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Research Article

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Posted Date: November 9th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11161477/v1

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Additional Declarations: No competing interests reported.

National plans for rare diseases in the European Union and their implementation through e-health information strategies

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Word Counts:

- **Abstract:** 237 words
- "**Research in Context" box:** 188 words
- **Main Manuscript:** 3865 words (excluding Abstract, "Research in Context" box, Keywords, tables, figures, and references)
- **Declarations of interest:** none.
- **Funding:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abstract

Background: Rare diseases present complex public health challenges across the European Union (EU) due to fragmented scientific knowledge and prolonged diagnostic pathways. Supranational recommendations emphasize the integration of strategic national frameworks backed by digital innovations .

Objective: This study conducts a comparative evaluation of centralized and decentralized information strategies and e-health implementation models in pioneering EU member states (France, the Netherlands, Germany) against the contemporary healthcare baseline of Bulgaria.

Methods: A mixed-methods research architecture was deployed, utilizing a qualitative Comparative Policy Analysis of macro-level strategic indicators alongside an empirical cross-sectional quantitative study. Primary data were extracted via 50 standardized in-depth interviews among a representative sample of rare disease patients at a tertiary medical hub in northeastern Bulgaria. Temporal contextualization was maintained via expert content analyses spanning the 2022–2025 period.

Results: Centralized frameworks (France) and highly interoperable net-based systems (the Netherlands) successfully reduce clinical info-asymmetries through operational registries and dedicated helpline infrastructures. Conversely, empirical Bulgarian data expose severe structural deficits: 61.3% of rare disease patients are completely unfamiliar with their Electronic Health Record, and over 83% remain unaware of e-health tools. However, a profound 90% digital readiness rate exists within the patient community.

Conclusions: Advancing the technological capacity of healthcare ecosystems fails to translate into patient benefit without target-funded digital navigation tools. Bulgaria requires an immediate structural upgrade, establishing unified portal architectures to transform passive data networks into functional tools for patient empowerment.

Keywords: national plans, rare diseases, e-health, comparative analysis, health literacy, European Reference Networks.

Research in Context

(1) What is already known about the topic? Rare diseases affect nearly 36 million individuals in the EU, necessitating coordinated cross-border actions and strategic frameworks [1]. National plans across several member states successfully utilize e-health platforms, electronic health records, and shared clinical registries to alleviate information deficits and decrease diagnostic delays [2, 3] .

(2) What does this study add to the literature? This paper provides a clear structural comparison between vertical institutionalized data networks (France) and highly interoperable, network-based university alliances (the Netherlands, Germany) [6, 9, 12]. It introduces unique empirical datasets capturing a profound health literacy gap in Bulgaria, proving that high consumer digital readiness (90%) is structurally bottlenecked by the absence of outpatient communication channels and software isolation of certified expert centers [5].

(3) What are the policy implications? Healthcare administrators must evolve national health databases from passive archives into interactive, patient-oriented knowledge hubs. Policies must ensure mandatory software interoperability with European Reference Networks, paired with the sustainable financing of specialized central web portals and national helplines to foster patient health literacy and enable true integrated care [11, 13, 14, 15].

Background

In the contemporary public healthcare system, rare diseases occupy a specific place due to their heterogeneity, progressive nature, and complex clinical manifestation. According to the official definition of the European Union, any disease affecting no more than 5 per 10,000 individuals in the general population is considered rare. Although the frequency of each individual nosological unit appears negligible, the aggregate number of affected individuals within the EU is immense - nearly 36 million people [1]. In 80% of cases, the pathology has a proven genetic origin and predominantly affects the pediatric population. These quantitative expressions transform rare diseases from isolated clinical cases into a global public health priority.

Due to the low prevalence of individual diagnoses, medical and scientific knowledge in this field remains fragmented and concentrated within a narrow circle of specialists. This leads to serious barriers for patients, who face a prolonged diagnostic odyssey within the healthcare system, accompanied by misdiagnoses, occasionally inappropriate therapies, and a high degree of psychosocial vulnerability. Recognizing this deficit, the European Commission and the Council of the EU identified rare diseases as an area with high added value for joint supranational actions [1]. A key pillar of this unified policy is the recommendation for each member state to develop, adopt, and implement a specific National Plan or strategy for rare diseases.

