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Review

Second-Opinion Systems for Rare Diseases: A Scoping Review of Digital Workflows and Networks

Vinícius Lima [1,*], Mariana Mozini [1] and Domingos Alves [2]

[1] Health Intelligence Laboratory, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto 14049-900, Brazil; mtmozini@gmail.com
[2] Department of Social Medicine, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto 14049-900, Brazil; quiron@fmrp.usp.br
* Correspondence: viniciuslima@alumni.usp.br

Abstract

Introduction: Rare diseases disperse expertise across institutions and borders, making structured second-opinion systems a pragmatic way to concentrate subspecialty knowledge and reduce diagnostic delays. This scoping review mapped the design, governance, adoption, and impacts of such services across implementation scales. Objectives: To describe how second-opinion services for rare diseases are organized and governed, to characterize technological and workflow models, to summarize benefits and barriers, and to identify priority evidence gaps for implementation. Methods: Using a population–concept–context approach, we included peer-reviewed studies describing implemented second-opinion systems for rare diseases and excluded isolated case reports, purely conceptual proposals, and work outside this focus. Searches in August 2025 covered PubMed/MEDLINE, Scopus, Web of Science Core Collection, Cochrane Library, IEEE Xplore, ACM Digital Library, and LILACS without date limits and were restricted to English, Portuguese, or Spanish. Two reviewers screened independently, and the data were charted with a standardized, piloted form. No formal critical appraisal was undertaken, and the synthesis was descriptive. Results: Initiatives were clustered by scale (European networks, national programs, regional systems, international collaborations) and favored hybrid models over asynchronous and synchronous ones. Across settings, services shared reproducible workflows and provided faster access to expertise, quicker decision-making, and more frequent clarification of care plans. These improvements were enabled by transparent governance and dedicated support but were constrained by platform complexity, the effort required to assemble panels, uneven incentives, interoperability gaps, and medico-legal uncertainty. Conclusions: Systematized second-opinion services for rare diseases are feasible and clinically relevant. Progress hinges on usability, aligned incentives, and pragmatic interoperability, advancing from registries toward bidirectional electronic health record connections, alongside prospective evaluations of outcomes, equity, experience, effectiveness, and costs.

Keywords: rare diseases; second opinion; telemedicine; tele-expertise; cross-border healthcare; health information exchange; interoperability; platform architecture

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1. Introduction

Rare diseases collectively affect more than 300 million people worldwide, yet each individual condition has a very low prevalence and limited evidence base [1,2]. Patients with rare diseases often endure a prolonged diagnostic odyssey, which can last several

years and involve multiple misdiagnoses and repeated consultations before a correct diagnosis is reached [3]. This is compounded by a shortage of specialized clinicians, concentration of expertise in a few tertiary centers, and inequitable access to advanced diagnostic tools such as genomic sequencing [4]. Health systems may lack standardized referral pathways, interoperable registries, and coordinated care models, resulting in fragmentation, duplication of efforts, and unmet patient needs [5].

Second medical opinions (SOs) represent an essential mechanism to address these challenges. By enabling patients and healthcare providers to obtain an additional expert assessment of diagnosis or treatment options, SOs can increase diagnostic accuracy, improve treatment planning, reduce unnecessary interventions, and enhance patient trust. In the context of rare diseases, SOs are especially critical because expertise is scarce and dispersed, clinical guidelines are often absent or incomplete, and management decisions may have life-changing consequences [6].

The digital transformation of healthcare has facilitated new structured models of second opinion delivery, such as tele-expertise, virtual multidisciplinary team meetings (vMDTs), e-consult platforms, and secure reference networks. Unlike direct-to-patient teleconsultations, these systems prioritize clinician-to-clinician exchange, often incorporating formal workflows, eligibility criteria, patient consent, governance, and data protection rules, as well as standardized documentation of recommendations [7,8]. Reported benefits include diagnostic revision, treatment modification, shared care coordination, capacity building of local providers, and increased equity of access [6,8,9].

Despite these advances, the literature remains fragmented. Initiatives differ in scope (disease-specific vs. cross-disease), modality (synchronous vs. asynchronous), governance models, financing, and outcome reporting. Terminology is inconsistent, with overlapping use of second opinion, tele-expertise, virtual consultation, or reference network, hindering synthesis and comparability. Furthermore, there is limited mapping of which systems are available, how they operate, what outcomes they achieve, and which barriers and facilitators shape their implementation [10].

It is also essential to distinguish SOs from related concepts. Teleconsultation generally refers to direct clinical interactions between a patient and a healthcare provider via telecommunication tools [11]. Tele-expertise, also known as e-consult, involves clinician-to-clinician exchanges, often asynchronous, to obtain specialist input without the patient being present [12]. vMDTs represent another modality, where multiple experts discuss a case together in real time, usually through secure online platforms [13]. Although terminology varies across contexts, all these models can serve as structured mechanisms of SOs if they follow defined processes of case submission, discussion, and recommendation.

In this context, a scoping review is warranted to map and characterize digital systems, processes, and platforms that deliver second medical opinions in rare diseases. Specifically, this review aims to: (i) describe the types of models; (ii) characterize the populations and actors involved; (iii) extract key components of system design and operation; (iv) summarize reported outcomes; (v) identify barriers, facilitators, and gaps for future research and policy.

