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Managing healthcare transformation towards P5 medicine

Edited by
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Managing healthcare transformation towards P5 medicine

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Editorial: Managing healthcare transformation towards P5 medicine

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personalized medicine, healthcare transformation, health ecosystem, precision medicine, translational medicine, P5 medicine

Editorial on the Research Topic
Managing healthcare transformation towards P5 medicine

After publishing a paper on "Challenges and solutions for designing and managing pHealth ecosystems" (1) in the Frontiers in Medicine Research Topic "Personal Health Systems", Frontiers in Medicine invited Bernd Blobel to edit a related Research Topic on the paper's topic. Contrary to traditional Frontiers in Medicine Research Topics based on open calls, the intended highly interdisciplinary volume is designed as a foundational textbook, established by papers on invitation only, that way guaranteeing a comprehensive, consistent and interrelated set of chapters. Therefore, Blobel et al. as Editor of the Research Topic "Managing healthcare transformation towards 5P medicine" first framed the topic regarding the objectives and challenges of transformed health ecosystems, their structures and functions, the involved domains including their methodologies and knowledge representation styles, as well as enabling technologies in a multidisciplinary approach to the transformation of health and social systems. After having defined the titles of the chapters to be included, he approached the internationally most acknowledged experts on those defined topics. Due to the special nature of the volume, a specific editor and reviewer pool had to be established first. Thus, he appointed Dipak Kalra as Research Topic Co-Editor. All papers have been first submitted to the Editor for check, harmonization, completion, etc., before running the formal submission process, followed by the formal review managed by the Co-Editor. Following the ethical rules of Frontiers, for all papers with the involvement of one of the editors as co-author, George Mihalas has been appointed as Research Topic Guest Editor. Without the latter's incredible engagement, the volume at hand wouldn't have been realizable.

Health and social care systems around the world are facing radical organizational, methodological and technological paradigm changes to meet the requirements for responding cost-effectively to increasing health demands, improving quality and safety of care, efficiency and efficacy of care processes and strengthening health systems resilience post-COVID. In this context, they are trying to tackle—usually without increased budgets—the challenges of ongoing demographic changes toward aging, multi-diseased societies, development of human resources, a health and social services consumerism, medical and biomedical progress, and exploding costs for health-related R&D as well as health services delivery. Furthermore, they intend to achieve sustainability of global health systems by

transforming them toward intelligent, adaptive and proactive systems focusing on health and wellness with optimized quality and safety outcomes.

The targeted outcome is a transformed health and wellness ecosystem combining the approaches of translational medicine, 5P medicine (personalized, preventive, predictive, participative precision medicine) and digital health toward ubiquitous personalized health services realized independent of time and location, preferably more strongly engaging and empowering the patient and citizen in maintaining their own health. It considers individual health status, conditions, genetic and genomic dispositions in personal social, occupational, environmental and behavioral context, thus turning health and social care from reactive to proactive. This requires the advancement communication and cooperation among the business actors from different domains (disciplines) with different methodologies, terminologies/ontologies, education, skills and experiences from data level (data sharing) to concept/knowledge level (knowledge sharing). The challenge here is the understanding and the formal as well as consistent representation of the world of sciences and practices, i.e., of multidisciplinary and dynamic systems in variable context, for enabling mapping between the different disciplines, methodologies, perspectives, intentions, languages, etc. This co-operation amongst disciplines and perspectives is vital if we are to correctly and successfully develop and deploy increasingly sophisticated digital solutions in increasingly complex health and care systems. Based on a framework for dynamically, use-case-specifically and context-aware representing multi-domain ecosystems including their development process, systems, models and artifacts can be consistently represented, harmonized and integrated.

The response to that problem is the formal representation of health and social care ecosystems through a system-oriented, architecture-centric, ontology-based and policy-driven model and framework, addressing all domains and development process views contributing to the system and context in question (Blobel et al.). The representational challenges regarding ontologies and linguistics are specifically addressed (Kreuzthaler et al.). Such transformed health ecosystems must be designed and implemented in a secure and trustworthy way (Ruotsalainen et al.), meeting ethical requirements and principles (Maeckelberghe et al.). For providing implementable solutions and realizing them, the system must be properly modeled (Oemig and Blobel).

The described methodological paradigm changes must be accompanied by technological ones to enable healthcare transformation toward intelligent and increasingly autonomous ecosystems. Here, artificial intelligence (AI) and robotics must be mentioned (Denecke et al.). A special challenge of P5 medicine is the deployment of digital therapeutics. Their adoption and related success factors are specifically considered by Prodan et al..

This Frontiers Research Topic concludes with practical demonstrators such as healthcare transformation in low- and middle-income countries by using artificial intelligence (López et al.) or the deployment of the described methodologies in EU projects with a focus on SARS-CoV-2 pandemic (Paleari et al.).

Author contributions

BB drafted the editorial. Both authors made substantial contributions to the work and approved it for publication.

Acknowledgments

The editors thank all authors and reviewers for their valuable contribution to the success of this volume. They especially thank the Guest Editor George Mihalas for his strong and excellent engagement in managing all papers with the involvement of the authors, that way meeting the ethical principles of the journal. Without this effort as well as the valuable organizational support and cooperation by Frontiers in Medicine, this volume would not have been possible.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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ORIGINAL RESEARCH
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Transformation of Health and Social Care Systems—An Interdisciplinary Approach Toward a Foundational Architecture

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Objective: For realizing pervasive and ubiquitous health and social care services in a safe and high quality as well as efficient and effective way, health and social care systems have to meet new organizational, methodological, and technological paradigms. The resulting ecosystems are highly complex, highly distributed, and highly dynamic, following inter-organizational and even international approaches. Even though based on international, but domain-specific models and standards, achieving interoperability between such systems integrating multiple domains managed by multiple disciplines and their individually skilled actors is cumbersome.

Methods: Using the abstract presentation of any system by the universal type theory as well as universal logics and combining the resulting Barendregt Cube with parameters and the engineering approach of cognitive theories, systems theory, and good modeling best practices, this study argues for a generic reference architecture model moderating between the different perspectives and disciplines involved provide on that system. To represent architectural elements consistently, an aligned system of ontologies is used.

Results: The system-oriented, architecture-centric, and ontology-based generic reference model allows for re-engineering the existing and emerging knowledge representations, models, and standards, also considering the real-world business processes and the related development process of supporting IT systems for the sake of comprehensive systems integration and interoperability. The solution enables the analysis, design, and implementation of dynamic, interoperable multi-domain systems without requesting continuous revision of existing specifications.

Keywords: health transformation, ecosystem, 5P medicine, architecture, knowledge representation and management, modeling, integration, interoperability

INTRODUCTION

In the context of the ongoing transformations of health and social care systems to improve the safety and quality of patients' care and population health as well as the efficiency and efficacy of care delivery services under the well-known constraints, appropriate organizational and methodological paradigm changes, supported by technological innovations, are inevitable (1).

Regarding the organizational paradigm, there is a transition from organization-centric through disease-specific process-controlled care to person-centric care. This process is accompanied by technological evolutions, such as the advancement from centralized to highly distributed and mobile technologies, deploying nano-, molecular-, and bio-sensors and actuators, healthcare internet of things (IoT), also referred to as the internet of medical things (IoMT) (2), smart systems, knowledge representation, and management as well as a social business. Also, big data and analytics, learning technologies and artificial intelligence, and autonomous systems, enabled by cloud, cognitive as well as edge, and nowadays also by quantum computing, must also be mentioned here.

Regarding the methodological paradigm, care evolves from the empirical approach of general care addressing health problems with one solution fitting all through the evidence-based medicine approach of dedicated care for a stratified population with specific, clinically relevant conditions to, in combination with the aforementioned new technologies, holistic or translational medicine. Holistic medicine aims at the entirety of physical, emotional, mental, spiritual, and social wellness, focusing on prevention by fixing the underlying cause of a

TABLE 2 | Technologies, methodologies, and principles for transforming healthcare ecosystems (29).

- Mobile technologies, biotechnologies, nano- and molecular technologies
- Big data and business analytics
- Integration of analytics and apps
- Assisting technologies → Robotics, autonomous systems
- Natural Language Processing → Text analytics → Intelligent media analytics
- Conceptualization → Knowledge representation (KR) and knowledge management (KM) → Artificial intelligence (AI) → Artificial common (general) intelligence → Intelligent autonomous systems
- Security and privacy, governance, ethical challenges, Education → Asilomar AI Principles
- Cloud computing, cognitive computing, social business
- Edge computing as a "family of technologies that distributes data and services where they best optimize outcomes in a growing set of connected assets" (Forrester Research)
- Virtual reality and augmented reality, thereby blurring "the boundaries between the physical and digital worlds" (Gartner)
- Creation of IoT-Platforms and app-ecosystems
- Patient-generated health data ecosystem → multiple, dynamic policies
- Web content management → Digital experience management
- Databases → NoSQL technologies → Data warehouses → Graph DBs → Data lakes
- EHR (including genomic data) → data exchange → semantic interoperability
- Use Case Analysis → Specification → Implementation → Tooling → Testing → Certification

TABLE 1 | The objectives and characteristics of pHealth ecosystems as well as the methodologies/technologies for meeting them (28).

Objective	Characteristics	Methodologies/technologies
Provision of health services everywhere anytime	• Openness • Distribution • Mobility • Pervasiveness • Ubiquity	• Wearable and implantable sensors and actuators • Pervasive sensor, actuator and network connectivity • Embedded intelligence • Context-awareness
Individualization of the system according to status, context, needs, expectations, wishes, environments, etc., of the subject of care	• Flexibility • Scalability • Cognition • Affect and Behavior • Autonomy • Adaptability • Self-organization • Subject of care involvement • Subject of care centralization	• Personal and environmental data integration and analytics • Service integration • Context-awareness • Knowledge integration • Process and decision intelligence • Presentation layer for all actors • Affective and cognition-aware computing
Integration of different actors from different disciplines/do-mains (incl. the participation/ empowerment of the subject of care), using their own languages, methodologies, terminologies, ontologies, thereby meeting any behavioral aspects, rules and regulations	• Architectural framework • End-user interoperability • Management and harmonization of multiple domains including policy domains	• Terminology and ontology management and harmonization • Knowledge harmonization • Language transformation/ translation
Usability and acceptability of pHealth solutions	• Preparedness of the individual subject of care Security, privacy and trust framework • Consumerism • Subject of care empowerment • Subject of care as manager • Information based assessment and selection of services, service quality and safety as well as trustworthiness • Lifestyle improvement and Ambient Assisted Living (AAL) services	• Tool-based ontology management • Individual terminologies • Individual ontologies • Tool-based enhancement of individual knowledge and skills • Human Centered Design of solutions • User Experience Evaluation • Trust calculation services

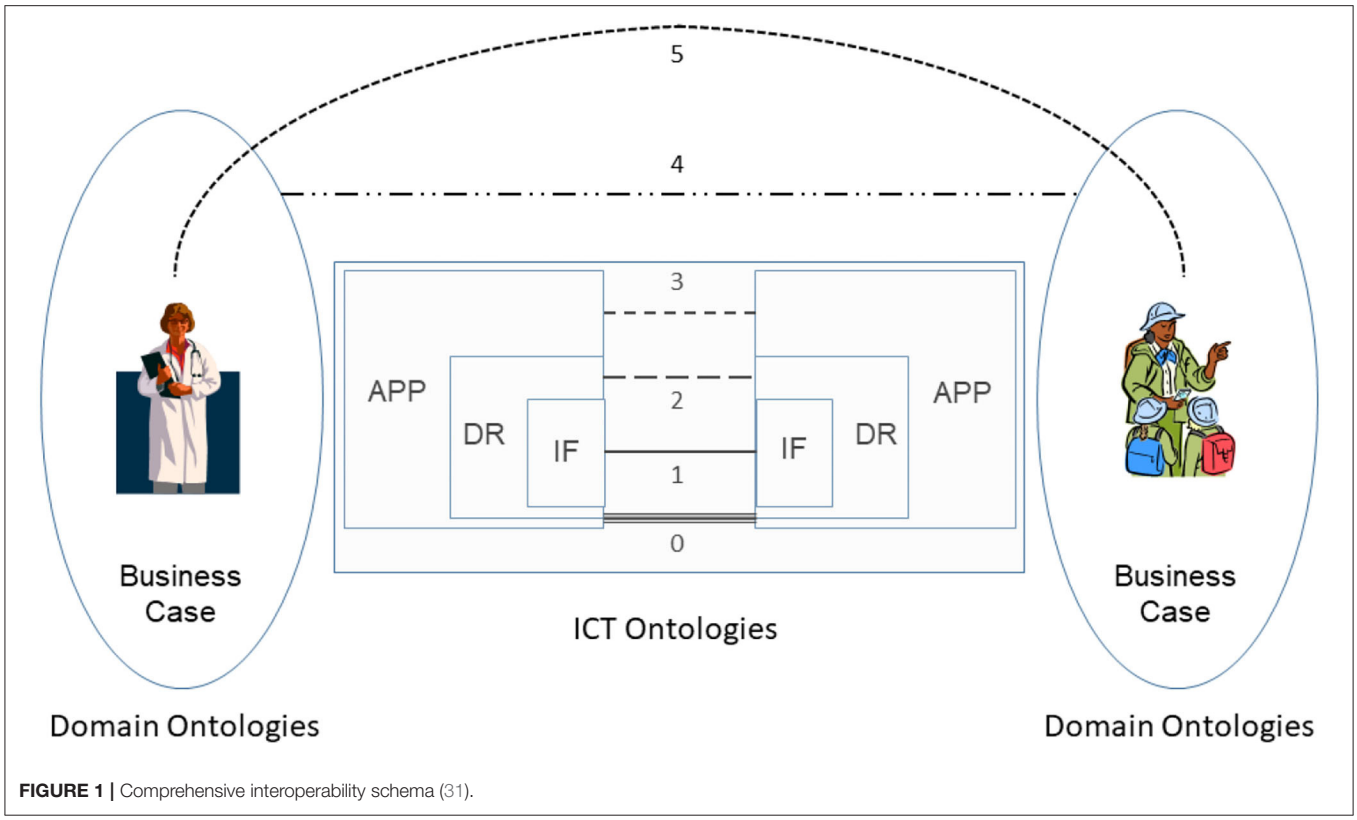

FIGURE 1 | Comprehensive interoperability schema (31).

TABLE 3 | Interoperability levels of the comprehensive interoperability schema.

Information perspective		Organizational perspective
Interoperability level	**Instances**	**Interoperability level**
Technical interoperability (0)	Technical plug&play, signal- & protocol compatibility	Light-weight interactions
Structural interoperability (1)	Simple EDI, envelopes	Information sharing
Syntactic interoperability (1)	Messages and clinical documents with agreed upon vocabulary	
Semantic interoperability (2)	Advanced messaging with common information models and terminologies	Coordination
Organizations/Service interoperability (3)	Common business process	Agreed Cooperation
Knowledge-based interoperability (4)	Multi-domain processes	Cross-domain Cooperation
Skills-based interoperability (5)	Multi-domain individual engagement	Moderated end-user collaboration

*The numbers in the brackets correspond to those in the interoperability schema (**Figure 1**) (32).*

disease instead of improving just symptoms (3), and empowering individuals and communities (4). Translational medicine is a bi-directional, interdisciplinary concept aiming at translating biomedical discoveries into clinical benefits and stimulating research by clinical observations, frequently called the "bench-to-bedside" or "bedside-to-bench" process (5). Advancing the practice of medicine from an inexact science to precision medicine, the deployment of genomics is foundational (6). A holistic, translational medicine approach including omics disciplines, such as genomics, nutrigenomics, metabolomics, proteomics, etc., allow us to consider individual health status, genetic, environmental, occupational, and social conditions, and context (stratification of population by risk profiles), so as to understand the pathology of diseases including the individual predisposition to diseases and responsiveness to treatment. By combining all interactomes, i.e., interacting factors and components impacting health of an individual, such as genomes, epigenomes, proteomes, microbiomes, metabolomes, pharmacomes, transcriptomes, cognitive-affective behavioromes, personalized, preventive, predictive, and participative care according to the precision medicine paradigm (5P medicine) can be enabled (1, 5, 7, 8). The approach is not only deployed for the evolution of health and social care, but also for advancing the underlying scientific foundations, such as clinical studies, as mentioned already in the context of the bi-directionality of the translational medicine concept (9). Recently, Cleveland Clinic started cooperation with IBM not only to deploy its quantum computers for studying genomics, emerging pathogens, virus-related diseases, and public health threats, but also for synthesizing needed data in imaging for rare diseases, using

a type of deep learning called generative adversarial networks (GANs) (10). Quantum computing also allows for new insights to understand the bindings and reactions of molecules in the design of new medications for personalized medicine (11). Another example of disruptive technologies in translational medicine is the deployment of next-generation sequencing (NGS) in clinical diagnostic and the definition of new therapeutic options at the molecular level, thereby extending and completing traditional pathological methodologies, such as histo-morphology, clinical chemistry, etc. (12).

Another term representing the described evolutionary process is "digital health." According to the definition of the Healthcare Information and Management Systems Society (HIMSS), "Digital health connects and empowers people and populations to manage health and wellness, augmented by accessible and supportive provider teams working within flexible, integrated, interoperable, and digitally-enabled care environments that strategically leverage digital tools, technologies and services to transform care delivery" (13).

The resulting personalized, ubiquitous, pervasive, and precision health services are provided independent of time and location. Personalized pervasive health includes the individualization of diagnosis and therapy with the help of bioinformatics, genomics, but also social sciences, public health, etc. While precision medicine provides the right treatment to the right patient at the right time, precision public health can be simply viewed as providing the right intervention to the right population at the right time. By advancing the methodologies for measuring disease, pathogens, exposures, behaviors, and susceptibility, population health could advance disease prevention (14). Precision cardiology, for example, integrates diverse, wide-ranging phenotyping and genomic data on patients to better understand the mechanisms at play in inherited heart diseases, so as to support a better understanding of the links between genetic variations and clinical manifestations (15). Analyzing cellular functions, e.g., by functional proteomics is used not only to develop new immune therapies and to assess the outcome of the patients regarding disease progression, anti-tumor, or COVID-19 immunization response *via* pre- or post-treatment immune profiling but also transplants rejection based on the analysis of cellular functions, by influencing research as well as practical care (16, 17). Another example in this context is the prediction of drug resistance in melanoma cells by deploying single-cell proteomics and metabolomics to analyze melanoma cell states in response to specific stimuli (18). The tumor microenvironment (TME) comprises cancer cells, the

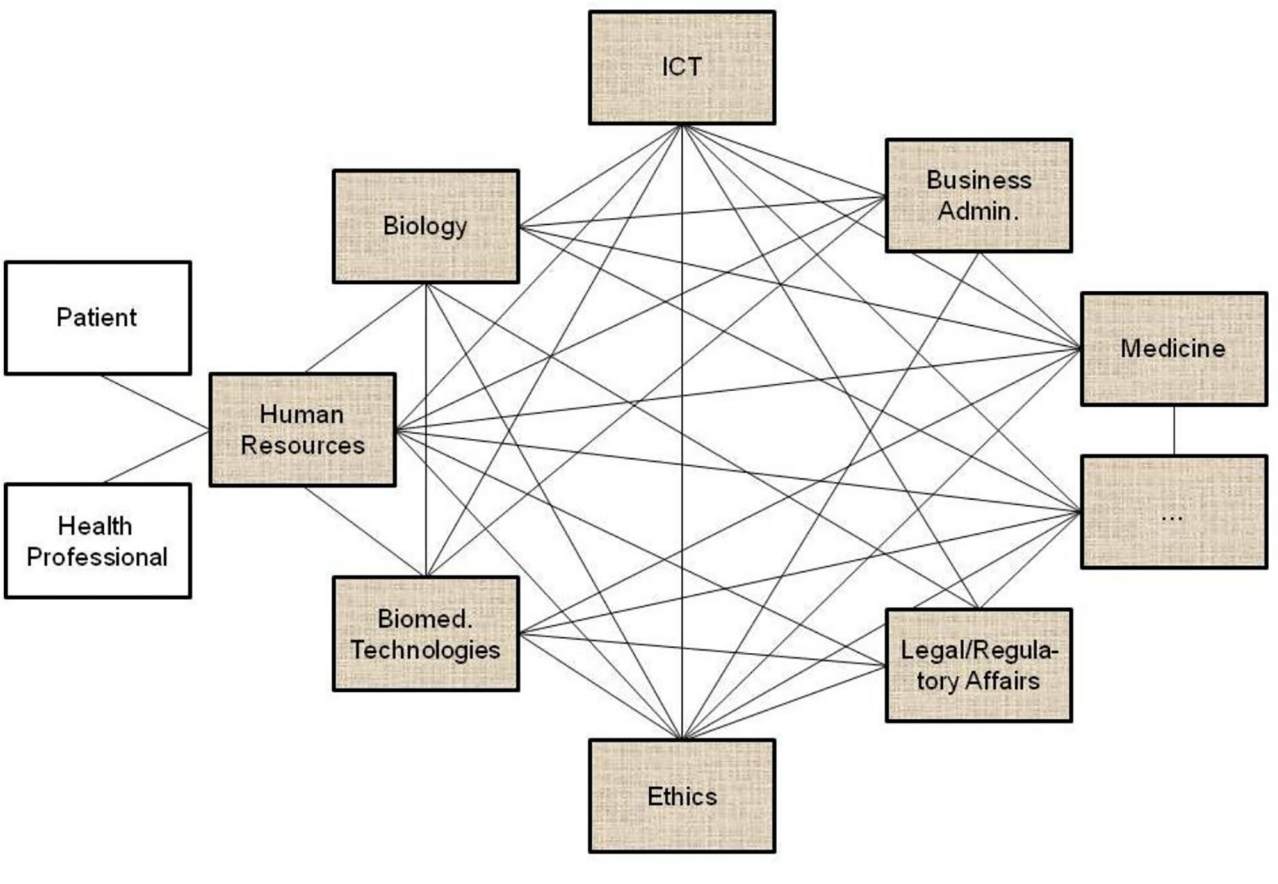

FIGURE 2 | Domain-domain interoperability requesting a permanent bilateral harmonization process (the un-shaded blocks present two relevant examples of human resources in pHealth ecosystems, but there are, of course, many more).

cytokine environment, extracellular matrix, immune cell subsets, and other components (19).

Precision medicine, and the ecosystem that supports it, must embrace patient-centeredness and engagement, digital health, genomics and other molecular technologies, data sharing, and data science to be successful (20).

Furthermore, the progress of digital health tools, including mobile health apps and wearable or even implantable sensors, actively and passively collecting data and information, could help improve human health and push new approaches to the management of health conditions, thereby enhancing human data science. In that context, digital therapeutics, consumer wearables and mobile apps, connected biomedical apps, smartphone cameras, connected virtual assistants in home care, but also health system disease management apps, care teams cooperation tools, interactive programs, personal health records, telemedicine and virtual visits to the doctor, and clinical trial tools have to be mentioned (21, 22). Here, intelligent clothing using nanotube fibers to monitor heart metrics also comes into play (23).

The ability to relate data across populations requires mastering data accuracy and semantic correctness, establishing a robust data infrastructure for integration by data exchange including its verification, ultimately supporting interoperability. Thereby, the digital twin technology can also support the move to precision (and accuracy) medicine and public health (24). The paradigm changes have been frequently discussed in different documents and summarized [e.g., in (1, 25–29)].

In summary, concept-oriented, context-aware, transformed health, and social care ecosystems consider the continuum from the cell up to society or even from elementary particle to the universe. Operations of such ecosystems require communication and cooperation of principals (person, organization, device, application, component, and object) as defined by the Object Management Group (30). Those principals belong to multiple domains, including medicine, natural sciences, engineering, and also social, legal, and political sciences, and the entire systems sciences world (systems medicine, systems biology, systems pathology, etc.). They are guided by different perspectives and objectives, follow different policies, deploy different methodologies, and use different languages/terminologies. A major principle is the empowered patient and his/her social environment. Such transformed ecosystems must be inevitably integrated with appropriate security and privacy solutions,

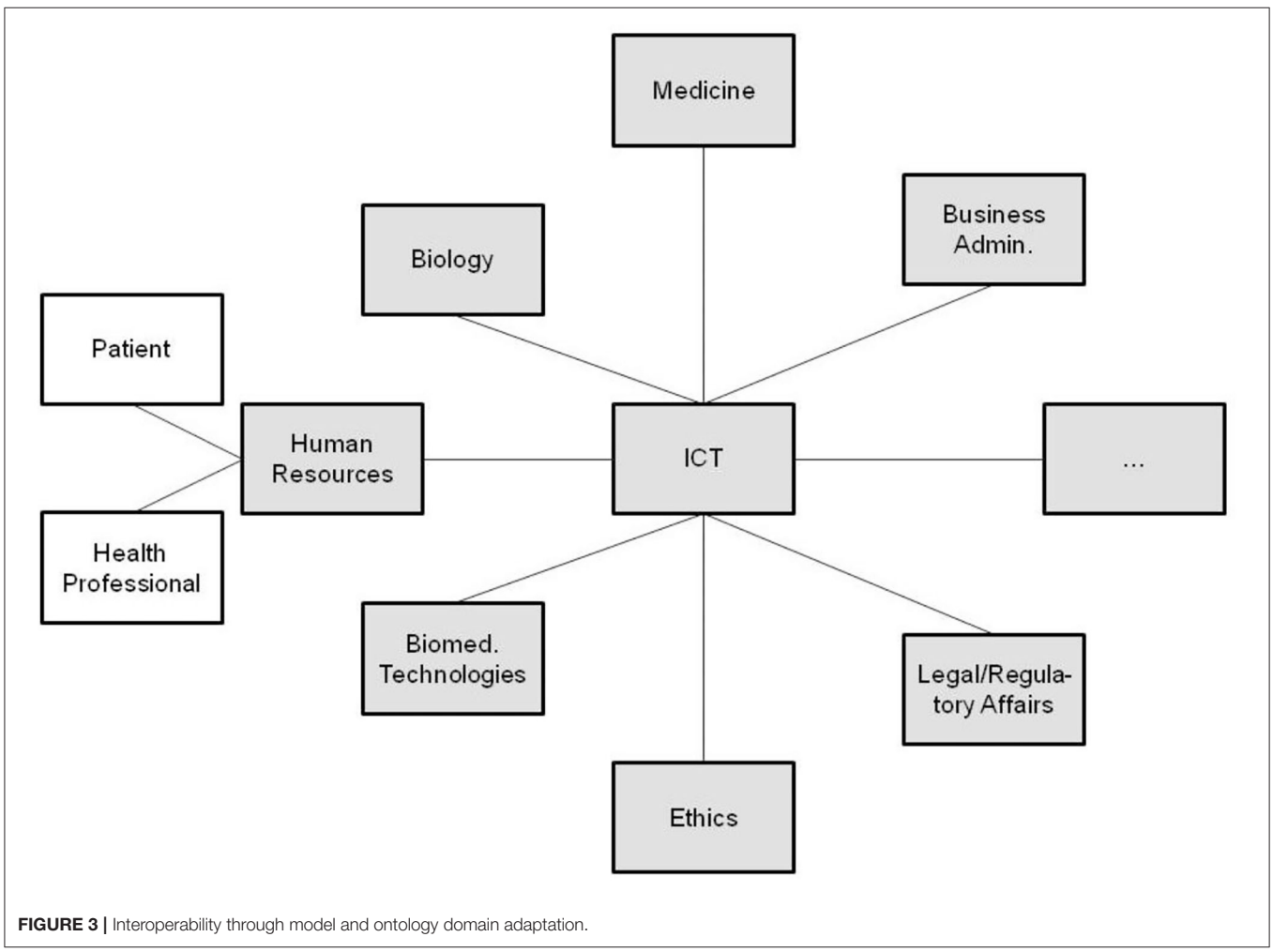

FIGURE 3 | Interoperability through model and ontology domain adaptation.

the establishment of trust, and the assurance of ethical and humanistic as well as equity, non-discrimination, and fairness principles. **Table 1** summarizes the objectives of pHealth ecosystems and characteristics as well as methodologies and technologies for meeting them (28), while **Table 2** aggregates technologies, methodologies, and principles for transforming healthcare ecosystems (29).

In the next section, we will discuss challenges and solutions for communication and cooperation between actors of transformed ecosystems, before we introduce approaches for representing and managing transformed health and social care ecosystems.

INTEROPERABILITY CHALLENGE UNDER THE NEW ORGANIZATIONAL, METHODOLOGICAL, AND TECHNOLOGICAL PARADIGMS

Interoperability has been traditionally addressed as an information technology (IT) challenge. As a result, the following interoperability levels from technical plug & play (0) through an interface (IF) enabled data/information exchange (1), sharing of semantics at data representation (DR) level (2) up to service sharing at application (APP) level (3) have been established [the numbers in the brackets correspond to those in the interoperability schema (**Figure 1**)]. The concepts and relations of the involved information and communication technology (ICT) systems components are represented using ICT ontologies.

At its core, interoperability of transformed health and social care ecosystems demands to integrate the knowledge of the business domains involved in the business case. A methodology to achieve interoperability would not be complete without taking into account human factors, such as education, skills, experiences, and social and psychological factors. In addition, commonsense knowledge must also be considered for interoperability (31). Therefore, the described advanced health and social services approach require the explicit and formalized representation of involved knowledge and skills as well as the application of pervasive, cognitive, and autonomous computing technologies for healthcare. **Figure 1** presents the comprehensive interoperability challenges, where the ICT-related stuff is the simplest one.

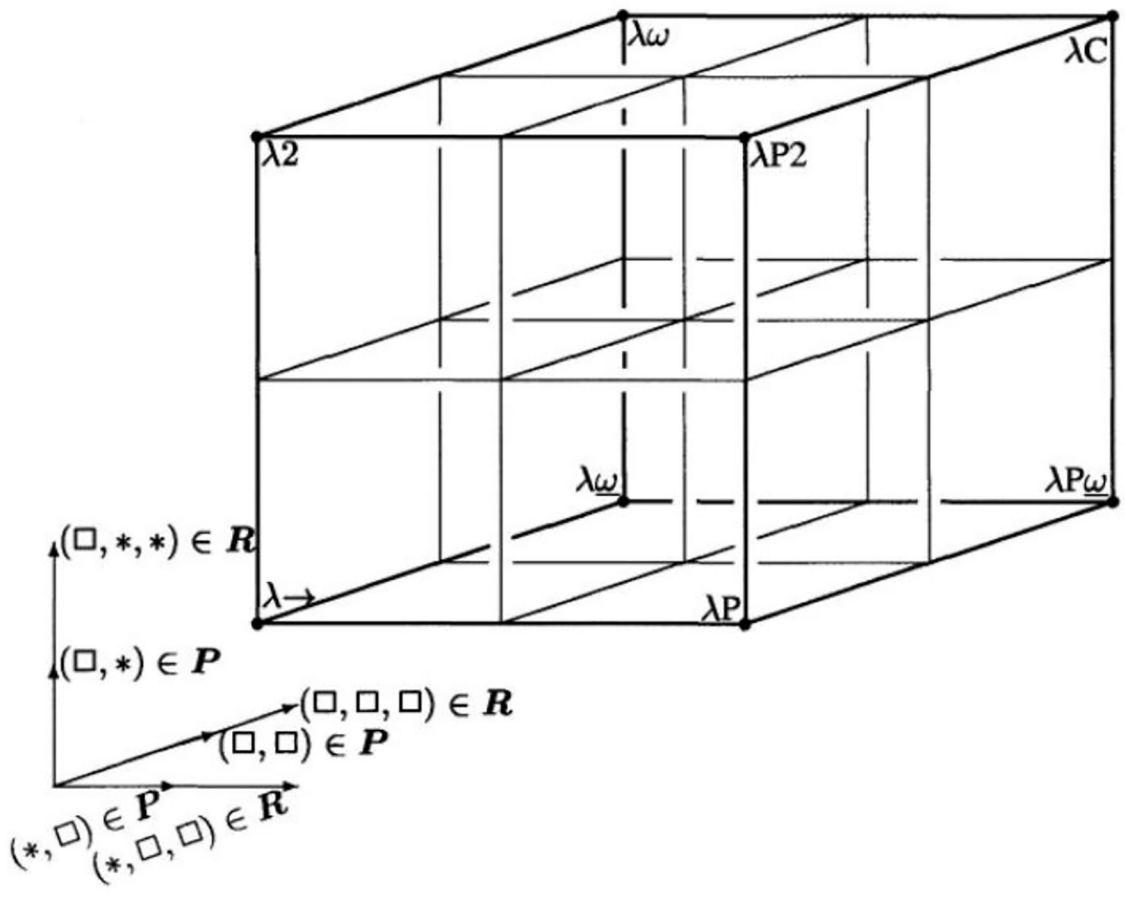

FIGURE 4 | Barendregt Cube with parameters [after (42)]. *Is a generic name for an element in a series of constants, defined by Barendregt. *Represents the sorts of types in Type Systems.

The resulting interoperability levels are shown in **Table 3**, considering both the informational and the organizational perspectives.

The system represented by the subject of care and the processes of analyzing and managing his/her health comprises different levels of structural and functional complexity. The structural complexity or granularity ranges from elementary particles through atoms, molecules, cell components, cells, tissues, organs, bodies, and communities, up to population (1). Regarding the domain-specific functional, or in general, interrelational aspects of that system and its components, we have to deal with quantum-mechanical effects in the atomic and subatomic world, biochemical processes, physical interrelations throughout the continuum, social relationships in the macro-world, etc. (1). Knowledge related to those facts has been reviewed, e.g., in (25, 27–29).

All the domain experts involved in the aforementioned transformed health services settings describe not only the specific aspects of that system in a specific context, using their specific languages and methodologies, but also specific expression means covering natural languages, figures, equations, formulas, codes, etc. As a result, the information flow and the background knowledge of the different domains have to go through a peer-to-peer interoperability adaptation process (**Figure 2**). Thereby, all the existing components and their representational models and standards connected or contributing to the system (shaded in the figure) have to be newly harmonized when some components or contexts are changing, or new components have been added to the therefore highly dynamic system.

An alternative approach to integrating the interrelated but different perspectives and aspects is the deployment of one domain's language, ontology, representational style, models, architectures, and standards (e.g., ICT languages,

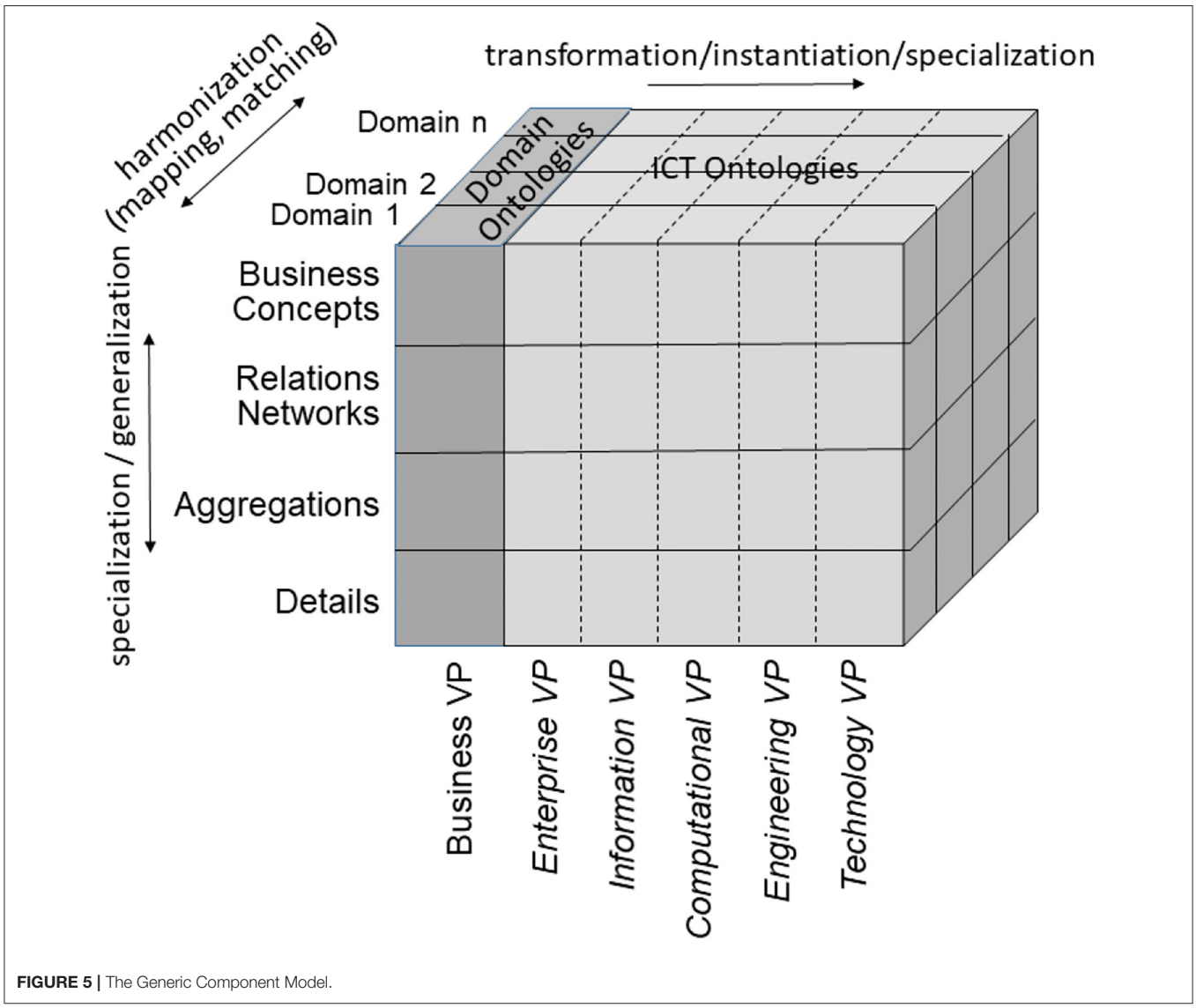

FIGURE 5 | The Generic Component Model.

ontologies, and notations) as a reference or master all the interrelated components must be adapted to (**Figure 3**). Such a process is tough and demands sometimes cumbersome compromises from the parties involved. The problems faced by this approach include complexity, completeness, expressivity, and consistency of domain-specific knowledge representation languages and ontologies, which start growing when moving from implicit knowledge up to fully explicit knowledge representation, i.e., from natural language up to machine language and universal logic (32–34). While more expressive knowledge representation language and reasoning systems like traditional programming languages with their context-free grammar enable a simpler and compact expression of knowledge, they usually need more complex logic and algorithms for constructing equivalent inferences to represent transformed health ecosystems, thereby running not only into a complexity, consistency, computability and decidability, but also a completeness problem. Less expressive knowledge representation languages, such as natural languages with their context-sensitive grammar optimize restrictions to special structure vs. generative power, thereby enabling a rich and nevertheless decidable representation of real-world concepts with the support of common sense knowledge. Hence, they allow not only for an efficient representation of meaning, shared knowledge, skills, and experiences, but also facts and knowledge about a system and its domain-specific subsystems, architecture, and behavior. Therefore, many domain ontologies deploy natural-language-based domain-specific terminologies and concept representations, extensively exploited in the best practices of good modeling discussed in the Chapter "Modeling digital health systems" in this volume. More details about knowledge representation and management languages, their grammars, and relationships can be found in the study by Blobel et al. (29).