However, the efficacy and practical value of these strategic documents depend heavily on their information architecture [2]. Access to timely, verified, and comprehensible medical information is a determining factor for improving the quality of life of patients and their

families. In an era of digital transformation, the concept of e-health becomes a fundamental tool for overcoming the information asymmetry between physician and patient [3]. Through the implementation of electronic health records, telemedicine, and mobile applications, modern healthcare systems aim to enhance the health literacy of the population and optimize clinical triage.

Despite general European guidelines, digitalization and information dissemination processes develop with varying dynamics across different member states, predetermined by economic factors, human resources, and levels of digital culture. Within this rapidly evolving landscape, emerging technologies such as artificial intelligence represent pivotal frontiers in optimizing rare disease diagnostics and managing complex clinical datasets [4]. Bulgaria, although having drafted its National Plan, still faces serious information challenges, low levels of health literacy, and a fragmented e-health infrastructure [5]

The present study aims to perform a comparative analysis of the information strategies and e-health models in selected European countries, and based on empirical data, define the current state, deficits, and opportunities for upgrading the Bulgarian model to benefit patients with rare diagnoses [5]. The selection of France, the Netherlands, and Germany is intentional, driven by the circumstance that they represent pioneers and leaders in building information infrastructures for rare diseases, employing distinct yet complementary models.

Methods

To achieve the research objectives and ensure scientific rigor, an interdisciplinary multi-methodological approach combining qualitative macro-analytical tools and quantitative statistical methods was applied.

A qualitative Comparative Policy Analysis was utilized to compare the national plans, information architectures, and e-health models across three purposefully selected EU member states (France, the Netherlands, and Germany), with Bulgaria serving as the contextual baseline. The choice of these countries is justified by their pioneering role in establishing digital ecosystems for rare conditions. The macro-level policy analysis was structured around four specific indicators: the degree of institutional centralization of data, the software architecture of registries, the levels of cross-border data exchange via European Reference Networks (ERNs), and the established tools for navigation and enhancing the health literacy of the patient community.

These structural comparisons were supplemented by an empirical quantitative investigation, consisting of a cross-sectional study among rare disease patients and their representatives in Bulgaria. This quantitative component evaluated the subjective awareness and readiness of respondents for digital engagement across five key electronic resources: electronic health records, telemedicine, tele-rehabilitation, mobile applications for medical nutrition, and online medical libraries. Primary data were processed and analyzed using descriptive statistics and frequency distributions [5].

To ensure temporal relevance and track ongoing structural shifts, an expert content analysis with dynamic tracking for the period 2022–2025 was integrated. This involved a comprehensive review of current strategic documents and reports detailing Bulgaria's ongoing involvement in the European digital consortia JARDIN and ERDERA, allowing the baseline empirical findings to be contextualized within the contemporary macro-framework of Bulgarian e-health [14, 15].

Results

The comparative analysis of European practices outlines several successful models for managing medical information in rare conditions. Tracking international experience proves that the effectiveness of a national plan is not exhausted by its administrative adoption but depends on the embedded digital and communication algorithms designed to overcome information deficits. Within the European Union, two primary approaches are observed-highly centralized (institutional) and decentralized (network-based), both relying on high-tech integration and specific instruments to increase health literacy.

France: The Model of Centralized Expert Networks

The French Republic occupies a strategic, pioneering position in the European scientific space, having normatively established its first national plan for rare diseases (*Plan National Maladies Rares*) as early as 2004 [6]. The evolution of French state doctrine over the subsequent two decades, developed and presented across three consecutive national plans, consolidates a model characterized by imperative state regulation, a strictly vertical managerial structure, and deep institutional linkage between clinical and financial datasets [7]. The foundation of this comprehensive strategy rests on multi-sectoral synergy across three main components: scientific research, highly specialized clinical infrastructure, and socio-economic support for the patient community [7].

At the organizational core of the French model lies the construction of a hierarchically certified national network composed of Reference Centers (*Centres de référence*) and their associated Competence Centers (*Centres de compétences*), distributed by specific nosological groups. These structures are digitally and administratively integrated with the global nomenclature platform Orphanet, which originated in France [2]. However, the information architecture is not a passive archive but a dynamic public health management tool. The French plan introduces mandatory epidemiological coding and national registries for rare diseases via the national database BAMARA, enabling precise monitoring of prevalence, human resource planning in healthcare, and targeted allocation of public financial resources [8].