Guided by a population–concept–context framing, this review addresses people living with rare diseases and the clinicians who care for them (population), structured second-opinion systems and their workflows, governance, technology, adoption, and reported impacts (concept), and real-world healthcare services and networks operating at regional, national, cross-border, and international levels (context). Our objective is to map how second-opinion services for rare diseases are designed and governed, how they are adopted and used, and what outcomes are reported.

2. Materials and Methods

Scoping reviews are ideal for providing an overview of a given topic, determining its coverage, and clearly indicating the volume of literature and studies available [14]. This review followed the methodological framework initially proposed by Arksey and O'Malley [15] and further refined by the Joanna Briggs Institute (JBI) [16], which recommends a five-stage process. In the following subsections, each stage is described in detail. Reporting adhered to the PRISMA extension for Scoping Reviews (PRISMA-ScR) checklist (see File S1) [17]. No review protocol was registered for this scoping review.

Although no protocol was registered, we predefined the Population Concept Context framing, eligibility criteria, and research questions before screening. We piloted and refined the data charting form on a subset of studies, conducted independent dual screening and extraction, and documented reasons for full-text exclusions to maintain transparency and minimize methodological drift. No post hoc changes were made to eligibility criteria after screening commenced and any clarifications were limited to wording.

2.1. Stage 1: Identifying the Objective and Research Questions

For this review, SO is considered in a more structured, system-based sense: a formalized process in which clinicians present a patient case to another specialist or to a multidisciplinary panel, often supported by digital platforms, standardized workflows, and documented recommendations. This excludes isolated individual requests or case reports, which lack systematization and reproducibility.

For this review, a structured second opinion system was operationally defined as an implemented service model that includes a defined workflow for case submission and expert review using a digital platform or standardized referral proforma, produces a documented recommendation (for example a written report or recorded decision), and reports at least one additional system feature such as formal triage or eligibility rules, designated coordination roles, explicit consent and data protection procedures, or auditable record keeping. In contrast, isolated individual requests refer to one-off, informal clinician-to-clinician exchanges or single-case descriptions that lack a repeatable process, governance, or documented outputs.

Additionally, a dedicated bespoke platform was not required. Digital second opinion systems could be supported by a purpose-built platform or by standardized digital workflows using secure institutional tools, such as encrypted email with structured referral templates, shared document repositories, or secure portals, provided that the process is repeatable, governed, and produces documented outputs.

Therefore, the objective of this review was to explore and characterize structured systems, processes, and platforms designed to deliver second medical opinions (SMOs) in the context of rare and orphan diseases. The following research questions guided the review:

- Q1. What types of digital systems, processes, or platforms have been developed and implemented to provide second medical opinions in rare and orphan diseases, and at what organizational scale (national, regional, international)?
- Q2. What are the main design features, workflows, and governance elements of these systems, including interoperability and ethical/legal safeguards?
- Q3. What outcomes, benefits, and limitations have been reported in clinical practice and policy, including diagnostic/therapeutic impact, time to decision, user satisfaction, and cost/resource implications?
- Q4. What barriers, facilitators, and sustainability factors have been identified for the implementation and long-term adoption of these systems, and what research gaps remain?

These research questions were finalized before database searching and screening, and informed the Population–Concept–Context (PCC)-based eligibility criteria and the data charting framework.

2.2. Stage 2: Identifying Relevant Studies

At this stage, the search strategy (i.e., the selected databases and keywords) and the eligibility criteria for assessing each primary study were defined to narrow the search and identify relevant studies.

Search strategy. The literature search was carried out in August 2025. The selected databases include PubMed/MEDLINE, Scopus, Web of Science Core Collection, Cochrane Library, IEEE Xplore, ACM Digital Library, and LILACS. In all databases, we combined terms for second medical opinion and virtual/multidisciplinary consultations with terms for rare diseases.

These databases were selected to balance biomedical indexing with technology-focused sources. Nevertheless, database selection may introduce disciplinary bias by favoring work indexed in biomedical and mainstream informatics outlets, potentially underrepresenting conference proceedings not fully indexed, grey literature, and implementation reports published outside traditional academic venues.

No date limits were applied. No study design or publication type filters were used, consistent with a scoping review approach. Results were restricted to English, Portuguese, or Spanish at the search stage using database filters and, where applicable, language operators in the search syntax. Therefore, records in other languages were generally not retrieved for screening.

The complete reproducible PubMed/MEDLINE strategy is reported below:

("Second Opinion"[Mesh] OR "second opinion"[tiab] OR "second opinions"[tiab]
OR tele-expertise[tiab] OR e-consult*[tiab] OR "virtual consultation*"[tiab]
OR "virtual case discussion*"[tiab] OR "multidisciplinary team"[tiab] OR vMDT[tiab])
AND ("Rare Diseases"[Mesh] OR "rare disease*"[tiab] OR "orphan disease*"[tiab] OR Orphanet[tiab])
AND (english[lang] OR portuguese[lang] OR spanish[lang])

Although engineering-oriented databases were included (e.g., IEEEXplore, ACM Digital Library), low-level computer science implementation terms or specific standards were intentionally excluded because they are inconsistently reported and indexed in the rare disease literature and could reduce search sensitivity by missing clinically described services that lack explicit engineering terminology.