The aforementioned statements clearly demonstrate that it is impossible to represent and justify the highly complex, highly dynamic, multi-disciplinary/multi-domain transformed healthcare system by just one domain terminology/ontology or, even worse, by using ICT ontologies exemplified in the next section. The deployment of domain-specific reference ontologies representation tools furthermore excludes the addressed other domains' experts which should when thinking of the medical domain experts' role in health informatics, be in the lead, but cannot understand and deploy that environment. ICT ontologies

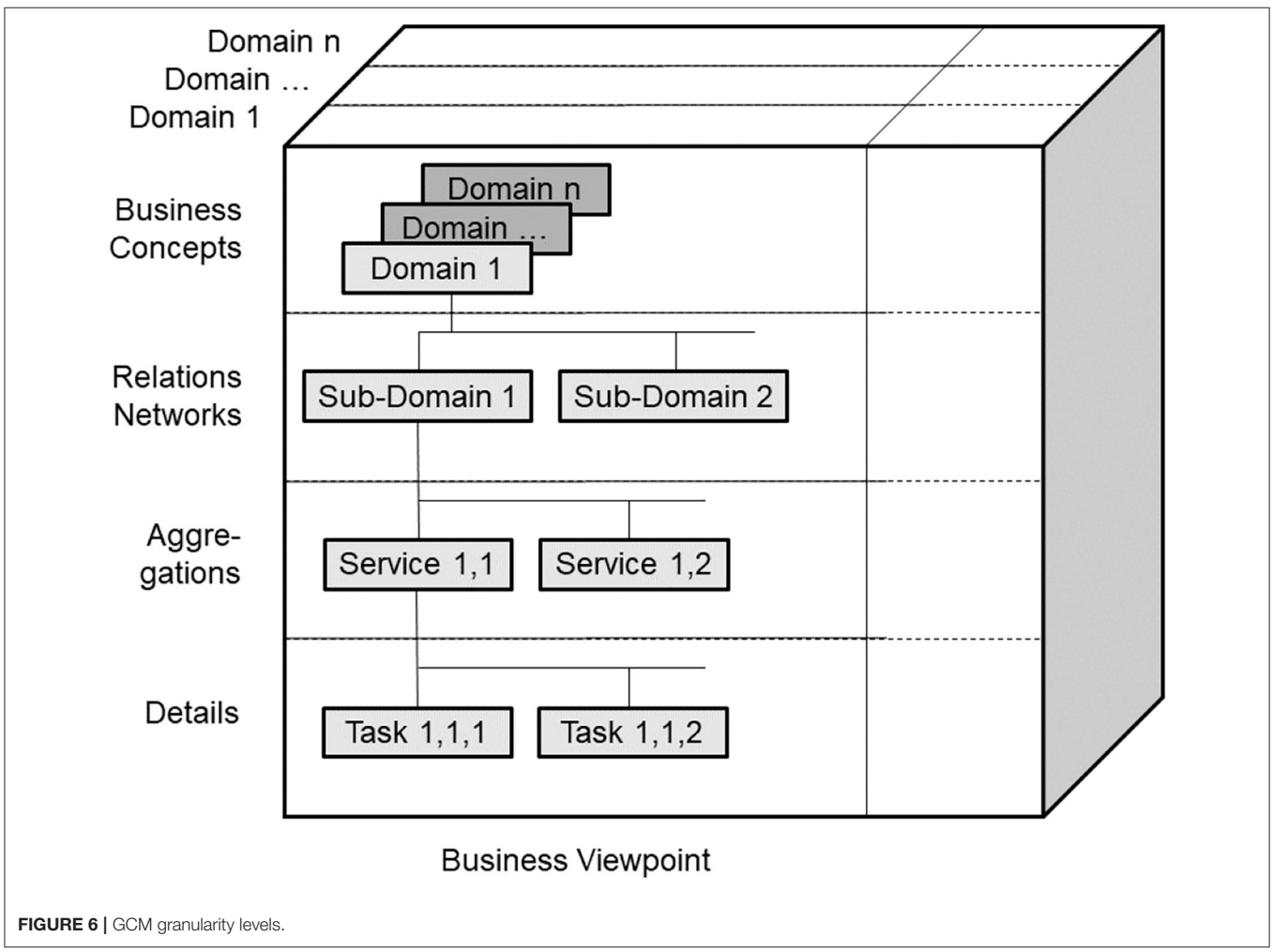

FIGURE 6 | GCM granularity levels.

can hardly manage dynamic systems, resulting in the permanent revision of existing components to be integrated into the system.

MASTERING THE KNOWLEDGE REPRESENTATION AND MANAGEMENT CHALLENGE IN MULTIDISCIPLINARY, COMPLEX, AND DYNAMIC ECOSYSTEMS

Focusing on different knowledge classes, such as classification-based knowledge, decision-oriented knowledge, descriptive knowledge, procedural knowledge, reasoning knowledge, or assimilative knowledge, knowledge has been defined in multiple ways (29). Davenport defines knowledge as "… information combined with experience, context, interpretation, and reflection. It is a high-value form of information that is ready to apply to decisions and actions" (35). As a result, we have to accept multiple knowledge spaces to represent the same real-world system. When representing reality according to the theory of knowledge or cognitive theory, we have to advance the cognition/sense-perception of reality toward its conceptualization (36). Doerner describes domain knowledge as reproducible and reliable models of a domain, repeatable formulated and justified in the discourse domain (discipline) by domain experts using their domain-specific methodologies, terminologies, and ontologies (37). A domain model represents that domain's perspective on reality to facilitate reasoning, inferring, or drawing conclusions. It formally describes objects, properties, relations, and interactions of a domain, enabling rational and active business in the represented domain. One important methodology to resolve the aforementioned knowledge representation problem is using domain-specific ontologies to formally represent the knowledge or concepts of each of the domains involved.

When conceptually modeling ecosystems, three levels of knowledge representation must be distinguished and consecutively processed: (a) epistemological level (domain-specific modeling), (b) notation level (formalization, concept representation), and (c) processing level (computational, implementations) (37). While the epistemological level of domain-specific modeling has been discussed so far, we will now focus on the concept of representation and formalization of the transformed health and social care ecosystem. The processing level will be considered in the Chapter "Modeling digital health systems" in this volume.

At the notation level, we need a formal knowledge/concept representation that is able to bridge between different

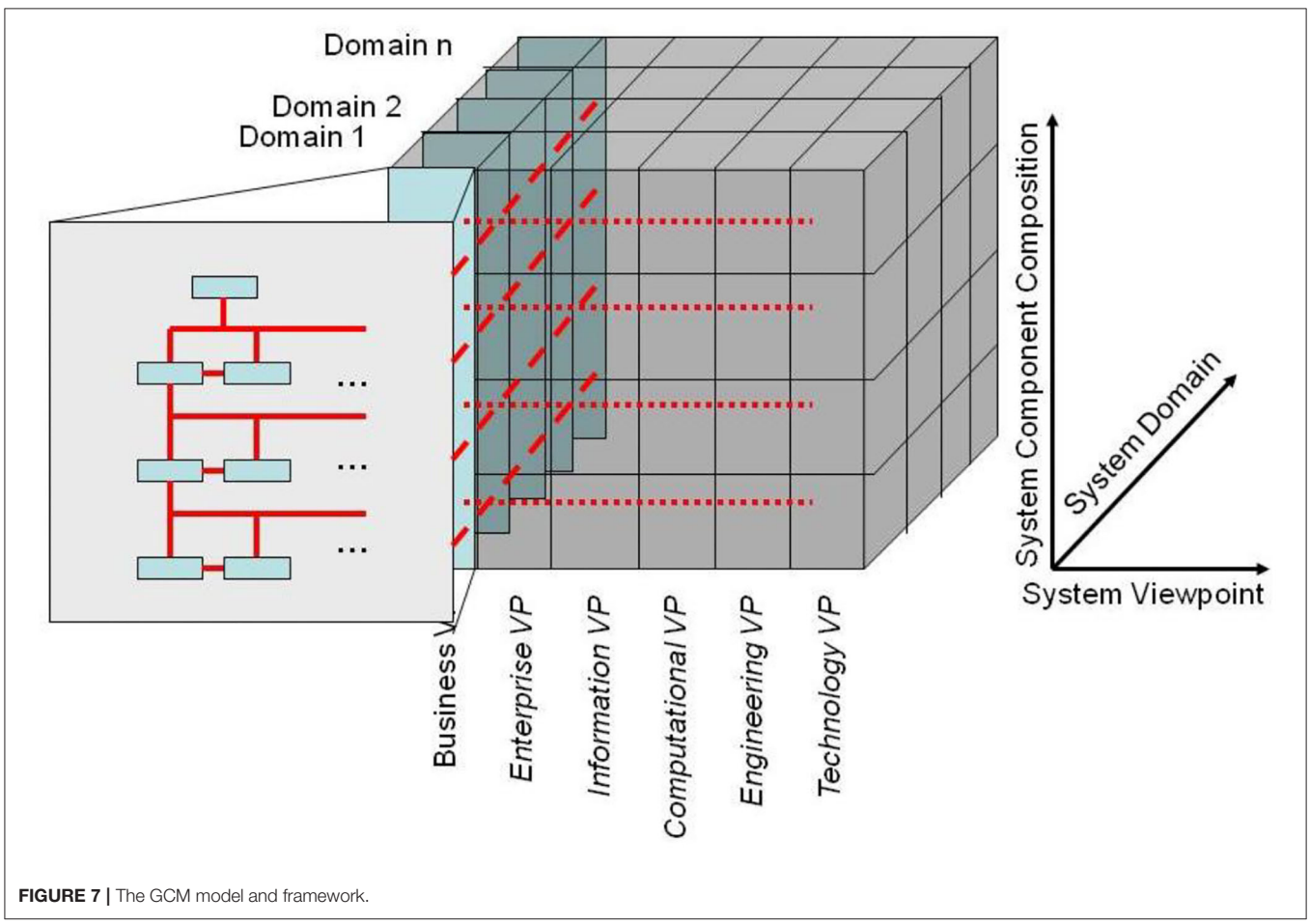

FIGURE 7 | The GCM model and framework.

domain-specific formal languages by uniformly representing concepts and relations of their elements. This can be done by generalizing the different ontological commitments required for those languages, i.e., the types of, and the relations between, things that the elements of the language represent (38). In model-based engineering, the Concept Representation Language has been developed to meet this challenge (38).

In the recent past, formal logic has moved from its traditional disciplines of philosophy and mathematics to disciplines, such as computer science, cognitive science, artificial intelligence, linguistics, and several more. 25 years ago already, we developed a similar approach, not limited to ICT systems but appropriate for multidisciplinary health ecosystems, using universal type theory, originally introduced in the early years of the last century (39), and universal logics to represent any system in the universe. In mathematics, logic, and computer science, a type system is a formal system in which every term has a "type" that defines its meaning and the operations that may be performed on it (40). The advantage of type theory vs. set theory is the type theory's property of a formal language and its computability. Furthermore, it allows for the representation of any system and the relationships of its components in just one notation layer similar to the object-oriented paradigm. Both representations of the body of mathematics can be transformed into each other (41). To compare and integrate type systems, Barendregt has specified the Barendregt Cube as the combination of eight important type systems presented in a uniform way (39). For adapting other practical type systems, allowing for the grouping of sets belonging, e.g., to one domain or subsystem, the Barendregt Cube has been advanced to the Barendregt Cube with parameters, presented in **Figure 4** (42).

The mathematical language of the Universal Type Theory and its representation by a Parameterized Barendregt Cube provides a proper solution for those challenges enabling to represent any formal language or informal language. To allow for the implementation of the system model for a given harmonization challenge, it might be required to go back to the most comprehensive description mode. However, for most of the scenarios, a simplified approach for representing the existing models and standards is sufficient.

For advanced interoperability of a complex, multi-disciplinary system with multiple actors performing at different skill levels, domain-specific components providing domain-specific perspectives on the system, represented using terms, concepts, and relationships of those ontologies of the domains must be structurally and functionally interlinked correctly according

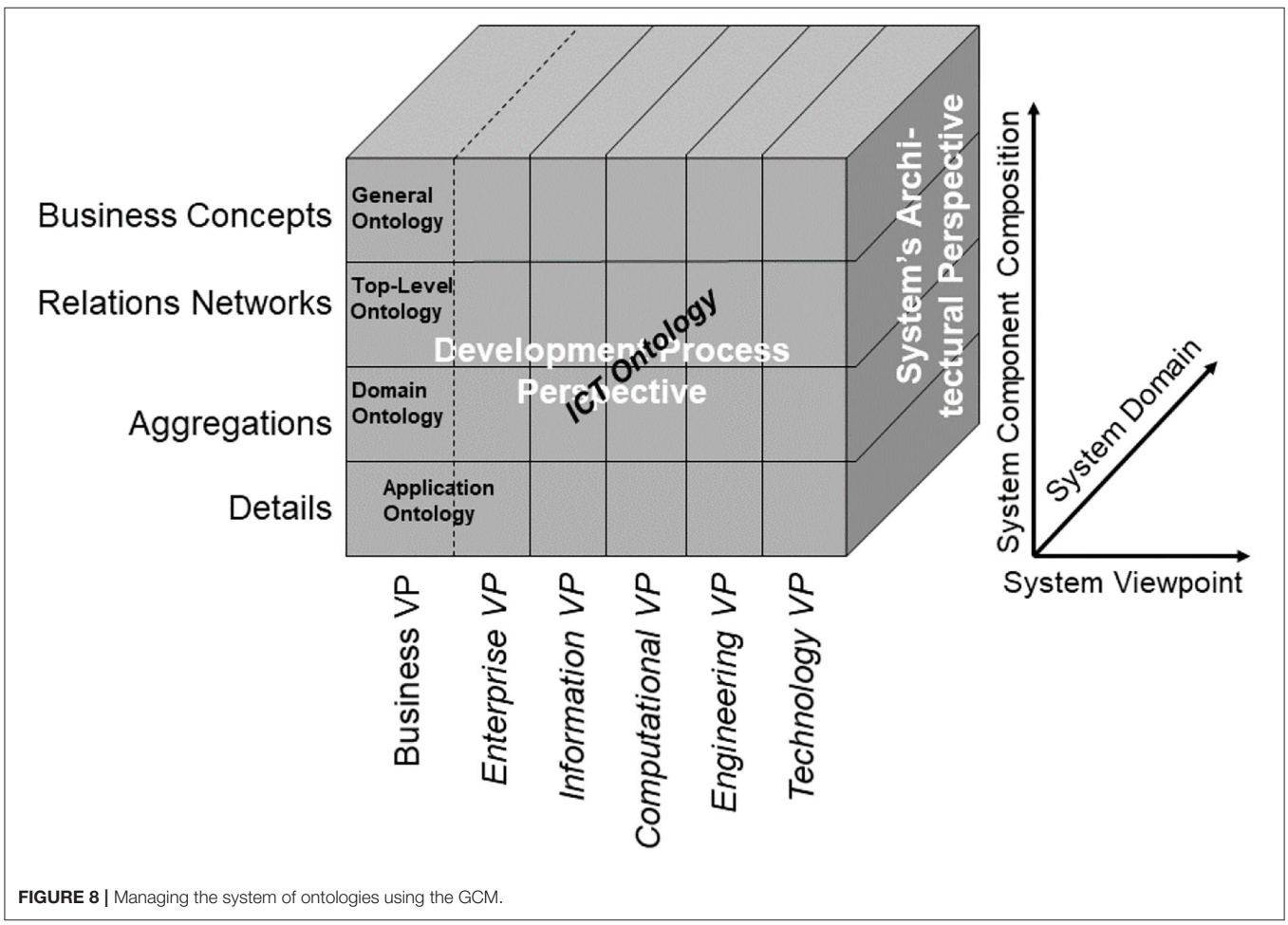

FIGURE 8 | Managing the system of ontologies using the GCM.

to the real-world system architecture. For that reason, an abstract and generic architectural model is needed that allows to represent any real-world system in any context, i.e., for any objectives, properties, perspectives, or interests bound to the considered business case and its processes. Furthermore, the definition and deployment of ontologies must be advanced through an architectural consideration of the real-world system represented to place and interrelate the ontological concepts correctly. This allows for the correct and consistent integration of different concepts of ontologies and avoids incorrect relations/equivalences of concepts provided by different domain ontologies for specific real-world elements (see also **Figure 7**). The same holds also for concept representations/models in the ICT viewpoints. As they lack contextual and implicit knowledge, simply mapping ICT concepts and models provided for different domains without considering the related granularity levels and specific contexts, unfortunately frequently practiced, is error-prone, can lead to wrong decisions and life-threatening actions.

According to ISO 21838 (43), a domain is a collection of entities of interest to a certain community or discipline. Consequently, a domain in our approach covers specific knowledge spaces, which could be the knowledge space of a discipline or the knowledge space of an individual actor/principal. The domain ontology of the latter is not a widely agreed one, but an individual ontology. The provided ontology harmonization enables meaningful communication between specialized health professionals, frequently talking, e.g., in Latin, and laymen, using street languages (44). Meanwhile, first steps for overcoming those limitations in the ontology ecosystem by enhancing it with an architectural framework have been performed (45–47). To meet the aforementioned challenge, the mathematical representation of the Barendregt Cube has been combined with the approach of the engineering discipline of systems theory. The advantage of a systems theory approach is due to the essence of systems engineering as follows: A system groups structurally and/or functionally interrelated components, which are separated from the environment by system boundaries. Systems can be recursively defined by composing (aggregating) them to super-systems or decomposing (specializing) them to sub-systems. As systems interact with their environment, sub-systems interact with each other and with the super-systems they belong to. The challenge is to represent the architecture of a system of systems structurally and functionally. For that purpose, domain-specific epistemological models must be generalized by transforming them into a universal knowledge representation (KR) notation, which has to be validated on the real-world system and thereafter adopted, if needed (37). Meanwhile, the approach is internationally acknowledged as ISO 23903:2021

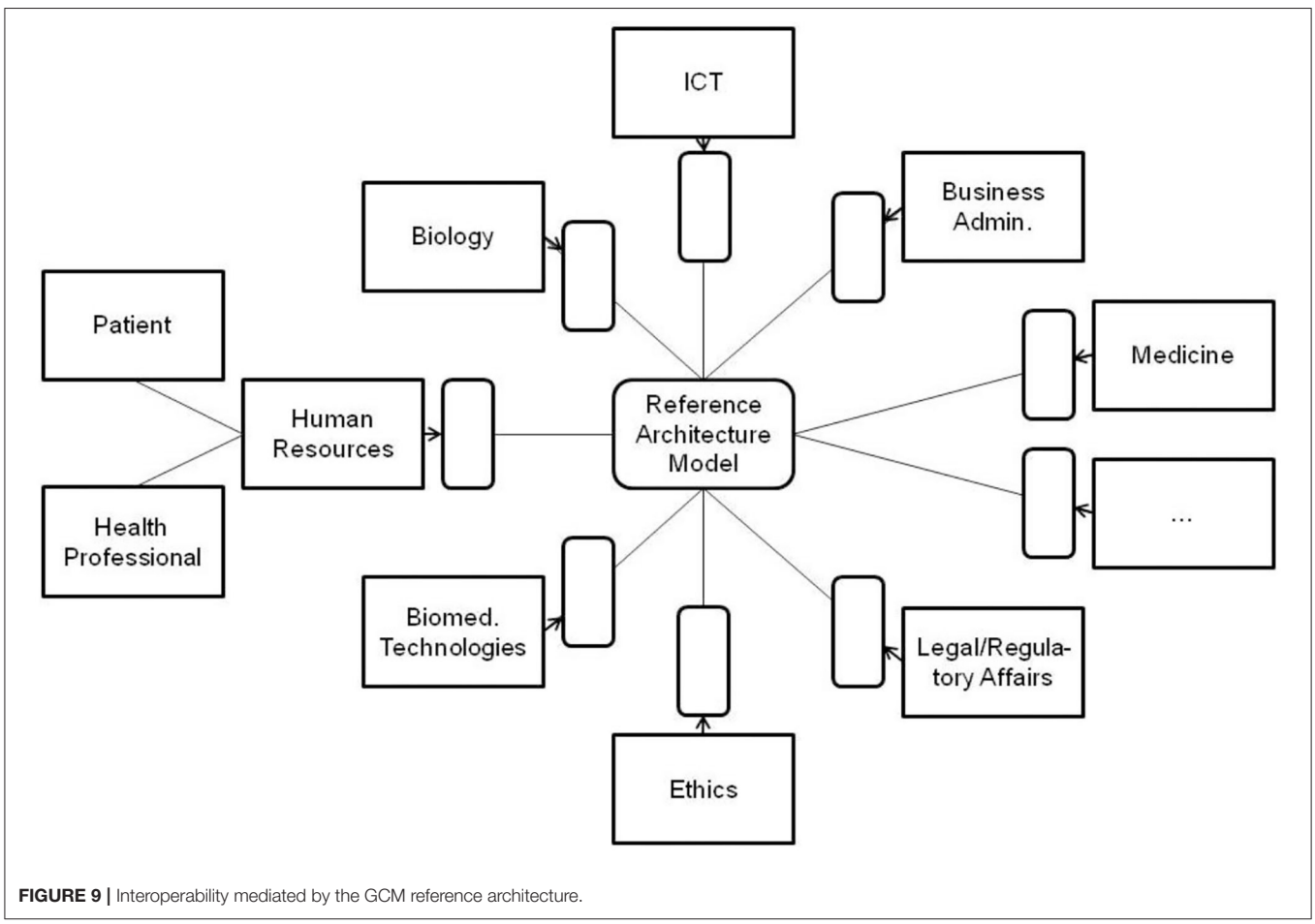

FIGURE 9 | Interoperability mediated by the GCM reference architecture.

"Interoperability and Integration Reference Architecture - Model and Framework" (48), standardizing the Generic Component Model (GCM) (49–53). It presents any real-world system using three dimensions (**Figure 5**):

a) the decomposition (composition) of the system in (of) its components (subcomponents), etc. (**Figure 6**);
b) the perspectives or the aspects of that system, represented by the domains addressing those perspectives/aspects, using the domain-specific ontologies (**Figure 6**);
c) the evolution of the system, in the context of digital health, the development process of implementing the system in an ICT environment following, but extending, the ISO 10746 ODP-RM (54) or the Rational Unified Process (55), respectively.

The GCM is a top-level architectural model and framework of a system of systems, formally describing the system components, their functions, and interrelations structurally and behaviorally, thereby representing specific aspects (domains) by related subsystems. For each business case, the subsystem components, their functions, and interrelations are instantiated by naming and representing them using the specific ontologies of the domains involved in that business case. For enabling this representation of a real-world system by its ICT-independent domain ontologies, the GCM provides a Business Viewpoint additionally to the five ODP-RM viewpoints. For the other viewpoints, ISO 10746 defines ICT-specific languages and representation styles, such as Business Process Modeling Language (BPML) and Business Process Modeling Notation (BPMN) (56), the Unified Modeling Language UML (57), or programming languages. For healthcare-specific aspects, healthcare-specific ICT ontologies standardized in ISO 13606 (58), ISO 12967 (59), ISO 13940 (60), openEHR Archetypes (61), ISO 13972 (62) or the outcome of the HL7® Clinical Information Modeling Initiative (CIMI) (63), and also implementable specifications following the HL7® RIM ontology (64), such as HL7®V3 (65), and nowadays HL7® FHIR® resources (66, 67) are widely deployed.

As we can consistently model and compute only systems of reasonable complexity, the system analysis or design has to address partial systems when considering higher granularity levels of the system in question. The architectural dimension of system component composition/decomposition, combined with the recursivity of the approach, allows for describing the continuum of systems from elementary particles to the universe in a generalized and standardized way. By considering just that detail of the continuum needed for managing the business objectives, like an amplifier glass magnifies just that part of the continuum the glass focuses on, so that the aforementioned complexity problem is overcome. At all levels of the complexity of

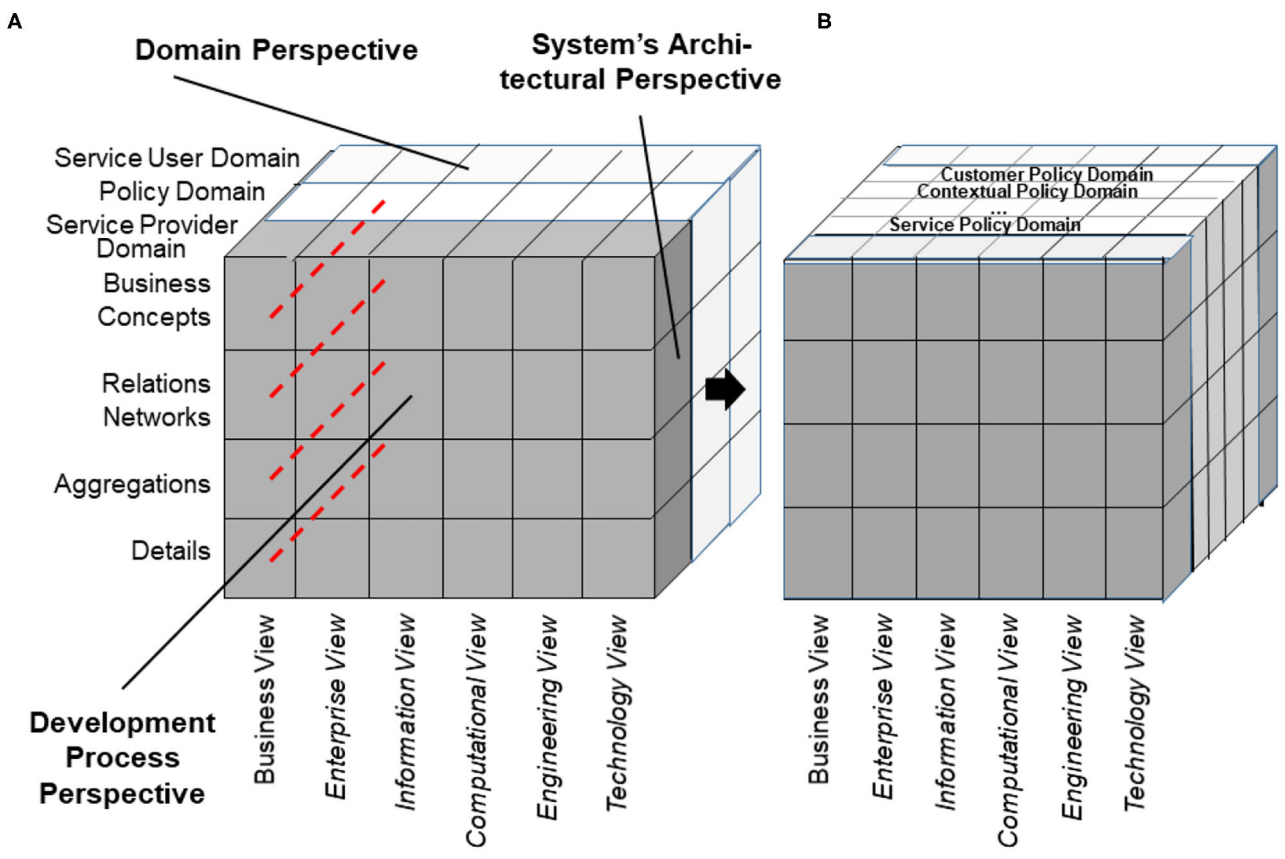

FIGURE 10 | Architectural representation of the policy domain **(A)** and its specializations **(B)**.

the system, the GCM defines the same generic granularity levels: business concepts, relations networks, aggregations, and details (**Figure 6**). The business concepts represent the conceptual domains of the system involved in the business case. The relations networks represent the subdomains within each domain. The aggregations level represents the services and concepts within a subdomain. The details describe the actions/tasks making up the services.

In the Business Viewpoint, the GCM domains are represented by the use of domain-specific ontologies. However, in order to ensure that all domain specific ontologies are consistently organized and as far as possible are future proof, they all need to be derived from an over-arching domain-neutral ontology representing the architecture of a real-world system in question from an abstract system-theoretical perspective. In that way, the domain-specific ontologies representing the domain-specific aspects of the system can be correctly and consistently integrated (mapped, matched), nevertheless reflecting all the domain-specific knowledge available. The resulting model can be easily transformed into corresponding ICT concepts.

The GCM (or ISO 23903) framework describes how to use the GCM in interoperability and integration settings. For properly representing the structure and behavior of the system, only components at the same granularity level can be interrelated, thereby reflecting the constraints ruling the interrelations of the components within (System Component Composition/Decomposition Dimension) and between the involved domains (System Domain Dimension) (as shown in **Figure 7**). For mapping components at different architectural granularity levels, they must be generalized or specialized first to comply with the mandatory framework. The same holds also for the systems development process through different viewpoints.

As demonstrated, the GCM can also be used to advance basic sciences, such as the development and engineering of domain-specific ontologies and their relations to other concept representations. As aforementioned generic ontology, a top-level ontology according to ISO/IEC 21838, following the Basic Formal Ontology (BFO) from the Open Biological and Biomedical Ontology (OBO) Foundry, should be deployed (43). **Figure 8** presents the system of ontologies deploying the GCM.

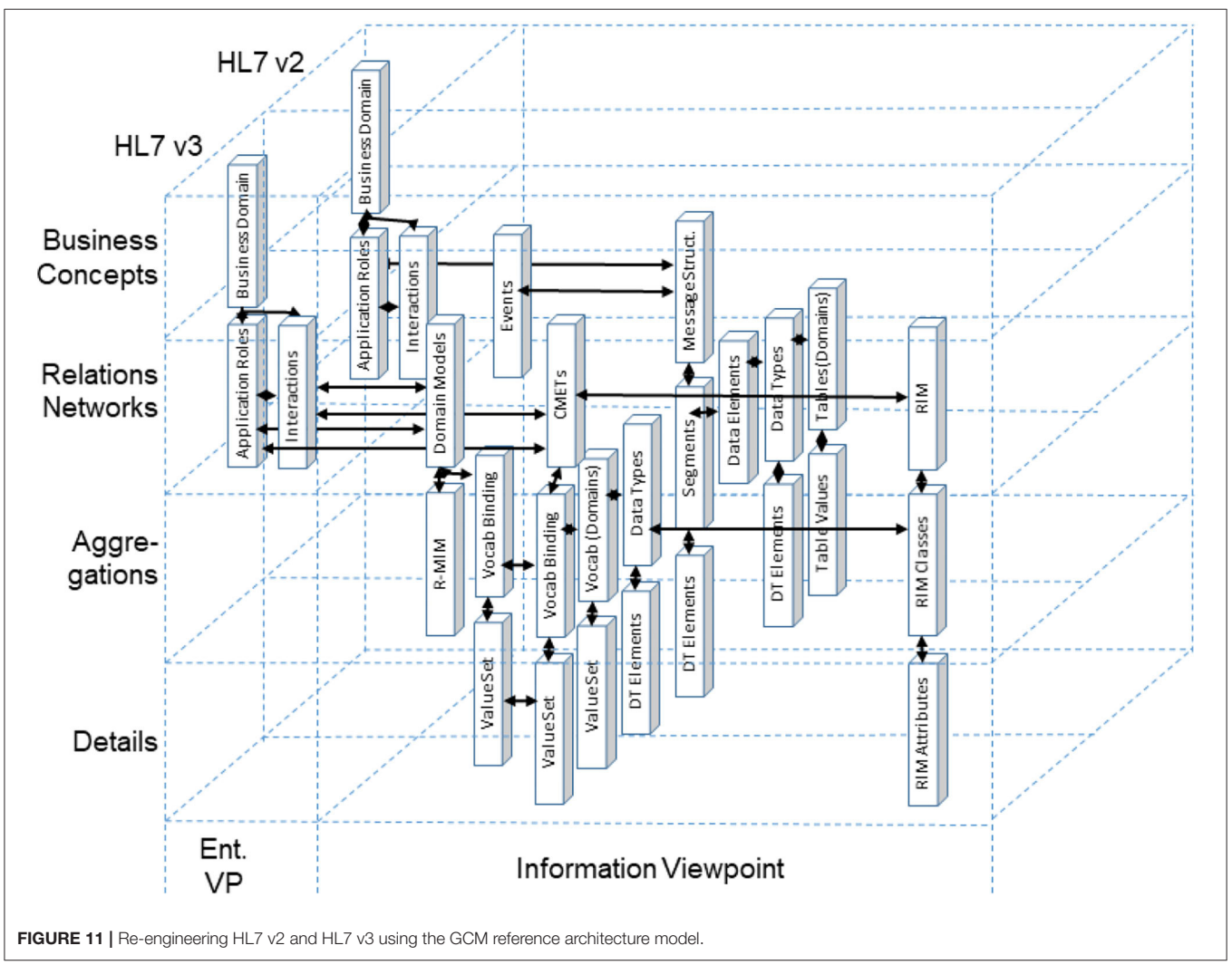

FIGURE 11 | Re-engineering HL7 v2 and HL7 v3 using the GCM reference architecture model.

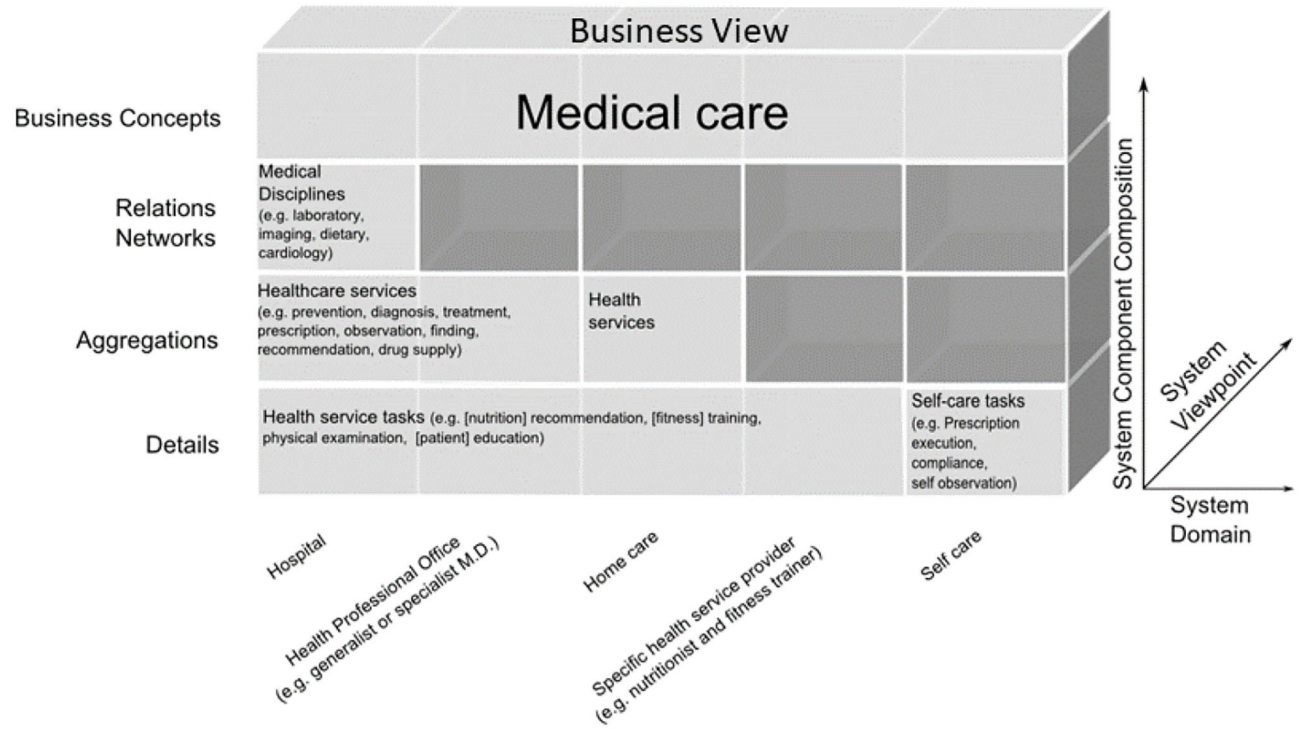

FIGURE 12 | T2D domains in the GCM business view representation (67).

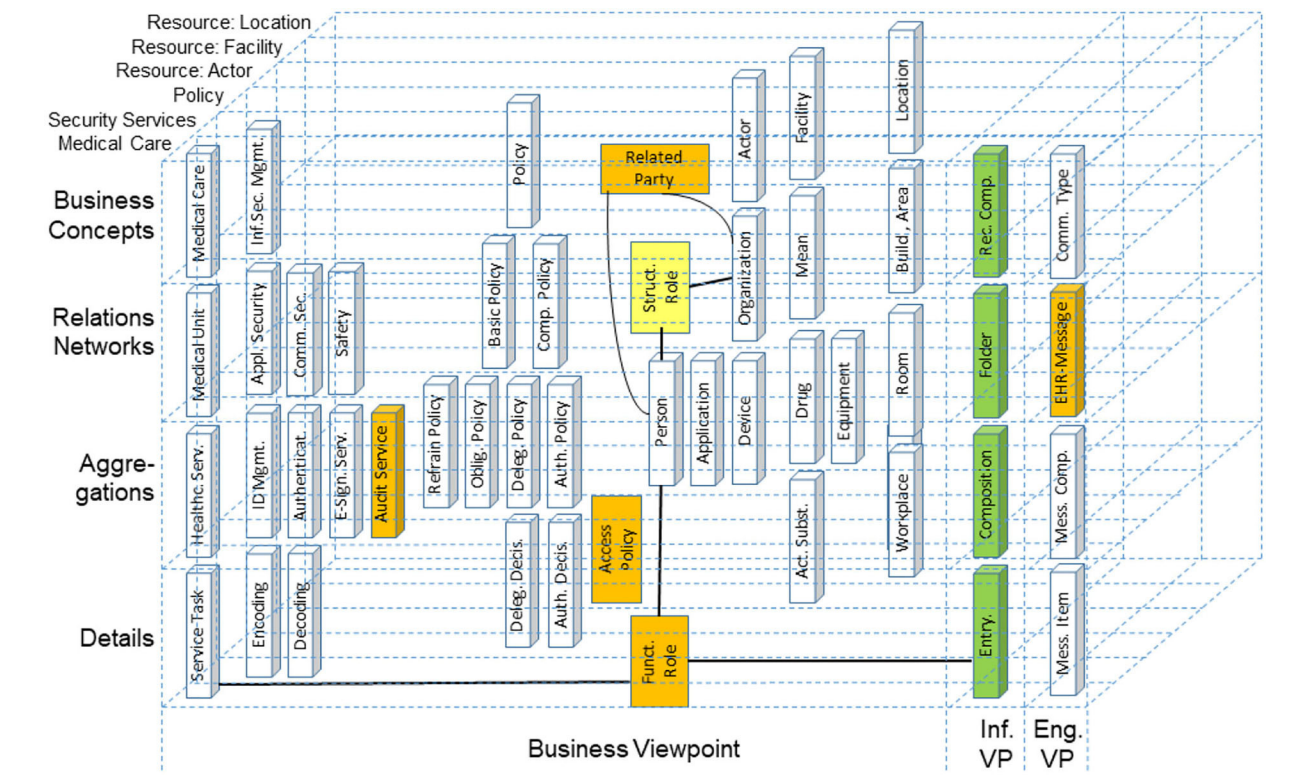

FIGURE 13 | Reengineering the ISO 13606-1 reference model in the context of the HL7® composite security and privacy domain analysis model.