A key methodological and applied achievement in the French strategy is the interconnection between these specialized databases and patients' personal electronic health records, directly reflecting on the safety of the therapeutic process. Information provisioning is detailed down to the level of operational micro-management through the implementation of a specialized tool known as "Emergency Cards for Rare Diseases" (*Cartes d'urgence maladies rares*). These digital and physical assets are equipped with encrypted secure access, facilitating immediate clinical triage [8]. They guarantee that in acute states, any medical professional across the country, regardless of the degree of regional decentralization, gains unhindered access to the patient's personalized therapeutic protocol, contraindications for pharmacological products, and direct communication lines with the treating reference center. This eliminates the risks of medical errors arising from information asymmetry outside specialized clinics [8].

Parallel to the clinical sector, the French national plan encompasses an extensive social architecture. The strategy integrates "medico-social platforms" that ensure a smooth transition of individuals with disabilities into the educational system and the labor market, coordinated by regional Departments for Persons with Disabilities (*Maisons Départementales*

des Personnes Handicapées). The research pillar of the plan is funded directly through targeted state subsidies for clinical trials of orphan drugs, completing the managerial cycle—from early neonatal screening and phenotype identification to long-term palliative care and social integration of the family system.

The Netherlands: A Horizontal Model of Digital Interconnection and Consumer Health Literacy

The Netherlands presents one of the most progressive and technologically advanced examples in the European Union regarding horizontal digital integration and ensuring high interoperability of clinical datasets. Unlike the strictly vertical, state-centralized approach of France, the Dutch national strategy for rare diseases relies on a flexible, decentralized ecosystem that unites eight recognized University Medical Centers into a single, coordinated information network. This organizational model represents a dynamic knowledge management tool realized through two main technological pillars—cross-border data exchange and enhancing health literacy within the patient community [9].

The primary methodological and applied achievement in the Dutch doctrine is the full automated integration of national expert centers with European Reference Networks (ERNs) [10]. The country's information architecture is designed to sustain continuous bidirectional data transfer through a specialized European clinical platform, the Clinical Patient Management System (CPMS). Through this secure digital environment, Dutch medical teams can conduct virtual consultative panels in real time, generating multidisciplinary meetings with leading European experts [10].

The technological capacity of the system permits the sharing of anonymized datasets, including highly specialized imaging studies, histological parameters, and complex sequenced genetic maps. In this manner, the Dutch model materializes the fundamental principle of digital medicine, according to which "knowledge travels, not the patient," leading to a tangible reduction in the time interval for definitive diagnosis and minimizing systemic costs [10].

Parallel to the clinical-technological pillar, the Dutch strategy places an extraordinary emphasis on overcoming information asymmetry by optimizing the literacy of patients and their families [11]. Official national portals, such as those coordinated by the VSOP (Dutch Alliance of Parent and Patient Organizations for Rare and Genetic Diseases), serve as interactive communication mediators. They perform semantic transformation of complex scientific guidelines and genetic nomenclatures, translating them into accessible, non-specialized language [11].

The state actively subsidizes and integrates certified national helplines that provide emergency triage, psychological navigation, and care coordination outside the hospital environment. This multi-sectoral approach shields the family system from isolation, limits the risks of excessive anxiety, and transforms the patient into an informed and equal partner in the therapeutic process.

Germany: A Federal Model of Shared Digital Registries and Academic Consolidation

Germany offers a distinct administrative, legal, and organizational approach to health information management, entirely predetermined by its decentralized state structure and the autonomy of individual federal states, healthcare facilities, and regional health insurance

funds. Unlike the strictly vertical model of France and the horizontal network of the Netherlands, the German healthcare system faced the challenge of coordinating a highly fragmented environment of independent university hospitals. The solution to this institutional dilemma was the creation of the National Action Alliance for People with Rare Diseases (NAMSE), whose strategy concentrates on building shared digital registries and unified platforms for data exchange between clinics [12].

The foundation for implementing this approach in the German model is the digital linkage of the research capacity of university hospitals to achieve better care coordination[12]. A key practical achievement in this direction is the development and implementation of the Central Information Portal for Rare Diseases (ZIPSE) [13]. In contrast to the Dutch focus on real-time cross-border consultations, the German ZIPSE system functions as a unified national database and an official source of verified medical information. The platform is designed to aggregate large arrays of clinical, genetic, and epidemiological data, introducing unified standards for information verification [13].