Eligibility criteria. Eligibility criteria were defined in accordance with the PCC framework. We included studies that: (i) explicitly addressed second medical opinions in the context of rare or orphan diseases, involving patients, caregivers, or healthcare professionals; (ii) described or evaluated a structured system, platform, or organizational process for delivering second opinions (e.g., virtual multidisciplinary team meetings, e-consult/tele-expertise platforms, reference networks, or web-based submission systems); (iii) were implemented in real healthcare settings. We excluded isolated case reports, telemedicine or telegenetics initiatives not explicitly focused on second opinions, conceptual proposals without implementation, and studies conducted outside the field of rare diseases.

It is important to state that eligible initiatives included both purpose-built platforms and standardized digital workflows implemented using institutional tools, provided they met the operational definition of a structured system, including a defined submission and review workflow and documented recommendations. Informal, ad hoc email exchanges without standardized procedures, governance, or documented outputs were excluded. Also, we did not impose minimum thresholds for case volume or number of participating

institutions. In addition, maturity indicators were not systematically extracted because they fell outside the predefined charting domains and were inconsistently reported across studies, which would limit the validity of cross-study comparisons.

Forward and backward searching. To complement database searches, forward and backward citation tracking was performed on all included studies to identify additional relevant articles that may have been left out.

2.3. Stage 3: Study Selection

All references were imported into Rayyan (Rayyan Systems Inc., Cambridge, MA, USA) for data management and deduplication [18]. Two reviewers independently screened titles and abstracts for eligibility. Borderline cases and articles deemed potentially relevant underwent full-text screening, which was also performed independently by two reviewers. Any disagreements were resolved through discussion, and if consensus could not be reached, a third reviewer adjudicated the decision. Reasons for exclusion at the full-text stage were documented. PRISMA-ScR flow diagram was used to report the selection process.

Eligibility criteria were defined a priori using the PCC framework and applied consistently throughout the screening process. No substantive changes were made to inclusion or exclusion criteria after screening commenced. Any adjustments were limited to clarifying operational definitions to improve reviewer consistency.

2.4. Stage 4: Charting the Data

A standardized data extraction form was designed to capture the information required to address the research questions. The data charting process was piloted on a subset of studies and refined accordingly. The data extraction domains were defined a priori from the research questions. Piloting was used to refine the charting form for clarity and consistency, without expanding or narrowing the predefined eligibility criteria or the scope of the review. Table 1 indicates the type of data that were extracted from each included article.

Table 1. Data extraction strategy.

Research Question	Data to Be Extracted	Rationale/How It Answers the Question
Q1	- Name of system/platform - Country/region - Organizational scale (national, regional, European, international) - Disease area - Year of implementation - Technological modality (synchronous, asynchronous, hybrid)	Identifies the range of SO systems, their geographical reach, and their characteristics, thereby enabling classification and mapping.
Q2	- Workflow description (submission process, triage, case presentation, panel discussion, documentation of recommendations) - Governance (who moderates, consent procedures, GDPR/data protection, roles of specialists) - Interoperability/integration with registries - Reporting standards used (if any)	Provides insight into how the systems are structured and the organizational/ethical frameworks that support them.

Table 1. *Cont.*

Research Question	Data to Be Extracted	Rationale/How It Answers the Question
Q3	- Reported outcomes: diagnostic revision, treatment modification, time to decision, access/equity - Adoption metrics: number of cases, users, institutions - User/patient satisfaction - Cost/resource implications - Time-related indicators (e.g., turnaround time for SO)	Shows the impact of SO systems and their value in clinical practice and policy.
Q4	- Reported barriers: technical (platform usability, connectivity), organizational (time, workload), legal/ethical (consent, liability), financial (funding, reimbursement) - Reported facilitators: training, governance support, policy frameworks, interoperability - Sustainability factors (e.g., long-term funding, institutional integration) - Research gaps identified by authors	Allows identification of cross-cutting themes, challenges, opportunities, and gaps for future implementation and research.

Extracted information included bibliographic details (authors, year, country, publication type), disease area, type of system or process, workflow, and governance characteristics (e.g., case submission, consent, data security, documentation), reported outcomes (diagnostic accuracy, management changes, adoption, satisfaction, equity, costs), and barriers or facilitators. Data extraction was conducted independently by two reviewers, and discrepancies were resolved by consensus.

We did not systematically chart the sources of funding of the included studies, as this variable was outside the scope of our research questions; this decision is reported here for transparency.

2.5. Stage 5: Collating, Summarizing, and Reporting the Results

Data from the included studies were collated and synthesized descriptively. Findings were summarized in a table and in narrative form, organized by type of second opinion system, disease area, and reported outcomes. Similarities and differences across studies were examined to identify patterns, themes, and gaps. No formal quality appraisal was conducted, consistent with scoping review methodology.

Reported outcomes were extracted and presented as described in the primary sources. Because most evaluations were programmatic and not independently audited, outcome figures such as diagnostic revision rates, turnaround times, and cost estimates should be interpreted as program-reported metrics rather than as externally validated measures of effectiveness.

