochai, C., Krosschell, K.J., 2022. A post pandemic roadmap toward remote assessment for neuromuscular disorders: limitations and opportunities. Orphanet J. Rare Dis. 17, 5.
Nadipelli, V.R., Elwing, J.M., Oglesby, W.H., El-Kersh, K., 2022. Social determinants of health in pulmonary arterial hypertension patients in the United States: clinician perspective and health policy implications. Pulm. Circ. 12, e12111.
Nakshbandi, G., et al., 2021. Worldwide experiences and opinions of healthcare providers on eHealth for patients with interstitial lung diseases in the COVID-19 era. ERJ Open Res 7, 405–2021.
Paglialonga, A., et al., 2021. eHealth for patients with rare diseases: the eHealth working group of the European reference network on rare multisystemic vascular diseases (VASCERN). Orphanet J. Rare Dis. 16, 164.
Pareyson, D., et al., 2021. Neuro-telehealth for fragile patients in a tertiary referral neurological institute during the COVID-19 pandemic in Milan, Lombardy. Neurol. Sci. 42, 2637–2644.
Petracca, F., et al., 2021. An electronic patient-reported outcome mobile app for data collection in type A hemophilia: design and usability study. JMIR Form Res 5, e25071.
Project ECHO. https://hsc.unm.edu/echo/partner-portal/.
Radtke, H.B., et al., 2021. The impact of the COVID-19 pandemic on neurofibromatosis clinical care and research. Orphanet J. Rare Dis. 16, 61.
Rare Disease Project ECHO®. Rare Voices Australia https://rarevoices.org.au/rare-disease-project-echo/.
Riedl, M.A., et al., 2022. Optimization of care for patients with hereditary angioedema living in rural areas. Ann. Allergy Asthma Immunol. 128, 526–533.
Rojahn, K., et al., 2016. Remote monitoring of chronic diseases: a landscape assessment of policies in four European countries. PLoS One 11, e0155738.
Rujeedawa, T., et al., 2022. Reducing global health inequalities for a rare disorder: evaluating the international Prader-Willi Syndrome Organisation's Echo® programme. Orphanet J. Rare Dis. 17, 380.
Schubart, J.R., Bascom, R., Francomano, C.A., Bloom, L., Hakim, A.J., 2021. Initial description and evaluation of EDS ECHO: an international effort to improve care for people with the Ehlers-Danlos syndromes and hypermobility spectrum disorders. Am J Med Genet C Semin Med Genet 187, 609–615.
Schwartz, I.V.D., et al., 2021. SARS-CoV-2 pandemic in the Brazilian community of rare diseases: a patient reported survey. Am J Med Genet C Semin Med Genet 187, 301–311.
Servais, L., et al., 2021. First regulatory qualification of a novel digital endpoint in Duchenne muscular dystrophy: a multi-stakeholder perspective on the impact for patients and for drug development in neuromuscular diseases. Digit. Biomark. 5, 183–190.
Singh, R.H., et al., 2022. Using informatics to build a digital health footprint of patients living with inherited metabolic disorders identified by newborn screening. J. Publ. Health Manag. Pract. 28, E340–E344.
Sloan, M., et al., 2022. Telemedicine in rheumatology: a mixed methods study exploring acceptability, preferences and experiences among patients and clinicians. Rheumatology 61, 2262–2274.
Smith, M., et al., 2020. Telemedicine strategy of the European Reference Network ITHACA for the diagnosis and management of patients with rare developmental disorders. Orphanet J. Rare Dis. 15, 103.
Smyth, D., et al., 2022. Patient-reported experience of clinical care of osteogenesis imperfecta (OI) during the COVID-19 pandemic. Front. Public Health 10, 951569.
Soussand, L., et al., 2022. Impact of the COVID-19 pandemic on the care of rare and undiagnosed diseases patients in France: a longitudinal population-based study. Orphanet J. Rare Dis. 17, 430.
Tjeertes, J., et al., 2023. Enabling endpoint development for interventional clinical trials in individuals with Angelman syndrome: a prospective, longitudinal, observational clinical study (FREESIAS). J. Neurodev. Disord. 15, 22.
Tosi, L.L., et al., 2020. The rare bone disease TeleECHO program: leveraging telehealth to improve rare bone disease care. Curr. Osteoporos. Rep. 18, 344–349.
US Food & Drug Administration, 2023a. FDA guidance on Conduct of clinical trials of medical products during the COVID-19 public health emergency. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency.
US Food & Drug Administration, 2023b. Decentralized clinical trials (DCT) draft guidance - 06/20/2023. FDA. https://www.fda.gov/drugs/news-events-human-drugs/decentralized-clinical-trials-dct-draft-guidance-06202023.
van de Warrenburg, B.P., Tiemessen, M., Munneke, M., Bloem, B.R., 2021. The architecture of contemporary care networks for rare movement disorders: leveraging the ParkinsonNet experience. Front. Neurol. 12, 638853.
Walsh, J., Markus, H.S., 2019. Telemedicine for follow-up of rare neurological disease. Stroke 50, 750–753.
Wasilewska, E., et al., 2021. Is it possible to have home E-monitoring of pulmonary function in our patients with Duchenne muscular dystrophy in the COVID-19 pandemic?-A one center pilot study. Int. J. Environ. Res. Publ. Health 18, 8967.
Wasilewska, E., Sobierajska-Rek, A., Małgorzewicz, S., Soliński, M., Jassem, E., 2022. Benefits of telemonitoring of pulmonary function-3-month follow-up of home electronic spirometry in patients with Duchenne muscular dystrophy. J. Clin. Med. 11, 856.
Wijnen, R., Anzelewicz, S.M., Petersen, C., Czauderna, P., 2017. European reference networks: share, care, and cure-future or dream? Eur. J. Pediatr. Surg. 27, 388–394.
Winkler, M.F., Tappenden, K.A., Spangenburg, M., Iyer, K., 2021. Learn Intestinal Failure Tele-ECHO Project: an innovative online telementoring and case-based learning clinic. Nutr. Clin. Pract. 36, 785–792.
World Health Organization, 2010. Telemedicine: Opportunities and Developments in Member States: Report on the Second Global Survey on eHealth. World Health Organization.