In the context of regulating patient flows and enhancing health literacy, the German strategy utilizes the portal to curb the spread of unverified or misleading medical information on the internet. The platform provides patients, their families, and general practitioners with officially validated data regarding the location and activities of certified expert centers. These centers are divided into three tiers based on their degree of specialization, with current parameters of ongoing clinical trials and established therapeutic protocols integrated into their profiles. Table 1 presents the three levels of specialization of certified expert centers in Germany and the structure of information within the ZIPSE digital portal [13].

Table 1: Functional Differences and Parameters of Expert Centers in the ZIPSE Digital Portal.

Center Tier	Degree of Specialization	Specific Information in the Platform	Purpose of Differentiation
Type A Center	Highest / Reference (Coordinating functions for complex cases)	• Location and official coordinates • Current clinical trial parameters •Established therapeutic protocols	• Regulating patient flows • Curbing misleading online information • Enhancing health literacy
Type B Center	Intermediate / Specialized (Targeted at specific groups of rare diseases)	• Location and official coordinates • Current clinical trial parameters • Established therapeutic protocols	• Rapid orientation for general practitioners • Digitally linking research capacity

Center Tier	Degree of Specialization	Specific Information in the Platform	Purpose of Differentiation
Type C Center	Local / Associated (Follow-up and specific outpatient activities)	• Location and official coordinates • Established therapeutic protocols at the local level	• Balanced distribution of information to patients and families

Source: Adapted from data from the Central Information Portal for Rare Diseases in Germany (ZIPSE) and the National Action Alliance for People with Rare Diseases (NAMSE).

By providing this controlled access to official data, the system helps properly inform citizens and reduces the risks of anxiety or self-treatment attempts among individuals with lower health literacy.

In parallel, the German model is distinguished by a direct link between information registries and public funding for research and development in the field of orphan drugs. Through initiatives of the Federal Ministry of Education and Research (BMBF), anonymized digital data on rare diseases are used for studies and statistical analyses, overcoming the barrier of small patient cohort sizes in clinical research. This managerial approach closes the full cycle of e-health in Germany, encompassing all stages from clinical data processing to transforming medical information into a functional resource for the entire healthcare and pharmaceutical sector [12].

Information Environment and E-Health in Bulgaria

Bulgaria initiated the normative recognition of rare diagnoses with the adoption of its first National Plan for Rare Diseases (Genetic, Congenital Malformations, and Non-Hereditary Diseases) for the period 2008–2013. This strategic document laid the foundations of the country's institutional framework through the creation of the Commission for Rare Diseases under the Ministry of Health and the introduction of criteria for designating and certifying Expert Centers. Despite significant progress in clinical and organizational terms—manifested in the concentration of medical expertise and the provisioning of modern diagnostics—the national information strategy exhibits substantial deficits compared to the discussed European models.

The Bulgarian approach remains predominantly clinically oriented, lacking the support of a functional digital infrastructure for mass data exchange and targeted interventions to enhance awareness within the patient community. Although the national electronic healthcare system was established as an information resource for patients nationwide, the data included within it remain fragmented and incomplete, which exposes rare disease patients to risks of severe difficulties in coordinating their treatment and diagnostics.

Empirical research in Bulgaria uncovers a profound paradox related to the presence of acute information asymmetry between medical specialists and affected families, alongside critically low levels of health literacy. This research problem is defined by two primary systemic issues.

- Low Digital Engagement

The results of the empirical study conducted in 2022 reflect the state of the healthcare system during a period characterized by the lack of an operational and widely accessible national e-health infrastructure in Bulgaria. Table 2 presents data from the survey among patients with rare diseases [5].

Table 2: Consumer Health Literacy Profile of Rare Disease Patients Regarding Online

Online Sources	Aware / Familiar	Unaware / Unfamiliar
Electronic Health Record	38.7%	61.3%
Telemedicine	16.1%	83.9%
Tele-rehabilitation	16.1%	83.9%
Mobile App for Medical Nutrition	41.9%	58.1%
Online Medical Library	29.0%	71.0%

Resources. Source: Author's data, adapted from doctoral dissertation (Yordanova, 2022).

The data from the empirical study clearly define the scale of the existing information deficit, showing that over 60% of surveyed rare disease patients lack access, knowledge, or a realistic opportunity to utilize digital tools to track their conditions. This high percentage is a direct consequence of the absence of a unified, institutionally supported electronic system during the study period [5].