3. Results

Initially, 264 articles were retrieved from the selected databases, and 20 were identified through forward and backward citation searching (a total of 284 records). After removing 81 duplicates, 203 records remained for screening. Following the title and abstract assessment, 176 articles were excluded for failing to meet the inclusion criteria. The remaining 27 full-text articles were assessed for eligibility, of which 9 were excluded: 3 did not focus on rare diseases, 4 did not address second opinions, and 2 lacked a structured system or platform. Finally, 18 studies were included in this scoping review. Figure 1 presents

the PRISMA flow diagram, and a comparative per study table with all charted variables, including technology relevant fields such as modality and interoperability, is provided in Supplementary Spreadsheet S1.

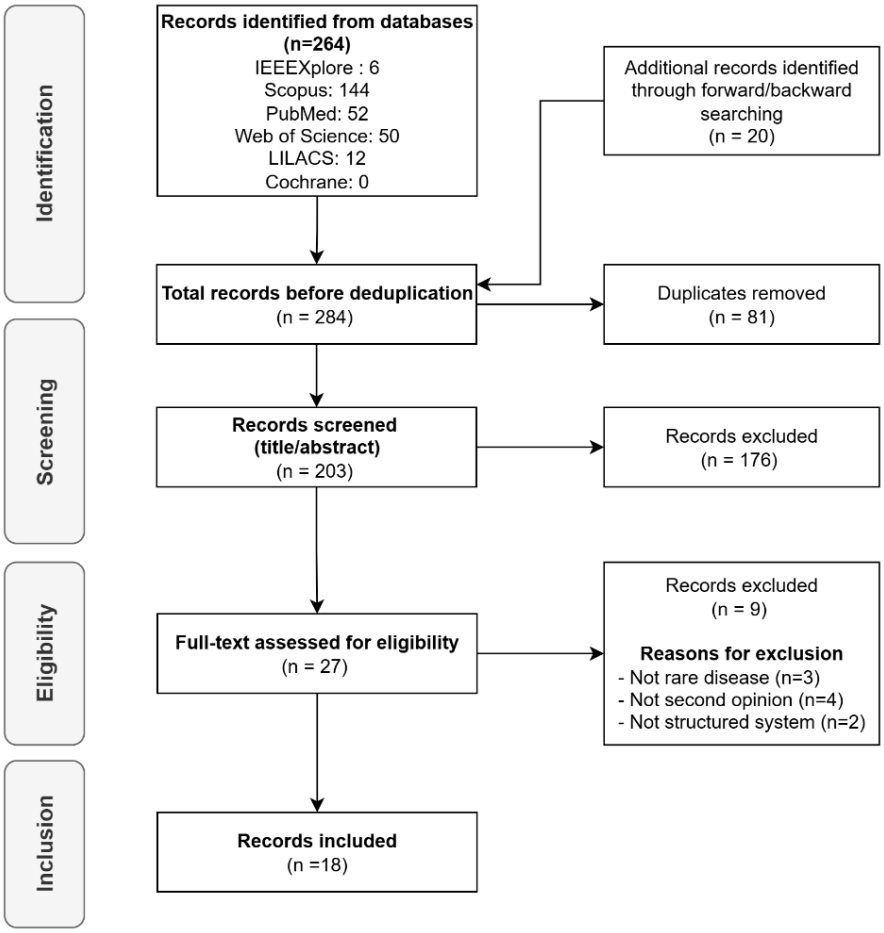


Figure 1. PRISMA flow diagram.

To avoid overlap, we organized results by implementation scale, a dimension that cleanly separates governance, legal frameworks, and interoperability models. Distribution by scale was as follows: European Research Networks (ERN) (8/18), National (5/18), Regional (2/18), and International (3/18). Regarding the technological approach, hybrid modalities predominated (9/18), followed by asynchronous (6/18) and synchronous contexts (3/18). Clinical domains were diverse, with concentrations in pediatric oncology (5/18) and clinical genetics/dysmorphology (5/18), alongside neurology/neuromuscular (3/18), endocrinology (2/18), immunology (1/18), urology (1/18), and cross-cutting platforms (1/18).

3.1. Cross-Border ERN Systems

ERN initiatives converge on the Clinical Patient Management System (CPMS) or direct precursors. Activity ranged from early implementation with a few dozen cases to mature programs with more than 150 panels. Examples include pediatric very-rare tumors integrating from EXPeRT to ERN PaedCan/CPMS (160 cases across 27 countries, 56 centers) [19], and ERN eUROGEN (152 panels; 81% closed) [20]. Endo-ERN reported growth to 144 panels with 326 registered and 270 active users [21], while EURO-NMD demonstrated a training-driven scale-up (panels 23→120 in 12 months) [22]. ERN-RND documented pan-European uptake (>40 CPMS discussions in early phase) [23], and ITHACA summarized its first-year telemedicine experience [24]. ExPO-r-Net mapped European pediatric tumor-board readiness

as a baseline for ERN deployment (121 institutions; virtual capability still limited at that time) [25].