INTEROPERABILITY AND INTEGRATION IN ECOSYSTEMS MEDIATED BY THE GCM REFERENCE ARCHITECTURE

The solution for meeting the described business objectives and challenges of the emerging health services paradigms and overcoming the aforementioned problems is the definition of a formally represented, system-oriented, ontology-based, policy-driven reference architecture model, and framework any component or domain-specific subsystem can adapt to. Such an approach allows for mapping different knowledge spaces, different representation styles, different maturity levels, etc., thus providing not only interoperability between and integration of different domains including different individual skills levels, but also different specifications without prior revision, thereby clearly qualifying it against solely ICT-level interoperability and integration efforts. This way, it can design and manage collaboration and cooperation of multidisciplinary systems including living and non-living principals. For solving ICT interoperability challenges, standard data interfaces or application programming interfaces (API) have been specified and implemented. While this approach was defining the structure and semantics of data to be exchanged between independently developed applications, in our solution, the structure and behavior of a system and its representation have to be specified. As the data and related applications in the information exchange paradigm remained unchanged, the existing models and standards remain unchanged in the interoperability and

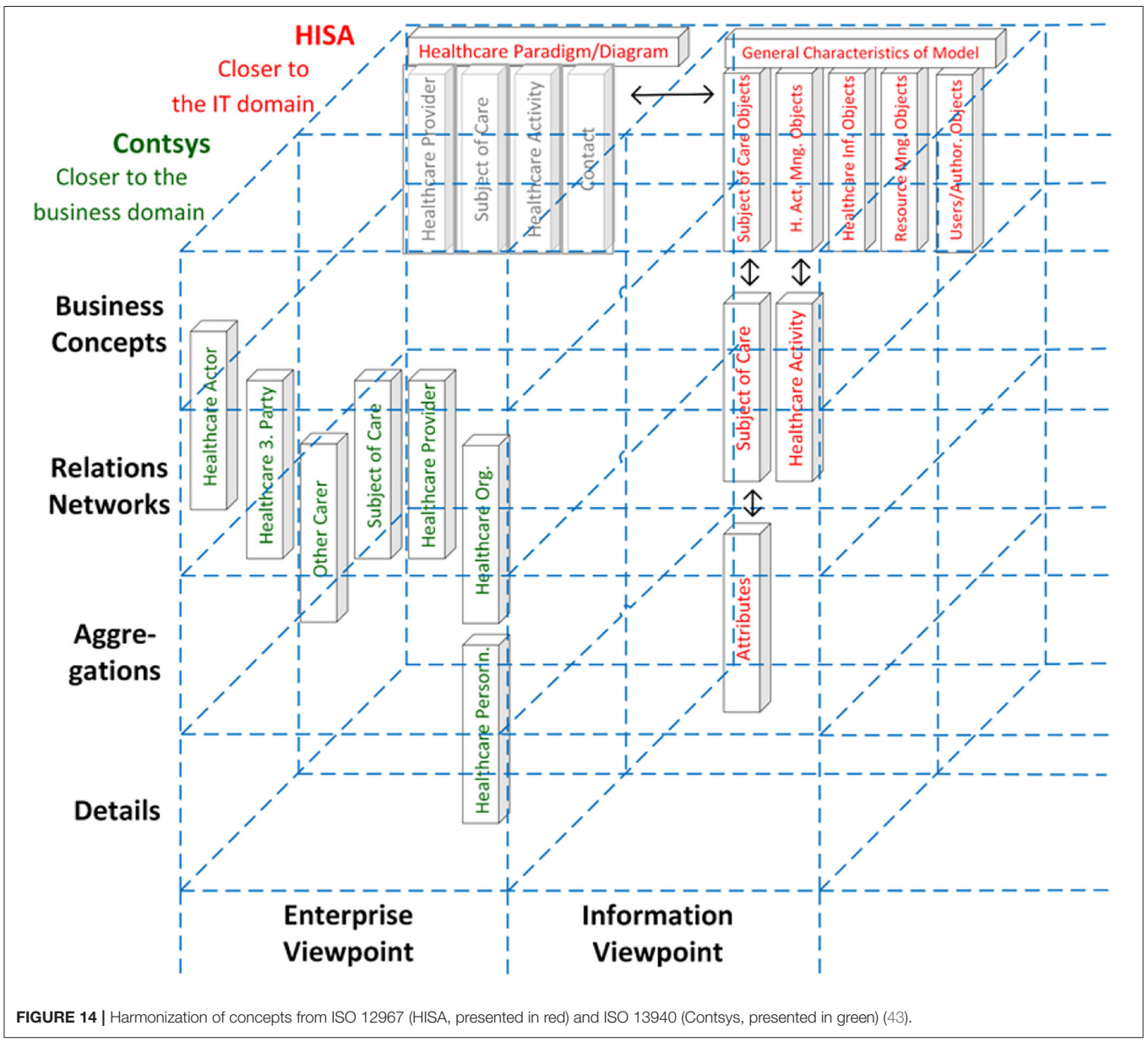

FIGURE 14 | Harmonization of concepts from ISO 12967 (HISA, presented in red) and ISO 13940 (Contsys, presented in green) (43).

integration approach of the comprehensive systems as well. The domain-specific subsystems to be integrated have just to be re-engineered once by correctly placing, representing, and interrelating their components in the GCM model according to the GCM framework to allow for interoperability- and integration-enabling harmonization (**Figure 9**) (48).

Thereby, constraining relationships have to be defined in a formalized way when not yet specified in the underlying ontologies deployed. For specific-use cases and specific models, it might be necessary that the model to be integrated must be refined to represent all the required GCM components.

A special domain is the policy domain, ruling and constraining the relations between the subsystems, thereby controlling the behavior of the system and also impacting its acceptance and usability. According to ISO 22600:2014 (68), a policy is a set of legal, political, organizational, functional, and technical obligations for communication and cooperation. The policy domain must be refined into policy-subdomains deploying specific ontologies. Among others, not only the individual's expectations and wishes (customer/user policy domain), security, privacy, trustworthiness, but also the ethical and legal concept spaces (contextual policy domain), and procedural requirements, such as the best medical practices (service policy domain), have to be mentioned here (**Figure 10**).

PRACTICAL DEPLOYMENT OF THE GCM MODEL AND FRAMEWORK

The GCM model and framework according to ISO 23903 has been widely implemented to enable interoperability between, and integration of, models, standards and solutions mainly in the health and social care domain. Some examples are shortly introduced as follows.

Based on the higher-level protocol specification of the University of California at San Francisco (UCSF), the globally most important data exchange standard in health settings, referring to Level 7 of the ISO/OSI protocol, is the Health Level 7 (HL7) standard HL7 v1, released in 1987 in the USA for testing, followed by HL7 v2.x for production in 1990 (64). Both standards define *ad hoc* specifications of data elements, data types, and messages implemented to exchange administrative, financial, and clinical information in the form of text messages. The *ad hoc* approach was advanced to the conceptual, model-driven approach of HL7 V3 with its HL7 V3 Development Framework (HDF) and its health information ontology defined in the HL7 Reference Information Model (RIM), standardized in ISO/HL7 21731 (63). For easing or even enabling the integration, both still applied specifications have to be architecturally and conceptually re-engineered, as demonstrated in **Figure 11** (69–71).

Another example is the automated development of interoperable Web services for Type 2 Diabetes (T2D) Care Settings including primary, secondary, and tertiary care, home care and self-engagement, dieticians, etc., based on the standardized approach (72–75) (**Figure 12**).

Many standards are dedicated to a specific topic or subdomain, such as technical specifications (devices, components) or specific technologies. Healthcare is by nature, interdisciplinary. This especially counts not only for security and privacy issues considering legal, social, ethical, and procedural issues, but also for individual perceptions, wishes, and expectations. Therefore, the GCM approach was first deployed in security and privacy standards for health, such as ISO 22600, ISO 21298 (76), or the HL7® Composite

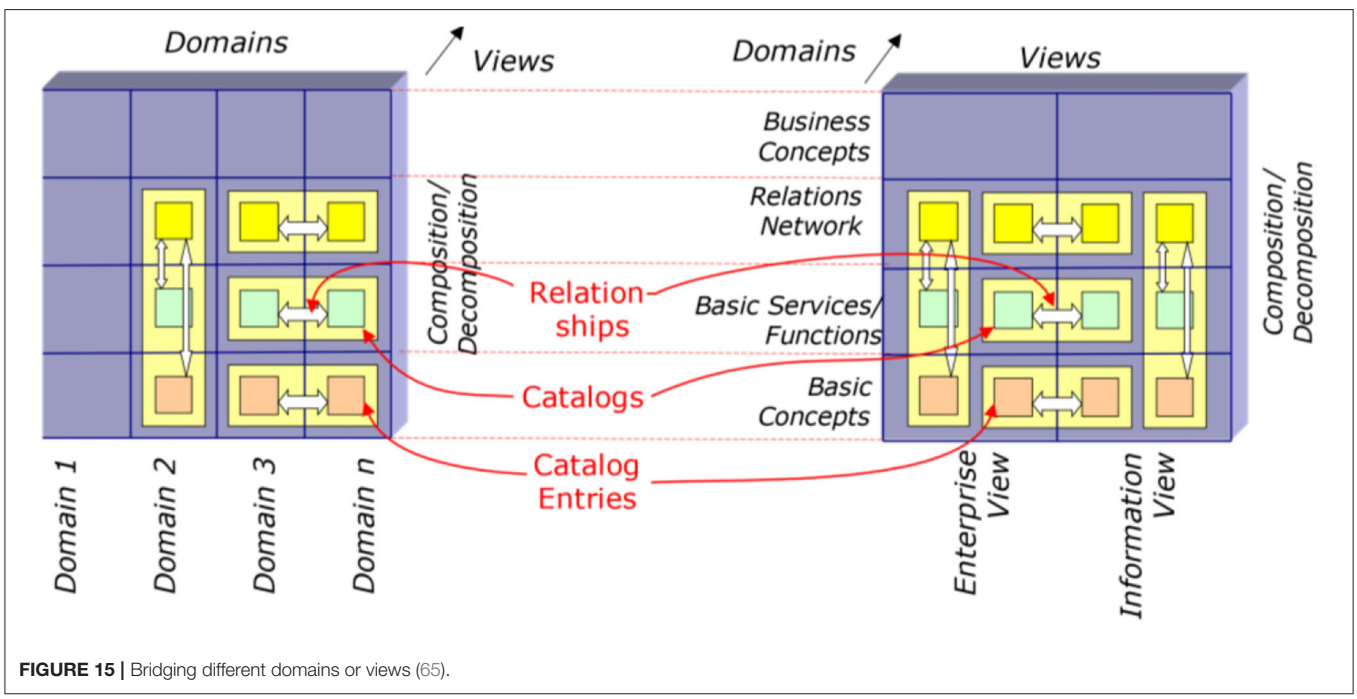

FIGURE 15 | Bridging different domains or views (65).

Security and Privacy Domain Analysis Model (77), recently replaced by the HL7/ANSI Security and Privacy Logical Data Model (78), and also in standards integrating security and privacy aspects in their solution, such as ISO 13606 (**Figure 13**).

The turn to transformed health and social care ecosystems and related standards increasingly required integrating work products from different Standards Developing Organizations (SDOs). This fact on the one side and the establishment of ISO 23903 on the other side resulted in the inclusion of the GCM model and framework in most of the ISO/TC 215 Health Informatics standards addressing more than one sub-domain for meeting their challenges. The latter is exemplified with the harmonization of concepts from ISO 12967 (HISA) and ISO 13940 (Contsys) (**Figure 14**).

An example of using the GCM for ontology management to ensure semantic interoperability between different EHR systems is demonstrated in the study by Adel et al. (79).

PRACTICAL USE OF THE GCM MODEL AND FRAMEWORK IN THE INFORMATION MODELING PROCESS

Figure 11 exemplifies the different information objects that are used within two example communication standards. According to the methodology provided by the GCM framework, relationships can only be established either horizontally or vertically, but not in a diagonal direction (**Figure 15**).

Following the GCM framework, we can only instantiate a GCM architecture for domains and components contributing to the considered business system use case. Therefore, we can only interrelate model or specification components that have a dedicated and semantically clear relationship. For communication standards, this mechanism can be used to map them as ICT ontology to an application domain (ontology), and therefore bridge them accordingly. Of course, because of the diverse semantics of the objects, this cannot be done directly but with the help of a mediator domain. In **Figure 16**, ACGT, the Advancing Clinico-Genomic Clinical Trials on Cancer Master Ontology is used for this purpose (71), but other application domain ontologies would work as well.

From a practical perspective, information modeling starts with platform-independent domain-specific information models, ideally facilitating BPMN or other formal languages, which are supported by graphical representations (tools) to help with an understanding by domain specialists. In a second step, such a model can be converted into an ontology-based representation form that allows for computational support to check consistency or completeness. Once that is in place, a correct bridging, either manually or semi-supported by tools, can start.

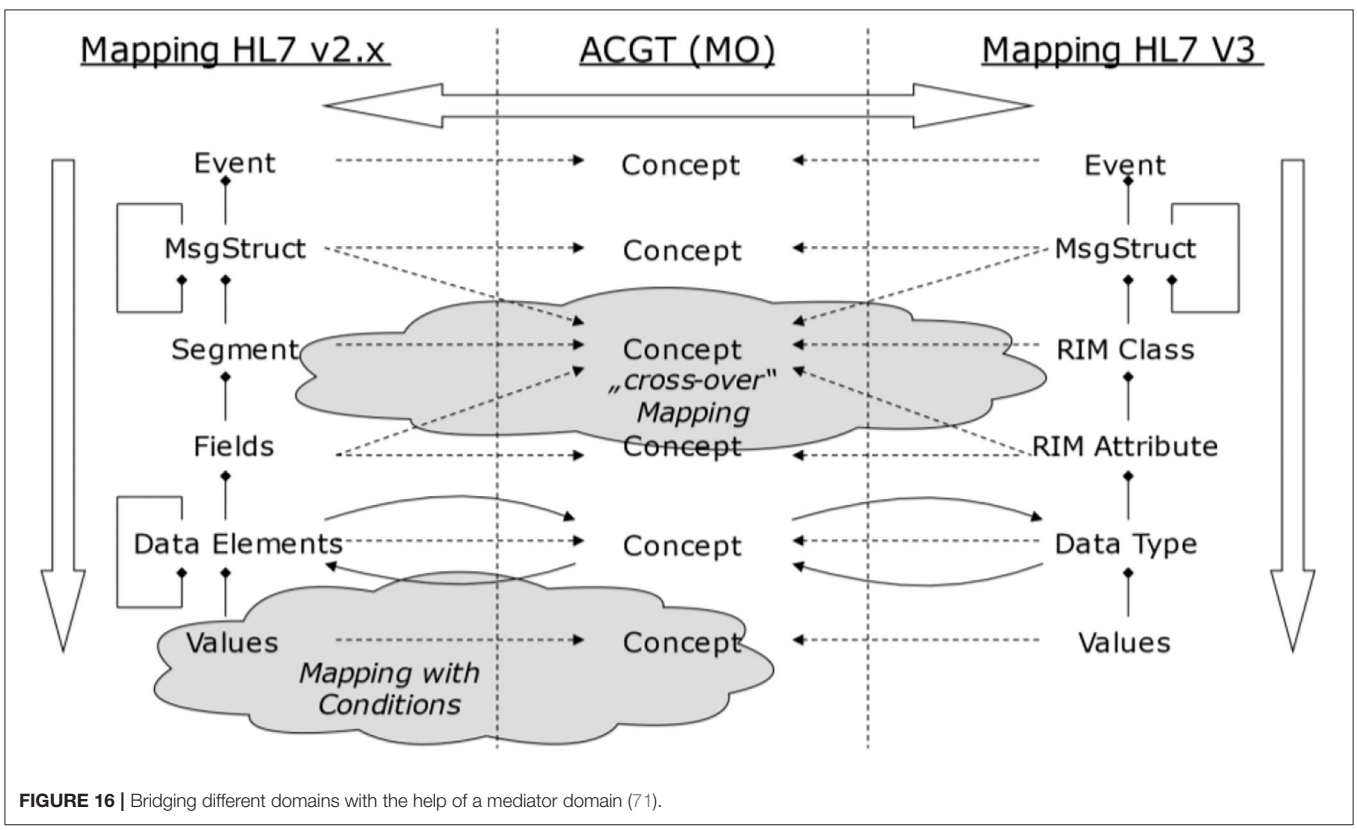

FIGURE 16 | Bridging different domains with the help of a mediator domain (71).

TABLE 4 | Comparing data model levels, dimensions of modeling, data model at different information level, and the ISO interoperability and integration reference architecture model, applied to specification examples (22).

Data model level	Dimen-sion of modeling	Data models at different information levels	Modeling actors	Model scope	ISO 23903 interop. & integration RA		Examples
Very-high-level data model	Know-ledge space	External	Business domains stakeholders	Scope, requirements and related basic concepts of business case	Business View		ISO 23903 Interoperability and Integration Reference Architecture
High-level data model	Know-ledge	Conceptual	Business domains stakeholders	Relevant information and representation & relationships of basic concepts	Enterprise View	DCM, CSO	
							ISO 10746 ODP-RM
Logical data model	Information	Logical	Data modelers and analysts	Layout & types of data and object relationships	Infor-mation View	HL7 V3 (CMETs), HL7 CIMI, openEHR Arche-types, FHIM	
					Compu-tational View	HL7 FHIR	
Physical data model	Data	Physical	Data modelers and developers	Implementation-related and platform-specific aspects	Engineer-ing View		

An important aspect is an alignment with a formal ontology like BFO. This ensures that wrong mappings can be detected by reasoners. For example, a mapping from an event to observation can be brought forward for manual inspection. Completeness, a second aspect, can be verified in this way as well.

Table 4 compares the different modeling paradigms.

DISCUSSION AND CONCLUSION

Collaboration is a challenge to meeting business objectives, and interoperability is a vital capability to achieving such collaboration. Therefore, it is not first a matter of the ICT domain, but one of the user domain. Interoperability requires sharing of knowledge and skills, which should be built on a hierarchical system of ontologies. Multi-disciplinary interoperability solutions interrelating life sciences, natural sciences, technology, legal and social sciences, etc., require an architecture-centric systems approach to the domains of discourse represented by their ontologies, thus enabling the formalization of representation and integration of the systems including correct ontology mapping. Based on the mathematical representation of the universe using the Universal Type Theory in combination with system-theoretical approaches, the GCM has been developed in the nineties and evolved to a reference architecture model. It not only allows for harmonizing/mapping of models and standards without requiring their revision or change, but also helps in understanding how, where, and why diverse specifications are different, or what their advantages/disadvantages are. So, not only just different specifications but also different versions of one specific specification or standard can be mapped. The approach enables both the analysis and design of complex, multi-disciplinary (multi-domain) systems, thereby meeting the challenges of advanced organizational, methodological, and technological paradigms for health and social services delivery (80).

The system-oriented, architecture-centric, ontology-based, policy-driven approach to transforming health and social care ecosystems integrates different domains and communities, thereby bridging the gap between different languages, representation styles, and skills. Therefore, the solution is foundational for managing our increasingly complex and dynamic reality, possibly helping to stop endless and fruitless discussions about why one specification should be preferred above the other. The approach presented in this paper, has been exemplified for health and social care, but can naturally be deployed in any other domains.

The aforementioned technologies and domain challenges will be addressed in specific papers in this volume, dedicated to those aspects.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

BB planned and designed the paper and authored its major part. FO authored the section "Practical Use of the GCM Model and Framework in the Information Modeling Process". All authors contributed to the article and approved the submitted version.

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Transformed Health Ecosystems—Challenges for Security, Privacy, and Trust

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A transformed health ecosystem is a multi-stakeholder coalition that collects, stores, and shares personal health information (PHI) for different purposes, such as for personalized care, prevention, health prediction, precise medicine, personal health management, and public health purposes. Those services are data driven, and a lot of PHI is needed not only from received care and treatments, but also from a person's normal life. Collecting, processing, storing, and sharing of the huge amount of sensitive PHI in the ecosystem cause many security, privacy, and trust challenges to be solved. The authors have studied those challenges from different perspectives using existing literature and found that current security and privacy solutions are insufficient, and for the user it is difficult to know whom to trust, and how much. Furthermore, in today's widely used privacy approaches, such as privacy as choice or control and belief or perception based trust does not work in digital health ecosystems. The authors state that it is necessary to redefine the way privacy and trust are understood in health, to develop new legislation to support new privacy and approaches, and to force the stakeholders of the health ecosystem to make their privacy and trust practices and features of their information systems available. The authors have also studied some candidate solutions for security, privacy, and trust to be used in future health ecosystems.

Keywords: ecosystem, security, privacy, trust, personal health information

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INTRODUCTION

The ongoing health transformation aims not only at better understanding the causes of diseases and how drugs function inside the human body, but also at offering high quality health services for all at a lower level of cost. Thereby, innovative technologies and methodologies are deployed, such as digitalization, new mathematical tools for advanced modeling, artificial intelligence (AI), and machine learning (ML). In that context, a wide spectrum of personal health information (PHI) is collected that exceeds many times the content of current electronic health record (EHR).

The intended outcome is the transformation of health and social care toward personalized, preventive, predictive, participatory, and precision medicine (5P Medicine) (1, 2). Other terms and definitions describing this development include Digital health, eHealth, and pHealth. All of them have many definitions. Digital health is an umbrella term covering concepts, such as mobile health (mHealth), health information technology, wearable devices, telehealth and telemedicine, and personalized medicine (3). It refers to the use of information and communications technologies (ICTs) in medicine and other health-related domains to manage illnesses and health risks, and to promote wellness (4). According to the WHO, eHealth transfers and exchanges health information between stakeholders and provides digitalized health services to support the delivery of health and the management of health systems (5). Moss et al. defined that "eHealth, or electronic health, refers to healthcare services provided with the support of information and communication technology" (6), and according to Eysenbach "e-health is an emerging field in the intersection of medical informatics, public health and business, referring to health services and information delivered or enhanced through the Internet and related technologies" (7). In this article the definition of Moss et al. is used. The core point in pHealth is personalized health. Ruotsalainen et al. have pointed that the pHealth user can be a patient, a customer, or a person managing own health/wellness, and pHealth collects a wide spectrum of PHI using sensors, and monitoring systems, and process that data using software applications and algorithms (2). pHealth services typically help a person to manage his/her own health, wellness, and lifestyle. Digital health, 5P Medicine, eHealth and pHealth, and mobile health have in common that they all are data-driven approaches. According to the National Institutes of Health (NIH), mobile health (mHealth) is "the use of mobile and wireless devices (cell phones, tablets, etc.) to improve health outcomes, health care services, and health research" (8).

The services of 5P medicine not only need data about care, treatments, and medication stored in the EHR, but also a wide spectrum of PHI, such as epigenetic data, personal health history, personally generated health information, the history of person's health-related behaviors, and person's individual characteristics. Personalized medicine refers to an approach that considers the patient's genetic features and his/her preferences, beliefs, attitudes, and knowledge in social context (9). According to Prosperi et al., precision medicine is the "approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person" (10). Gorini et al. presented an even wider approach called 5P eHealth (11). In it, a patient is characterized not only as a biological and genetic entity, but also as a person with specific needs and values, habits and behaviors, hopes and fears, beliefs, personality, cognitive dispositions, health beliefs, social support networks, education, socioeconomic status, health literacy, and all the other life conditions and events (i.e., persons' psychological characteristics). This means that the 5P eHealth creates the person's full psychocognitive profile (11).

To be successful, 5P approaches require PHI not only in the context of healthcare services delivery, but also before it, i.e., when we are "healthy." This kind of PHI does not exist in any today's EHR. Instead, it is necessary to collect PHI from many sources such as social media, Web browsers, personal health devices, and home care services (**Figure 1**). The combination of all those collected health data forms a "Virtual PHI" repository. This indicates a paradigm change, as the regulated EHR is not anymore in the center of the health ecosystem.

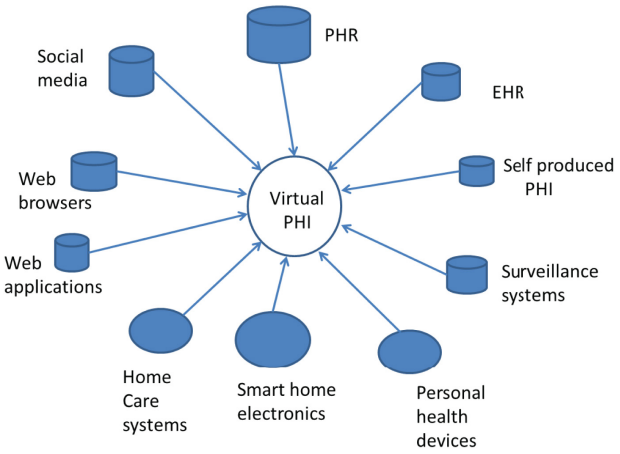

FIGURE 1 | Typical sources of the personal health information (PHI).

There is a big variety of sources of PHI, such as mobile phones, social networks, e-commerce applications, but also personal computer pedometers, smart health watches, smart wearables, and a smart toilet (12–14). Health and behavioral tracking takes increasingly place in public spaces, in cars, and in our work places (15). The collection of PHI using sensor technology is not limited to heart rate, body temperature, sleep patterns, or keyboard touching style. Even our emotions and behaviors can be monitored (16). Often, e-commerce services, surveillance systems, and commercial health applications collect, use, and store user related PHI, and monetize it.

Currently, eHealth, pHealth, and 5P medicine services are seldom stand-a-lone or end-to-end services. Instead, the ecosystems and the platform model are widely used. According to Iyawa et al., a digital ecosystem is "a network of digital communities consisting of interconnected, interrelated and interdependent digital species, including stakeholders, institutions, and digital devices situated in a digital environment, which interact as a functional unit and are linked together through actions, information and transaction flows" (17). The ecosystem metaphor requires that all stakeholders have a common goal, but in health ecosystems, this is not always clear. A precision medicine ecosystem links patients, providers, clinical laboratories, and researchers together for better care. An eHealth ecosystem adds government in the role of sponsor and regulator, and industry aiming at developing and selling medicine products (9). A platform is an ICT technical intermediate service that creates value for, and enables interaction between, customers and service providers. The platform operator orchestrates the services and communication between stakeholders in the ecosystem.

Currently, a typical platform is Web-services in a Cloud. Vimarlund and Mettler have defined the eHealth ecosystem as a two-sided health service market platform that combines service consumers (persons or patients) and service providers, enabling them to profit from interactions by finding each other's, and to reduce costs (18). Service examples include health portals, education, and self-care services.

Ecosystems built over platforms, clouds, and the Internet are widely used and, from economical, functional, and usability viewpoints, they can be successful in building blocks for pHealth, eHealth, and 5P services. Ecosystems can easily integrate stakeholders, such as service providers and service users and distributed information, which all can be located in different jurisdictional domains. Unfortunately, the architectural, functional, and technological features of ecosystems, especially when the large amount of sensitive PHI is communicated, processed, and stored, generate also meaningful security, privacy, and trust challenges. Some researchers have stated that in current digital information systems, it is almost impossible for the user to maintain privacy, today's security solutions are ineffective, privacy is an illusion, and trust is only a belief (19–22).

From data subjects' point of view, this kind of situation is unacceptable. It seems necessary to rethink the way privacy should be understood, what is its role in future information systems enabling 5P Medicine, eHealth, pHealth, and mHealth services can be, and how privacy can be implemented. In this paper, the authors study security, information privacy, and trust challenges existing in ecosystems supporting pHealth, eHealth, mHealth, and 5P services. Some answers to these problems will be presented in the next chapters.

PRIVACY, SECURITY, AND TRUST AS CONCEPTS

Security is a well-defined and standardized concept. According to the International Organisation for Standardisation (ISO), security implies the preservation of confidentiality, integrity, and availability of information (also authenticity, accountability, and reliability can be included) (23). Confidentiality is the property that information is not made available or disclosed to unauthorized individuals, entities, or processes, and data availability is the property that data are accessible and usable upon demand by an authorized entity.

Information privacy (aka privacy) and trust are fuzzy concepts with many definitions. At general level, privacy is a human right. Information privacy addresses the question what we like others or other information systems to know about us. Most common privacy approaches are privacy as right and ability to control (make choices), privacy as legal construct, privacy as contextual integrity, and finally risk based privacy (24, 25). Privacy is often understood as the exclusion of others. The control approach to privacy is linked to the self-determination and freedom to hide personal secrets, but also freedom from surveillance and tracking (25). The notice-and-choice-model for privacy (consent) is widely used in the European Union (EU) and the United States. It is based on the idea that data collectors have (moral or legal) responsibility to inform data subjects (DS) which data are collected (25) and how these are used, and that the DS can make rational and information-based decisions concerning which data they are willing to disclose, and to whom. Similarly, privacy as risk approach expects that the DS has the ability to make realistic risk assessment and then calculate expected benefits against the possible negative impacts of the data disclosure. Nissenbaum's privacy as contextual integrity approach is based on the assumption that every context (e.g., healthcare domain) can have own contextual privacy rules which regulate the information flow inside the context and with other contexts (26). It presents a social theory of privacy by representing privacy rules as a common agreement and not as a personal right. A common misconception is to understand privacy as confidentiality (i.e., security). Confidentiality means that a data controller or processor has responsibility to guarantee that only authorized persons or entities can access data. In the privacy as right approach, the DS has right to define own personal rules (policies) regulating the processing of PHI. Privacy is also a legal construct in many countries. According to Sokolovska, specific laws protecting information privacy exist in 120 counties (27). In the EU, the General Data Protection Regulation (GDPR) offers to the data subjects (the EU-citizen) some rights to control the processing of personal information.

Behavioral privacy is a quite new concept. It is derived from the fact that service user's online behaviors (e.g., lifestyle patterns) are increasingly sensed and recorded using sensors, surveillance systems, and computer browsers to predict the behavior of consumers, employees, and citizens (28). Using data mining and analytics, businesses organizations and governments are able to create detailed profiles of persons and use it in predictive analysis. Tracking people's movements online is an invasion of privacy. Online behavioral tracking is even more serious because people are not aware who is tracking them, why, and how collected information will be used (29).

Trust is a social norm (25), which acts as the glue making our society function. Trust does not exist only between persons, but also between a human and organizations, computers, and technology. The way trust is understood is culture and context dependent. Human trust is also a personal trait. General trust is based on belief or disposition, i.e., it is a tendency to trust others without proof. There are many other approaches to trust, such as perceived trust, subjective probability-based trust, trust as risk, and willingness to trust (30). Our perception, previous experiences, other's opinions, and proposals impact the trust formulation that is both a cognitive and an affective process inside our brain. Trust is also transformative: if we trust an organization, we often trust other similar organization (e.g., hospital). In digital information systems, such as the health ecosystem, the person has to trust in organizations, technology, and computational features of the system, as well as in communication and computer applications. Computational trust imitates the human trust creation process, and its goal is to calculate the level of trust in a context (31).

According to Lilien and Bhargava, privacy and trust can be a symbiotic or an adversarial relationship. Both require knowledge of other (30). When the trustee (e.g., a health service provider)

makes information describing its privacy features available to the trustor (e.g., a service user), it gains trust. At the same time, the high level of trust indicates to the trustee that their PHI is processed fairly, and there is low or no need to require additional privacy safeguards.

SECURITY, PRIVACY, AND TRUST CHALLENGES IN HEALTH ECOSYSTEMS

In this chapter, security, privacy, and trust challenges in health ecosystems are studied from different perspectives, such as ecosystem, data subject, privacy and trust models, privacy law, information architecture, and computation as well as from the 5P medicine viewpoint.

Ecosystem's Perspective

As mentioned earlier, the health ecosystem combines different kinds of stakeholders, such as the data subject (a person or patient), public and private healthcare service provider organizations and providers, researchers, and research organization, commercial vendors, such as tele-operators and Web service providers, platform managers, pharmaceutical organizations, or private organizations offering health and wellness management services. Some of the service providers have a physical location, but others are virtual organizations. The service provided is often non-tangible, e.g., they address just lifestyle and health management related information. Service providers and other stakeholders can have different business models (e.g., offering health services or monetization of PHI, and selling it) and security and privacy policies. They can also locate in different jurisdictions. This all makes it difficult for the service user to know which privacy and security rules apply, when and by whom PHI is used, and how to control data disclosure and secondary use of PHI. In the ecosystem, there exists meaningful power asymmetry between the DS at the one side and data collectors and processors at the other side. This makes it difficult to balance the DS's privacy needs and data processors' business needs (25). Furthermore, the collection of DS's behavioral data as well as health tracking is a widely used practice in health ecosystems, and the DS has in real life no way to control it.

Additionally, a huge amount of PHI is collected by stakeholders to produce services for customers. According to Prosperi et al., PHI, such as omics data, information on medications, EHR data, transcriptions, behavioral, social, environmental and genetic data, shopping and bank information, the content of social media, data created by wearable devices, the content of school and employment records, income information, and social security records, can be collected for further use (10) (as shown in ref. Blobel et al. Transformation of health and social care systems—an interdisciplinary approach toward a foundational architecture, in this volume). This PHI forms a very sensitive Health Big Data record that raises concerns regarding global surveillance and possible misuse. Other challenges include how and where this data can be securely stored and made available for a long time, how information privacy can be guaranteed, who owns the data, and who can access at what granular level the data. A big challenge is how to recognize and prevent the possible misuse of PHI and prevent future social, psychological, and economical harm of possible secondary use and misuse of it.

The data ownership of PHI is certainly a difficult question because PHI used in the ecosystem is a combination of regulated healthcare data (e.g., the content of the EHR), self-produced health information, data collected in ecommerce and business relationships, and hidden collected behavioral data. According to Evans, the legal ownership of health data should be non-exclusive (32). In real life, many organizations (e.g., organizations offering social network services) see that the ownership of self-disclosed data belongs to them. Confusion over the ownership of PHI and conflicting opinions on privacy rules make it difficult to manage privacy in the ecosystem and to know what its overall level of privacy is.

Privacy management in today's healthcare is based on the approach of well-defined context, where data flow through its borderline is strictly controlled following healthcare domain specific regulations. Unfortunately, this approach will not work in the health ecosystems because a part of PHI needed is located outside the healthcare domain, borderlines in the ecosystem are virtual and dynamic, and laws regulating information processing in commercial organizations vary. Furthermore, stakeholders collecting and using PHI in the health ecosystem often have different business models and privacy policies.

Successful service requires the linking of information collected from many separate information sources at different times (**Figure 1**). The linking requires the availability of DS's unique identifier or pseudonym. In ecosystems, there is no guarantee that all data sources use the same identifier, i.e., different identifiers are often used. This fact that the DS requires opportunities to access own (identifiable) raw data rises concerns regarding privacy and possible re-identification (32).

Data Subject's View

A person needs privacy to overcome the lack of trust, but also to prevent others to have power over him or her. The insufficient level of privacy causes the loss of autonomy enabling increased behavioral, social, and political control, manipulation and discrimination from service providers and the government. Even though privacy is a human and constitutional right, it is often balanced against other's benefit or business objectives in real life. Unfortunately, long-term negative side-effects (harm) are frequently not taken into account in this balancing because they often take place later, and harm is difficult to monetize. DS's privacy needs can be also simply overridden by the service provider.

Before disclosing PHI to a stakeholder in the health ecosystem, the DS needs to know whom to trust, why and how much? Furthermore, the DS has to trust that necessary security and protection safeguards are in place, and all stakeholders in the ecosystem have fully implemented security and privacy requirements set by the laws of the DS's home country. A meaningful challenge is that the DS seldom has necessary and reliable information for trust building and therefore for making informed decision how much PHI they are to disclose.

Instead, belief-based trust or perceived trust are often expected by the service provider in real life (21), and the DS seldom has the possibility to define own privacy policies despite existing standards enabling such service (2, 22). Furthermore, the disclosure of PHI is in many cases not a free and a voluntary decision (25). Instead, the take-or-leave policy is widely used by the service providers, and behavioral data is invisibly collected using "mandatory" cookies.

The way human builds trust is a combined cognitive and affective process that can be, and is, widely manipulated. This fact together with the lack of reliable information of service provider's and network's security, privacy, and trust features leads to situations where the DS's feeling or opinion about the trustworthiness of the ecosystem is the only measure. Unfortunately, there is no guarantee to what extent this feeling describes the actual trustworthiness of the ecosystem. A problem in Big Data environment is that the person's information privacy is affected by other's decisions, and DS's consent is not sufficient to protect privacy (32).

The fact that precision medicine requires access not only to large-scale, detailed, and highly integrated PHI, but also to genetic information raises questions about who owns person's genetic information, what results are returned, and to whom (9).

Challenges With Privacy and Trust Models

Privacy as personal right and control is the most widely used approach in today's information systems. It is based on the idea that a well-defined context of information processing exists and a rational evaluation of privacy risks and benefits is possible. Control rules, which can both reject and enable the processing of PHI, are typically expressed in the form of computer-understandable policies. This approach has many weaknesses, such as: in a pervasive environment, such as the health ecosystem, the control approach, and notice-and-choice (consent) is hardly to implement despite existing related standards. Rational decision-making frequently fails because of the limited rationality of humans (33), and the risk-based approach to privacy fails every day. Researchers have found that actual privacy risks are impossible to measure, and therefore the perceptions of opinion are widely used as proxy for actual risks. Unfortunately, perceptions are often only beliefs or based on other opinions. Privacy as contextual integrity approach fails also because contexts in ecosystems do not have clear boundaries, and inside the contexts, privacy rules are often defined by the stakeholder itself and cannot be defined by the DS.

Trust is a human trait that can be easily manipulated. General trust is a tendency to trust (belief) without any proof, i.e., it is unreliable. Trust as risk fails similar to the privacy as risk approach discussed earlier. Perceived trust is often only an opinion, and it is unreliable as well. Trust as subjective probability is problematic because the DS can hardly measure reliable probabilities. Computational trust based on own experiences and direct measurements is a promising approach, but its challenge is to get the reliable information of stakeholders' and information systems' trust features and behaviors.