A detailed breakdown of these results reveals that the barrier facing patients is simultaneously technological and functional. On one hand, the lack of specialized digital infrastructure isolates individuals with rare diagnoses outside the hospital setting. On the other hand, the absence of adapted, layman-friendly digital sources predetermines low levels of consumer health literacy. When the majority of affected families are deprived of certified tools to manage their disease, they lose the opportunity for informed control over the therapeutic and diagnostic process. In the context of rare and complex pathologies, these preconditions sharply elevate the risk of therapeutic errors and delays in adequate medical response [5].

These findings align with reports from the Health Literacy Europe consortium, which traditionally place Bulgaria among the countries with the highest proportion of the population possessing limited health literacy due to the lack of institutional digital information sources. In the context of rare diseases as of 2022, these informational absences forced patients to rely entirely on passive, un-systematized sources, severely limiting their capacity for informed control over the therapeutic process outside the hospital environment [5].

Tracking these processes dynamically reveals that although by 2025–2026 Bulgaria possesses an operational National Health Information System (NHIS) and actively participates in European digital integration initiatives, including projects such as JARDIN and ERDERA, systemic deficits in the information environment remain identical to those identified in 2022 [14, 15]. Current expert analyses from 2025/2026 confirm that national rare disease registries still function in isolation, software connectivity for automatic data transfer to European Reference Networks is non-existent, and expert centers are forced to conduct their

informational activities without targeted state funding. This reinforces the conclusion that without a clear digital navigation strategy, technological progress does not automatically translate into improved patient health literacy at the micro-level.

- ⍰ Absence of Institutional Communication and Navigation Channels

In contrast to established best practices in the EU, where the state coordinates and long-term finances national portals and shared registries, Bulgaria exhibits a severe lack of officially maintained outpatient support channels. Currently, the country does not possess established instruments such as a functioning national helpline for rare diseases to serve as a primary unit for informational triage. Consequently, due to this institutional deficit and the lack of specialized digital navigators, the primary and often sole source of information for over 35% of patients remains the treating physician within the respective Expert Center.

This restrictive model reflects negatively across two main directions. On one hand, it leads to critical overloading of medical teams at the micro-level. Highly qualified clinical specialists are forced to expend limited time and human resources to fulfill an unnatural role as social navigators and administrative consultants. On the other hand, the patient community remains completely isolated and deprived of logistical, psychological, and palliative support the moment it steps outside the specialized clinic.

The lack of a unified, interoperable platform for linking expert centers, general practitioners, and regional social services renders the ambition of building integrated care impossible. In the Bulgarian reality, horizontal data transfer is missing, which breaks communication along the "expert – personal physician – patient" chain. Thus, the entire burden of care coordination is shifted onto family systems, forcing them to manage complex administrative processes independently, which contradicts the principles of advanced e-health and European standards of shared responsibility.

Discussion

A critical reading of the presented data outlines a profound systemic gulf between the technological provisioning of e-health and its actual functional value for the end-user. The comparative macro-analysis unequivocally proves that successful European models do not view digitalization as an end in itself or as a passive tool for administrative reporting. In France, through the centralized BAMARA system and emergency cards, digital information has been transformed into an operational resource for the micro-management of clinical risk [8]. In the Netherlands, horizontal integration with the CPMS platform transforms international data exchange into an accessible tool that shortens the patient's diagnostic pathway [10]. Against this background, the Bulgarian model, though formally upgraded with the National Health Information System (NHIS) by 2025–2026, continues to suffer from structural fragmentation. The core problem in Bulgaria does not stem from a lack of access to technology, but from the absence of a sustainable methodological framework for education, digital navigation, and systematic information of affected individuals.

The empirical results of the quantitative research reveal a paradox that warrants serious scientific interpretation. The fact that 61.3% of surveyed patients are unfamiliar with the capabilities of their electronic health record, while over 83% are completely uninformed about telemedicine solutions, must not be interpreted as a lack of consumer interest [5]. On the contrary, these values represent a clear managerial signal of "digital exclusion" of the

patient community from modernization processes. When the state implements macro-technological solutions without providing parallel outpatient communication channels - such as the state-subsidized lines of the VSOP in the Netherlands or the German ZIPSE portal - digitalization layout inevitably exacerbates existing inequalities in healthcare [11, 13]. The patient is left isolated in an unregulated, fragmented internet environment where the risk of misinterpreting complex medical terminology and genetic risks is immense. This informational insecurity generates a specific form of psychosocial vulnerability and a progressive distrust toward institutional sources.