Impacts. Across ERNs, reported impacts cluster around treatment/diagnosis decision-making and faster access to expertise. In EXPeRT/PaedCan, 93% of consultations influenced management; advice was thoroughly followed in 83% and partly in 14%, with typical responses in 2–3 days [19]. Endo-ERN users rated the usefulness high (approximately 8/10), with management changes or validations in roughly two-thirds of cases [26]. ERN eUROGEN emphasized optimization of care pathways [20]. Training effects, such as increased platform confidence and sustained usage, were consistently observed [21,22].

Governance, workflow, interoperability. ERN systems share a role-based workflow (case submission → panel coordination → multidisciplinary discussion → outcome document), under GDPR-compliant consent and audit trails. Video meetings are available, but most casework remains asynchronous (structured forms, threaded comments), with DICOM/image upload and standardized datasets. Interoperability with registries (e.g., EuRRECa/e-REC in Endo-ERN) is emerging; direct linkage of Electronic Health Records (EHR) is generally planned rather than routine.

Barriers and enablers. Recurrent barriers include platform complexity, time burden for panel creation, limited incentives, and uneven onboarding/awareness. Enablers include help desk support, targeted training, standardized consent across ERNs, and the multidisciplinary network effect. Sustainability leans on European Commission funding streams and the progressive integration of ERNs into national systems [20,21].

3.2. National Systems

National programs tailor governance and processes to local legal and service contexts. Italy's IEI-VCS/IPINet validated 68 cases, reaching a final diagnosis in ~51% (with many genetically confirmed) [27]. The UK's National Advisory Panels (NAPs) reviewed over 1100 referrals, with approximately 89% of recommendations implemented, and typical referral-to-panel and panel-to-recommendation intervals of 10 days and 4 days, respectively [28]. Germany's GPOH rare tumor network demonstrated early activity and substantial improvements in case registration and knowledge sharing [29]. Spain's national survey showed widespread vMDT presence but uneven virtual capacity and standardization [30]. Brazil's RD2O is a cross-cutting platform in development/pilot, aligned with national rare-disease networks [31].

Impacts. Reported national-level benefits include diagnostic yield (e.g., IEI-VCS), changes to or validation of local plans (UK NAPs), and faster access to reference expertise (GPOH). Surveys highlight where impact is latent but dependent on standardizing documentation, quoracy, and follow-through (Spain).

Governance, workflow, interoperability. Common patterns include standardized referral proformas, panel chairs/administrators, and clear statements that legal responsibility remains with the treating team. Interoperability varies, with national registries and PACS being common, while unified virtual platforms and EHR integration are less consistent.

Barriers and enablers. Key gaps are Standard Operating Procedures (SOPs), protected time, defined quorum, and secure data platforms to support auditing and learning. Enablers include national networks/registries, central reviews (such as radiology/pathology), and emerging guidance that formalizes referral and documentation processes.

3.3. Regional Systems

Subnational networks demonstrate how coordinated hybrid workflows can yield significant operational benefits. Italy's NOVHO (Lombardy) discussed 80 patients in 28 meetings across 6 centers [32]; the USA's Consultagene/Project GIVE enrolled 196 referrals in an underserved region with bilingual navigation and clinic-embedded tele-genetics [33].

Impacts. NOVHO reported a 66% reduction in time to assessment (≈89→30 days), 47% fewer hospital visits (141 avoided across 80 patients), and a 27.5% reduction in diagnostic revisions. GIVE increased access to genetics services and workforce capability (outcomes pending), illustrating the role of local cultural and language mediation.

Governance, workflow, interoperability. Both rely on structured submission, case management, and regular multidisciplinary case-conferences, with emphasis on local logistics (e.g., imaging sharing; clinic kiosks) rather than national infrastructure.

Barriers and enablers. Persistent barriers include IT constraints, time/scheduling issues, and limitations of remote physical examination. Enablers include clear roles, routine case rounds, and on-site coordination to bridge digital and in-clinic steps.

3.4. International Programs

Outside the ERN architecture, programs span bilateral telegenetics and pan-European crowdsourcing in dysmorphology. The DR-USA telegenetics program saw 66 individuals over five years with regular, scheduled clinics [34]. DYSCERNE's web-based diagnostic system handled 200 consecutive cases in a formal evaluation and sustained ~8 cases/month in service mode [35,36].

Impacts. Telegenetics achieved a 59% molecular diagnosis rate and approximately 70% management recommendations, with scheduling typically occurring within ~2 weeks. DYSCERNE's consensus clinical diagnosis rate was 22.5%, with a 36-day turnaround, frequent test recommendations (e.g., genetic testing in ~70%), and identification of new syndromic entities. Operating costs were about 127€/case, underscoring cost-effective reach.

Governance, workflow, interoperability. Submissions are standardized, consent is explicit for images/data, and expert panels provide written reports. Interoperability is modest (secure portals, archives); direct EHR linkage is generally absent.

Barriers and enablers. Sustainability beyond initial grants is the dominant challenge (expert time, platform upkeep, engagement), whereas enablers include clear protocols, educational spillover for submitters/reviewers, and network effects from multinational expertise.