Regulatory Challenges

Current advanced privacy regulations, such as the EU GDPR or the California Consumer Privacy Act uses privacy as DS's legal right and control approach. In this approach, the privacy right is a right to control (e.g., use consent) dissemination of personal data (25). This model that is widely used in the healthcare does not work in digital, distributed, and virtual ecosystem environment where regulations offer little protection (25). Furthermore, behavioral privacy is poorly or not at all protected. Current regulatory privacy models work in domains having clear boundaries and similar jurisdictional tradition. Unfortunately, this is not the case in health ecosystems, where many stakeholders other than the DS have legitimate interests in a person's PHI (32). Laws, e.g., the EU GDPR, often give the data collector or processor the right to define the data it has legitimate interest in, to define the content of legitimate interest, and to use so called "mandatory cookies." All those facts make it difficult for DS to control the use of own PHI in ecosystems. Health ecosystems running pHealth, eHealth, and 5P medicine are also Big Data environments, where informed consent is not capable to protect the DS against research-related privacy risks, and where cross-correlation among multiple datasets can enable re-identification (32). According to Evans, informed consent, giving the DS in real life situations only a take-it-or-leave-it right, is not adequate in the context of modern Big Data science and in precise medicine (32). Furthermore, in the context of genomics, consent does not work because it is nearly impossible to know the future uses of data at the time of collection (34).

The EU GDPR requires that organizations and entities which are actually in the control of health information should proactively use data protection principle [art. 5(2), art. 24], and assess, implement, and verify that data processing complies with the GDPR (art. 24) (35). Unfortunately, there is no legal obligation to explain the DS how this is done and which protection tools are implemented. Furthermore, laws do not enable the DS to know which data at granular level are collected, what privacy protection safeguards are in place, and which data are disclosed to other stakeholders in the ecosystem.

Architectural, Security, and Computational Challenges

In health ecosystems that use a platform to orchestrate communication between stakeholders and applications and also to store the collected PHI, it is necessary for the DS and other stakeholders to trust in platform technology and in platform managers. Between organizations, the trust builder is typically a legally binding service level agreement (SLA), where content and penalties are defined in a negotiation process. In addition, external certificates are frequently used. In a health ecosystem, this is a challenging task caused by the large amount of public private and commercial stakeholders. Furthermore, it is more than challenging for the DS because they have limited or no power to negotiate an SLA.

In the ecosystem, there are many security challenges, such as a Denial of Service (DoS) attack that impacts the availability of services and data. An unauthorized node in the network (e.g.,

a sensor node) may also send false information. The platform manager can be untrusted and make administration errors and include wrong users. There can be software bugs, malware, and malicious insiders. As service users do not have access to the platforms' internal operational details, the confidentiality and integrity of data can be at risk (36). Inside the platform, PHI is typically encrypted. This rises the problem of how to search encrypted data and how to manage securely the required encryption keys. Users of the ecosystem typically do not belong to one specific domain, but often to different jurisdictions. Different users need different access rights to PHI at different granularity level, using corresponding decryption keys. This makes authorization and key management a challenging task (36). Another challenge is how to guarantee long-term availability and integrity of PHI and how to proof data ownership during the whole retention time?

Cloud-based systems often use virtualization, i.e., multiple users run applications parallel on the same physical hardware. This generates security threats and privacy vulnerabilities to both the cloud infrastructure and cloud users (36).

Challenges Linked to 5P Services

As discussed in previous chapters, personalized, preventive, predictive, participatory, and precision medicine services require a large amount of PHI, such as genetic information, clinical information extracted from patients EHR, and different kinds of PHI collected by non-regulated health service providers and commercial Web-sites. This raises privacy and data ownership concerns discussed in earlier chapters. Technologies used for the predictive and personalized health services include mathematical algorithms, modeling, AI, and ML. Heterogeneous and noise data from different environments, used in AI and ML, can produce biased and wrong results, and ML can generate results that are difficult to interpret by a human (37). The use of genetic information together with the content of EHR and/or PHI for profiling can also cause discrimination.

Research and commercial organizations offering AI and ML services are increasingly actors in the health ecosystem. This raises privacy and trust concerns especially in a situation where PHI without encryption is disclosed to them for personalized analysis and predictions, but increasingly also in the context of clinical studies. Commercial and research organizations are seldom certified for privacy, and their trust features can be unknown. Data anonymization does not help because identifiable information is needed for personalized services, and anonymization is insufficient to guarantee the unidentifiability of genetic data due to the existing auxiliary information.

Modern medical and health research is often multi-disciplinary and international. This raises trust concerns, because it is difficult to know who the authorized users of data are, how secure the information systems of participants are, and how privacy can be managed. Another challenge is to grant only necessary access rights to remote users, and to verify whether researchers asking for data access are legitimate and trusted.

Health Big Data and modeling enable to create a digital copy (Digital Twin) of human organs or even of the patient, and to use this copy for personalized medicine and disease prediction. The concept of Digital Twin raises privacy questions, such as who is the owner of person's Digital Twin (e.g., DS, heath care provider, or somebody else), by whom Digital Twin can be used, and which are the rights of DS having Digital Twin (38).

PRIVACY AND TRUST SOLUTIONS

As discussed in previous chapters, researchers have found that current security tools cannot guarantee privacy. Control-based privacy solution and belief-based trust do not work in health ecosystems (21, 39). To meet those challenges, researchers have developed new conceptual, organizational, and regulatory, but also information technology solutions. An overview of promising solutions is shown in **Table 1**. Some of those solutions propose only small modifications to the currently used privacy and trust approaches, but others are rather radical.

Coiera et al. have developed an e-Consent mechanism to access PHI in electronic environment. This solution deploys the privacy as right and control approach and an e-Consent instead of traditional consent. In this solution, the e-Consent is a digital object that explains the specific conditions under which the PHI can be accessed, and by whom. According to Coiera, e-Consent can be general, general with special denials, or general denial with specific consents (40). A challenge in this approach is that it is difficult for the DS to manage granular and contextual e-consents, and therefore, this solution leads to very wide consents. Another related approach is addressed in the IEEE 7012 Project on Machine-Readable Privacy Terms the second author is member of Coiera and Clarke (41).

Another solution that is based on the patient's right to control, but does not use consent, is the patient controlled health data sharing proposal. Here, the patient (or the person) dynamically controls the access to PHI stored in personally owned PHI repository, or to the content of regulated EHRs. Fatokun et al., for example, have developed an EHR system where the healthcare provider can search for patient's data by requesting the patients' agreement to access it. In this solution, the patient can manage the use and sharing of PHI and the content of the EHR. By using the Ethereum Blockchain platform and smart contract to guarantee security and non-repudiation, all patient data are stored on the peer-to-peer node ledger (42). Encryption is still needed for privacy, and the management of encryption keys can be challenging for the DS.

Researchers have developed many cryptographic solutions to protect the PHI's integrity, availability, and confidentially. Data encryption is routinely used in cloud storages and during communication. In large data bases, encryption solution, such as differential privacy and K-anonymity are widely deployed to enable confidential data access and sharing. Homomorphic encryption seems to be the ultimate solution, but currently it supports only a few algorithms. Cryptography-based Blockchain technology has the power to guarantee the integrity and availability of data, but encryption is needed for confidentiality and privacy. Moreover, cryptographic technology is used for patient controlled data sharing. In a solution developed by Dubovitskaya et al., different hospitals are nodes in a

TABLE 1 | Examples of new privacy and trust solution for health ecosystem.

Privacy focused solutions	Patient controlled EHR sharing	Use of cryptography	Computer understandable privacy policy
	Blockchain-based EHR repository	Blockchain- and smart-contract-based SLA	Privacy as control, and use of e-consent
	Mapping law and DS's privacy needs	Privacy as regulatory property	Policy and ontology driven systems
Trust focused solutions	Privacy as trust, trust as fiduciary duty	Measurement of the level of computational trust	Collective agreement
Combination of privacy and trust	PHI as personal property and trust as fiducial duty, Blockchain based SLA		

permissioned Blockchain-based system aimed at EHR data sharing. Patients and doctors use a web-interface to initiate EHR sharing transactions. In this solution, original EHR data are stored outside a storage cloud, and a public key infrastructure based on encryption and digital signatures are used to enable secure storing and sharing of EHR data. The patients share their data using a Web service by specifying which data are shared to whom (43). In another solution developed by Chen et al., requested PHI is mapped to the privacy laws and requirements, to data users' identity and to data owners' disclose policy. Based on the results of mapping, decision to share or not to share data can be made. If needed, K-anonymity is used to secure the shared data (44). Cryptographic solutions can offer the high level of privacy, but the management of encryption keys is challenging as mentioned before already, and trust is only a strong disposition, or it should be created using other methods.

Security, privacy, and trust problems discussed earlier are caused by the complex, highly dynamic, and multi-disciplinary transformed health ecosystem. Those characteristics are not limited to the aforementioned security, privacy, and trust aspects or properties of, and perspective on, ecosystems. It of course also holds for designing, implementing, and managing the entire transformed health ecosystem itself. In the introductory paper of this volume, Blobel et al. noted that a more general system oriented view is needed, i.e., the challenge is to formally represent the specific aspects, intentions, and interests of all stakeholders (users) in their current and usually multiple contexts, to interrelate them and to integrate them properly in the business process to best meet the harmonized business objectives. A sustainable, future-proof approach to this challenge is the representation of the transformed health ecosystem as a system of systems by a system-oriented, architecture-centric, ontology-based, policy-driven model and framework, which has been meanwhile standardized in ISO 23903:2021 Interoperability and integration architecture—model and framework (45). This approach represents any system by its (knowledge) domains, i.e., user-specific and domain-specific perspectives and representation means (languages and ontologies), by generic granularity levels to allow correct and consistent interrelations, and finally by its evolution, e.g., a solution or software development process. The behavior of systems is ruled and controlled by domain-specific policies, which could be a process policy, a legal policy, a privacy policy including an individual privacy policy, but also moral or ethical principles and frameworks. As mentioned before, those different domains must use-case-specifically, currently and therefore dynamically represent using the corresponding domain ontologies (45–48). For the ontological representation of policies, ISO 22600:2014 should be used (49).

In addition, there are researchers who see that the current widely used privacy as right and control approach should be replaced by a new approach. Waldman has presented a privacy as trust approach, and Dobkin and Balkin as another approach, where trust is based on the regulated specific information fiduciary (25, 50, 51). These approaches require new legislation, and in real life it is difficult to know that the data collector/processor behave as required in the duty. Ritter et al. have proposed a regulation for data as property. In this approach, data ownership is clearly defined, but also at the same time property rules which define the right to own information (52). Natural persons and a legal entity can own data property, and only public data are understood as open data. Property also means that the data must be anonymized if a person does not accept the use of PHI. Also here, new law is needed, and encryption for privacy.

Since ownership right may not be sufficient against all privacy risks in digital environment and do not prevent against re-identification, Ruotsalainen et al. have proposed a model that combines the PHI as personal property approach and trust as regulated fiducial duty. In this solution, DS and data processor make a digitalized SLA using Blockchain smart contract technology. In this solution, the smart contract stores also trust duty requirements (21). A specific law for informational trust duty is needed, and the DS needs the information of trustee's privacy and trust features before signing the smart contract.

Prosperi et al. have proposed a "health avatar" solution where avatar is a virtual representation of a person with all associated health information. The avatar captures and integrates health-related data, from genomics to omics, mobile, and wearable technology generated data, and environmental information (10). According to Prosperi, "Within the context of appropriate ethics bylaws and informed consents, health avatars could directly feed individual-level health information to multiple research projects." In this innovation, the avatar is an active computer application that is programmed to collect data and make privacy decision according to DS's will. A challenge is that data processors can regard avatars dangerous, and it is challenging for them to give restricted access control rights to

the avatar. Evans has presented a radical approach to reject all traditional regulatory norms and replace them with collectively agreed norms (consumer-driven data common approach) (32). A weakness in this approach is that collectively accepted norms can be difficult in a heterogeneous group. Furthermore, norms provision and DS's privacy needs can be conflicting.

There are other less radical proposals, such as offering the DS information to measure the level of privacy in the ecosystem. This approach can be used as the front end for different access control and data sharing solutions, such as the use of computer understandable privacy policies. The challenge is that the measurement of the actual level of privacy in a health ecosystem is a demanding task caused by the number of different stakeholders and many contextual factors impacting privacy (e.g., technology used, how security and privacy requirements are defined in laws, how standards are implemented in information systems, how stakeholders' privacy policies and business models differ, how information is used, what is the sensitivity of data, and how the level of trustworthiness vary between stakeholders) (53). Another problem is that there is often the lack of reliable privacy and trust information in real life.

Distributed storage architecture is an architectural solution for the trustworthy disclosure and use of PHI. It splits the PHI into different blocks and stores them in different databases (or in blockchain ledgers), and the DS can grant separate access to each data block. This solution enables the detailed disclosure of extremely sensitive PHI, such as genomic data (54). In this solution, encryption is needed, and the management of granular encryption keys remains a challenge.

DISCUSSION AND CONCLUSION

The ability to protect information privacy and high organizational trust has been for long a "*de facto*" requirement in healthcare. The ongoing health transformation toward personalized preventive, predictive, participative precision medicine, and healthcare challenges what PHI is collected, stored, used, and shared, and how privacy and trust are understood and created. Personalized and preventive services and new medical research need PHI that considerably exceeds the content of the today's EHR. Digital measurement tools (e.g., sensors and monitoring devices) and communication technology have all together enabled the collection of personal related data almost on-line, supporting the aforementioned 5P medicine services. Furthermore, health and increasingly healthcare services are moved to ecosystems. At policy level, parallel to this transition, to gain economical, administrative, and social benefits, the general interest seems to move from strong protection to the balancing of information privacy and the free movement of health data (55). Furthermore, medical and health industry and e-commerce increasingly see PHI as "new oil" and commodity.

This development raises many privacy and trust challenges. Currently, it is nearly impossible for the health service user to guess, which privacy and trust principles and security and privacy solutions will best fulfill their privacy and trust needs, and at the same time to respond to the security, privacy, and trust challenges existing in the health ecosystem. In this paper, the authors have studied security, privacy, and trust challenges in health ecosystems from different viewpoints (ecosystem; data subject; regulatory, privacy, and trust models; architectural, security, and computation; and 5P Medicine) and recognized many issues to be solved. Novel privacy and trust solution prosed in the literature are also studied. Some of them are only enhancements to the current practice (e.g., e-consent), others rely on technology (use of cryptography), and some present a radical change (e.g., privacy as trust approach). All discussed proposals have their own limitations (Chapter 4), and none of them is widely accepted or used. Hence, there is much space for new innovations. The authors' proposal for health ecosystems is the combination of privacy as personal property and trust as fiducial duty approaches in such a way that the duty to trust is created using legally binding smart contracts (56).

In any case, the authors state that for making pHealth, eHealth, and 5P Medicine successful, trustworthy, and secure, and therefore acceptable for people, it is necessary to redefine the way information privacy and trust in health ecosystems are currently understood and managed. To achieve this, widely accepted consensus, new laws, and political will are inevitable.

The redefinition of privacy and trust should be an international and multi-professional consensus, for example, under the guidance of the WHO. New regulations are also needed to enable the DS to evaluate (or calculate) the actual level of privacy and trust of the health ecosystem, and to force the ecosystem's stakeholders to openly publish detailed privacy, security, and trust information concerning their information systems and processes. Since stakeholders in health ecosystem can locate in different jurisdictions, created laws (e.g., the law for specific fiducial duties) should be internationally accepted.

If the current, from the DS's point of view, unsatisfactory situation will persist (i.e., nothing is done by regulators and policy makers and industry), the danger that our PHI will become commodity which is monetized comes true, and privacy and trust in health information system remains only a myth.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

PR wrote the main part of this manuscript. The content and the title of this article were developed together by the authors. BB wrote part of the section "Privacy and Trust Solutions" and did a lot of the editing and fine tuning work necessary. Both authors contributed to the article and approved the submitted version.

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Success Factors for Scaling Up the Adoption of Digital Therapeutics Towards the Realization of P5 Medicine

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Introduction: Digital therapeutics (DTx) can be a valuable contribution to the successful scale up of P5 Medicine (personalized, participatory, predictive, preventive, precision medicine) as they offer powerful means of delivering personalization and active patient participation in disease self-management. We investigated how the approval and adoption of DTx within health systems have been approached in five selected European countries and regions, with a view to proposing success factors scaling up their adoption.

Methodology: Preliminary research established best countries or region candidates as being Germany, UK, France, Belgium, and the Spanish Region of Catalonia. The research was informed by a literature review, interviews with public bodies and industry, and a multi-stakeholder workshop to validate the findings and fill in existing gaps.

Results: To authorize the use of digital technologies, the countries and regions passed legislation and developed policy instruments, appointed bodies to assess and certify the products and formalized mechanisms for permitting reimbursement. While DTx is not a commonly used nomenclature, there are digital health technology types defined that have similar requirements as DTx. Assessment and certification frameworks are usually built around the Medical Device Regulation with additional criteria. Reimbursement considerations often observe reimbursement of therapeutic devices and/or medicines. To be integrated into reimbursement systems, countries require manufacturers to demonstrate clinical value and cost-effectiveness. As there are currently very few DTx approved in practice, there is resistance toward clinical acceptance and organizational change, and change management is highly needed to integrate DTx into healthcare systems. The integration and secondary use of DTx data is not encountered in daily practice. Although some enablers exist, there remain technical and legal barriers.

Discussion: DTx strategies should be considered as an integral part of digital health strategies and legislation, and specific DTx pathways with clear and transparent assessment and guidelines that balance regulation and innovation should be defined. To help manufacturers, countries should recommend and list methods that are widely accepted and ensure scientific robustness, aligned to the MDR requirements to support

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transfer of relevant and comparable data across countries. To facilitate rapid uptake of innovation, countries should add flexibility to the framework by allowing temporary market authorization to enable data collection that can support the clinical and socio-economic evaluation and data gathering phase. Certification should trigger rapid price setting and reimbursement mechanisms, and dynamic ways to adjust price and reimbursement levels in time should be established. Relevant stakeholders should be approached on the potential impacts of DTx through transparent communication and change management strategies should be considered. These findings should be validated with a wider range of stakeholders.

Keywords: digital therapeutics, P5 Medicine, scaling up, adoption, success factors, assessment, certification, regulation

INTRODUCTION

The digital transformation of society comes about at different speeds, depending on the observed sector. Healthcare is traditionally delivered in-person; however, digital support tools are increasingly relied upon during different phases of care (e.g., diagnosis, communication, treatment) (1, 2). Electronic Health Records (EHRs), e-prescriptions and e-referrals are only a few examples of services and tools aimed to digitize healthcare. This development is further strengthened by the recent emergence of digital therapeutics (DTx). Sometimes referred to as "apps on prescription," DTx are regulated digital, and often, mobile applications that deliver evidence-based therapeutic interventions to either prevent, manage, or treat a disease (3–6).

Digital therapeutics can be a valuable contribution to the successful scale up of P5 Medicine (medicine that is personalized, participatory, predictive, preventive and palliative). As argued by Blobel et al. (see the first paper in this volume), digital transformation (in partnership with organizational and workflow transformation) is essential to realizing this vision (7). Digital tools such as apps, wearables, and sensors, especially those that offer active guidance to patients on personal actions, escalation actions and treatment dosing, offer powerful means of delivering personalization and active patient participation in illness self-management. As they are not intended to replace existing therapies, digital therapeutic solutions are often used in combination with medications, other devices or therapies and are mainly targeted at patients as the users (3). They are therefore adopted as part of a care plan, through a joint decision by clinicians and patients and ideally as a fully integrated component of the plan, embedded within the health and care system.

As DTx do not fall within the scope of wellness and lifestyle apps, manufacturers undergo regulatory approval processes in order to receive marketing authorization that enables their adoption by health systems (4). Approved DTx may be prescribed by healthcare providers or procured on a larger scale (8, 9). However, two aspects are key to support a wide-spread and swift adoption of DTx into routine care: firstly, care providers need to be aware of the therapy and its ambition and, secondly, regulators need to implement reimbursement support for patients and healthcare providers in case interactions are part of the therapy (6). Potentially, DTx will introduce major changes to the accessibility of care for patients and their health outcomes (10, 11). This will, however, depend on the successful demonstration of their clinical and economic value proposition compared to existing interventions. Experts point out that low-price technology interventions do not necessarily trigger cost-savings, but in fact increase their demand and thus overall healthcare spending (12, 13).

Despite positive evidence, successful implementation and scaling-up of digital health solutions still seems to be a sluggish process and remains a much debated topic, with a very fragmented landscape (e.g., the fragmentation of national EHRs and ePrescription services, health data silos). Adoption of digital health technologies takes place across many dimensions of the health and care system and within diverse organizational processes. The enablers and success factors for adoption therefore need to be studied from a plethora of stakeholder and dimension perspectives.

Frameworks for scaling up digital health interventions have been proposed. For example, Yamey (14) analyses success factors for scaling up global health interventions. These include "choosing a simple intervention widely agreed to be valuable, strong leadership and governance, active engagement of a range of implementers and of the target community, tailoring the scale-up approach to the local situation, and incorporating research into implementation" (15). Labrique et al. (16) identified five key areas critical for the success of scaling digital health in low and middle-income countries. These comprise the initiative addressing unmet needs and offering tangible benefits, stakeholder engagement to implement new initiatives, a technical profile driven by simplicity, interoperability and adaptability, alignment with broader health care policy, and sustainable funding to support long-term growth (16). Desveaux et al. (17), approached the issue of digital health implementation from a policy perspective. To overcome policy-level barriers, they identified several key areas, that include the need for a system-level definition of innovation, a clear overarching mission, and clearly defined organizational roles. Operationally, the authors identified a need for standardization of processes, a shift in emphasis of change management, and alignment of funding structures (17).

A study that examined barriers and facilitators to the implementation of digital health at scale through the evaluation of a national digital health programme in the UK identified three levels of issues influencing the readiness for digital health: the macro-level (market, infrastructure and policy), meso-level (organizational), and micro-level (professional or public). Clinical endorsement, champions who promoted digital health and public and professional willingness were identified as factors that support implementation of digital health (18). Another recent study from 2022 examined key considerations for adoption and implementation of digital health tools within large, complex health systems (19). These were aimed to support health systems' decision-making on how to best approach the selection and evaluation of digital health tools, how to ensure the availability of sufficient resources for deployment and long-term use and the creation of implementation strategies. The dimensions described include optimal product selection, how clinical value and return on investment are demonstrated, internal champions, tool alignment with institutional priorities, executive sponsors, data assets, long-term operational anchoring and implementation-required resources.

Perspectives from a stakeholder workshop in Switzerland identified a culture of innovation and patient-centric approaches as a push factor, but that adoption was hindered by fear of change and unwillingness to share data (20).

Key success factors for policy-makers to consider when using demand-driven open innovation as a policy instrument involve improved citizen centricity through clinical staff engagement, promoting knowledge transfer through better and more communication between health system actors, time to market entry, customer relevance and making explicit to stakeholders process roles, responsibilities and funding structures (21). Another paper that explored success factors scaling-up digital innovations in healthcare pointed out that actors and factors on different levels influence success factors (micro, meso, macro and technology/innovation level) (22). The authors highlighted the importance of leadership as a trigger for innovation, a culture for change, common goals for change, interdisciplinary co-creation of solutions that address the needs for change through innovation from multiple perspectives, and the need for sound regulation and actions to maintain or increase trust in scaled-up solutions (ibid.).

However, none of these papers consider DTx specific-success factors and remain in the general digital health domain. As DTx are a rather novel form of therapy, a few countries have implemented DTx-specific assessment frameworks in addition to regulatory compliance with the Medical Device Regulation (MDR). The success factors for DTx adoption are therefore likely to be a combination of the success factors for obtaining approval and some that are the same as for any other digital health intervention. This topic has not been investigated to date. This paper explores how the approval and adoption of DTx within health systems have been approached in five selected European countries and regions, with a view to proposing success factors for scaling up their adoption.

METHODOLOGY

The analytical framework was established in the beginning of the investigation and covered eight dimensions: system-wide strategic policies, the legal scope and nomenclature of DTx, assessment and certification schemes, clinical and socio-economic evaluation, integration into reimbursement systems, integration into healthcare systems, data integration and use of DTx and secondary use of data and data reusability. These eight dimensions were derived by examining the main categories of criteria within multiple European assessment frameworks (15), in the context of the authors' background knowledge of the general digital health success factors summarized in the previous section.

To ensure that all dimensions were covered, prior research was conducted to assess European countries in terms of availability of DTx assessment frameworks, certification and reimbursement approaches and number of approved DTx. Five countries or regions were identified to be most advanced in the field of DTx: Germany (specific DTx legislation, a clear "fast-track" certification and reimbursement scheme in place, several DTx solutions with both permanent and preliminary market authorization), Belgium (mHealth Belgium initiative and strategic focus on mHealth, pilot projects on DTx to determine appropriate framework for DTx integration, three-tiered validation approach), France (certification and reimbursement process for connected medical devices (CMD) based on a registry of procedures and services, with a guide for, or specific features of, clinical evaluation of a CMD in view of its application for reimbursement), National Health Service (NHS) England (several innovation and digital health technology frameworks on required evidence for reimbursement negotiations for health apps with Clinical Commissioning Groups and NHS Trusts) (23–29), and the region of Catalonia (existing certification framework for health and wellbeing apps, mConnecta platform is an interoperable infrastructure that integrates mobile data from mobile apps, wearables and medical devices with the EHR data) (30, 31). Data from this prior review was fed back to the finalization of the analytical framework. A mixed-methods approach was employed to facilitate the analysis. Firstly, the collection of information involved a systematically approached desk research of policy instruments, websites, templates, and guidelines. Secondly, 15 semi-structured interviews were conducted with at least two interviews from each of the five countries or regions, involving at least one expert from public authorities and one from industry. Experts were identified through internet search: public officials were contacted through the national bodies responsible for DTx assessment and certification, and industry experts were contacted through contact forms on companies' websites which produce and market DTx in that country or through public workshop documents (list of speakers or attendees). Thirdly, findings from the literature and the interviews were validated during a dedicated multi-stakeholder expert workshop, whose attendees received a summary of all collected information. At the workshop, the interim findings were presented, discussed, and remaining gaps were filled to the extent possible. The discussion was organized around four main areas: (1) evaluation and assessment,

(2) reimbursement and procurement, (3) European alignment, and (4) secondary use of DTx data. The workshop hosted 25 experts from industry, public authorities, EU-initiatives, and networks and represented experts from all studied countries. The workshop input validated and consolidated the results across all methods and countries under the analytical framework. Furthermore, key discussion points facilitated the identification of success factors for enabling better integration of DTx into healthcare systems.

RESULTS

System-Wide Strategic Policies

To authorize the use of digital technologies within the health system, the five countries and regions have passed legislation and developed policy instruments, appointed bodies with authority to assess and certify the products, and formalized mechanisms for permitting reimbursement. Countries such as Belgium and France included policy on DTx (referred to as connected medical devices or CE-certified mHealth apps) as part of a broader eHealth or digital health strategy. The Belgian national e-Health Action Plan 2013–2018 contains the general strategy of the architecture of the national health data platform (24). In the context of the plan, the Belgian authorities developed a dedicated mHealth assessment process following an assessment pyramid model (26). In France, DTx are an integral part of the "National Health Strategy 2022" and associated digital transformation, which promotes health reform measures, the reinforcement of governance, security, and interoperability, and the stimulation of innovation in digital care provision (32). NHS England created specific programs to enable rapid uptake of digital innovations (e.g., Accelerated Access Collaborative Programme, Medical Technologies Evaluation Programme, NHS Innovation Accelerator and Digital Health London), through which DTx adoption is supported in order to achieve common health policy goals such as cost reductions and improved quality of care (33–36). Germany does not have an overarching strategy to digitize the health and care sector, but rather particular laws to create the legal basis for digital innovation. The legal basis for reimbursement of digital health applications was established through the 2019 Digital Health Care Act (Digitale-Versorgung-Gesetz), which states that insured persons in the statutory healthcare insurance system are entitled to healthcare through digital health applications (33). The autonomous region of Spain, Catalonia, has defined via the 2015 Catalan Master Plan a Strategic Plan and an Action Plan to support the development of mHealth in Catalonia, through which it addresses certification and integration of mHealth apps, yet currently does not have policies to enable reimbursement of digital health applications (31).

The Legal Scope and Nomenclature of DTx

"Digital therapeutics" is not a commonly used nomenclature in European legislation and policy. Different terms are used to refer to DTx in the five explored countries and regions: connected medical devices, digital health applications, digital health technologies, or mHealth apps. Variations can also be observed in the exact scope of what types of DTx are covered by legislation. Commonly found scoping criteria for inclusion of DTx into the relevant legislation were that they should be digital, have a patient-facing interface, address prevention, management or treatment of a medical disorder or disease, and possibly undertake analytic processing besides simply data collection and display. General health and wellbeing apps were not addressed by the studied countries, except Catalonia. In France, DTx fall under the category of medical devices and apps are classified to assist with clarifying which level is in scope of the legislation and approval process (29). The Belgium framework considers mHealth applications that are CE-marked as medical devices of all classes (37). According to NICE (the Evidence standards Framework for digital technologies—ESH) (28), in the UK DTx fall under the category of digital health technologies (38). Germany has defined DiGA (Digitale Gesundheitsanwendungen—Digital health apps)—a medical device of the MDR risk class I or IIa, whose main function is based on digital technologies achieving the medical purpose, where "DiGA supports the recognition, monitoring, treatment or alleviation of diseases or injuries and represents a "digital assistant" in the hands of patients" (23). Generally, inclusion of prevention was not explicitly stated but secondary and tertiary prevention for a particular disease was widely included. Primary prevention might be partly included in specific cases but mostly it is not considered to fall within this context.

Assessment and Certification Schemes

All five explored countries and regions apply Health Technology Assessment (HTA) processes for digital health solutions that fall under the MDR. There are several types of assessment frameworks that a DTx solution can undergo: DiGA frameworks, frameworks for CE-marked health apps, classical HTA evaluation approaches for medical devices, frameworks for digital technologies, and frameworks for general health and wellbeing apps. While safety aspects and clinical effectiveness are partly ensured by certification as CE-medical devices under the new MDR, all five explored countries and regions have additional requirements related to risk assessment, safety evidence, data protection, health outcomes impact, or health economic implications (39). Germany is at the forefront of DTx assessment with its DiGA assessment process (23). The Digital Health Applications Regulation (DiGAV) describes the regulations and requirements for testing the eligibility of DiGAs for reimbursement by the statutory health insurance system (40). The Federal institute for Drugs and Medical Devices BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte) is the responsible body for the evaluation and certification of DiGAs. From the moment of application, BfArM is obliged to perform the assessment within 3 months. In case of acceptance, the application is published in a specific DiGA directory (41). The procedure is designed as a fast track: if positive effects on care evidence are not available, then the DTx is preliminary listed and the evidence can be submitted within the next 12 months, with a further extension of maximum 12 months if justified. NHS England has a series of indicator frameworks for digital technologies (soft regulations) designed by NICE and

NHSx—the Digital Technology Assessment Criteria (DTAC) (42). In the pyramid-based Belgian framework and certification process, at each of the three pyramid levels the DTx is evaluated for certain criteria by different institutions (26). In France, health technologies and medical devices are evaluated by the "Medical Device and Health Technology Evaluation Committee" (CNEDiMTS, part of Haute Authorité de Sante, HAS) according to internal assessment guidelines for medical device (29). The TICSalutSocial foundation, part of the Catalan Ministry of Health, created the "Accreditation Service and TICSS guarantee certification" framework through which a set of criteria was established for general health and wellbeing apps, but where the CE-mark is currently considered optional (43).

Clinical and Socio-economic Evaluation

The evaluation of socio-economic and clinical evidence in Germany, France, Belgium, and the NHS England feature typical Health Technology Assessment (HTA) elements, including security, safety, and effectiveness.

The German DiGA assessment introduces the concept of positive care effect, which is split into two categories: medical benefits and patient-relevant improvements (5). Both categories refer directly to the patient and need to be demonstrated by appropriate endpoints (e.g., morbidity, mortality, or QoL). The positive care effects need to be demonstrated through clinical studies that show positive effect with a comparison group through controlled trials or randomized controlled trials. If sufficient evidence for a positive healthcare effect does not yet exist but all other requirements are fulfilled, the DTx company can apply for a provisional listing in the directory, as described earlier. The French CNEDiMTS published a "Guide to the specific features of clinical evaluation of a connected medical device (CMD) in view of its application for reimbursement" in January 2019 (44). The evaluation is currently built around Medical Device assessment and split into two stages: clinical value and real-world results. In the French evaluation procedure, a randomized clinical trial (RCT) is the preferred form of clinical evidence although lower level of clinical evidence can be submitted. The current model is based on a committee-based approach which makes case-specific decisions possible (45). The UK frameworks have different focus areas: the DTAC by NHSx focuses on technical questions while ESF by NICE describes clinical and socio-economic efficacy requirements, where clinical data needs to be acquired through experimental and comparative studies (28–42). The Belgian model is built around the MDR which requires clinical effectiveness evidence (46). The framework also considers changes to current care processes, costs, and clinical evidence. However, the specifics of the evidence is left open and many kinds of methods (e.g., RTCs, studies based on real-world use, or expert opinion) can be applicable, and the model leaves most room to maneuver for the applicant compared to other countries. The Catalan TICSS framework does not capture clinical or socio-economic evaluation of health apps (47).

Manufacturers in all countries are expected to support the costs of clinical studies. Randomized Clinical Trials are an expensive and time-consuming undertaking and smaller companies may not always be able to provide this gold-standard of clinical evidence. The investigation revealed that DTx companies' developers suffer from the lack of recognition of excellence, and they welcome assessment and evaluation, but processes must be efficient, realistic, and transparent. Much of what needs to be assessed is performed under regulatory MDR compliance. The main challenge from the manufacturers' point of view regarding clinical and socio-economic evidence is to have realistic requirements in terms of the evidence they must present. One challenge relates to the definition of health benefits and corresponding evidence: should it be clinical outcomes, improvements in the process of care or both? The latter can be challenging because it involves organizational change as well as an organizational adoption of the DTx. While pilots of DTx are feasible, it is harder and expensive to provide large-scale evidence. Therefore, there is need of a reasonable and sufficient level of population evidence that can demonstrate a realistic level of outcome-change based on a probably cautious organizational commitment to an unapproved DTx. Since healthcare systems are under increasing pressure for cost savings, many countries emphasize cost savings instead of added value.

The investigated countries and regions varied in the extent to which the expected standards for approval were openly available with the assessment criteria that a DTx developer needs to meet, but companies we interviewed valued having access to the most complete and precise guidance they could obtain to help them to submit the evidence that would be required. The evidence generated within the country in question is considered the gold standard and using data from another country requires clarification and reasoning from the developer.

Integration Into Reimbursement Systems and Market Stimulation

DTx solutions can be commercialized through licensing agreements with hospitals, companies, or individuals, after being certified as CE-devices and proving clinical effectiveness through RCT studies. Reimbursement is a strong incentive, and it always requires that the DTx is prescribed by a health professional and being selected among solutions that have had a successful prior positive HTA-type assessment. However, approval and reimbursement are usually separate decisions, sometimes made by separate bodies based on separate applications, and an approved DTx could be used by a healthcare provider if it perceives a clinical and business case (without reimbursement). A clear link between certification and reimbursement has been defined for the German DiGA and mHealthBelgium frameworks. The two frameworks employ a bottom-up approach, where application is open for all DTx solutions. The ones that are certified under the specific assessment process are listed in a directory and reimbursed. In France, NHS England and Catalonia, there is currently no direct link between certification and reimbursement.

The German model of reimbursement for DTx is registry-based. After the solution is certified and approved by BfArM, price negotiations are conducted and established between manufacturers and the National Association of Statutory Health

Insurance Funds (GKV-SV) (48). BfArM plays a consultancy role and informs the GKV-SV of the need for corresponding remuneration amount. In the first year, the manufacturer is free to set their price for that year according to value-based pricing principles and market competition (i.e., intensity of positive healthcare effects, preliminary manufacturer price, solution pricing in other countries). After the first year, the price setting is determined with a framework agreement designed by the GKV-SV. Reimbursement for DiGAs is currently part of a special budget but will become part of a budget that is allocated to primary care at regional levels. Besides the DiGA prescription, General Practitioners (GPs) can be reimbursed for additional services related to DiGA. The price negotiations in the future will show how attractive the market will be, and eventually determine the long-term success of the DiGA-framework.

In Belgium, solutions that pass the third level of assessment (M3 level of the pyramid) are reimbursed after approval of their funding request by the National Institute for Health and Disability Insurance (NIHDI). The evidence required for reimbursement of the solutions follows a template (dossier) to assess the care pathway or process related to the app's purpose, i.e., explore the current pathway and how it changes with the use of the app. The reimbursement plan can consider the different verticals (budget lines) of the health payment system. There is currently one application reimbursed, and an agreement has been established between the NIHDI and the healthcare providers (hospitals and physiotherapists) (49).

In France, DTx reimbursement is currently following similar patterns as medical devices, which resembles drug reimbursement (50). Once CNEDiMTS completes the technical review of the actual clinical benefit and clinical added value compared with existing therapies, the Economic Committee for Health Products (CEPS) negotiates the prices to be paid by the statutory insurance system. Manufacturers and CEPS then sign a contract stipulating a price for the therapy and forecasting script volumes. If actual prescription volumes exceed this forecast, manufacturers must rebate between 50 and 80% of additional revenues back to the French government. After these negotiations, the National Union of Health Insurers (UNCAM) registers new therapies on a list of reimbursable products and sets a reimbursement rate that corresponds to therapies' clinical benefits rating: for important benefits, and 100% for major benefits. Since reimbursement rates are set by UNCAM, net price increases do not occur in the 5 years after drugs initially gain market access. By rewarding added value within limits, the French drug pricing system strikes a robust balance between lower prices and innovation. Medical Devices that receive permission to be reimbursed are included in the list of products and services qualifying for reimbursement (List des Produits et Prestations Remboursables—LPP) (51).

In NHS England, there is no direct connection between the DTAC or ESH frameworks certification and reimbursement. A positive endorsement from NICE can support the acceptance and adoption of the health app by providers and Clinical Commissioning Groups (CCGs) (25). CCGs are primary care-led groups that include the GP groups in a particular area and represent statutory NHS bodies responsible for the planning and commissioning of health care services for their area, that might provide reimbursement for a digital technology depending on their strategy. Therefore, DTx solutions may strive to achieve certification by NICE/NHS and be purchased at a national or regional level by CCGs. However, through dedicated programs such as NHS Innovation Accelerator, the NHS selects innovations to be integrated in the health and care system (52).

The Spanish public health system has no defined framework for reimbursement of digital health solutions. The Catalan system is purchasing health products and services through public or pre-commercial procurement (PCP) by launching specific tenders. The current approach for general reimbursement is a top-down approach, their strategy being focused on the reimbursement of the care pathway, and not isolated elements. The current pathway in focus is diabetes, and a tender for diabetes is soon to be published by the main healthcare provider, CatSalut. The tender covers multiple aspects related to diabetes care needs (i.e., glucometers), but also contains requirements for diabetes apps: passing the TICSS Certification Process, providing the CE-certification and proof of possibility of integrating the solution with the mConnecta platform (30). The Catalan evaluation approach is based on assessing how elements can improve the existing pathways in an integrated-care way, considering both the system and the patient. If the solutions are funded through the public tender, they can be integrated into the health system.