Another critical aspect that Bulgarian health policy overlooks is software interconnection at the expert level. While the German NAMSE model successfully links digital registries with targeted funding for research and development regarding orphan drugs, Bulgarian Expert Centers are placed in software isolation [12]. The lack of an automated connection for bidirectional data transfer to European Reference Networks (ERNs) forces Bulgarian specialists to perform manual, time-consuming, and unfunded labor to extract and translate clinical arrays [10]. This explains why our country's participation in strategic projects such as JARDIN and ERDERA remains predominantly at a formal, political level, without reflecting on the quality of care at the micro-level [14, 15]. Without horizontal data transfer along the "expert – general practitioner – regional social services" chain, the concept of integrated care remains unachievable, and the entire administrative and logistical burden is transferred onto family systems. The Bulgarian model urgently requires a conceptual transformation where the NHIS evolves from a passive archive into an active, patient-oriented platform for knowledge management.

Limitations of the Study

Several limitations of this study must be acknowledged. First, the empirical phase relies on a relatively small cohort (N = 50) of rare disease patients and their representatives recruited from a single tertiary medical center [5].While this limits the generalizability of the quantitative findings on a strictly national scale, the study was conceptualized as a **pilot inquiry**. In the context of rare and low-prevalence conditions, where patient recruitment is inherently restricted, these pilot data provide crucial, first-of-its-kind baseline insights into the digital literacy gaps and technological readiness of Bulgarian patients, which are vital for designing larger multicenter studies in the future.

Conclusions

The comparative analysis demonstrates that successful National Plans and information strategies within the European Union view e-health not merely as an isolated software product or administrative accounting tool, but as a mechanism for social integration, overcoming information asymmetry, and systematically elevating consumer health literacy. While the pioneered models of France, the Netherlands, and Germany successfully close the loop between digital infrastructure, research capacity, and ultimate patient navigation, the Bulgarian model continues to suffer from acute fragmentation and a lack of horizontal communication. Technological progress and the deployment of the National Health Information System in our country do not yet automatically reflect on the quality of life and awareness at the micro-level, leaving the patient community in a state of deep information deficit [6, 9, 12] .

To overcome these challenges and optimize the managerial model in Bulgaria, future strategic and regulatory documents in the sphere of rare diagnoses should emphasize three primary directions:

- **Institutionalization of a Central Digital Source:** A conceptual transformation of the national information environment is required by designing and constructing an official, state-supported, and targeted-funded digital portal for rare diseases. This platform must be fully integrated with the international Orphanet nomenclature and function as a verified data source [2]. A key function must be the semantic transformation of complex medical and genetic terminology into accessible language for non-specialists to curb the spread of misleading information online and provide reliable navigation regarding the location and capacity of certified Expert Centers.
- **Technological Integration with European Structures:** The Bulgarian healthcare model must transition to international knowledge exchange. This necessitates ensuring software and operational interoperability between national registries and European Reference Networks through platforms for secure transfer of clinical, epidemiological, and genetic datasets [10]. The process must be backed by targeted state funding for the informational activities of Expert Centers to guarantee that Bulgarian patients have equal access to cross-border virtual consultations, innovative clinical trials, and established international therapeutic protocols in real time. Currently, this interaction remains largely formal and restricted to the political level through participation in European projects [14, 15]. At the practical level, automated software linkage is absent, forcing medical professionals to manually extract, translate, and enter fragmented data into European platforms.
- **Functional Patient Empowerment:** Technological modernization is ineffective without a parallel enhancement of the capacity of its end-users. The development and implementation of targeted national programs for digital training, navigation, and psychological support aimed at rare disease patients and their families are recommended [5]. By building outpatient communication channels, including national helplines and specialized modules within the electronic record, the goal is to achieve true empowerment of the family system. The objective is to transform the patient into an informed, literate, and equal partner of medical specialists in the therapeutic and diagnostic process.

In the specific world of rare diseases, where diagnostic time is critical, ensuring the unhindered transfer of knowledge and high health literacy is the only secure pathway toward saving human lives and guaranteeing a dignified future for affected families.

Declarations

Clinical trial number: Not applicable.

Ethics approval and consent to This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics approval was granted by the Research Ethics Committee at Medical University "Prof. Dr. Paraskev Stoyanov" – Varna, Bulgaria (approval protocol available upon request). Informed consent was obtained from all individual participants or their legal representatives included in the study.

Consent for publication Not applicable (The manuscript does not contain any individual person's data in the form of identifiable images, videos, or voice recordings).
Availability of data and materials The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.
Competing interests The author declares that she has no competing interests.
Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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