4. Discussion

This scoping review synthesizes the evolution of structured second-opinion systems for rare diseases from locally organized advisory groups into multi-level, digitally enabled networks with reproducible workflows and auditable governance. Across ERNs, national programs, regional initiatives, and international collaborations, a standard operating model emerged: structured submission, eligibility screening and triage, moderated multidisciplinary deliberation that is primarily asynchronous with optional video, and a signed-off recommendation with responsibility retained by the treating clinician, yet implementation choices diverged according to scale, legal frameworks, and available infrastructure [19,21,22,24,28,34,36]. Interpreting these findings together suggests that ERN-style governance and consent models may enable cross-border collaboration at scale. At the same time, national and regional services can move more quickly on local logistics and workforce embedding, while international outreach programs can close equity gaps in underserved settings.

A first implication concerns the quality and timeliness of decisions. Multiple ERN reports, spanning very rare pediatric tumors, endocrinology, neurology, neuromuscular disease, and urology, describe consistent influence on diagnostic and therapeutic plans, high perceived usefulness, and accelerated access to subspecialty expertise through CPMS or its precursors [19,20,22–25]. At the national level, the UK National Advisory Panels achieved widespread adoption, with high levels of recommendation implementation, underscoring the value of standardized intake, chaired moderation, and rapid post-meeting

documentation [28]. Regional initiatives, such as the virtual hospital for rare cerebrovascular diseases, reduced time to assessment and unnecessary hospital visits while revising a substantial share of diagnoses, illustrating how subnational networks can reconfigure care pathways when case volumes concentrate across a few centers [32]. International telegenetics programs demonstrate both a high diagnostic yield, with sequencing accessible and pragmatic turnaround times, and the development of local capability through case-based learning [33–36].

A second implication relates to governance, data protection, and interoperability. ERN deployments share role-based access control, GDPR-aligned multi-stage consent, structured datasets, and traceable outcome notes, lowering transaction costs for cross-border working [21,24]. Where integration exists today, it most often connects panels to disease registries rather than to hospital EHRs; many programs describe bidirectional EHR interoperability as a near-term goal rather than a routine capability [20,21]. Concrete interoperability examples reported across the included systems include DICOM-based image upload and sharing within expert workflows [27,37], integration with imaging repositories and PACS [25], and linkage to disease registries [21], whereas direct EHR connectivity is less commonly implemented and is more often described as a near term goal, including via open standards such as HL7 FHIR.

National and regional services demonstrate that interoperability is not a binary concept: imaging repositories and PACS integration are standard, but unified virtual platforms and EHR links remain uneven, and medico-legal clarity outside ERNs requires explicit local arrangements [28–30]. International programs rely on secure portals and explicit image/data consent, trading deep systems integration for reach and feasibility in resource-constrained contexts [34–36].

Cross-border second opinion services operate under a set of combined legal, organizational, and technical security constraints that shape what is feasible in practice. At the legal and governance levels, personal health data exchange requires risk-based security, including measures such as encryption, confidentiality, integrity, availability, and the resilience of processing systems, alongside clear responsibilities for controllers and processors and incident handling [38].

Operationally, this translates into a small set of recurring control families, namely strong identity and access management (role-based access control, least privilege, and managed onboarding and offboarding), explicit consent and minimization for data and images, secure transmission and storage with appropriate key management, and auditability through tamper-evident logging to support traceability, accountability, and medico-legal defensibility [39,40]. Finally, cross-border services must plan for resilience and incident response, given the increased attack surface and dependency chain introduced by multi-party collaboration, including obligations under cybersecurity policy frameworks applicable to critical sectors such as health [41].

A third implication concerns adoption and sustainability. Across settings, uptake is most substantial where helpdesks, hands-on training, and clear SOPs reduce cognitive and administrative load; where expert effort is recognized in job planning; and where panel coordination is resourced rather than informal [21,22,28]. Conversely, recurring frictions, such as platform complexity, time-intensive panel creation, inconsistent incentives, and uneven institutional buy-in, quickly translate into underuse, even when perceived clinical value is high [20,21,30]. International crowdsourcing in dysmorphology further highlights the importance of sustainable funding and reviewer capacity; a modest cost per case can still be untenable if revenue and incentives are not aligned with demand [35,36]. Regional and outreach programs surface additional equity-relevant constraints (e.g., technology

access, digital literacy, and limits of remote examination) that can be mitigated but not eliminated through on-site coordination and bilingual navigation [33,34].

Figure 2 summarizes a potential reference architecture for digital second opinion services. The diagram synthesizes recurring functional components and data flows described or implied across the included implementations, including identity and access management, consent and data minimization, case intake and workflow coordination, clinical documentation handling, imaging exchange, communication modalities, audit logging and traceability, and interoperability connectors. This conceptual reference model is intended to support implementation-oriented discussion and does not represent system-specific deployed architectures.