With regards to market stimulation, besides Germany, most countries focus on health care improvement rather than market stimulation. Germany is a notable difference as they allow reimbursement with provisional evidence within the first 12 months and relatively free pricing for the initial year, after which the pricing levels are renegotiated.

In terms of how DTx can be procured, there is a need for agreement on the patient-reported outcome data that could be used to determine models of payment (registry based, licensing, reimbursement per use, prescription). Shifts in budget and service allocation are often not considered in price negotiations and should be, from a system perspective, taken into account (e.g., in cases where care is shifted from a hospital to a different organization, team or even to the supplier of DTx). Most of the reimbursement scenarios observed during the study are reimbursement of a novel care pathway that incorporates a DTx, and not a direct reimbursement of the technology solution (except for the German model). One key question that policymakers should consider is whether reimbursement should be made to a single healthcare organization which then has the business justification for a procurement of the DTx. This model has anecdotally been shown to be unfavorable to DTx that support cross-organizational collaborative care, since no one healthcare organization is a complete beneficiary to justify the procurement. On the other hand, not every DTx applies to cross-organizational care and regulation and reimbursement structures should account for this variation.

Another issue from the manufacturers' perspective is that there currently seems to be a lack of dedicated processes and transparent guides for DTx assessment. A solid business case for manufacturers further reduces barriers for DTx development. The model for both traditional therapeutics (i.e., mostly drugs)

and DTx requires large investments, making this market feasible only for larger players. To facilitate market access for SMEs and a wider pool for innovation while following strict clinical evidence standards is not an easy equation to solve. Solutions to this challenge could most likely be achieved through public funding programs directed specifically to trialing DTx.

Finally, a step forward toward a promising DTx reimbursement, integration and pricing pathway could be a value-based approach, i.e., payment/reimbursement for additional value added compared to existing practices. However, challenges remain. Value-based models could solve some challenges with DTx as the healthcare providers would have to find solutions to prevent escalation and to work across the current siloes. Value-based healthcare focuses on health outcomes instead of activity (i.e., paying for the number of procedures). This is widely recognized as a promising solution to many health-system challenges but the practical application of it is difficult. The difficulty for DTx companies lies in the lack of direct control over the use of their solutions. The DTx itself can have immense potential but realization of this value depends on the way it is used and the broader way of working at the healthcare provider. One key driver of price is not only the absolute value a product delivers but also its relative value to other existing DTx solutions. Therefore, there will be a future point in time where several DTx solutions are on the market and the demand for any new solutions must carefully be assessed in terms of market competition. This could introduce a soft cap on the amount of DTx for a certain disease type or patient group to prevent health system expenditure from increasing. Existing DTx solutions should also be re-assessed, and their price be adjusted according to performance data which could be obtained from insurance datasets.

Integration Into Healthcare Systems

Evaluation, certification, and reimbursement are essential steps for the DTx to reach its' end user: the patient. There is scarce information on DTx prescription practices as the phenomenon is rather new. In Germany, DiGAs can currently be prescribed by primary care physicians and psychotherapists. However, hurdles have been identified in relation to the general workflow of the prescription process, as DiGAs are currently prescribed on paper. There is also resistance from German physician organizations to raise awareness on DiGAs. Currently the system works according to a bottom-up approach: developers target directly their customers; the latter find out about the solutions. Patients usually then ask their physicians for a prescription, but alternatively seek direct reimbursement from the statutory health insurance companies. While information campaigns are on-going, a strong impact has not been observed yet. The German government is exploring possibilities on how to incentivize the prescription and use of DiGAs. In Belgium, medical doctors are allowed to prescribe DTx, which are targeted toward broad patient groups as per results of the notification form (53). In UK, DTx solutions can be prescribed by GPs if their CCG/NHS trust groups have commissioned them. In France, DTx included in the LPP can be prescribed by physicians to patients. In Catalonia, the prescription of health apps was piloted and physicians are able to prescribe health apps but without patient reimbursement (54).

Integrating and yielding the most value out of DTx is difficult and requires change management from the health system, and mainly on the engagement of clinicians in how DTx can fit into clinical workflows and practice. There is resistance toward clinical acceptance and organizational change, and issues that have been raised include anxieties amongst clinicians about their professional responsibility for care pathway elements which are placed in the hands of patients, and with certain levels of care guidance being provided by the technology and not by them. Secondly, there is a concern about the investment of time and expertise required to educate patients about how to use the technology and about how to manage those elements of their care which are supported by the technology, including the criteria that should trigger them to escalate a concern to a clinician. Who will pay for this time investment and who has the relevant training to provide it? Will this be an extra burden on each medical practitioner, or will there be enough budget to employ someone who coaches the patients and can support them with any issues at home? Another important resistance factor amongst clinicians is about what reimbursement they will get for elements of care that the technology looks after and therefore the possibilities of financial losses for services that are being replaced by the digital technologies. Ideally, these issues should be researched in more detail with a wider range of health and care professionals.

Data Integration and Use of DTx Data

Data integration is generally addressed through wider strategies. In France, data integration is expected to be achieved through the integrated approach of the new health data strategy, operationalized by several organizations, and enabled by the national Health Data Hub (HDH) (55). The patients' health data space and the professional one is linked *via* interoperability services by the L'ANS competence center.

In most of the surveyed countries, the approval of a DTx required interoperability with the national Electronic Health Record, eHealth platform, or certain interoperability standards, and sometimes to specific Application Programming Interfaces (APIs). In Belgium for example, interoperability standards compliance is required and verified before approval of the health app as part of a second level of the assessment process, which specifies that if data is to be shared or processed, this should take place via open standards proposed by the eHealth platform (26).

However, most of the studied countries and regions are still exploring how to import the DTx data and to incorporate it as part of the longitudinal health record of each patient. The level of interoperability between different functions of EHR varies among the countries based on different indicators such as the level of usage by different care organizations, the type of data, or characteristics of data exchange. For example, Germany shows more widely a low level of health data exchange e.g., the ePrescription system is still on piloting phase (56). A rather similar case applies for France, as the use of national EHR systems, and the level of usage is slightly higher than that of Germany. Given that most EU countries' national-level EHR systems are in the phase of being rolled-out and interoperability

to all care sectors, facilities and practices is not fully established, integration of DTx data into routine care and Health Information Systems (HIS) is and will remain more a vision than reality in the near future.

As such, many DTx operate in their own "data bubble" due to the limits of the health system and its infrastructure consisting mostly of EHRs. An interesting approach to DTx data integration is represented by the interoperable mConnecta platform developed by the Catalan government (30). The platform collects data produced by devices that are not normally collected within the framework of formal healthcare provision services (e.g., EHR). mConnecta stores data from mobile apps, wearables, and medical devices and integrates the generated data with the EHR, and with available data for standard care on primary and hospital settings. At the moment of data collection, the platform was being piloted in two hospitals and two primary care settings.

Secondary Use of Data and Data Reusability

Secondary use of health data, and DTx data in particular, is a complex topic as the structure of data often hinders effective data use and overly strict data protection laws limit the use and extents of secondary purposes. Several strategies and policies address the secondary use of health data. In the National Data Strategy recently published by UK, secondary use of health data is seen as a top priority, and strategy goals related to use of health data in research have been defined. Currently, health data is used at the NHS level mostly for research and monitoring purposes, but DTx data is not used for this purpose even though there is interest (57). In Belgium, the Data for Better Health Strategy proposes strategic actions and addresses challenges to support secondary use of health data (58). However, the role of the healthdata.be platform, whose mission is to facilitate the data exchange between healthcare professionals and researchers to increase public health knowledge, is unclear with regards to DTx data (59). In France, innovation from health data is facilitated by the newly established Health Data Hub (HDH), which interfaces with data providers and data consumers and through a general, however non-exclusive practice, of entering into contact with data consumers. The HDH handles both personal and anonymized data (4 categories of data: personal for care, personal for research, research under specific conditions, RWD and anonymized data). It also supports the hospitals and other data generating organizations to collect data meeting the quality and interoperability requirements for an eventual multi-purpose use. Hospitals partner with the HDH, and they in return get back the results of the research they contributed to, but also other HDH supported research. Appropriate governance is in place to make sure there is equal access of all industry and full transparency of such access. Industry can get access to data from the HDH if there is a clear and validated protocol for the purpose and way of use. Industry may contribute some budget globally into a fund, reinvested into supporting the functions of the HDH. In Germany, secondary use of DTx data is allowed (40), and secondary use for research purposes upon patient consent will be possible once the technical infrastructure in Germany allows data transfer between the patient's EHR and the Research Data Center (60), the central organization of primary datasets for legitimate research purposes.

None of the countries had yet put in place a formalized approach to the reuse of data originating from DTx, for secondary purposes yet it was usually an aspiration for the health system to do this. Although health data research centers exist, the lack of technical capabilities (interoperability with EHRs, structured data) strongly prevents the effective re-use of data. We did not encounter a scenario in which the developer of the DTx is permitted to commercially utilize the data they collect.

There is an increasing interest, especially from the medical device and Artificial Intelligence (AI) sector, to have access to patient-generated data. Therefore, DTx generated data is a valuable resource. The obstacles to reusing the data seem to lie between legislative restrictions and the implementation of rich enough interoperability and control over the data despite existing standards, methodologies and solutions (see other papers in this volume). There is very little DTx data reuse culture. A major identified benefit of shared DTx data would be decentralized clinical trials where manufacturers obtain (given the consent of all involved patients) real-world datasets which can be used as an evidence base for any impact assessment without conducting patient recruitment. From the patient's perspective, consent management could be improved through support models or platforms to make it as easy as possible to consent to their data being used for specific trials or studies. Another possibility is to integrate patient-generated data into the same approval processes and secondary use models designed for EHR data.

KEY FINDINGS AND RECOMMENDATIONS FOR ENABLING BETTER INTEGRATION OF DTX INTO HEALTHCARE SYSTEMS

Success Factors for Scaling Up DTx Adoption

Navigating the health system, its organizations and understanding its structures can be challenging especially for new market entrants, but also for established players when new frameworks are introduced. While regulating market access is the main responsibility of regulators, there are needs for guidance and clear paths for DTx providers to understand the different market entry options, responsibilities of relevant bodies and the processes toward DTx certification and deployment as well as the steps within these processes. The investigation revealed several factors that could enable rapid uptake of innovation and ensure a better healthcare market access. These main success factors are summarized as recommendations in **Table 1** and discussed in the rest of this section.

Inclusive National Strategies for DTx

Currently, DTx solutions are not part of national or regional strategies but rather only parts of certain

TABLE 1 | Summary of the success factors identified through this research.

Inclusive national strategies for DTx
• DTx should be recognized as a key enabling technology and should be included into broader digital health strategies to ensure a harmonized and integrated approach in the digital health ecosystem.
Regulation for innovation
• Countries should define a framework and criteria for assessing DTx that optimizes and balances regulation and innovation. • Frameworks needs to consider the adoption process from the provider perspective in addition to the regulatory perspective. • Features of the evaluation procedures should include a publicly available standardized catalog of the required evidence, indicator types and a defined set of accepted methods.
Clinical evidence
• Assessment of clinical impacts needs to highlight the necessary changes to care processes and new interactions between care stakeholders. • The required evidence should be aligned with the requirements stipulated in the European Medical Device Regulation, to create a portfolio of evidence that is valid and relevant across the EU. • Assessment frameworks should provide temporary reimbursement for a CE marked DTx to enable placing in the market and use of the solution by patients and clinicians for a limited period of time, so DTx providers can gather real-world evidence to support clinical and health economic evaluation.
Socio-economic evidence
• Changes to the way of clinical practice and workflow in general need to be considered and pose opportunities for extending the cost-efficiency of the DTx itself. • The healthcare system should provide necessary information, especially on health systems costs, to the DTx provider, for the benefit of both parties.
Additional assessment criteria
• DTx are patient-facing, therefore additional criteria for interoperability, privacy, and security by design, on top of Medical Device Regulation certification, as well as usability and accessibility criteria should be explicitly specified.
Clear-cut assessment and certification pathways for DTx solutions linking approval and reimbursement
• There should be a clear link between DTx certification and reimbursement, and namely, certification should trigger rapid price setting and a reimbursement mechanism. • HTA pathways for DTx solutions should be established, together with clear guidelines, requirements, and information on the process (e.g., length of processing and regular status updates).
Fostering innovation through the DTx industry
• High research costs can partially be leveled through public funding during the data generation phase, and national innovation programmes should be put in place to encourage partnerships between industry and health care providers to work together. • Manufacturers should be offered possibilities to generate data from real patients, where clinical pathways can appropriately accommodate the DTx innovation, while reimbursing the solution at an appropriate level. • The risks for public payers can be managed by requiring strict scrutiny for entry but at the same time allowing providers to discover the optimal ways of working under real clinical conditions. • Accompanying guidelines for providers significantly improves the transparency of the acceptance process, reduce the business risks for providers and are expected to stimulate innovation. • DTx frameworks should aid small and large companies already in the phase of data generation through initial financial support (through funds or commercial revenue in combination with an initial marketing authorization). • New agile business models, such as pay for use, or the prescription of apps, could be valid and useful alternatives to current licensing-based revenue streams for companies. • Payers interested in such models may consider implementing dynamic ways to adjust price and reimbursement levels. This can be achieved, for instance, by basing the price on volumes of usage or reimbursement after a defined period of use by patient.
Strategies for change management and capacity building for the involved stakeholders
• Change resistance can be managed on a general level by increasing the understanding of the potential impacts of DTx and by transparently communicating the (desired) changes and their implications. • Information of the approvals and assessment of DTx should be visible to all stakeholders involved in decision making and potential adoption. • Enable patients and clinicians to decide on the relevance of a DTx for their individual needs by facilitating the comparison of DTx solutions for specific conditions or within a certain care pathway, based on quality criteria that they can easily understand.
Secondary use of DTx data and use of RWE data
• Decentralized clinical trials could offer manufacturers the possibility to use real-world datasets to generate evidence for impact assessment without having to recruit trial patients. • Consent management could be improved through support models or platforms. • Whilst secondary data use is probably not a direct success factor for a DTx developer, this secondary use can be a success factor for learning from the data to better design and implement more personalized care.

innovation programs or laws, which contributes to lower uptake of DTx solutions. Given the complexity of the solutions, DTx should be recognized as such and should be included into broader digital health strategies to ensure a harmonized and integrated approach in the digital health ecosystem.

Regulation for Innovation

Countries should define a framework and criteria for assessing DTx that optimizes and balances regulation and innovation. Many such frameworks are publicly available both from official national frameworks, trade organizations (e.g., DTxAlliance), and working

groups (e.g., EUnetHTA), on which governments can build.

A DTx framework needs to consider the process from the provider perspective in addition to the regulatory perspective. Key aspects to be addressed are transparency (of the process and of the criteria) and efficiency. Requirements, processing time and status of the application should be clear and visible, preferably accessible online. The process from submitting the application to certification should not take more than a few months at maximum.

For DTx providers, the one key support feature of any evaluation and assessment procedure is a publicly available standardized catalog of the required evidence, indicator types and a defined set of accepted methods. Compared to the wide field of medical device assessment, a more streamlined and speedier process is overall preferred to enable the innovative potential of any DTx solution. Recognized methods such as Randomized Controlled Trials, Cost-Benefit Analysis and Cost Effectiveness Analysis are regarded as appropriate and rigorous tools for the generation of evidence, but other forms of evidence should be accepted depending on the specifics.

Clinical Evidence

In terms of clinical evidence generation, demonstration of improved quality of care and better clinical outcomes through DTx is the desirable goal. Clinical trials are an industry-standard with long-standing acceptance and scientific robustness and can be regarded as the gold-standard for quantifying clinical impacts. However, DTx fail to achieve their full potential if they remain isolated within existing care pathways. Assessment of clinical impacts will however need to also highlight the necessary changes to care processes and new interactions between stakeholders. The exact type of required evidence can be aligned to the requirements stipulated in the European Medical Device Regulation to create a set of evidence that is valid and relevant also across countries. A potential solution to balance clinical evidence and real-world results is to offer provisional acceptance period based on clinical evidence. This period can be utilized by the DTx provider to gather information on the real-world effects.

Socio-economic Evidence

For socio-economic evidence health systems and healthcare providers need to provide data and support to DTx providers to achieve the best results for all parties. Using general cost estimates does not suffice when comparing DTx to an existing and specific care pathway. Changes to the way of clinical practice and workflow in general need to be considered and pose opportunities for more cost-efficiency. The obligation to furnish this evidence, including the cost of its production, is always to be borne by the developer. On the other hand, available socioeconomic data collected for other primary purposes (e.g., reimbursement of health care) is not always of suitable quality for the purposes of DTx assessment. A national framework could provide temporary reimbursement for a CE marked DTx to enable placing in the market and use of the solution by patients and clinicians for a limited period of time, while real data can be collected to support clinical evaluation. The healthcare system should provide necessary information, especially on costs to the DTx provider for the benefit of both parties.

Additional Criteria

DTx are patient-facing, therefore additional criteria for interoperability, privacy, and security by design, on top of Medical Device Regulation certification as well as usability and accessibility criteria should be explicitly specified. For all of these, industry standards (such as ISO 82304-2 for health software) do exist, and they provide the blueprint for these requirements (61).

Clear-Cut Assessment and Certification Pathways for DTx Solutions Linking Approval and Reimbursement

DTx providers use several business models to commercialize their products, including license agreements and direct negotiation with hospitals. Current HTA pathways are rather slow and complicated to navigate and do not necessarily lead to reimbursement for DTx products. This makes it difficult for developers to scale up, is unfriendly to new market players, and inhibits innovation. To facilitate rapid uptake of innovation, there should be a clear link between DTx certification and reimbursement, and namely, certification should trigger rapid price setting and a reimbursement mechanism.

HTA pathways for DTx solutions should be established, together with clear guidelines, requirements, and information on the process (e.g., length of processing and status). Depending on the specifics of the country, a process analogous to pharmaceuticals may be sensible, but this process should be much more streamlined and shorter than with pharmaceuticals and should focus on the effects of specific DTx within the care pathways they are designed to be applied in. Experts remarked that re-using pathways for pharmaceuticals for DTx can endanger DTx, if the existing shortcomings of pharmaceutical pathways are transferred to DTx pathways.

Fostering Innovation Through the DTx Industry

The costs (patient recruitment costs, personnel costs for long trials, development costs) significantly raise product development costs and may discourage potential DTx providers. High research costs can partially be leveled through public funding during the data generation phase, and national innovation programs may be put in place to encourage partnerships between industry and health care providers to work together on ICT enabled re-engineering of clinical processes and demonstrating the value of the DTx innovation at hand.

An alternative approach would be offering manufacturers a possibility to generate data from real patients, where clinical pathways can appropriately accommodate the DTx innovation, while reimbursing the solution at an appropriate level. The risks for public payers can be managed by requiring strict scrutiny for entry but allowing providers to discover the optimal ways of working under real clinical conditions. The German DiGA model with its real-world evidence process, where the manufacturer receives initial approval and reimbursement for a year to collect additional data, is one example of balancing risks, level of evidence and overall duration of the assessment procedure. Accompanying guidelines for providers significantly

improve the transparency of the process, reduce the business risks for providers and are expected to stimulate innovation.

Companies have been developing and marketing DTx solutions as Medical Devices for many years and are expected to continue to do so. However, the introduction of new and more lucrative business models and market entry pathways have a great potential to spur innovation. As such, DTx frameworks should aid small and large companies already in the phase of data generation through initial revenue (through funds or commercial revenue in combination with an initial marketing authorization). This step would lower the bar for smaller companies to enter the market with less capital and provides an incentive to enter a clinical and economic evaluation and assessment process which requires thorough and costly data collection methods (such as RCTs).

New agile business models, such as pay for use, or the prescription of apps could be a solid alternative to current licensing-based revenue streams for companies. Payers interested in such models may consider implementing dynamic ways to adjust price and reimbursement levels. This can be achieved, for instance, by basing the price on volumes of usage or reimbursement after a defined period of use by patient.

Strategies for Change Management and Capacity Building for the Involved Stakeholders

Traditional healthcare systems, with their complex networks of stakeholders and responsibilities, have developed a certain resistance to radical change. This should be considered (with sensitivity but as an obstacle) when conceiving new frameworks, even though change itself cannot be avoided. However, change resistance can be managed on a general level by increasing the understanding of the potential impacts of DTx and by transparently communicating the (desired) changes and their implications. This is a task for both the regulators and payers, and for DTx providers. Clinicians broadly trust published studies and data on drug effectiveness and treatment risks. Information of the approvals and assessment of DTx should be visible to clinicians and handled in a similar manner.

Patients are expected to adapt quickly to changes introduced by DTx, provided that they can trust them. Health and wellness apps already play a significant role in mHealth, while there currently is a lagging of DTx in the healthcare system. One way for enabling patients and clinicians to decide on the relevance of a DTx for their individual needs would be to filter and compare DTx solutions for specific conditions or within a certain care pathway, based on quality criteria that they can easily understand.

Secondary Use of DTx Data and Use of RWE Data

Data collected by DTx is not fully harnessed in Europe. Although in certain cases it is planned, no DTx data is used in the health system for other uses than the primary use within the DTx, although strategies for the secondary use of health data have been defined. Real-world evidence is an interesting topic, but its potential is mostly left unused. Better access to data bears huge potential to realizing additional benefits for businesses and governments. Decentralized clinical trials could offer manufacturers the possibility to use real-world datasets to generate evidence for impact assessment without having to recruit patients and consent management could be improved through support models or platforms. Whilst secondary data use is probably not a direct success factor for a DTx developer, this secondary use can be a success factor for learning from the data to better design and implement more personalized care. This source of valuable data might incentivize health systems to promote wider DTx adoption.

Strengths and Limitations

The approach to the investigation sought a thorough analysis of the current situation regarding adoption of digital therapeutics in five selected countries and regions.

The investigation included interviews with experts with intimate knowledge of relevant national and regional DTx efforts. In most cases, the interviewees were representatives of the bodies responsible for running or setting up DTx national or regional programs, or representatives of DTx providers who were or are planning to take part in those programs with DTx solutions they have been developing. However, the topic of digital therapeutics is a fast-moving one, and despite best efforts, it may be possible that brand-new developments are not considered. Some of the interviewed experts might be unfamiliar with other relevant initiatives within their national systems. For example, only recently did President Emmanuel Macron announce his desire for France to replicate the German DIGA approach, the implications of which are only now starting to be revealed. DTx adoption and research into good national and regional practices is an exciting area which requires further attention in the years to come.

Pertinent good practices and examples may be available in other European countries, and some of them have been communicated to the investigators, e.g., through the multi-stakeholder expert workshop which hosted experts from many EU countries and who reflected on their own national experiences. While many expert inputs at the workshop confirmed the general conclusions of the investigation as well as the identified success factors and barriers to DTx adoption, the investigation cannot generalize its conclusions and recommendations across Europe, since they have only been derived from the five investigated countries and regions. Further work is needed to validate these findings and success factors more broadly across Europe, although the authors suspect many of them findings will be generally applicable.

Recommendations for Future Work

The findings in this paper are preliminary and based on a limited sample of countries and experts per country. It may be noted that these success factors and potential recommendations to decision makers are more specific to the context of DTx adoption than the general success factors for digital health adoption that were identified from the literature reported earlier. Our findings should be validated by wider range of stakeholders: a greater number and diversity of stakeholders from more European countries. We believe that the success factors found through our

research represent the main factors on a high level. The practical approaches to these factors should be investigated further. This field is advancing quickly, and the value and feasibility of different models will be tested in the coming years. Effort should be placed on cross-country recognition of evidence and certification.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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EU-Funded Telemedicine Projects – Assessment of, and Lessons Learned From, in the Light of the SARS-CoV-2 Pandemic

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The SARS-CoV-2 health emergency has demonstrated the need for developing structured telemedicine systems to protect citizens from the spread of the virus. Thereby, their importance and the necessity to tailor their diffusion at large scale for providing services both at a distance and in time has been shown. For these reasons, the European Union advocates the digital transition of health systems for the next 5 years. The main aim of this work is to revisit the telemedicine research projects financed by European Community during the period 2000-2020 with particular respect to the results derived from their application. The analysis showed that some integration of tele-care and tele-health could be obtained with tele-monitoring systems and the implementation of Electronic Personal Record (EPR). Furthermore, telemedicine allows enhancing health care in critical environments, to protect health and life of the most vulnerable patients, and to encourage cross-border dialogue. The criteria of "from distance" and "timely delivered" are granted, but the effectiveness of the overall offered services highly depends on the availability and the quality of the input data. Unfortunately, this remains a relevant problem in the SARS-CoV-2 pandemic.

Keywords: tele-health, tele-care, telemedicine, tele-monitoring, tele-rehabilitation

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TELEMEDICINE DEFINITION AND APPLICATION IN EUROPE

Telemedicine concerns all health practices, provided remotely, considered as an innovative medical service in contrast to traditional face-to-face practice. It allows breaking down the geographical distances and aims at equalizing access to care using information and communication technologies (ICTs), thereby enabling the secure transmission and sharing of medical data and information for monitoring and controlling patients' clinical status.

Telemedicine services are classified as specialist telemedicine that comprises tele-visit and teleconsulting; tele-health; tele-care; and tele-rehabilitation. In particular, tele-visit is a medical action, which involves the health professional and the patient resulting in a remote electronic prescription of specialist visits or therapies. Teleconsulting, instead, is an information exchange activity between physicians and/or health workers on a specific clinical case for the provision of a second opinion. It plays a key role in emergency cases. Tele-health mainly concerns the

management of patients with chronic diseases and allows general practitioners to monitor and manage them. Tele-care is related to the provision of health care services at citizens' home, especially addressing the elderly population. Tele-rehabilitation is a medical action that aims at recovering cognitive and physical performance status of patients. In addition, tele-monitoring can be considered as an operative procedure, which aims at the control of physiological parameters, such as insulin or blood pressure, through the use of wearable devices. **Figure 1** represents the different components of telemedicine.

Throughout the last two decades, the European Community has been supporting telemedicine through the funding of several research projects powered by technological development and the consequent increase in interest in telemedicine. In fact, despite the opportunities and benefits related to Telemedicine services, to date their large-scale spread has been mostly slowed down by the high costs of technologies, the absence or inadequate laws for eHealth and privacy, the lack of capability to use ICT for elderly patients, the frequently unpredictable evolution speed of the patient status, but sometimes also the lack of qualified actors. Therefore, here we assess selected EU projects on telemedicine applications through the evaluation of their results to explore valid and persisting returns envisaged from their application/implementation. **Figure 2** represents the flow diagram including the path we followed to select at least 20 projects. **Table 1** shows the projects we have found by searching on https://ec.europa.eu/regional_policy/en/projects and https://artemis-ia.eu/projects-1.html, using the following keywords: "telemedicine," "tele-health," "tele-care," "tele-monitoring," "tele-rehabilitation" and "tele-visit" through the period 2000-2020. Moreover, we checked for reported project outcomes and the clinical area of intervention. Interestingly, almost all the selected projects applied telemedicine services to address general chronic disease management, and a few of them deployed telemedicine as a tool to diagnose and treat patients in a remote or rural areas. Chronic disease management continues to be one of the greatest healthcare challenges for providers. In fact, as chronic diseases continue to overstress health systems over time. Thus, telemedicine systems can improve efforts in chronic disease management, enhancing patients' engagement, improving the quality of care and the efficiency of used human and economic resources.

THE CORONAVIRUS LESSON FOR HEALTHCARE TRANSFORMATION

The Coronavirus has confronted almost all countries around the globe with a series of unprecedented health, social, ethical and economic challenges. The pandemic has brought to light the consequences of a series of old problems that have exacerbated numerous situations of vulnerability, marginalization and suffering. In Italy, the pandemic has violently hit the most vulnerable people, while worsening the significant inequalities that plague our country, as evidenced by the social differentials that can be found in the excess mortality caused by COVID-19 (18). The health emergency has highlighted the strengths and criticalities of the sanitary system. The austerity policies adopted during the years have made it more efficient, but unprepared to deal with one demand shock like that imposed by the pandemic. The territorial services failed to stem the emergency in a timely manner. The hospitals challenged with COVID-19 cases have proved to be in difficulty in dealing with a pressure, due to the constant dwindling of economic resources, health personnel, and beds, which have been shorten over the last decades. In Italy, the protraction of expenditure control of health services recorded between 2009 and 2018 a particularly large reduction of the resources allocated to health, which has extended the gaps in terms of public health expenditure per capita. In 2018, the expenditure per capita was in Germany twice as much, and France 60 percent higher, than the Italian one (19).

Government Responses

In order to support the recovery and resilience of Member States, the European Union approved the Next Generation EU program (20, 21), which allocates 750 billion € (20–22). One of the aims of this ambitious project, which will have closed by 2026, was to improve the digital transition of healthcare systems (20–22). Italy is the first beneficiary of this innovation program, because it was the most affected Member State, and it approved its National Recovery and Resilience Plan (21, 22). It promotes smart, sustainable and inclusive growth both through investments aimed at enhancing physical and human capital, and reforms, which should have an impact on productivity and competitiveness over the medium and long term. The European Union shall make available to Italy a financial contribution in the form of non-repayable support, to be legally committed by 31 December 2022. Moreover, the Mission 6.1 of the plan is focused on proximity networks, facilities and telemedicine for territorial healthcare assistance (22). The objective of this component is to strengthen the Italian NHS, enhancing the protection against environmental and climate-change related health risks, and better responding to the communities' needs regarding local care and assistance (22). In fact, local healthcare assistance is fragmented and subject to regional disparities that result in different levels of healthcare provisions and health outcomes across regions. The provision of integrated home care services is considered low, and the different healthcare and social service providers are considered to be only weakly integrated. The Investment 1.2 on Home as the first place of care and telemedicine consists in a large-scale adoption of telemedicine solutions and supporting healthcare innovation (22). The goal is to increase the number of people treated in home care to 10% of the population over 65 through investment in hardware and increased service provision, and the establishment of Territorial Coordination Centers (22).

The governance of the Italian Recovery and Resilience Plan is divided into several levels. The Ministry of Health is entrusted with the leadership of the project, together with the government working group, which must ensure that the execution is consistent with the political direction, the timing of the Plan and the needs of the territories (21, 22). AGENAS, the Italian National Agency for Regional Health Services, is responsible for implementing the Mission 6 (21), and its technical working group

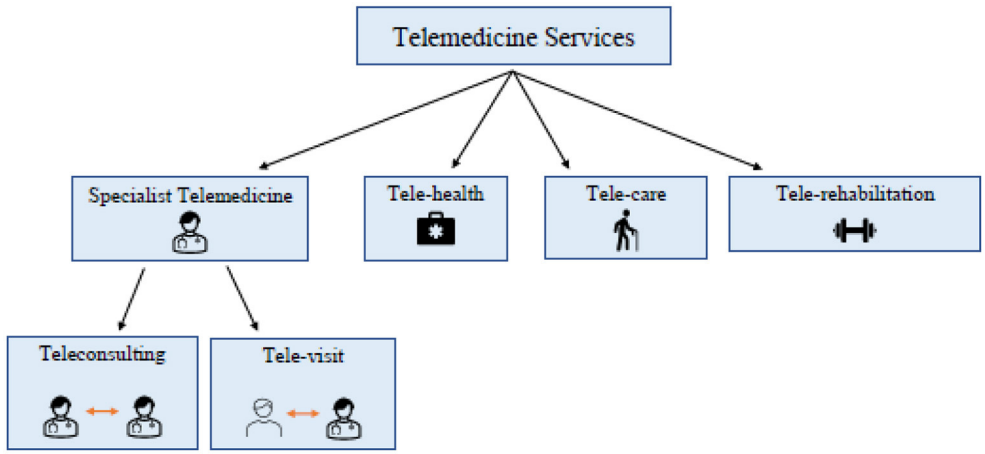

FIGURE 1 | Schematic representation of the different telemedicine components.

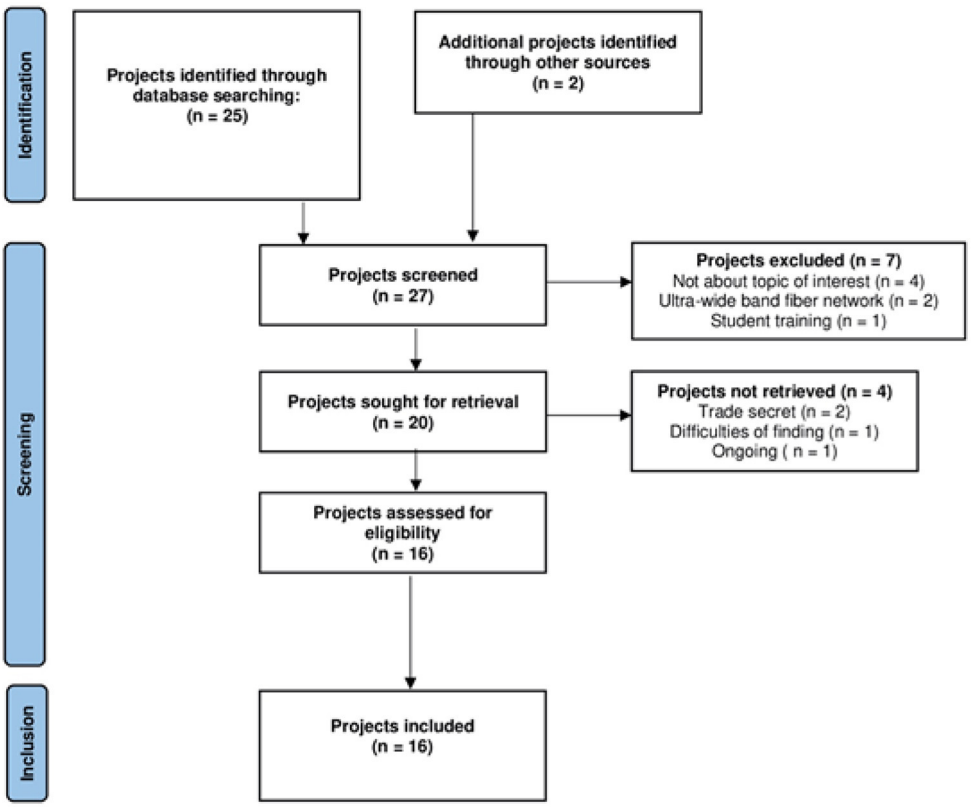

FIGURE 2 | Flow diagram of project search and selection.

will be in charge to draw up the projects' guidelines, evaluate the proposals, oversee the regional procedures, and receive and verify the reports sent by the Regions.

As exposed above, the COVID-19 pandemic has highlighted the importance of technology, which allows developing structured and organized systems based on telemedicine services (23). At the outbreak of the COVID-19 pandemic in Italy, no appropriate rules within telemedicine have been implemented. The only one, dated in 2014 (24), was very vague and generic, limiting itself to the presentation of indications on the definitions, regulatory aspects and tariff services without a real boost to the application of telemedicine services. This

caused the diffusion of local and isolated experiences. Indeed, each Italian Region has adopted protocols based on telemedicine services to delimit the virus spread, establishing the need to define a national standard. In November 2021, the number of active telemedicine experiences in Italy were 369 and unequally spread at the national level as presented in **Figure 3**. Considering the Italian Regions, Liguria has implemented tele-visit through a dedicated platform and individual experiences of tele-monitoring and tele-consulting for cardiological, nephrological, and diabetic area, whilst there is no documented experience of tele-rehabilitation. Moreover, in our Region, the Policlinic Hospital San Martino has implemented telemedicine service for cancer patients, but only for cases that do not require a clinical visit but only a consultation to view laboratory or radiological tests performed externally.

SPECIALIST TELEMEDICINE PROJECTS

Among the projects selected for this study, 6 are focused on Specialist Telemedicine and briefly described below (**Table 2**). Since the early 2000's especially with Tel Lappi project, Finland has approved political strategies aimed at setting the foundations for a teleconsulting system through the acquisition of the equipment for videoconferencing for strengthening the emergency system in the Lapland Hospital District (1). Moreover, the health personnel involved in this project was trained to correctly use these technologies (1). As already stated, teleconsulting simplifies emergency procedures in problematic and rural areas. The SOS MAM project and the following e-Res@Mont project have developed a teleconsultation platform around the Mont Blanc thanks to the co-operation between France, Italy and Switzerland. This innovative platform permits nurses from mountain huts to exchange medical opinions with doctors based on the hospital in Aosta, the main city of the Region, during emergencies. Furthermore, to prevent potential connectivity problems, researchers have developed an offline application to support nurses' clinical evaluation when the connection is absent (12). Starting from 2002, the Pomerania Euroregion, the border area between Germany and Poland (4), was the protagonist of several European projects (i.e., The Telemedicine Pomerania project and Telemedicine in the POMERANIA Euroregion project), which aimed at implementing videoconferencing network between the 2 countries. Interestingly, since 2012 on the German side, a multidisciplinary tele-tumor conference takes place every week in several hospitals, while on the Polish side this program is not implemented (4). However, tele-conferencing for board meetings is successfully developed (4) to improve the co-operation and the medical information exchange between the two nations. The Development of Cross-Border Telediagnostic and Teleconsultation Network in Health Institutions (TELEDIAG) project is an example of cross-border teleconsultation network between Serbia and Romania (8). As stated by the project researchers, teleconsulting offers many advantages such as time-savings during emergency state (1, 12), because rescuers can execute medical procedures under the guidance of doctors who are hospital based. Moreover, it leads to an economic saving because some activities can be realized moving data and not people (1, 12), and reducing travels at all (1, 4).

TELE-REHABILITATION PROJECTS

In 2009, Scotland, Finland and Sweden have developed rudimental services based on ICTs to support rehabilitation for elderly and chronic patients with web services, audio and music programs, and videogames (5). Subsequently, the 9 remote exercise classes for rehabilitation of the ITTS (Implementing Transnational Telemedicine Solutions) project focused on the generation of a rehabilitation program. In this project, rehabilitation was based on videoconferences between physiotherapists and home-based patients, becoming a common medical practice in Scotland and Northern Ireland (9). The Gamification Against Phantom Pain (GAPP) project has set up a prototype of a tele-rehabilitation platform for patients with phantom limb pain. Thanks to this mobile platform, patients are able to exchange messages with therapists and select their training program centered on mirror therapy (13), which can be remotely executed during daily life practices. Moreover, this mobile application helps therapists to monitor and manage the phantom limb pain.

INTEGRATION OF TELE-CARE AND TELE-HEALTH PROJECTS

Tele-care integration can be realized through the installation of ICT solutions, such as sensors, automatic controllers, tele-alarm systems and portable devices (25), inside the homes, for instance, of elder, chronically ill, and disabled citizens. During the course of the iAge (e-inclusion in Aging Europe) project, it has been shown that most of the homes in the Netherlands are not suitable for disabled citizens due to uncomfortable bathrooms and narrow hallways (10). To overcome these architectural limitations, opened elevators, bathroom equipment and electronic doors could be installed (25). Furthermore, there are three projects centered on the implementation of tele-care solutions. The ITTS project has established 2 tele-care programs: one for chronic patients and the other for patients with multi-morbidity. This project aims at improving patients' independence through the installation of several technologies in their home, such as epilepsy and disability discrimination sensors (9). Another example of tele-care integration is represented by the iAge project, which has involved the North Sea Regions. This project encompasses pilot programs aiming at the creation of a comfortable home environment based on ICTs and home automation for the elderly population. This project has developed the Home Automation Living Platform (HALP) allowing elderly people to live safely alone in their houses. In fact, the system, through the use of sensors, is able to manage all the devices present in the house and detect eventual falls (10). Moreover, the Italian SmartCare project of tele-care integration supported by ICT is focused on elderly with chronic diseases with particular attention to heart failure. The results of the study show that the use of ICT can reduce the

TABLE 1 | Projects characteristics.

Project name	Countries	Project duration	Medical field	Outcome	Reference
TEL LAPPI Project	Finland	2000–2006	Radiology; Emergency system	Video conferencing, emergency care and electronic feedback system, as well as digital photographing and image transfer, were initialized in the Lapland Hospital District and member municipalities in the area near the hospital. Moreover, the long-term storage of images was readied and data protection was improved.	(1) https://ec.europa.eu/regional_policy/en/projects/Finland/telemedicine-services-in-lapland
IANUS	Spain	2007–2013	All medical fields	IANUS allows the recording of clinical data, this avoid of repeating procedures potentially harmful to patients. The most important result is the wide availability of clinical data for health care professionals. As a result, the gap between primary and secondary care is bridged.	(2) https://ec.europa.eu/regional_policy/en/projects/Spain/electronic-medical-record-system-ianus-improves-regional-health-care
The New Business Model for Ambulatory Monitoring of Patients Suffering from Congestive Heart Failure	Germany	2007–2013	Cardiology	The project has developed an outpatient model for the monitoring of chronic patients allowing the reduction of hospitalizations.	(3) https://ec.europa.eu/regional_policy/en/projects/Germany/high-tech-medicine-for-heart-patients-2
Telemedicine in the POMERANIA Euroregion	Germany Poland	2007–2013	Radiology; Oncology; Diabetology; Clinical pathology	Tele-tumor conferencing, Tele-radiology service and Tele-pathology service have been successfully established both in Germany and in Poland. Tele-ear nose throat service, Tele-ophthalmology service and Tele-stroke service have been only established in Germany. Data exchange between the two nations has improved.	(4) https://ec.europa.eu/regional_policy/en/projects/Poland/telepom-uses-ict-to-improve-medical-care-in-rural-areas-at-the-german-polish-border
The Telemedicine Pomerania project	Germany Poland	2010–2012			(4) https://ec.europa.eu/regional_policy/en/projects/Germany/telemedicine-pomerania-improves-healthcare-in-sparsely-populated-regions
The Competitive Health services project	Finland Partners: Ireland - Norway Scotland Sweden	2008–2010	Diabetology; Cardiology; Chronic patient with aphasia, dyslexia and Parkinson's disease	In Finland, the use of teleradiology has rapidly increased becoming common practice; three fourths of health centers used telelaboratory services and the coverage was 64% in 2007. Scotland has demonstrated to have a solid base of existing eHealth initiatives, both at national level and locally in the Highland region. In 2008, Sweden recorded 45 afoot e-health services, some based on tele-consultation and tele-monitoring. In Norway, telemedicine services were used for remote diagnosis and advices of treatment, second-opinion, communication between staff and access to radiology report system.	(5) https://ec.europa.eu/regional_policy/en/projects/Finland/healthcare-goes-electronic-under-northern-skies
ICT for Health	Belarus; Germany; Denmark; Estonia; Finland; Lithuania; Latvia; Norway; Poland; Russia; Sweden	2009–2012	Patients with chronic disease	Health technologies have allowed patients to improve the prevention and the treatment of their chronic diseases. Thanks to self-monitoring technologies patients have increased the responsibility for their own health.	(6) https://ec.europa.eu/regional_policy/en/projects/Belarus/ict-for-health-strengthening-social-capacities-for-the-use-of-e-health-technologies-by-the-aging-population

(Continued)

TABLE 1 | Continued

Project name	Countries	Project duration	Medical field	Outcome	Reference
CHIRON - Cyclic and person- centric Health management: Integrated appRoach for hOme, mobile and clinical eNvironments	United Kingdom - Slovenia - The Netherlands - Hungary - Belgium - Greece - Italy - Spain	2010–2013	Cardiology	This project has developed a prototype of middleware aimed at tele-monitoring chronic patients with congestive heart failure. It fully satisfies the requirements indicated by the personnel.	(7) https://artemis-ia.eu/project/17-chiron.html
Development Of Cross-Border Telediagnostic And Teleconsultation Network In Health Institutions (TELEDIAG)	Serbia - Romania	12/2010–02/2012	Radiology Oncology; Clinical pathology	The project has allowed creating a cross-border telediagnostic and teleconsultation network among 14 health units of the cross-border partners. Moreover, every health units have installed a software for telemedicine and specialized equipment.	(8) https://ec.europa.eu/regional_policy/en/projects/Romania/telediag-enables-faster-more-precise-diagnosis-and-better-treatment-for-patients-on-the-romanian-serbian-border
ITTS - Implementing transnational Telemedicine Solutions	Finland - Norway - Sweden - Ireland - Scotland	09/2011–03/2014	Diabetology Cardiology; Obese people; Patient with Inflammatory Bowel Disease; Patient with multimorbidity	ITTS project allowed implementing telemedicine solutions into everyday practice and the spread of knowledge among countries. The evaluation demonstrated that remote solutions are positively accepted by patients, there are positive returns on investment and the use of telemedicine can be sustainable.	(9) https://ec.europa.eu/regional_policy/en/projects/Finland/calm-cool-and-connected-telemedicine-project-boosts-health-care-in-the-northern-periphery
iAge: e-inclusion in Aging Europe	Netherlands Scotland Norway Germany Belgium Denmark	2012–2014	Elderly people	This project has enabled the development of the Home Automation Living Platform (HALP), which ensures elderly patients to stay alone in their houses as long as possible.	(10) https://ec.europa.eu/regional_policy/en/projects/Belgium/boosting-the-economic-and-social-e-inclusion-of-the-growing-over-65-group
SmartCare	Italy	2013–2016	Cardiology	SmartCare project has allowed reducing days of hospitalization for chronic patients, mainly for those with heart failure. Moreover, it has ensured a sustainable use of local nursing resources.	(11) https://ec.europa.eu/regional_policy/en/projects/Italy/smartcare-using-ict-to-enable-older-people-to-live-independently-for-longer
SOS MAM	France Switzerland	2013–2015	Patients with acute mountain sickness – mountain tourists – mountain dwellers	The project allowed setting up a telemedicine call center for expedition teams. Currently 10 medicine doctors work through an association called Altidoc to maintain telemedicine system. Through Altidoc they provide teleconsultations before departure and telemedical guidance to groups during their expeditions. The follow-up project is called e-Res@MONT.	(12) https://ec.europa.eu/regional_policy/en/projects/France/sos-mam-telemedicine-for-a-mountain-environment
GAPP - Gamification Against Phantom Pain	Germany	2015–2018	Patients with phantom limb pain	The project has allowed creating a tele rehabilitation platform for patients with phantom limb pain.	(13) https://ec.europa.eu/regional_policy/en/projects/Germany/gapp-german-project-treats-phantom-limb-pain-with-the-help-of-virtual-reality
Beratung zum Eintritt in den Gesundheitsmarkt in den USA	Germany	2015–2016	Diabetology	ESYSTA® system has simplified interaction and communication between doctors and patients, has significantly improved blood glucose control due to the optimized self-management by the patients and has simplified the documentation process for patients.	(14) https://ec.europa.eu/regional_policy/en/projects/Germany/advice-on-entry-into-the-us-healthcare-market

(Continued)

TABLE 1 | Continued

Project name	Countries	Project duration	Medical field	Outcome	Reference
e-Res@MONT	Lead Partner: France Partners: Italy Switzerland	2016–2018	Patients with acute mountain sickness – mountain tourists – mountain dwellers	The e-Res@MONT teleconsultation platform reduces the distance between patients and medical staff in a challenging environment, and improves the timeliness of monitoring, diagnosis and treatment. The telemedicine platform can also be used for medical tourism while removing language and cultural barriers.	(12) https://ec.europa.eu/regional_policy/en/projects/France/making-it-work-for-mountain-medicine-services-around-mont-blanc
E-coordination of bone and joint care in Cher	France	2016–2018	N/A	N/A	https://ec.europa.eu/regional_policy/en/projects/France/a-telemedicine-platform-facilitates-access-to-bone-and-joint-care-in-the-center-val-de-loire-region
AIR CARDIO	Italy	2017–2020	Cardiology	The AIR CARDIO project has developed a digital platform, which allows doctors to monitor the health of children suffering from congenital heart disease. During the Covid-19 health emergency, this system has allowed patients to decrease the risk of infection.	(15) https://ec.europa.eu/regional_policy/en/projects/Italy/air-cardio-a-lifeline-for-babies-with-heart-disease-in-tuscany
Community Areas of Sustainable Care and Dementia Excellence in Europe (CASCADE)	Lead Partner: France Partners: Belgium - Netherlands - United Kingdom	2017–2021	Elderly people and people living with dementia	CASCADE has developed a sustainable approach to elderly/dementia care, which has also reduced the strain on hospital beds and increased the quality of care. CASCADE allows people living with dementia to stay in their homes for as long as possible.	(16) https://ec.europa.eu/regional_policy/en/projects/Belgium/cross-border-project-develops-holistic-approach-to-dementia-care
Moore4Medical	Switzerland Germany Ireland Hungary Italy Spain Austria Netherlands Finland	2020–2023	People with sleep disease.	Ongoing project that aims at creating a bed-monitoring platform to control indiscreetly patients during their daily life.	(17) https://artemis-ia.eu/project/198-Moore4Medical.html

days of hospitalization due to the monitoring of patients' clinical parameters (26). Since 2006, in Scotland, the Scottish Center for Tele-health has been established to support the development of clinical tele-health projects. Additionally, in 2005, strategies to improve both tele-health and tele-care in the rural NHS Highland Area have been approved for supporting direct patient care, educational programs and videoconferencing networks (5). Besides, tele-health integration can be realized through the development of solutions that strengthen the integration between primary care and community services. These models are well represented by the Community Areas of Sustainable Care and Dementia Excellence in Europe (CASCADE) project, that provides flexible solution via the creation of residential facilities for demented and elderly patients (16). In addition, the New Business Model for Ambulatory Monitoring of Patients Suffering from Congestive Heart Failure project has developed a health care center based on telemedicine solutions (3). Importantly, it has been shown that the creation of these structures for chronically diseased citizens avoids the risk that non-acute patients occupy the wrong hospital bed (21).

ICT solutions enable the integration of tele-health and tele-care through tele-monitoring systems and Electronic Personal Record (EPR). Tele-monitoring system can improve health care through the use of appropriate platforms and medical devices, like blood pressure meter and pulse-oximeter (17), which are able to manage the safe transmission of patients' data to physicians for the control/treatment of chronic diseases. In 2008, Sweden established two ICT-based tele-monitoring services: the Care@Distance for patients with heart insufficiency and the Checkup-remote Monitoring of Physiological Parameters developed for those who have to check parameters frequently (11). Another example of tele-monitoring systems is the CHIRON prototype, which is composed of a home platform connected with medical devices and sensors, and the ICU client, which is a web application for personnel to check the patient's health status (7). Two European projects have developed tele-monitoring tools still available on the market. The first is the ESYSTA® system created by a German company that is a wireless system used to control blood glucose and insulin values in diabetic patients (14). The second is the AIR CARDIO platform realized by GPI Spa, which enables to manage children affected by congenital heart disease (15). These systems can simplify the communication between doctors and patients and improve the responsibility of patients (14)

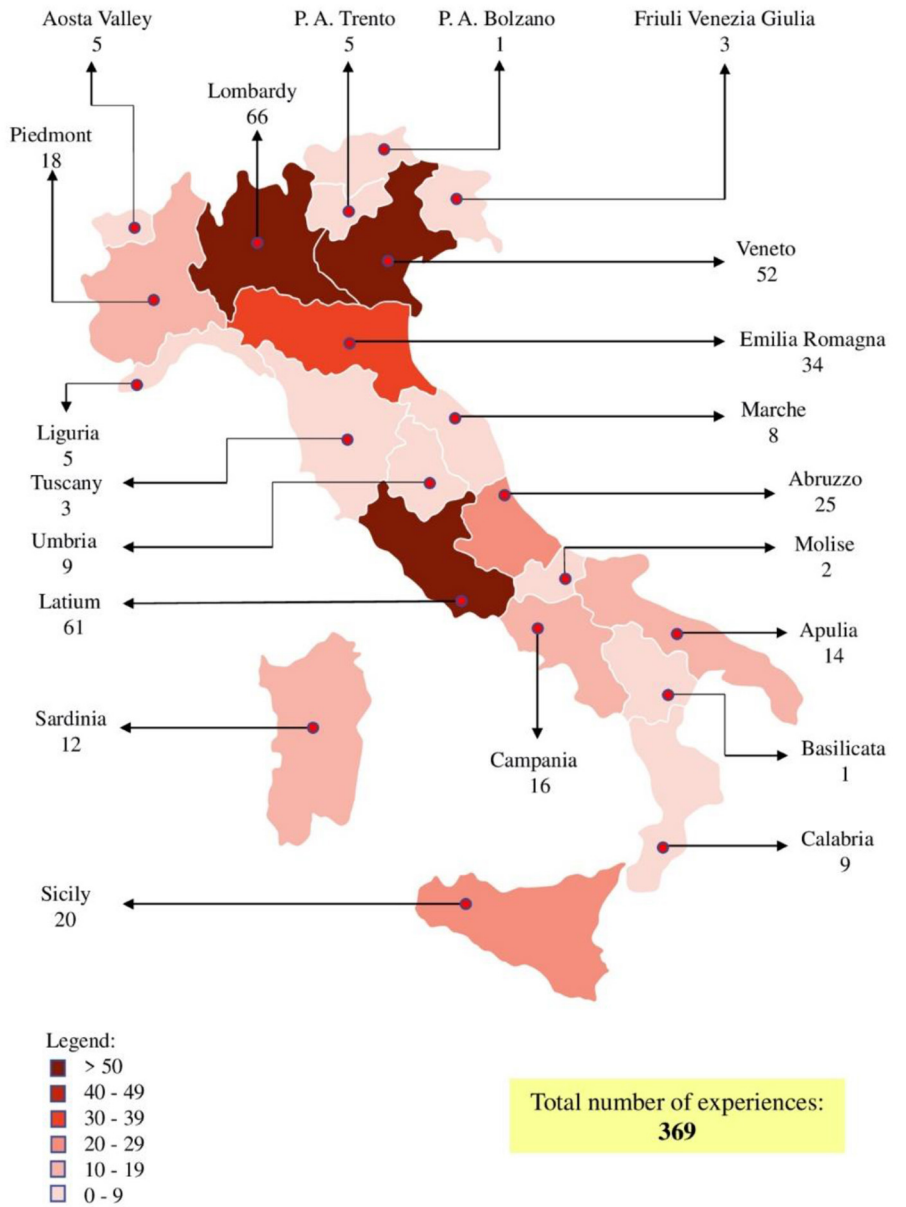

FIGURE 3 | Distribution of active Telemedicine experiences in Italy.

in the management of their illness. However, these benefits can only be achieved through a better acceptance of ICT solutions on the part of older citizens who show an aversion and unfamiliarity toward such technologies (21). For this reason, the ICT for Health in the Baltic See Region project has developed educational programs for chronic patients, in particular for the elderly, to improve their ICT skills, showing an increasing acceptance of e-Health among the users (6). Currently, the Moore4Medical project is developing a bed-monitoring platform using remote sensing of clinical parameters without direct contact of the device with the chronic patient. This innovative approach facilities monitoring of patients with sensitive skin (17).

As already mentioned, the EPR represents a digital archive of medical information which can be shared between different health service providers and patients (3), improving the organization of health systems. The ICT for Health project has established a multi-lingual EPR to support citizens, in particular chronically ill ones, in their travels abroad, and the sharing of medical document in the Baltic See Region (6). In Galicia, in 2013, 2,785,430 patients allowing the recording/consultation of clinical data (i.e., diagnostic images) and the e-prescription of

TABLE 2 | Projects classification.

Specialist telemedicine	Tele-health	Tele-care	Tele-rehabilitation
TEL LAPPI Project (1)	The Competitive Health services project (5)	Beratung zum Eintritt in den Gesundheitsmarkt in den USA (14)	GAPP - Gamification Phantom Pain (13)
SOS MAM (12)	ICT for Health (6)	SmartCare (11)	The Competitive Health services project (5)
e-Res@MONT (12)	The New Business Model for Ambulatory Monitoring of Patients Suffering from Congestive Heart Failure (3)	AIR CARDIO (15)	ITTS - Implementing transnational Telemedicine Solutions (9)
Telemedicine in the POMERANIA Euroregion (4)	IANUS (2)	iAge: e-inclusion in Aging Europe (10)	
The Telemedicine Pomerania project (4)	Community Areas of Sustainable Care and Dementia Excellence in Europe (CASCADE) (16)	The Competitive Health services project (5)	
Development Of Cross-Border Telediagnostic And Teleconsultation Network In Health Institutions (TELEDIAG) (8)	Beratung zum Eintritt in den Gesundheitsmarkt in den USA (14)	IANUS (2)	
	AIR CARDIO (15)	ITTS - Implementing transnational Telemedicine Solutions (9)	
		ICT for Health (6)	
		CHIRON - Cyclic and personcentric Health management: Integrated appRoach for hOme, mobile and clinical eNvironments (7)	
		Moore4Medical (17)	

medicine possessed the EPR-IANUS. The results of this project have highlighted how the usage of this system has improved the integration between primary and secondary care thanks to the accessibility of medical data to all healthcare professionals (6, 7, 11, 14, 15).

STUDY LIMITATIONS

This study is mainly affected by two limitations: the trade secret and the difficulty of retrieving the material. With respect to the trade secret, the beneficiaries of the selected projects are companies. Thus, it was not possible to receive project details. This specifically concerns the German Getemed for The New Business Model, developer of the Ambulatory Monitoring of Patients Suffering from Congestive Heart Failure project, the German Emperra GmbH E-Health Technologies realizing the "Beratung zum Eintritt in den Gesundheitsmarkt in den USA" project, and the Italian GPI SpA with the AIR CARDIO project.

Through the trade secret approach, industries defend their products and knowledge, which cannot be handed over to others. The infraction of this privacy agreement classifies as crime. For this reason, the flow of information is reserved and confidential. The second limitation concerns the difficulty of finding the essential material for the studies' assessment because of the lack of project webpages and published documents. To solve this problem, we have tried to contact the different project referents or the beneficiary corporations resulting just in few replies. Moreover, it is important to point out that many selected projects took place several years ago, When the researchers of the contacted institutes were not working on it anymore, it leads to difficulties in finding the required materials. These limitations have restricted our study causing the inability in analyzing the outcomes of the projects and making it impossible to properly compare all the selected projects.

CONCLUSIONS

In the present work, we have assessed 20 telemedicine projects developed in Europe during 2000-2020 to evaluate the strengths and the limits of these kind of emerging health services. Among them, several are based on teleconsulting: the Tel Lappi, SOS MAM, the e-Res@Mont, the Telemedicine Pomerania project, the Telemedicine in the POMERANIA Euroregion and the Development Of Cross-Border Telediagnostic and Teleconsultation Network In Health Institutions (TELEDIAG) (**Table 2**). With the exception of the first one, all the others are cross-border projects between neighboring countries. This aspect underlines the role played by teleconsulting, expandable to the telemedicine approach, to break down even the national borders, enabling the transparent spread of scientific knowledge and the co-operation among nations.

The development of home tele-care, which guarantees elder people to remain self-sufficient in their homes, has significant benefits such as cost savings for healthcare (13), because it

allows the reduction of hospitalizations and the increase of their independence (10). It is important to know that for optimizing the realization of those e-Health approaches it is fundamental to identify, what the requirements and the needs of the final users are (10) in order to implement appropriate care models. For instance, the implementation of EPR also would ensure a better integration between hospitals and community services. A paradigmatic example is represented by the ICT for Health project that foresees a European portal for cross-border travel that would allow citizens, in particular chronic patients, to travel safely in European countries.

Through tele-monitoring, tele-health and tele-care technologies, the patients' responsibility on the management of their diseases can increase as their sense of safety (6). Moreover, tele-monitoring systems can enhance the healthcare for citizens who live in rural or problematic areas, enabling the continuity of care without patients' moving.

The Coronavirus has not only highlighted the criticalities of the health systems, but it has also pointed out the importance of telemedicine, which allows the reduction of waiting list, continuous monitoring, increasing the productivity of personnel, the reduction of traveling and the protection of patients from the spread of COVID-19. All these features make it possible to reorganize health systems, making them more sustainable and allowing economic saving. To face the health emergency, each Italian region has resorted to solutions based on telemedicine services, leading to the birth of many projects delivered irregularly (**Figure 3**). Such fragmentation is due to the lack of inter-regional dialogue, which makes standardization difficult (21). Currently, the Italian recovery and resilience plan is an essential occasion to enhance and homogenize telemedicine throughout the national territory. Another problem will be the certification of telemedicine activities and their correct storage, which allows personnel to recall the documents reported by facilitating territorial collaboration. The governance of telemedicine's diffusion will include the definition of technological and interoperability standards, national guidelines, and continuous check. Therefore, the Italian Recovery and Resilience Plan aimed at uniformly spreading telemedicine by promoting culture for appropriate and compassionate use.

In the last 20 years, ICTs have assumed an increasingly predominant role in health systems, allowing the integration of tele-care and tele-health, improving the lifestyle of citizens. Moreover, the pandemic emergency period has shown the centrality of health as a universal good and the fundamental importance of the NHSs, highlighting at the same time various areas on which to intervene. The historic opportunity now opens up to redefine the healthcare of tomorrow, with the obligation to make the best use of the incoming injection of economic resources derived from Europe. The challenge we face is to deal with the three fronts of acuity, chronicity and emergencies with effective solutions in an aging country. In fact, the data indicate that in Italy in 2040 there will be over 19 million elderly and 28 million chronic patients, with increases respectively of + 38.5% (+5.4 million elderly) and + 12% (+3 million chronic patients). To this, we must add the "suspended" Healthcare emergency: 46 million specialist visits, diagnostic tests, and 3 million fewer oncological screenings in 2020 compared to the previous year, which we will soon return to engage the NHS.

Therefore, digital health is the challenge to be mastered. The experiences achieved so far independently from the various territories have given rise to an infinite multiplication of platforms and projects with the result that Italy boasts a babel of software, devices and technologies. The fragility of digital has emerged and, to date, the inability to inform health care about oneself because digitalization is frequently insufficient or error-prone, generating more harm than benefit.

AUTHOR CONTRIBUTIONS

LP: conceptualization, methodology, validation, investigation, writing—original draft, writing—review and editing, and supervision. VM: data curation, investigation, writing—original draft, and writing—review and editing. GP, SS, CB, BB, and MG: writing—review and editing, supervision, and funding acquisition. All authors contributed to the article and approved the submitted version.

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A Review of Artificial Intelligence and Robotics in Transformed Health Ecosystems

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Health care is shifting toward become proactive according to the concept of P5 medicine–a predictive, personalized, preventive, participatory and precision discipline. This patient-centered care heavily leverages the latest technologies of artificial intelligence (AI) and robotics that support diagnosis, decision making and treatment. In this paper, we present the role of AI and robotic systems in this evolution, including example use cases. We categorize systems along multiple dimensions such as the type of system, the degree of autonomy, the care setting where the systems are applied, and the application area. These technologies have already achieved notable results in the prediction of sepsis or cardiovascular risk, the monitoring of vital parameters in intensive care units, or in the form of home care robots. Still, while much research is conducted around AI and robotics in health care, adoption in real world care settings is still limited. To remove adoption barriers, we need to address issues such as safety, security, privacy and ethical principles; detect and eliminate bias that could result in harmful or unfair clinical decisions; and build trust in and societal acceptance of AI.

Keywords: artificial intelligence, robotics, healthcare, personalized medicine, P5 medicine

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THE NEED FOR AI AND ROBOTICS IN TRANSFORMED HEALTH ECOSYSTEMS

"Artificial intelligence (AI) is the term used to describe the use of computers and technology to simulate intelligent behavior and critical thinking comparable to a human being" (1). Machine learning enables AI applications to automatically (i.e., without being explicitly programmed for) improving their algorithms through experiences gained by cognitive inputs or by the use of data. AI solutions provide data and knowledge to be used by humans or other technologies. The possibility of machines behaving in such a way was originally raised by Alan Turing and further explored starting in the 1950s. Medical expert systems such as MYCIN, designed in the 1970s for medical consultations (2), were internationally recognized a revolution supporting the development of AI in medicine. However, the clinical acceptance was not very high. Similar disappointments across multiple domains led to the so-called "AI winter," in part because rule-based systems do not allow the discovery of unknown relationships and in part because of the limitations in computing power at the time. Since then, computational power has increased enormously.

Over the centuries, we have improved our knowledge about structure and function of the human body, starting with the organs, tissues, cells sub-cell components etc. Meanwhile, we could advance it up to the molecular and sub-molecular level, including protein coding genes, DNA sequences, non-coding RNA etc. and their effects and

behavior in the human body. This has resulted in a continuously improving understanding of the biology of diseases and disease progressions (3). Nowadays, biomedical research and clinical practice are struggling with the size and complexity of the data produced by sequencing technologies, and how to derive from it new diagnoses and treatments. Experiment results, often hidden in clinical data warehouses, must be aggregated, analyzed, and exploited to derive our new, detailed and data-driven knowledge of diseases and enable better decision making.

New tools based on AI have been developed to predict disease recurrence and progression (4) or response to treatment; and robotics, often categorized as a branch of AI, plays an increasing role in patient care. In a medical context, AI means for example imitating the decision-making processes of health professionals (1). In contrast to AI that generates data, robotics provides touchable outcomes or realize physical tasks. AI and robotics use knowledge and patient data for various tasks such as: diagnosis; planning of surgeries; monitoring of patient physical and mental wellness; basic physical interventions to improve patient independence during physical or mental deterioration. We will review concrete realizations in a later section of this paper.

These advances are causing a revolution in health care, enabling it to become proactive as called upon by the concept of P5 medicine –a predictive, personalized, preventive, participatory and precision discipline (5). AI can help interpret personal health information together with other data to stratify the diseases to predict, stop or treat their progression.

In this paper, we describe the impact of AI and robotics on P5 medicine and introduce example use cases. We then discuss challenges faced by these developments. We conclude with recommendations to help AI and robotics transform health ecosystems. We extensively refer to appropriate literature for details on the underlying methods and technologies. Note that we concentrate on applications in the care setting and will not address in more detail the systems used for the education of professionals, logistics, or related to facility management– even though there are clearly important applications of AI in these areas.

CLASSIFICATION OF AI AND ROBOTIC SYSTEMS IN MEDICINE

We can classify the landscape of AI and robotic systems in health care according to different dimensions (**Figure 1**): use, task, technology. Within the "use" dimension, we can further distinguish the application area or the care setting. The "task" dimension is characterized by the system's degree of autonomy. Finally, regarding the "technology" dimension, we consider the degree of intrusion into a patient and the type of system. Clearly, this is a simplification and aggregation: AI algorithms as such will not be located in a patient etc.

Classification Based on Type of System

We can distinguish two types of such systems: virtual and physical (6).

- Virtual systems (relating to AI systems) range from applications such as electronic health record (EHR) systems, or text and data mining applications, to systems supporting treatment decisions.
- Physical systems relate to robotics and include robots that assist in performing surgeries, smart prostheses for handicapped people, and physical aids for elderly care.

There can also be hybrid systems combining AI with robotics, such as social robots that interact with users or microrobots that deliver drugs inside the body.

All these systems exploit enabling technologies that are *data* and *algorithms* (see **Figure 2**). For example, a robotic system may collect data from different sensors–visual, physical, auditory or chemical. The robot's processor manipulates, analyzes, and interprets the data. Actuators enable the robot to perform different functions including visual, physical, auditory or chemical responses.

Data

Two kinds of data are required: data that captures the knowledge and experience gained by the system during diagnosis and treatment, usually through machine learning; and individual patient data, which AI can assess and analyze to derive recommendations. Data can be obtained from physical sensors (wearable, non-wearable), from biosensors (7), or from other information systems such as an EHR application. From the collected data, digital biomarkers can be derived that AI can analyze and interpret (8).

Algorithms

AI-specific algorithms and methods allow data analysis, reasoning, and prediction. AI consists of a growing number of subfields such as machine learning (supervised, unsupervised, and reinforcement learning), machine vision, natural language processing (NLP) and more. NLP enables computers to process and understand natural language (written or spoken). Machine vision or computer vision extracts information from images. An authoritative taxonomy of AI does not exist yet, although several standards bodies have started addressing this task.

AI methodologies can be divided into knowledge-based AI and data-driven AI (9).

- *Knowledge-based AI* models human knowledge by asking experts for relevant concepts and knowledge they use to solve problems. This knowledge is then formalized in software (9). This is the form of AI closest to the original expert systems of the 1970s.
- *Data-driven AI* starts from large amounts of data, which are typically processed by machine learning methods to learn patterns that can be used for prediction. Virtual or augmented reality and other types of visualizations can be used to present and explore data, which helps understand relations among data items that are relevant for diagnosis (10).

To more fully exploit the knowledge captured in computerized models, the concept of *digital twin* has gained traction in the

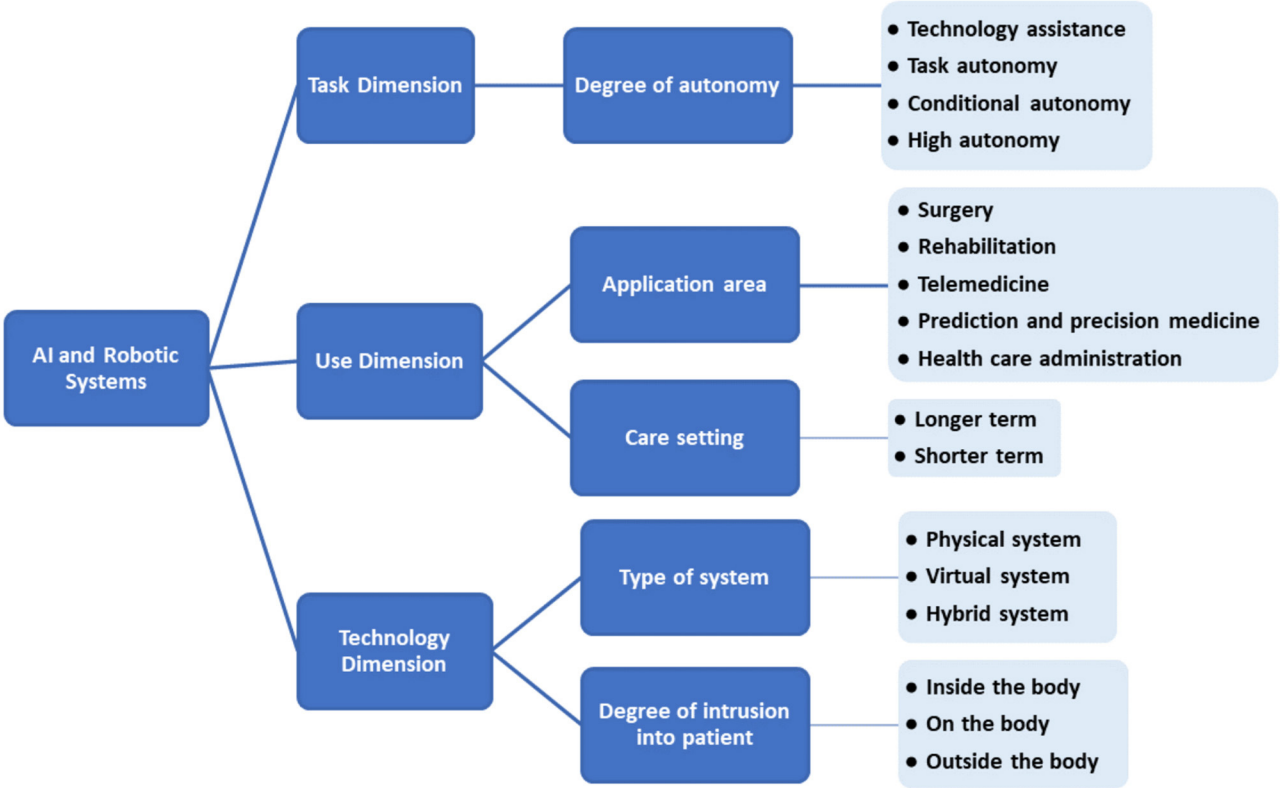

FIGURE 1 | Categorization of systems based on AI and robotics in health care.

medical field (11). The terms "digital patient model," "virtual physiological human," or "digital phenotype" designate the same idea. A digital twin is a virtual model fed by information coming from wearables (12), omics, and patient records. Simulation, AI and robotics can then be applied to the digital twin to learn about the disease progression, to understand drug responses, or to plan surgery, before intervening on the actual patient or organ, effecting a significant digital transformation of the health ecosystems. Virtual organs (e.g., a digital heart) are an application of this concept (13). A digital twin can be customized to an individual patient, thus improving diagnosis.

Regardless of the specific kind of AI, there are some requirements that all AI and robotic systems must meet. They must be:

- *Adaptive.* Transformed health ecosystems evolve rapidly, especially since according to P5 principles they adapt treatment and diagnosis to individual patients.
- *Context-aware.* They must infer the current activity state of the user and the characteristics of the environment in order to manage information content and distribution.
- *Interoperable.* A system must be able to exchange data and knowledge with other ones (14). This requires common semantics between systems, which is the object of standard terminologies, taxonomies or ontologies such as SNOMED CT. NLP can also help with interoperability (15).

Classification Based on Degree of Autonomy

AI and robotic systems can be grouped along an assistive-to-autonomous axis (**Figure 3**). Assistive systems augment the capabilities of their user by aggregating and analyzing data, performing concrete tasks under human supervision [for example, a semiautonomous ultrasound scanner (17)], or learning how to perform tasks from a health professional's demonstrations. For example, a robot may learn from a physiotherapist how to guide a patient through repetitive rehabilitation exercises (18).

Autonomous systems respond to real world conditions, make decisions, and perform actions with minimal or no interaction with a human (19). They be encountered in a clinical setting (autonomous implanted devices), in support functions to provide assistance[1] (carrying things around in a facility), or to automate non-physical work, such as a digital receptionist handling patient check-in (20).

Classification Based on Application Area

The diversity of users of AI and robotics in health care implies an equally broad range of application areas described below.

[1]https://cmte.ieee.org/futuredirections/2019/07/21/autonomous-systems-in-healthcare/

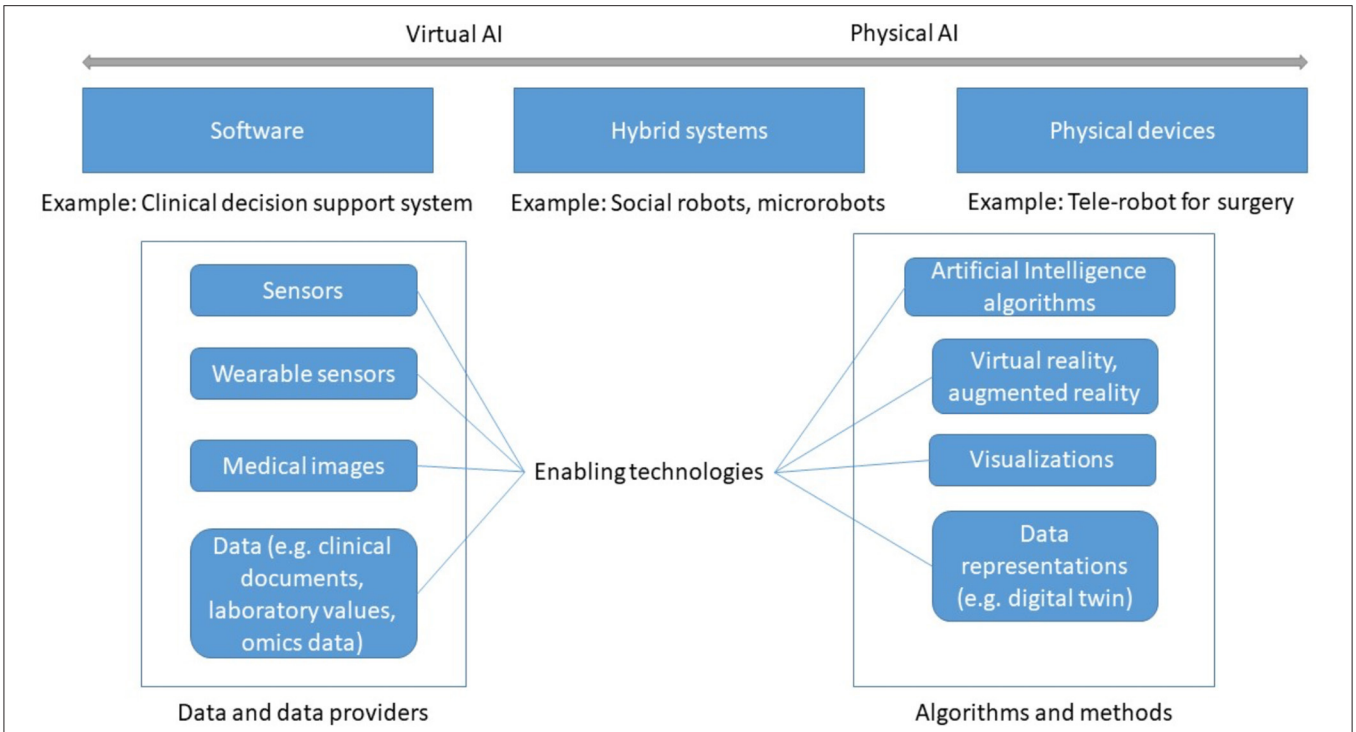

FIGURE 2 | Types of AI-based systems and enabling technologies.

	Technology assistance	Task autonomy	Conditional autonomy	High autonomy
Description	Caregiver is involved in task; system aids and enhances effectiveness and efficiency	Caregiver initiates task and controls execution by system	Caregiver defines and initiates a task; system executes task with supervision by human	Technology decides for action and executes it with caregiver execution
Example	System analyses patient data and highlights important facts	System analyses patient data and calculates a risk score	System analyses patient data and makes recommendations for examinations, physician always has to approve	System analyses patient data and makes / orders examinations without physician approval

FIGURE 3 | Levels of autonomy of robotic and AI systems. [following models proposed by (16)].