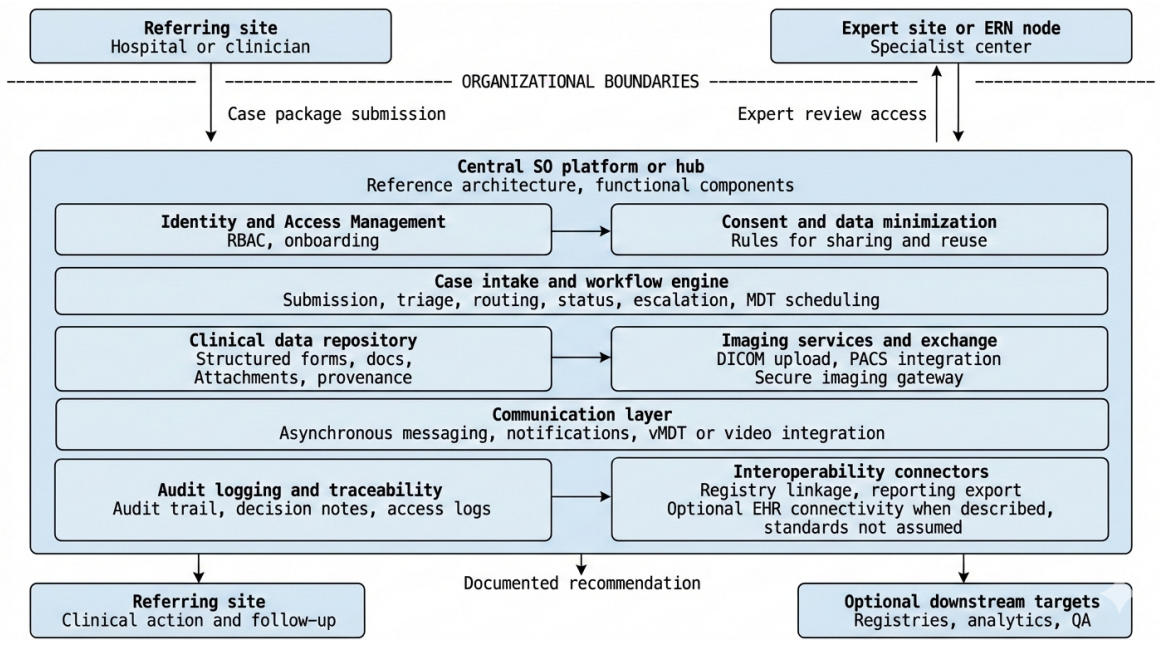


Figure 2. Reference architecture for digital second opinion services for rare diseases.

The rationale for using a scoping review rests on the field's heterogeneity. The interventions vary widely in scope (ERN, national, regional, international), technical modality (asynchronous, synchronous, hybrid), disease area, governance, and outcome definitions. Guidance explicitly recommends scoping reviews when topics are conceptually broad, evidence is methodologically diverse, and many sources are descriptive or programmatic rather than comparative, making meta-analysis inappropriate or premature [14]. Accordingly, a scoping approach is best suited to map the breadth and nature of evidence, clarify concepts and workflow components, and identify gaps and priorities for future evaluative research [15].

Additionally, focusing the scoping review exclusively on second opinion systems for rare diseases is justified by the low prevalence, dispersed expertise, and high diagnostic uncertainty. Rare diseases frequently require cross-border or inter-institutional deliberation to reach and validate management decisions. This creates a structural need for system-level SO services, explaining why the most mature digital infrastructures and governance models have emerged in ERNs.

Notwithstanding these constraints, the review identifies concrete, testable priorities. Usability and incentives should be aligned so that expert participation is technically straightforward, formally recognized in service planning, integrated with clinical workflows, and consistent with professional well-being [42]. Interoperability should progress from registry bridges toward safe, standardized, and, where appropriate, bidirectional EHR connectivity

that enables longitudinal follow-up and comparative effectiveness while preserving privacy, leveraging open standards such as HL7 FHIR/SMART to enable longitudinal tracking and comparative analysis with privacy protection [43]. Evaluation should shift from perceived usefulness to prospective, patient-level metrics, supported by consistent data elements and audit trails across programs, anchored in consolidated implementation/evaluation frameworks, and aligned with WHO guidelines for digital health assessment [44,45]. Finally, equity-oriented design, including bilingual navigation, clinic-embedded kiosks, and clear escalation pathways for in-person evaluations, should be treated as core infrastructure rather than optional features in regions where structural access barriers exist [46,47].

Digital health maturity frameworks could, in principle, inform future evaluations of rare disease second opinion services. However, we did not conduct a formal maturity assessment in this scoping review. First, maturity models are often designed for different units of analysis, for example, national digital health capabilities or hospital-wide electronic medical record adoption, which may not map directly onto interinstitutional second opinion workflows [48]. Second, the included literature reports heterogeneous and frequently incomplete technical and operational indicators, limiting the validity of scoring or benchmarking across initiatives. In future work, researchers may consider applying an appropriate maturity framework, complemented by data stewardship lenses such as the FAIR principles, to support standardized reporting on interoperability, governance, and reuse of data artifacts, provided that the necessary indicators are prospectively collected and transparently reported.

Regarding the role of AI and automation, although most second opinion initiatives identified in this review rely primarily on structured workflows and expert deliberation, emerging models increasingly consider AI and automation as enabling components [31,32]. AI and automation may become relevant in the next phase of scale-up, especially to reduce coordination burden and improve throughput, for example, by supporting de-identification, structured data capture, multilingual drafting, and case summarization before expert review. Any such use should remain human-supervised and be embedded in auditable workflows with clear accountability, bias monitoring, and privacy safeguards, consistent with emerging international guidance on the governance of generative AI in health. Prospective evaluations should explicitly test whether automation improves timeliness and equity without compromising clinical rigor, and whether interoperability and traceability are strengthened rather than diluted.