Robotics and AI for Surgery

Robotics-assisted surgery, "the use of a mechanical device to assist surgery in place of a human-being or in a human-like way" (21) is rapidly impacting many common general surgical procedures, especially minimally invasive surgery. Three types of robotic systems are used in surgery:

- Active systems undertake pre-programmed tasks while remaining under the control of the operating surgeon;
- Semi-active systems allow a surgeon to complement the system's pre-programmed component;
- Master–slave systems lack any autonomous elements; they entirely depend on a surgeon's activity. In laparoscopic

TABLE 1 | Classification by care setting.

Care setting		Description	Example
Longer term	Home care	Personal living environment	Remote monitoring of individuals for identifying early indications of heart failure decompensation, which allows for optimization of therapy to prevent hospitalizations (56)
	Assisted living facility	Residential facility with self-contained living units; site support 24 x 7 and capacity to arrange health care services	A smart kitchen for ambient assisted living (57)
	Nursing home	Facility providing residential accommodation with health care	Social robots to treat individuals with dementia in order to improve symptoms (58)
Shorter term	Inpatient hospital	Provides diagnostic, therapeutic and rehabilitation services by or under supervision of physicians	Virtual nurse for hospital discharge planning (59)
	Hospice	Facility that offers palliative and supportive care for terminally ill persons and their families	Conversational agent to collect patient reported outcome measures from individuals in palliative care (60)
	Inpatient psychiatric facility	Inpatient psychiatric services for the diagnosis and treatment of mental health disorders	AI to predict risk or severity of depression (61)

Selected care settings where robotic systems may be used [adapted from (62)].

surgery or in teleoperation, the surgeon's hand movements are transmitted to surgical instruments, which reproduce them.

Surgeons can also be supported by navigation systems, which localize positions in space and help answer a surgeon's anatomical orientation questions. Real-time tracking of markers, realized in modern surgical navigation systems using a stereoscopic camera emitting infrared light, can determine the 3D position of prominent structures (22).

Robotics and AI for Rehabilitation

Various AI and robotic systems support rehabilitation tasks such as monitoring, risk prevention, or treatment (23). For example, fall detection systems (24) use smart sensors placed within an environment or in a wearable device, and automatically alert medical staff, emergency services, or family members if assistance is required. AI allows these systems to learn the normal behavioral patterns and characteristics of individuals over time. Moreover, systems can assess environmental risks, such as household lights that are off or proximity to fall hazards (e.g., stairwells). Physical systems can provide physical assistance (e.g., lifting items, opening doors), monitoring, and therapeutic social functions (25). Robotic rehabilitation applications can provide both physical and cognitive support to individuals by monitoring physiological progress and promoting social interaction. Robots can support patients in recovering motions after a stroke using exoskeletons (26), or recovering or supplementing lost function (27). Beyond directly supporting patients, robots can also assist caregivers. An overview on home-based rehabilitation robots is given by Akbari et al. (28). Virtual reality and augmented reality allow patients to become immersed within and interact with a 3D model of a real or imaginary world, allowing them to practice specific tasks (29). This has been used for motor function training, recovery after a stroke (30) and in pain management (31).

Robotics and AI for Telemedicine

Systems supporting telemedicine support among others the triage, diagnostic, non-surgical treatment, surgical treatment, consultation, monitoring, or provision of specialty care (32).

- Medical triage assesses current symptoms, signs, and test results to determine the severity of a patient's condition and the treatment priority. An increasing number of mobile health applications based on AI are used for diagnosis or treatment optimization (33).
- Smart mobile and wearable devices can be integrated into "smart homes" using Internet-of-Things (IoT) technologies. They can collect patient and contextual data, assist individuals with everyday functioning, monitor progress toward individualized care and rehabilitation goals, issue reminders, and alert care providers if assistance is required.
- Telemedicine for specialty care includes additional tools to track mood and behavior (e.g., pain diaries), AI-based chatbots can mitigate social isolation in home care environments[2] by offering companionship and emotional support to users, noting if they are not sleeping well, in pain or depressed, which could indicate a more complex mental condition (34).
- Beyond this, there are physical systems that can deliver specialty care: Robot DE NIRO can interact naturally, reliably, and safely with humans, autonomously navigate through environments on command, intelligently retrieve or move objects (35).

Robotics and AI for Prediction and Precision Medicine

Precision medicine considers the individual patients, their genomic variations as well as contributing factors (age, gender, ethnicity, etc.), and tailors interventions accordingly (8). Digital health applications can also incorporate data such as emotional state, activity, food intake, etc. Given the amount and complexity of data this requires, AI can learn from comprehensive datasets to predict risks and identify the optimal treatment strategy (36). Clinical decision support systems (CDSS) that integrate AI can provide differential diagnoses, recognize early

[2]https://emag.medicalexpo.com/ai-powered-chatbots-to-help-against-self-isolation-during-covid-19/

TABLE 2 | Mapping of use cases to our classification.

Use case	Application area	Autonomy	Intrusion	Care setting
Sepsis onset prediction	Prediction and precision medicine	Technology assistance	Outside the body	Shorter term
Monitoring in the ICU	Surgery	Technology assistance	Outside the body	Shorter term
Tumor detection from image analysis	Prediction and precision medicine	Technology assistance	Outside the body	Shorter term
COVID-19 detection	Prediction and precision medicine	Technology assistance	Outside the body	Shorter term
Patient triage and symptom checker	Prediction and precision medicine	Task autonomy	Outside the body	Shorter term
Cardiovascular risk prediction	Prediction and precision medicine	Technology assistance	Outside the body	Shorter term
Gait analysis	Prediction and precision medicine, Rehabilitation	Technology assistance	Outside the body	Shorter term
Home care robots	Telemedicine	Technology assistance, task autonomy	Outside the body	Longer term
Biomechatronics	Rehabilitation	Task autonomy	On the body	Longer term

warning signs of patient morbidity or mortality, or identify abnormalities in radiological images or laboratory test results (37). They can increase patient safety, for example by reducing medication or prescription errors or adverse events and can increase care consistency and efficiency (38). They can support clinical management by ensuring adherence to the clinical guidelines or automating administrative functions such as clinical and diagnostic encoding (39), patient triage or ordering of procedures (37).

AI and Agents for Management and Support Tasks

NLP applications, such as voice transcription, have proved helpful for clinical note-taking (40), compiling electronic health records, automatically generating medical reports from patient-doctor conversations or diagnostic reports (41). AI algorithms can help retrieving context-relevant patient data. Concept-based information retrieval can improve search accuracy and retrieval speed (42). AI algorithms can improve the use and allocation of hospital resources by predicting the length of stay of patients (43) or risk of re-admission (44).

Classification Based on Degree of Intrusion Into a Patient

Robotic systems can be used inside the body, on the body or outside the body. Those applied *inside* the body include microrobots (45), surgical robots and interventional robots. Microrobots are sub-millimeter untethered devices that can be propelled for example by chemical reactions (46), or physical fields (47). They can move unimpeded through the body and perform tasks such as targeted therapy (localized delivery of drugs) (48).

Microrobots can assist in physical surgery, for example by drilling through a blood clot or by opening up obstructions in the urinary tract to restore normal flow (49). They can provide directed local tissue heating to destroy cancer cells (50). They can be implanted to provide continuous remote monitoring and early awareness of an emerging disease.

Robotic prostheses, orthoses and exoskeletons are examples of robotic systems worn *on* the body. Exoskeletons are wearable robotic systems that are tightly physically coupled with a human body to provide assistance or enhance the wearer's physical capabilities (51). While they have often been developed for applications outside of health care, they can help workers with physically demanding tasks such as moving patients (52) or assist people with muscle weakness or movement disorders. Wearable technology can also be used to measure and transmit data about vital signs or physical activity (19).

Robotic systems applied *outside* the body can help avoid direct contact when treating patients with infectious diseases (53), assist in surgery (as already mentioned), including remote surgical procedures that leverage augmented reality (54) or assist providers when moving patients (55).

Classification Based on Care Setting

Another dimension of AI and robotics is the duration of their use, which directly correlates with the location of use. Both can significantly influence the requirements, design, and technology components of the solution. In a longer-term care setting, robotics can be used in a patient's home (e.g., for monitoring of vital signs) or for treatment in a nursing home. Shorter-term care settings include inpatient hospitals, palliative care facilities or inpatient psychiatric facilities. Example applications are listed in **Table 1**.

SAMPLE REALIZATIONS

Having seen how to classify AI and robotic systems in health care, we turn to recent concrete achievements that illustrate their practical application and achievements already realized. This list is definitely not exhaustive, but it illustrates the fact that we're no longer purely at the research or experimentation stage: the

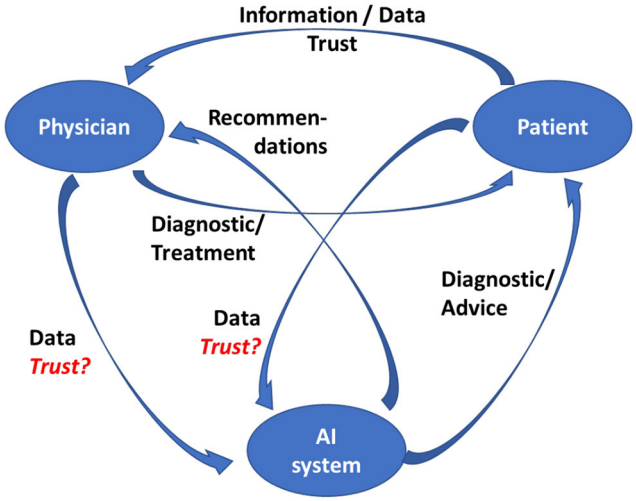

FIGURE 4 | Physician-patient-AI relationship.

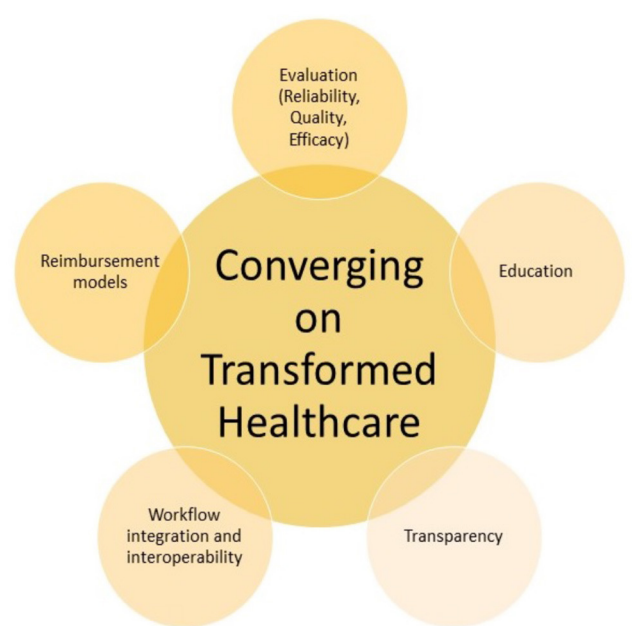

FIGURE 5 | Roadmap for transformed health care.

technology is starting to bear fruit in a very concrete way–that is, by improving outcomes–even when only in the context of clinical trials prior to regulatory approval for general use.

Sepsis Onset Prediction

Sepsis was recently identified as *the* leading cause of death worldwide, surpassing even cancer or cardiovascular diseases.[3] And while timely diagnosis and treatment are difficult in other care settings, it is also the leading cause of death in hospitals in the United States (Sepsis Fact Sheet[4]) A key reason is the difficulty of recognizing precursor symptoms early enough to initiate effective treatment. Therefore, early onset prediction promises to save millions of lives each year. Here are four such projects:

- Bayesian Health[5], a startup founded by a researcher at Johns Hopkins University, applied its model to a test population of hospital patients and correctly identified 82% of the 9,800 patients who later developed sepsis.
- Dascena, a California startup, has been testing its software on large cohorts of patients since 2017, achieving significant improvements in outcomes (63).
- Patchd[6] uses wearable devices and deep learning to predict sepsis in high-risk patients. Early studies have shown that this technology can predict sepsis 8 h earlier, and more accurately, than under existing standards of care.
- A team of researchers from Singapore developed a system that combines clinical measures (structured data) with physician notes (unstructured data), resulting in improved early detection while reducing false positives (64).

Monitoring Systems in the Intensive Care Unit

For patients in an ICU, the paradox is that large amounts of data are collected, displayed on monitors, and used to trigger alarms, but these various data streams are rarely used together, nor can doctors or nurses effectively observe all the data from all the patients all the time.

This is an area where much has been written, but most available information points to studies that have not resulted in actual deployments. A survey paper alluded in particular to the challenge of achieving effective collaboration between ICU staff and automated processes (65).

In one application example, machine learning helps resolving the asynchrony between a mechanical ventilator and the patient's own breathing reflexes, which can cause distress and complicate recovery (66).

Tumor Detection From Image Analysis

This is another area where research has provided evidence of the efficacy of AI, generally not employed alone but rather as an advisor to a medical professional, yet there are few actual deployments at scale.

These applications differ based on the location of the tumors, and therefore on the imaging techniques used to observe them. AI makes the interpretation of the images more reliable, generally by pinpointing to the radiologists areas they might otherwise overlook.

- In a study performed in Korea, AI appeared to improve the recognition of lung cancer in chest X-rays (67). AI by itself performed better than unaided radiologists, and

[3]https://www.med.ubc.ca/news/sepsis-leading-cause-of-death-worldwide/

[4]https://www.sepsis.org/wp-content/uploads/2017/05/Sepsis-Fact-Sheet-2018.pdf

[5]https://medcitynews.com/2021/07/johns-hopkins-spinoff-looking-to-build-better-risk-prediction-tooing,ls-emerges-with-15m/

[6]https://www.patchdmedical.com/

the improvement was greater when AI was used as an aid by radiologists. Note however that the sample size was fairly small.
- Several successive efforts aimed to use AI to classify dermoscopic images to discriminate between benign nevi and melanoma (68).

AI for COVID-19 Detection

The rapid and tragic emergence of the COVID-19 disease, and its continued evolution at the time of this writing, have mobilized many researchers, including the AI community. This domain is naturally divided into two areas, diagnostic and treatment.

An example of AI applied to COVID-19 diagnostic is based on an early observation that the persistent cough that is one of the common symptoms of the disease "sounds different" from the cough caused by other ailments, such as the common cold. The MIT Opensigma project[7] has "crowdsourced" sound recordings of coughs from many people, most of whom do not have the disease while some know that they have it or had it. Several similar projects have been conducted elsewhere (69).

Another effort used AI to read computer tomography images to provide a rapid COVID-19 test, reportedly achieving over 90% accuracy in 15 s (70). Curiously, after this news was widely circulated in February-March 2020, nothing else was said for several months. Six months later, a blog post[8] from the University of Virginia radiology and medical department asserted that "CT scans and X-rays have a limited role in diagnosing coronavirus." The approach pioneered in China may have been the right solution at a specific point in time (many cases concentrated in a small geographical area, requiring a massive detection effort before other rapid tests were available), thus overriding the drawbacks related to equipment cost and patient exposure to radiation.

Patient Triage and Symptom Checkers

While the word triage immediately evokes urgent decisions about what interventions to perform on acutely ill patients or accident victims, it can also be applied to remote patient assistance (e.g., telehealth applications), especially in areas underserved by medical staff and facilities.

In an emergency care setting, where triage decisions can result in the survival or death of a person, there is a natural reluctance to entrust such decisions to machines. However, AI as a predictor of outcomes could serve as an assistant to an emergency technician or doctor. A 2017 study of emergency room triage of patients with acute abdominal pain only showed an "acceptable level of accuracy" (71), but more recently, the Mayo Clinic introduced an AI-based "digital triage platform" from Diagnostic Robotics[9] to "perform clinical intake of patients and suggest diagnoses and hospital risk scores." These solutions can now be delivered by a website or a smartphone app, and have evolved from decision trees designed by doctors to incorporate AI.

[7]https://hisigma.mit.edu

[8]https://blog.radiology.virginia.edu/covid-19-and-imaging/

[9]https://hitinfrastructure.com/news/diagnostic-robotics-mayo-clinic-bring-triage-platform-to-patients

Cardiovascular Risk Prediction

Google Research announced in 2018 that it has achieved "prediction of cardiovascular risk factors from retinal fundus photographs via deep learning" with a level of accuracy similar to traditional methods such as blood tests for cholesterol levels (72). The novelty consists in the use of a neural network to analyze the retina image, resulting in more power at the expense of explainability.

In practice, the future of such a solution is unclear: certain risk factors could be assessed from the retinal scan, but those were often factors that could be measured directly anyway–such as from blood pressure.

Gait Analysis

Many physiological and neurological factors affect how someone walks, given the complex interactions between the sense of touch, the brain, the nervous system, and the muscles involved. Certain conditions, in particular Parkinson's disease, have been shown to affect a person's gait, causing visible symptoms that can help diagnose the disease or measure its progress. Even if an abnormal gait results from another cause, an accurate analysis can help assess the risk of falls in elderly patients.

Compared to other applications in this section, gait analysis has been practiced for a longer time (over a century) and has progressed incrementally as new motion capture methods (film, video, infrared cameras) were developed. In terms of knowledge representation, see for example the work done at MIT twenty years ago (73). Computer vision, combined with AI, can considerably improve gait analysis compared to a physician's simple observation. Companies such as Exer[10] offer solutions that physical therapists can use to assess patients, or that can help monitor and improve a home exercise program. This is an area where technology has already been deployed at scale: there are more than 60 clinical and research gate labs[11] in the U.S. alone.

Home Care Robots

Robots that provide assistance to elderly or sick persons have been the focus of research and development for several decades, particularly in Japan due to the country's large aging population with above-average longevity. "Elder care robots" can be deployed at home (with cost being an obvious issue for many customers) or in senior care environments (74), where they will help alleviate a severe shortage of nurses and specialized workers, which cannot be easily addressed through the hiring of foreign help given the language barrier.

The types of robots used in such settings are proliferating. They range from robots that help patients move or exercise, to robots that help with common tasks such as opening the front door to a visitor or bringing a cup of tea, to robots that provide psychological comfort and even some form of conversation. PARO, for instance, is a robotic bay seal developed to provide treatment to patients with dementia (75).

[10]https://www.exer.ai

[11]https://www.gcmas.org/map

Biomechatronics

Biomechatronics combines biology, mechanical engineering, and electronics to design assistive devices that interpret inputs from sensors and send commands to actuators–with both sensors and actuators attached in some manner to the body. The sensors, actuators, control system, and the human subject form together a closed-loop control system.

Biomechatronic applications live at the boundary of prosthetics and robotics, for example to help amputees achieve close-to-normal motion of a prosthetic limb. This work has been demonstrated for many years, with impressive results, at the MIT Media Lab under Prof. Hugh Herr[12] However, those applications have rarely left the lab environment due to the device cost. That cost could be lowered by production in large quantities, but coverage by health insurance companies or agencies is likely to remain problematic.

Mapping of Use Cases to Classification

Table 2 shows a mapping of the above use cases to the classification introduced in the first section of this paper.

ADOPTION CHALLENGES TO AI AND ROBOTICS IN HEALTH CARE

While the range of opportunities, and the achievements to date, of robotics and AI are impressive as seen above, multiple issues impede their deployment and acceptance in daily practice.

Issues related to trust, security, privacy and ethics are prevalent across all aspects of health care, and many are discussed elsewhere in this issue. We will therefore only briefly mention those challenges that are unique to AI and robotics.

Resistance to Technology

Health care professionals may ignore or resist new technologies for multiple reasons, including actual or perceived threats to professional status and autonomy (76), privacy concerns (77) or the unresolved legal and ethical questions of responsibility (78). The issues of worker displacement by robots are just as acute in health care as in other domains. Today, while surgery robots operate increasingly autonomously, humans still perform many tasks and play an essential role in determining the robot's course of operation (e.g., for selecting the process parameters or for the positioning of the patient) (79). This allocation of responsibilities is bound to evolve.

Transparency and Explainability

Explainability is "a characteristic of an AI-driven system allowing a person to reconstruct why a certain AI came up with the presented prediction" (80). In contrast to rule-based systems, AI-based predictions can often not be explained in a human-intelligible manner, which can hide errors or bias (the "black box problem" of machine learning). The explainability of AI models is an ongoing research area. When information on the reasons for an AI-based decision is missing, physicians cannot judge the reliability of the advice and there is a risk to patient safety.

Responsibility, Accountability and Liability

Who is responsible when the AI or robot makes mistakes or creates harm in patients? Is it the programmer, manufacturer, end user, the AI/robotic system itself, the provider of the training dataset, or something (or someone) else? The answer depends on the system's degree of autonomy. The European Parliament's 2017 Resolution on AI (81) assigns legal responsibility for an action of an AI or robotic system to a human actor, which may be its owner, developer, manufacturer or operator.

Data Protection

Machine learning requires access to large quantities of data regarding patients as well as healthy people. This raises issues regarding the ownership of data, protection against theft, compliance with regulations such as HIPAA in the U.S. (82) or GDPR for European citizens (83), and what level of anonymization of data is necessary and possible. Regarding the last point, AI models could have unintended consequences, and the evolution of science itself could make patient re-identification possible in the future.

Data Quality and Integration

Currently, the reliability and quality of data received from sensors and digital health devices remain uncertain (84)–a fact that future research and development must address. Datasets in medicine are naturally imperfect (due to noise, errors in documentation, incompleteness, differences in documentation granularities, etc.), hence it is impossible to develop error-free machine learning models (80). Furthermore, without a way to quickly and reliably integrate the various data sources for analysis, there is lost potential for fast diagnosis by AI algorithms.

Safety and Security

Introducing AI and robotics into the delivery of health care is likely to create new risks and safety issues. Those will exist even under normal functioning circumstances, when they may be due to design, programming or configuration errors, or improper data preparation (85).

These issues only get worse when considering the probability of cyberattacks:

- Patient data may be exposed or stolen, perhaps by scammers who want to exploit it for profit.
- Security vulnerabilities in robots that interact directly with patients may cause malfunctions that physically threaten the patient or professional. The robot may cause harm directly, or indirectly by giving a surgeon incorrect feedback. In case of unexpected robot behavior, it may be unclear to the user whether the robot is functioning properly or is under attack (86).

The EU Commission recently drafted a legal framework[13] addressing the risks of AI (not only in health care) in order to improve the safety of and trust in AI. The framework distinguishes four levels of risks: unacceptable risk, high risk, limited risk and minimal risk. AI systems with unacceptable

[12]https://www.media.mit.edu/groups/biomechatronics/overview/

[13]https://digital-strategy.ec.europa.eu/en/policies/regulatory-framework-ai

risks will be prohibited, high-risk ones will have to meet strict obligations before release (e.g., risk assessment and mitigation, traceability of results). Limited-risk applications such as chatbots (which can be used in telemedicine) will require "labeling" so that users are made aware that they are interacting with an AI-powered system.

Biases

While P5 medicine aims at considering multiple factors–ethnicity, gender, socio-economic background, education, etc.–to come up with individualized care, current implementations of AI often demonstrate potential biases toward certain patient groups of the population. The training datasets may have under-represented those groups, or important features may be distributed differently across groups–for example, cardiovascular disease or Parkinson's disease progress differently in men and women (87), so the corresponding features will vary. These causes result in undesirable bias and "unintended of unnecessary discrimination" of subgroups (88).

On the flip side, careful implementations of AI could explicitly consider gender, ethnicity, etc. differences to achieve more effective treatments for patients belonging to those groups. This can be considered "desirable bias" that counteracts the undesirable kind (89) and gets us closer to the goals of P5 medicine.

Trust–An Evolving Relationship

The relationship between patients and medical professionals has evolved over time, and AI is likely to impact it by inserting itself into the picture (see **Figure 4**). Although AI and robotics are performing well, human surveillance is still essential. Robots and AI algorithms operate logically, but health care often requires acting empathically. If doctors become intelligent users of AI, they may retain the trust associated with their role, but most patients, who have a limited understanding of the technologies involved, would have much difficulty in trusting AI (90). Conversely, reliable and accurate diagnosis and beneficial treatment, and appropriate use of AI and robotics by the physician can strengthen the patient's trust (91).

This assumes of course that the designers of those systems adhere to established guidelines for trustworthy AI in the first place, which includes such requirements as creating systems that are lawful, ethical, and robust (92, 93).

AI AND ROBOTICS FOR TRANSFORMED HEALTH CARE–A CONVERGING PATH

We can summarize the previous sections as follows:

1. There are many types of AI applications and robotic systems, which can be introduced in many aspects of health care.
2. AI's ability to digest and process enormous amounts of data, and derive conclusions that are not obvious to a human, holds the promise of more personalized and predictive care–key goals of P5 medicine.
3. There have been, over the last few years, a number of proof-of-concept and pilot projects that have exhibited promising results for diagnosis, treatment, and health maintenance. They have not yet been deployed at scale–in part because of the time it takes to fully evaluate their efficacy and safety.
4. There is a rather daunting list of challenges to address, most of which are not purely technical–the key one being demonstrating that the systems are effective and safe enough to warrant the confidence of both the practitioners and their patients.

Based on this analysis, what is the roadmap to success for these technologies, and how will they succeed in contributing to the future of health care? **Figure 5** depicts the convergent approaches that need to be developed to ensure safe and productive adoption, in line with the P5 medicine principles.

First, AI technology is currently undergoing a remarkable revival and being applied to many domains. Health applications will both benefit from and contribute to further advances. In areas such as image classification or natural language understanding, both of which have obvious utility in health care, the rate of progress is remarkable. Today's AI techniques may seem obsolete in ten years.

Second, the more technical challenges of AI–such as privacy, explainability, or fairness–are being worked on, both in the research community and in the legislative and regulatory world. Standard procedures for assessing the efficacy and safety of systems will be needed, but in reality, this is not a new concept: it is what has been developed over the years to approve new medicines. We need to be consistent and apply the same hard-headed validation processes to the new technologies.

Third, it should be clear from our exploration of this subject that *education*–of patients as well as of professionals–is key to the societal acceptance of the role that AI and robotics will be called upon to play. Every invention or innovation–from the steam engine to the telephone to the computer–has gone through this process. Practitioners must learn enough about how AI models and robotics work to build a "working relationship" with those tools and build trust in them–just as their predecessors learned to trust what they saw on an X-ray or CT scan. Patients, for their part, need to understand what AI and robotics can or cannot do, how the physician will remain in the loop when appropriate, and what data is being collected about them in the process. We will have a responsibility to ensure that complex systems that patients do not sufficiently understand cannot be misused against them, whether accidentally or deliberately.

Fourth, health care is also a business, involving financial transactions between patients, providers, and insurers (public or private, depending on the country). New cost and reimbursement models will need to be developed, especially given that when AI is used to assist professionals, not replace them, the cost of the system is additive to the human cost of assessing the data and reviewing the system's recommendations.

Fifth and last, clinical pathways have to be adapted and new role models for physicians have to be built. Clinical paths can already differ and make it harder to provide continuity of care to a patient who moves across care delivery systems that have different capabilities. This issue is being addressed by the BPM+ Health Community[14] using the business process,

[14]https://www.bpm-plus.org/

case management and decision modeling standards of the Object Management Group (OMG). The issue will become more complex by integrating AI and robotics: every doctor has similar training and a stethoscope, but not every doctor or hospital will have the same sensors, AI programs, or robots.

Eventually, the convergence of these approaches will help to build a complete digital patient model–a digital twin of each specific human being – generated out of all the data gathered from general practitioners, hospitals, laboratories, mHealth apps, and wearable sensors, along the entire life of the patient. At that point, AI will be able to support superior, fully personal and predictive medicine, while robotics will automate or support many aspects of treatment and care.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

KD came up with the classification of AI and robotic systems. CB identified concrete application examples. Both authors contributed equally, identified adoption challenges, and developed recommendations for future work. Both authors contributed to the article and approved the submitted version.

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Modeling digital health systems to foster interoperability

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Information systems are a complex thing, and they are mostly not used stand-alone anymore. In that context, many different issues must be considered. It starts with defining the system's purpose, includes the use cases and scenarios in combination with the necessary data ideally separated into distinct domains. Furthermore, it requires the selection of an appropriate set of supporting components/tools and a development environment including some technology to enable continuous integration. And the endeavor does not come to an end with the development of the system itself. To manage those challenges, thinking about design and architectural principles becomes a mandatory element. The situation gets more complicated with growing expectations regarding communication and cooperation between the more and more complex and dynamic ecosystem's actors. The resulting information system has to adhere to different, sometimes contradictory principles and requirements, frequently controlled by different authorities. This paper focuses less on developing information systems in general but concentrates on the aspects that must be considered when multiple requirements from different stakeholders for data exchange and knowledge sharing for advanced interoperability must be met. The latter is commonly underspecified due to missing proper verification of the correct interpretation of data. One intent of the paper is to promote the deployment of information models as a common basis to derive data exchange specifications establishing advanced interoperability. However, it also addresses the necessity to guarantee that the information models and implementable artifacts correctly represent the intended functions and objectives as well as the underlying concepts of the business system in its prevailing context. Therefore, we cannot limit our considerations on the data and information viewpoints.

KEYWORDS

information model, interoperability, data exchange, data set, communication standard

Introduction

To enable and facilitate interoperability among applications, many data exchange standards for different purposes such as HL7 version 2.x (1), HL7 Version 3.0 (2), HL7 CDA (2), HL7 FHIR (3), DICOM (4), openEHR/EN13606/archetypes (5, 6), EDIFACT (7), ebXML (8), xDT (9, 10), H.PR.I.M. (11), PN13 (12), NCPDP (13), X12 (14), ClaML (15), CTS2 (16), SNOMED CT (17), etc., have been developed by

different Standards Developing Organizations (SDOs). Despite structural and functional differences, they share the same design elements and underlying basic principles such as specific topologies, the Open Systems Interconnection model (17), etc., which will be following explained in more details (18). Nevertheless, most of those standards lack the same foundational basis – a data model resp. an information model.

A data model is sometimes mixed up with data structures or database models, although it organizes elements and defines how they relate to each other. In most cases, they should refer to real-world entities even though the interpretation of that is left to the reader. According to Lee, an information model is "a representation of concepts, relationships, constraints, rules, and operations to specify data semantics for a chosen domain of discourse" (19). Therefore, an information model needs a sophisticated formal representation. This paper especially focuses on the formalization of a model to enforce a correct interpretation of requirements controlling the system's development and implementation. Thereby, it follows the good modeling best practices described, e.g., by Langhorst et al. (20), especially considering the characteristics and increasing constraints of representation styles and languages throughout the development process, that way guiding justification and transformation of the different models. In other words, the paper adds theoretical and general linguistics as well as systems theory to the traditional way of discussing development processes.

Information Communication Technology (ICT) builds the foundation for data exchange. This paper focuses on the ICT perspective of interoperability in transformed health ecosystems represented according to the ISO 10746 Open Distributing Processing Reference Model (RM-ODP) (18) and its extension according to ISO 23903 Interoperability and Integration Reference Architecture (15). After roughly introducing and exemplifying the ICT-specific viewpoints (VPs) Enterprise VP, Information VP, Computational VP, Engineering VP and Technology VP, it especially elaborates on commonalities, differences and their relationship as a solid foundation. Furthermore, it focuses on the data sharing interoperability paradigm with its logical information models and associated implementable technology specifications. A second aspect of this paper is to demonstrate and explain the foundational equivalence of different standards, that way demonstrating the importance of information models as a common reference to achieve interoperability.

Viewpoints

Information Systems have to follow a well-defined life cycle, including design, development, implementation, test, and in some cases certification. According to the reference model for open distributed processing (RM-ODP) (18), these process steps can be aligned with different viewpoints which are roughly introduced as follows.

The enterprise view on digital health

The Enterprise View takes care of the business processes in a specific environment. It describes the IT-specific use cases and workflows that should be managed within – or across – organizations with a focus on purpose, scope and policies of the system. Commonly, transaction and interaction models explain how different (abstract) actors are working together and interacting to achieve a common goal. They are represented in common notation forms such as Business Process Markup Language (BPML, BPML+) and Business Process Model Notation (BPMN) (21).

The information view on digital health

The Information View defines the informational components of the system and their relationships in form of (domain) information models, expressed in class diagrams. It focuses on the semantics of information and information processing performed. The data/information is coupled with the processes described in the previous VP.

These viewpoints together are going to exemplify interaction and information models. The Unified Modeling Language (UML) (22) is one possible, but the most commonly applied formalism that can be used to express those diagrams.

The computational view on digital health

The Computational View enables the distribution of the system by decomposing it into objects according to structural and functional requirements, including necessary interfaces. This view concentrates on the computation to be performed.

The engineering view on digital health

The Engineering View takes care of the design of the information system under consideration by defining and interrelating implementable artifacts.

The technology view on digital health

Finally, the Technology View focuses on the specific technologies like IDEs, programming languages, libraries, etc., chosen to implement, run and maintain the system.

The business view on digital health

When designing digital health systems, we must always have in mind that the requirements for the solution as well

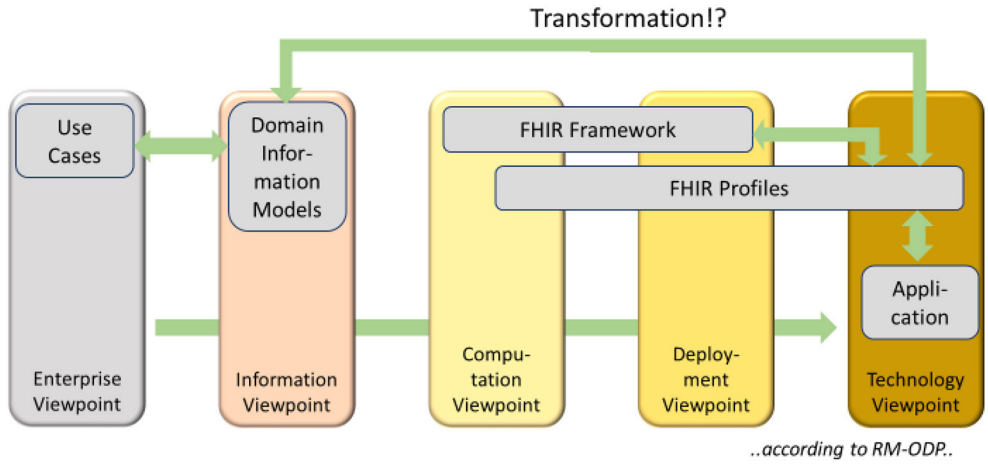

FIGURE 1
FHIR Framework (3) according to RM-ODP (18).

as the relevant concepts have to be defined by experts from the domains involved in the business system and the business process use cases. The concepts must be formally represented using those domains' ontologies. Therefore, the viewpoints of ISO 10746 must be extended by another, ICT-independent view – the Business View - as defined in ISO 23903 (see Chapter 9.2), which thereafter has to be transformed into the aforementioned views. The Business View guides all the other view (23). The Business View guides all the other views.

FHIR as a new foundational standard

One of the standards mentioned in the introduction is extraordinary and therefore worth a more thorough investigation during the course of this paper: the Fast Healthcare Interoperability Resources (FHIR) specifications (3). FHIR is the newest product family of HL7 International and currently transitioning from phase 1 (technology trigger) to phase 2 (peak of inflated expectations) according to Gartner's hype cycle. Furthermore, FHIR realizes a boot-strapping process, therefore allowing a self-definition using its own representation form. Finally, it is the foundation for a set of other standards and developments like CDS Hooks, "Smart on FHIR," etc.

FHIR as a foundational framework and implementable artifacts must be placed across the computational, engineering, and/or technology viewpoints, depending on what is judged (Figure 1). The easiest part is the technology, because FHIR is based on XML and/or JSON. Therefore, information systems must create FHIR instances in one of those representation forms.

The resources as defined by the FHIR framework belong to the computational and the engineering viewpoint, respectively, as they specify how the information must be separated and spread into certain components (engineering), and what kind of functionality they support (computational). FHIR profiles establish the semantic bridge to the information models because they define the semantics that is represented by specific FHIR resources in their use-case specific deployment. Therefore, FHIR profiles mostly belong to the technology viewpoint because technical aspects are described and specified in detail, but profiles also span over to the computation and engineering viewpoint due to their foundation.

Communicating data

Although RM-ODP is designed to support the development of information systems, it does not contain an explicit viewpoint in Figure 1 for expressing communicating systems even if each system has been designed according to the principles listed before. According to Figure 2, the aspect of two or more information systems sharing their data can be best represented and expressed in the technology view. They have to communicate according to the ISO/OSI-stack (26). In Chapter 8 (Figure 15), it is explained in which way this aspect is influencing interoperability and therefore reusability of data in form of information. The way the different viewpoints interact can be best seen in (27).

Designing and managing information models for interoperability

Information models are built as entities with relationships among them. These relationships lead to

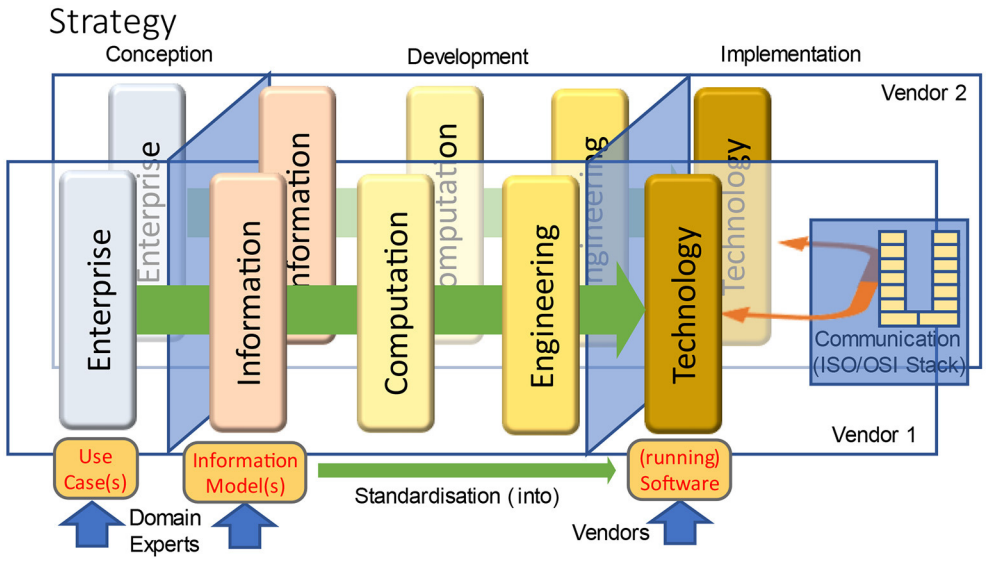

FIGURE 2
RM-ODP (18) and ISO/OSI-Stack (24, 25).