From an operational informatics perspective, future evaluations of second opinion platforms should also report a minimum set of service reliability and performance indicators to support scalability planning. Examples include availability or uptime, components of turnaround time (submission, triage, expert allocation, response), imaging and document-upload latency, case-routing efficiency, and capacity-related measures under peak load. These indicators were not synthesized in the present review, but their prospective collection would materially strengthen evidence on performance and scalability.

In sum, the field has established a workable minimum viable workflow for second-opinion services in rare diseases and demonstrated clinical relevance across scales. The next phase requires disciplined attention to human-centered design and incentives, pragmatic interoperability that builds from registries toward EHRs, and outcome frameworks that verify patient benefit and value for money. ERNs provide a template for governance and consent, national and regional services demonstrate how to operationalize logistics, and international outreach programs maintain a focus on equity. Together, these strands outline a realistic path to scale without compromising clinical rigor or fairness.

5. Limitations

This synthesis has limitations. The evidence base is mainly observational and programmatic; most studies rely on descriptive metrics and user-reported usefulness rather than controlled comparisons or patient-level outcomes, limiting causal inference. Because no formal quality appraisal was conducted, statements about feasibility and scalability should be interpreted as reported signals within specific implementations, not as definitive estimates of readiness for scale.

Interoperability and sustainability claims are often prospective, and several papers report planned EHR integration or anticipated funding solutions rather than audited implementations, which may inflate expectations. Detailed implementation characteristics such as specific APIs, messaging protocols, and storage architectures were inconsistently reported across primary sources; therefore, our synthesis emphasizes workflow, governance, interoperability signals, and implementation features at a level relevant to health service deployment, and we highlight technical reporting as a gap. Additionally, several quantitative outcomes and cost figures were program-reported and not independently validated, and they were often measured with heterogeneous definitions, which limits comparability and precludes strong causal inferences.

Our corpus comprises 18 studies provided for extraction, indicating purposive rather than exhaustive sampling. The review may under-represent negative or null experiences, relevant initiatives reported in other languages, and grey literature. Because reporting of workflow and documentation features varied, some initiatives may have been misclassified at the margins despite the operational criteria and independent dual review. We also did not systematically extract or compare maturity indicators such as case volume, number of sites, operational duration, or tech-specific performance and reliability metrics (for example, uptime, latency, throughput, error rates, or interoperability conformance testing) because these data were not consistently reported and were outside the scope of our charting framework. Therefore, we do not synthesize them as outcomes.

Database coverage may have introduced disciplinary bias. While we intentionally combined biomedical and technology-oriented databases, relevant work may still reside in venues with limited indexing, such as certain conference proceedings, preprints, and grey literature. As a result, some implemented systems may be underrepresented, particularly those reported in technical or operational channels rather than peer reviewed journals.

Finally, the lack of a prospectively registered protocol may raise concerns about methodological drift. However, this risk was mitigated through predefined questions and eligibility criteria, piloted charting, independent dual processes, and complete documentation of exclusions.

6. Conclusions

This scoping review demonstrates that structured second-opinion systems for rare diseases have evolved from ad hoc consultations into multi-level, digitally enabled services with reproducible and auditable workflows. Across cross-border networks, national programs, regional "virtual hospital" models, and international outreach, we observed recurring workflow components that appear across settings, including structured case submission, expert review, and documented recommendations. Despite variations in scale, legal context, and technology, the signals of benefit were consistent: faster access to subspecialty expertise, shorter decision times, frequent clarification or adjustment of diagnostic and therapeutic plans, and educational spillovers for the workforce.

For implementation, the clearest lessons are practical. Programs that pair strong governance with day-to-day enablers achieve steadier uptake and more reliable follow-through. Equity-oriented design, such as bilingual navigation, clinic-embedded kiosks,

and clear escalation to in-person assessment, should be treated as core infrastructure in settings where digital and geographic barriers are structural. For evaluation, the field should move beyond perceived usefulness toward prospective, patient-level outcomes and comparative effectiveness.

These conclusions are bounded by a heterogeneous, mostly descriptive evidence base and a purposive sample of studies. The available evidence suggests that systematized second opinion services for rare diseases may be feasible and clinically relevant across multiple settings, particularly when governance, coordination, usability, and interoperability are addressed. However, the literature remains largely descriptive and heterogeneous, and it does not yet support strong claims about maturity or readiness for scale across contexts. Scaling decisions should therefore be guided by prospective evaluation, standardized outcome reporting, and context-specific implementation assessment.

With disciplined attention to human-centered design, sustainable resourcing of expertise, and data standards that protect privacy while enabling measurement, these services provide a practical path to reduce unwarranted variation, accelerate diagnosis, and advance equity without shifting clinical responsibility away from the point of care.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/informatics13010006/s1, Spreadsheet S1: Comparative per study data extraction of the 18 included studies, including modality, workflow and governance, and interoperability or integration signals. File S1: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist (Reference [17] is cited in the supplementary material).

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