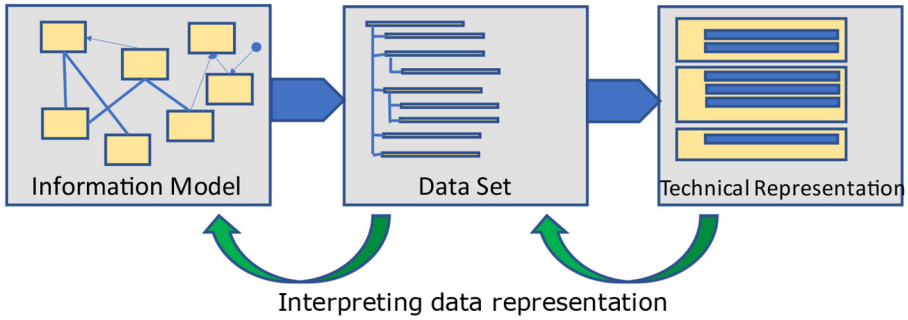

FIGURE 3
Derivation process.

closed loops - cyclic graphs. Frequently, the opinion dominates that information models as cyclic logical models are too complicated and therefore unnecessary for data exchange, and requirements of healthcare providers are adequately covered by data sets as a hierarchic definition of data elements alone. Therefore, most implementation guides for data exchange only provide hierarchic data element lists – named data sets (Figure 3) and do not introduce references and crosslinks to other information elements which are necessary in complex information systems. However, as long as only representations of forms/questionnaires are requested, the difference between data sets and data models will not show up and is ignored thereof – or at least not seen/realized.

For communicating data among different applications, the data set is taken and transferred into a technical, hierarchically equivalent representation that can be implemented – as sender and recipient – with the same or different expectations. Consequently, a sender is taking the data from its storage and converts it into that technical representation, whereas the recipient is implementing the opposite, namely extracting the data from that representation and converting it into its own data storage model (Figure 4). Only a few standards exist, that allow for direct storage using that exchange format, so that this transformation is obsolete. To answer the interoperability question, it must be verified that the underlying models from both the sender and the recipient perspectives adhere to the same information model. If this is not the case, some information details cannot be provided

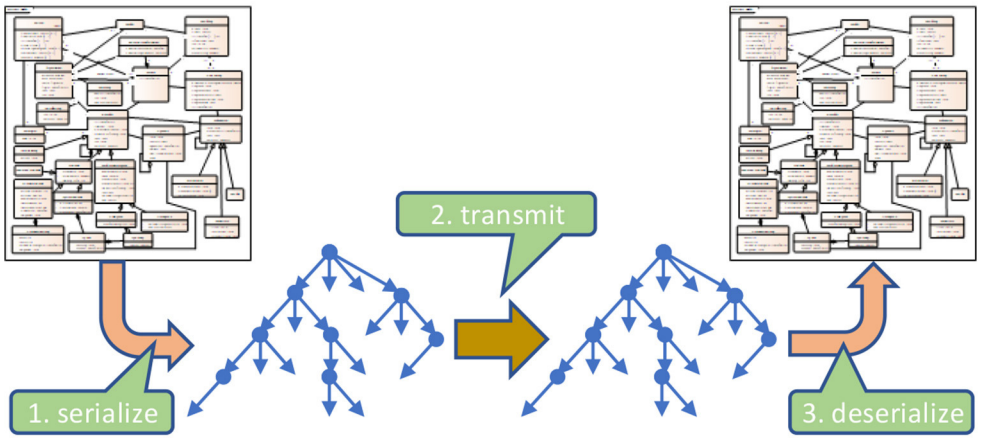

FIGURE 4
Communication.

or stored. The loss of information is the consequence. The driving force for data exchange specifications is the information model components and relations implicitly contained within the specification.

It should be clear, that the hierarchic structure of the information objects and the corresponding technical representation depends on both – the underlying information model and the standard that should be used for data exchange (Figure 5). It is necessary to find a bijective transformation from the hierarchical representation into the standard and back again without losing information.

If the standard being used allows for arbitrary variations of the structure, as it is the case, e.g., with XML at the highest level, this bijective transformation is easy because one is free in specifying the entities and attributes according to the direct needs. On the opposite, such a structure is individually created and therefore specific to the needs, so that no reasonable reuse is possible.

If the standard provides a set of dedicated structures, e.g., HL7 V3 or FHIR, the transformation is more complicated, because an alignment or mapping is needed. When the number of models resp. hierarchic data sets is greater than the number of available structures, certain marks must be established that can be used to identify what data set is represented. In high level data exchange standards like HL7 v2, V3, CDA or FHIR, these available structures are called profiles or templates.

Details

Communication scenarios are using one of two possible exchange paradigms: sending messages or documents. The first conveys information triggered by events for data processing and storing, discarding the original message afterwards. The second transmits a complete set of information elements for storage as a whole accompanied by metadata specifying the context. Independent of the paradigm, both facilitates a hierarchic tree-like structure, beginning with the message context or the root element of the document (Figure 6). All branches of the tree represent appropriate parts.

What attributes do the nodes with substructures or leaves provide?

The nodes of this tree enforce the overarching structure. For example, a message/document contains information about a patient. The patient data consists of his name and address. The name is comprised of first and given name as well as other details. In the end, real data is only provided with the leaves of this hierarchic structural representation, as non-terminal elements are simply introduced to group them for control purposes.

Depending on the paradigm and the underlying communication standard, the naming of the different branches (levels) varies (in Figure 7 marked by different colors). For example, a message is comprised of segments and fields, whereas a document contains sections and subsections. Some standards distinguish between (logical) data structures and (technical) data types. In the end, they all contribute to this data tree in form of different levels (Figure 7), and it does not matter how many individual levels are defined and what their technical purpose is. From their attribution, they obey the same rules.

The interesting part are the non-terminal nodes within that hierarchic structure. In Figure 8, one node is enlarged to explain the internals.

The nodes conceal architectural, development and runtime requirements (Figure 9). Unfortunately, data exchange specifications only express development and runtime

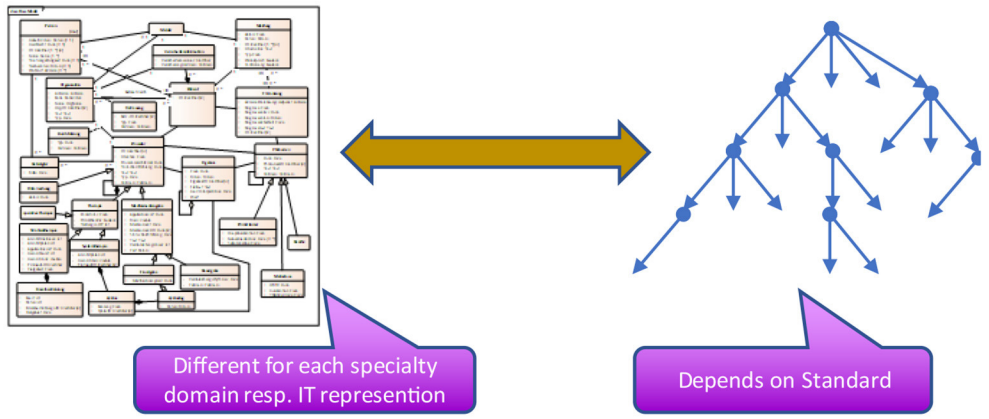

FIGURE 5
Projection to standards.

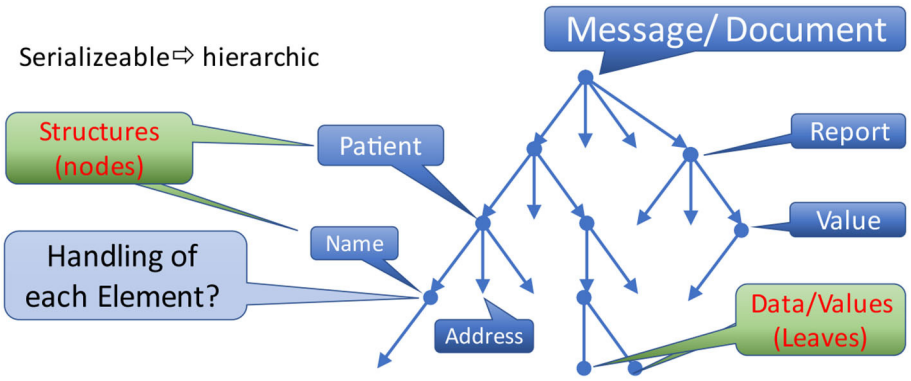

FIGURE 6
Hierarchic data structure.

requirements explicitly so that those can be considered during consecutive specification processes. The names of those constructs vary and may occur in different pre-coordinated types, e.g. "optionality," "must implement," "must support," "required," "mandatory," "repetitions," "cardinality," and some more.

Architectural requirements have an impact on structure and general capabilities of an application itself. The most obvious aspects are the structure as introduced in form of logical groups repeating those structural elements, and links to other sub-structures. The latter introduces cyclic graphs within the underlying information models. Extensions and null-values are two further architectural aspects that are often not interpreted as such. Both impact the design of applications, because the capability to store additional, most probably unexpected information or information about the absence of data is a central challenge for the basic design of an application, esp. for data storage. In this context, two standards must be mentioned:

a) HL7 Version 3/CDA (2) is the only standard that has a built-in capability for null-values for all data elements and attributes. Due to the underlying architectural framework, extensions are not directly allowed, or only within implementation guides facilitating a different namespace.
b) HL7 FHIR (3) allows for extensions at every part of a data instance. That opens the door for all kind of variations including different ways of conveying null-values (reasons for missing/absent data). Developers are challenged to consider these architectural requirements within their information systems.

Another interesting aspect is conditions (often also called predicates) that describe inter-dependencies among different nodes. As supporting a node is an architectural requirement, evaluating and supporting conditions is such a requirement as well.

In contrast to the nodes, leaves add even more requirements, because they are responsible for managing and maintaining

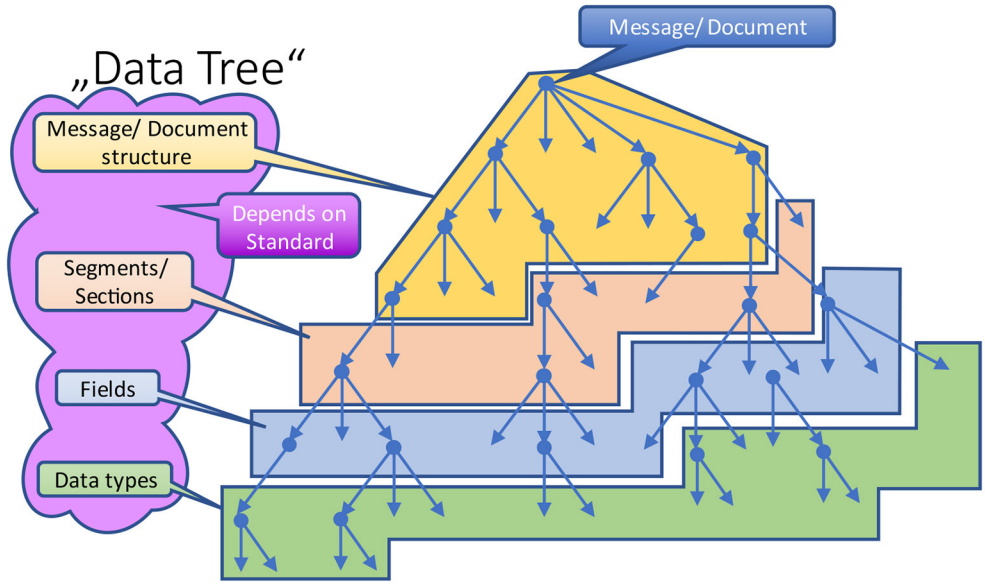

FIGURE 7
Abstract data tree.

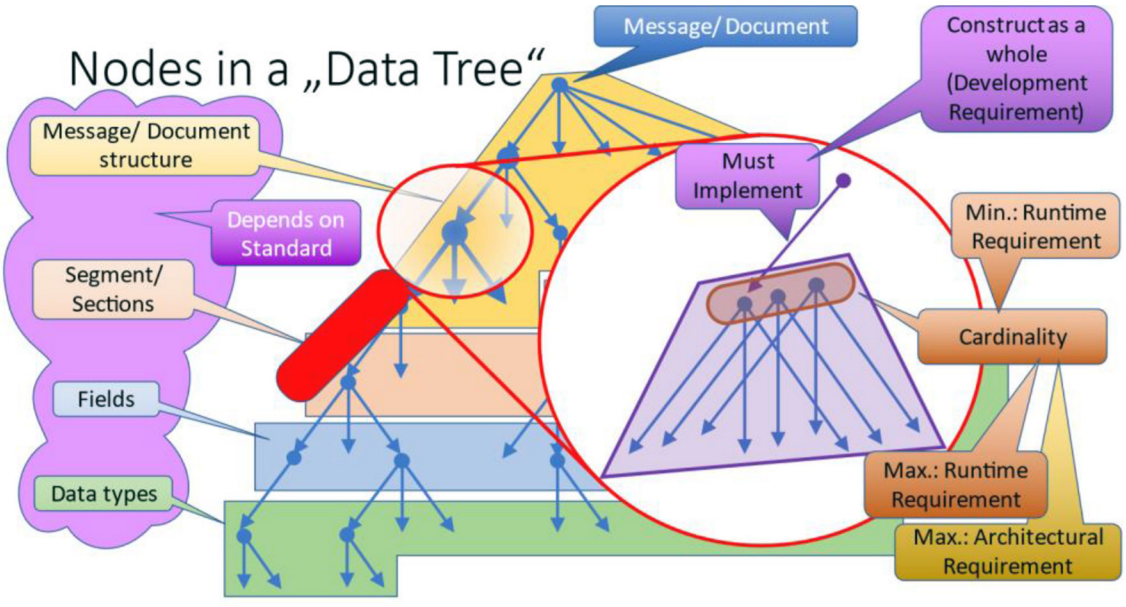

FIGURE 8
Nodes in a data tree.

particular values for data elements (Figure 10). So, different data types primarily handle textual and numeric information as well as coded information. The latter must be bound to appropriate vocabulary which is a dedicated and separate topic.

An important aspect for maintaining data items is the length of the value, although most interoperability specifications do not care about this anymore. Minimum and maximum length only make sense for rare use cases, esp. when the length is a real (physical) restriction, and the content of the use case is clearly defined. To overcome this problem, some standards have introduced a conformance length that informs about a reasonable value for a minimum length.

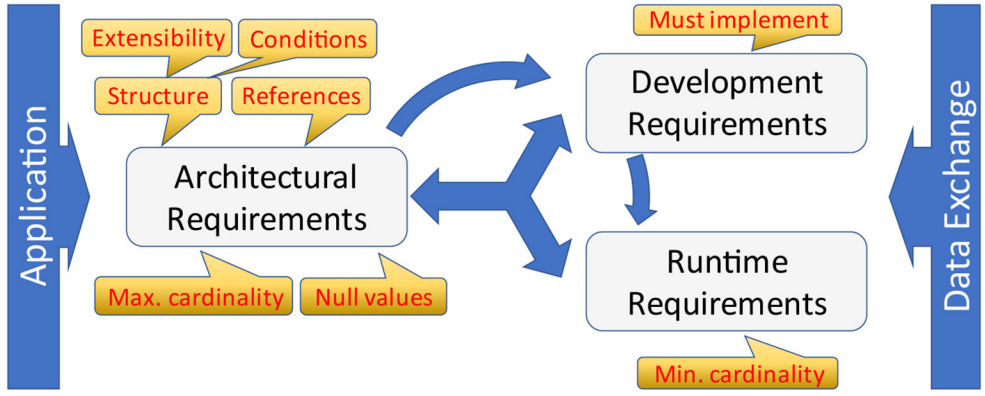

FIGURE 9
Architectural, development and runtime requirements.

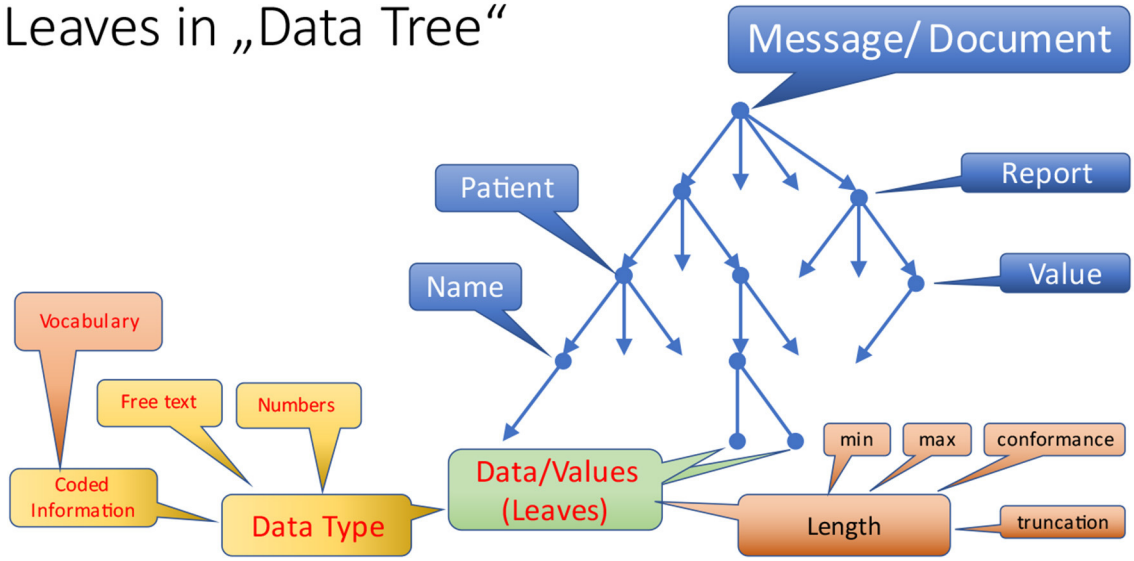

FIGURE 10
Leaves in a data tree.

As such, it can be treated as an advice for developers. The absence of length details is quite frequently accompanied by truncating the information during storage, because the target field in a database is too short, and most interfaces do not handle it adequately. In order to eliminate this problem, some standards have introduced a truncation flag, that indicates, in which way truncation is allowed or not. For example, truncating the house number in a street line information is certainly not nice, but cutting off relevant information in coded or textual information may cause severe misinterpretations leading to harm a patient.

Information model representation

As introduced previously, the structure resp. the hierarchy of data elements highly depends on the underlying information model (example in Figure 11), even if none is explicitly defined. As standards developers have such a model in mind when defining certain structures, this problem is not worth a discussion. For example, the family and given name parts are obviously associated with the name and not with an address. And a patient is going to have a name – or several names in the course of time – depending on the necessary details. Consequently, such simple aggregations do not cause major

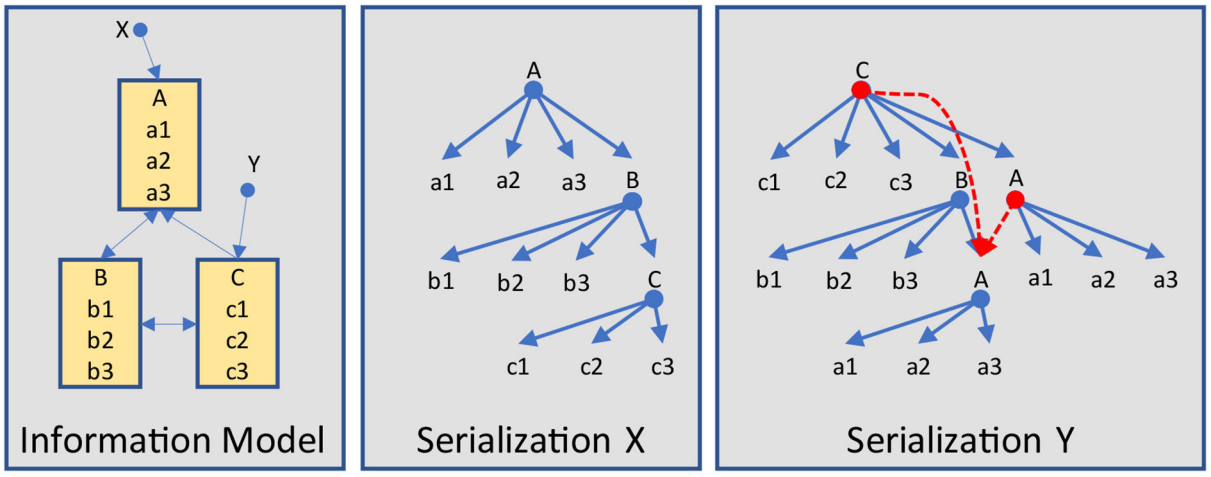

FIGURE 11
Serialization examples.

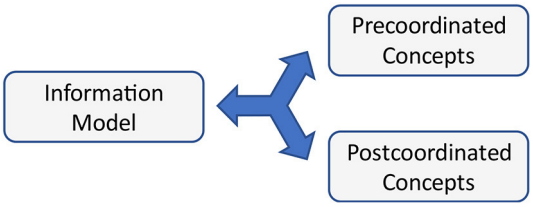

FIGURE 12
Equivalence of different modeling approaches.

or longer lasting discussions. The same applies to arbitrary structures that are used with forms, which are mainly driven by human readability, so that circular definitions do not occur.

Therefore, information models come into play when different aspects for reporting must be considered, that are taken from different parts of this model and reference other parts as is shown in Figure 11. Other good examples are taken from order entry workflows in combination with reports. In essence, the receiving application must "reconstruct" this model from the data it has received. As explained above, if the structure is not compatible, information loss is the consequence. Hence, explicitly providing the underlying model is the preferred solution against best guesses and implicit assumptions of developers.

Another problem is the handling of references to the same information item, as is demonstrated in Figure 11. Whether the information itself is included in the data, repeatedly represented, or simply referenced, offers different options and requires an explicit definition of how it should be handled.

Information model handling

The authors observe strong discussions about using a set of dedicated concept codes instead of defining appropriate information models (Figure 12). Of course, certain details of information models can be pre-coordinated into concept codes. This requires of course that both sides refer to the same coding scheme. Furthermore, codes hide specific contexts, objectives, and perspectives explicitly mentioned in the model and so guiding the interpretation. The deployment of codes only considers and covers the details that can be captured as different axes from a central concept. As an example, the different blood pressure measures allow for aggregating the cuff type, position, load, interpretation, and other details, as they are not exclusive and not repeating. Body weight does not allow for such an approach, because the different forms of amputations would result in a combinatorial explosion of possibilities if expressed explicitly.

Using pre- or post-coordinated concepts is of minor importance because of lossless conversions between them.

The size and assignment of models to a specific domain is of major importance. From a good modeling perspective, the individual information models should be kept small in order to simplify maintenance and promote consistency. Furthermore, they should not bridge different domains, as they might use different information objects for representing the same concept and vice versa. Especially the latter can be seen in many information systems, when clinical, medical, administrative and financial information is mixed, and therefore it is unclear what is exactly represented, and for what purpose it can be used.

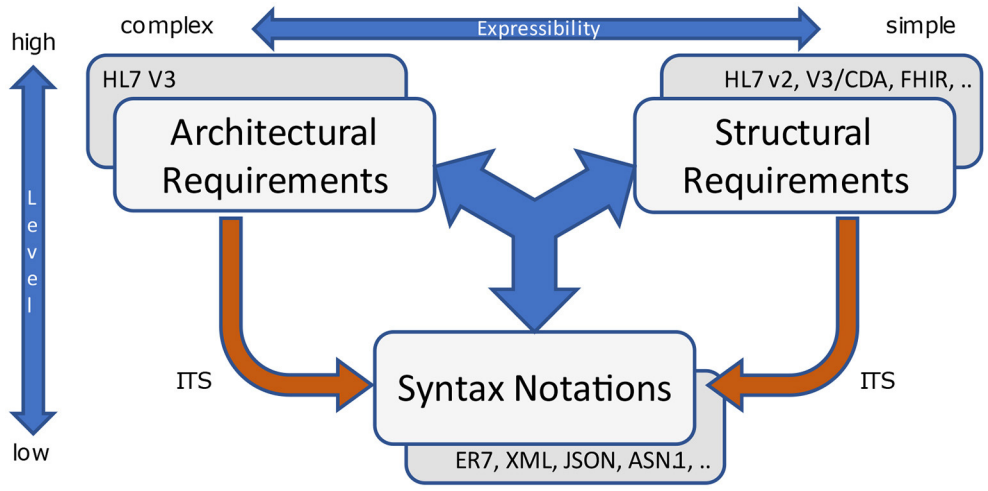

FIGURE 13
Representation forms.

Information models vs. ontological definitions

For correctly and consistently designing and interrelating information models, we have first to understand the concepts and relationships of the business system and its components, representing them using domain ontologies. Thereafter, we must model the business system from its ICT solution perspective at the enterprise level. For that purpose, we must use appropriate techniques and languages like BPMN. The formal representation of concept models using ontologies allows for describing the details in a computable form. Understandable models are an important step forward, as such models are frequently not provided, as mentioned above already. The more one think about contents, the less the semantic details are clear to the reader. In combination with (new) intelligent, knowledge-based techniques like Artificial Intelligence (AI), Machine Learning (ML) or big data, an ontological description becomes necessary. Snomed CT ontology (17) is a good example that demonstrates the possibilities when using the definitions for computation. The authors want to underline and motivate for concentrating on ontological definitions of information models using a computable form. The outcome helps with technical representations for storage and transmission as introduced above to enable advanced interoperability.

Information models' representation form

Another topic worth mentioning is the option for different representation forms. The authors remember a question from the nineties about "what is better, HL7 (v2.x) or XML?". This question is of course a rhetoric one, and abstracts from the levels that are used for representing data. Furthermore, it hides the disability to distinguish between those levels. Nowadays, modern representation forms are on a higher (ISO/OSI) level and facilitate XML, JSON, ASN.1 and others on the lower level as their implementable technology specification (ITS). Some also allow for bijective transformation between different syntactic representations (Figure 13).

Nevertheless, these aspects do not favor architectural and structural requirements against each other. Both are necessary to develop and implement information systems.

Information models, standards and applications

The relationship of information models to applications and data exchange standards has been explained before. Standards that are handled by adding constraints (Figure 14A) impose a greater adherence to the standards from the beginning, whereas adding constraints by extensions (Figure 14B) are easier to manage and to define so that the acceptance is higher. However, the latter does not exclude and avoid additional and new architectural requirements that are not foreseen by the base standard.

The principles for creating specifications according to Figure 14 are realized by specific standards in different practical ways (Figure 15), because the syntactic and semantic perspective must be analyzed separately. HL7 v2.x allows for extending the encoding syntax to add new contents by user-defined segments that must be considered during the parsing process. In HL7

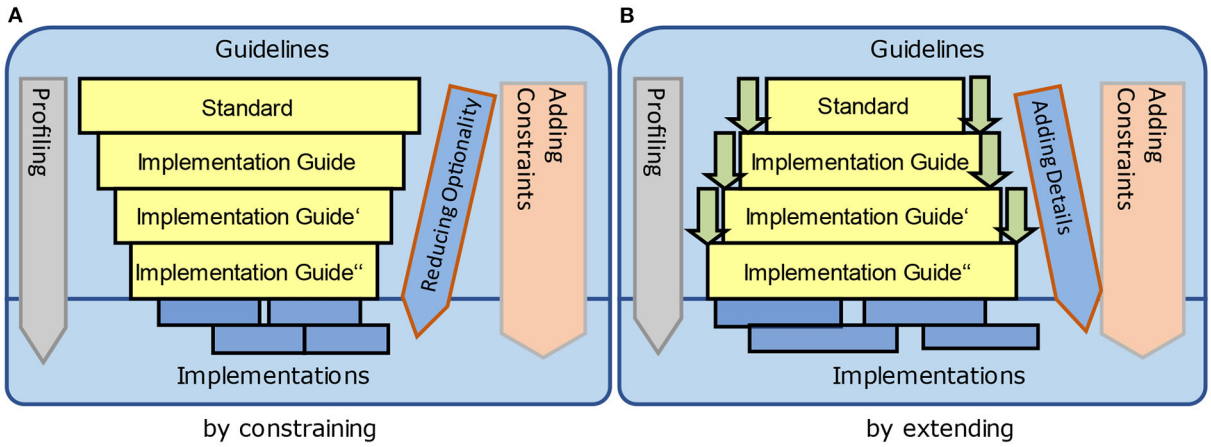

FIGURE 14
Creating specifications by adding constraints. **(A)** By constraining and **(B)** By extending.

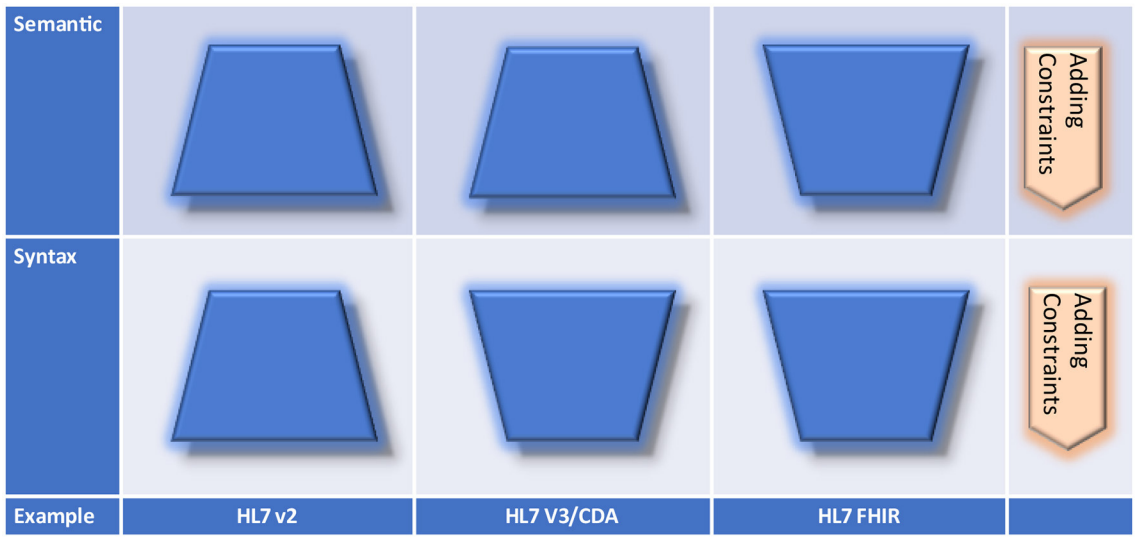

FIGURE 15
Creating specifications by standards.

Version 3/CDA, new content can be added by constraining the XML representation. The attribute/value-pair approach for extensions within FHIR is in principle a specific constraint for both – the syntax is closed although the semantics is open.

Another strong relationship is the use of internal information models as an architectural foundation to the application itself. The structure of the database for storing the information introduces such an information model, although it is not always made explicit. Consequently, a vendor is facing the challenge to convert from its internal structure the external one as defined by interoperability specifications. This challenge becomes even more complex, when a vendor must import data from different other applications, and export it to others as well (Figure 16). As previously explained, if the underlying structures differ and multiple im- and exports according to different data exchange standards are preformed, the probability to lose information is high or at least increasing.

In Figure 16, a communication scenario is presented, where all applications have to adhere to the same base specification. The interoperability challenge for a chain of communicating applications, thereby not losing or misinterpreting information, is even more difficult if the different base specifications and/or base standards have to be used, which facilitate different underlying information models.

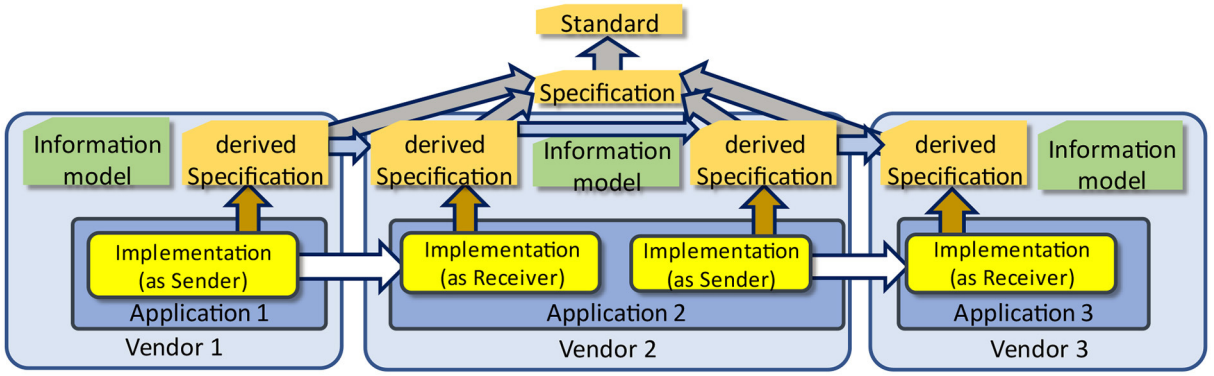

FIGURE 16
Information models within applications.

(Improved) Definition of interoperability

Figure 16 also triggers to reconsider the well-known definition of interoperability. IEEE Standard Computer Glossaries (1990) defines "interoperability" as

> … "the ability of two or more systems or components to exchange information and to use the information that has been exchanged."

Merriam Webster's Dictionary defines interoperability in a military context that associates the concept with using weapons. The latter reveals a hidden condition: This definition lacks an implicit verification that the data has been understood according to the sender's intention, which is symbolized by the green arrow in Figure 17. In other words, there must be some kind of feedback loop to verify the recipient's interpretation against the sender's understanding.

Using the aforementioned thoughts to reformat Figure 2 by unfolding and combining it with Figures 4, 17 results in Figure 18: The data being stored in one application according to the associated information model is communicated and transmitted to the other application and stored accordingly. Interoperable data exchange requires that the data is stored on both sides equivalently to each other, without the loss or falsification of data. Furthermore, the usage of this data has to be exactly the same. This guarantees that the concept of the business system component represented by the data is correctly understood on both sides. Without such a verification and confirmation, one can hardly name the process interoperable data exchange, although the data might be reused. For representing the business system on both sides, a generic component model (GCM) is used to represent the business system components and the related domains it serves (28).

Figure 19 provides an example demonstrating the difficulties using the FHIR Encounter Resource. In different domains, various types of "encounters" may occur that have to be stored with different details (attributes). Nevertheless, all of them can be communicated in FHIR using the same data structure. Therefore, there must be some clear and unambiguous indications in which way each of these communicated data has to be interpreted. Misinterpretations in any way may lead to severe risks for patient treatment.

All arguments favor information models for aligning a common understanding of data, so allowing a correct reuse.

Model transformation

Good modeling best practices

The different views on digital health systems discussed in the former sections are represented by different languages and different grammars. They range from business process notation languages with a grammar more constrained than natural languages, but less than the other ICT languages and ontologies, up to highly expressive traditional programming language with regular grammars, demonstrating a growing expressivity and formalization of languages. For ensuring context-sensitivity, the inclusion of tacit and implicit knowledge as well as decidability of the resulting system representation, the modeling process has to start in a top-down manner, where business domain experts define the view of the model as well as structure and naming of concepts to ensure the conceptual integrity of the model (29). Thereby, the good modeling design principles orthogonality, generality, parsimony, and propriety have to be guaranteed (30).

When modeling dynamic, multidisciplinary, transformed health ecosystems, the different perspectives of involved domains, different requirements of the intended users as well as behavioral, conceptual or contextual differences among the modelers might lead to different models of

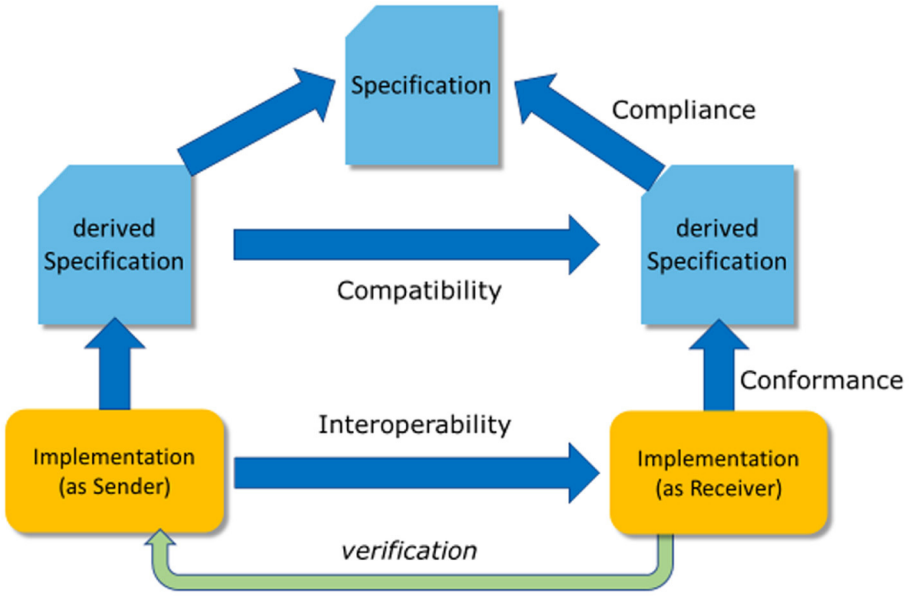

FIGURE 17
Enhanced definition of interoperability.

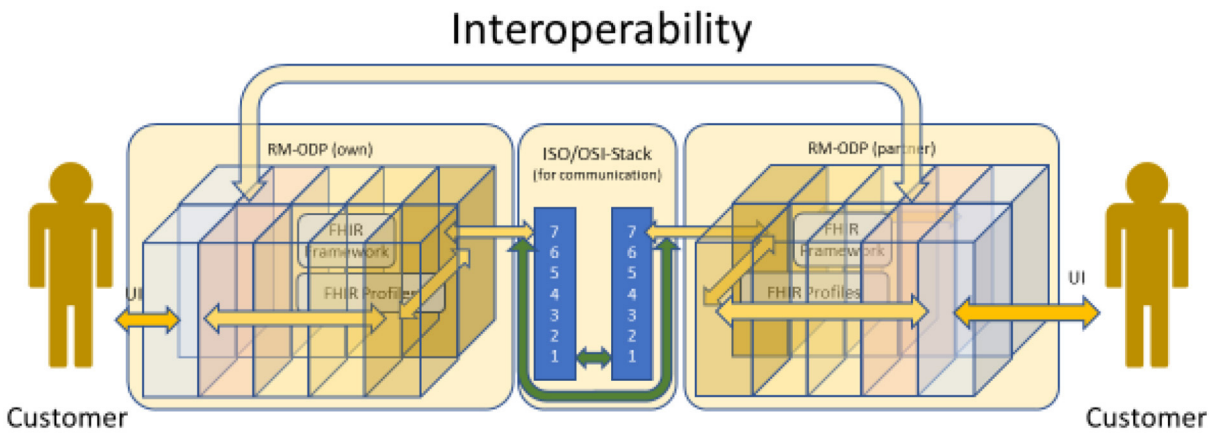

FIGURE 18
Unfolding the cube.

the same phenomenon. To guarantee that the integration of models represents the intended unambiguous, abstract conception of some parts or aspects of the real world, the models must be represented in an architecturally (i.e. structurally and behaviorally) correct and consistent way throughout all viewpoints. Newly created models and interrelations can only be justified at the real-world business system.

This aspect has to be considered when modeling business system components and using them for integration and/or interoperability.

Architectural approach to model transformation

or overcoming the aforementioned problems, a system-oriented, architecture-centric, ontology-based, policy-driven systems representation has been developed, based on the aforementioned GCM. The resulting generic integration and interoperability reference architecture based on universal type theory, universal logics and the system of ontologies has been meanwhile standardized as ISO 23903 (31). It represents every system of systems from the perspectives of the involved domains

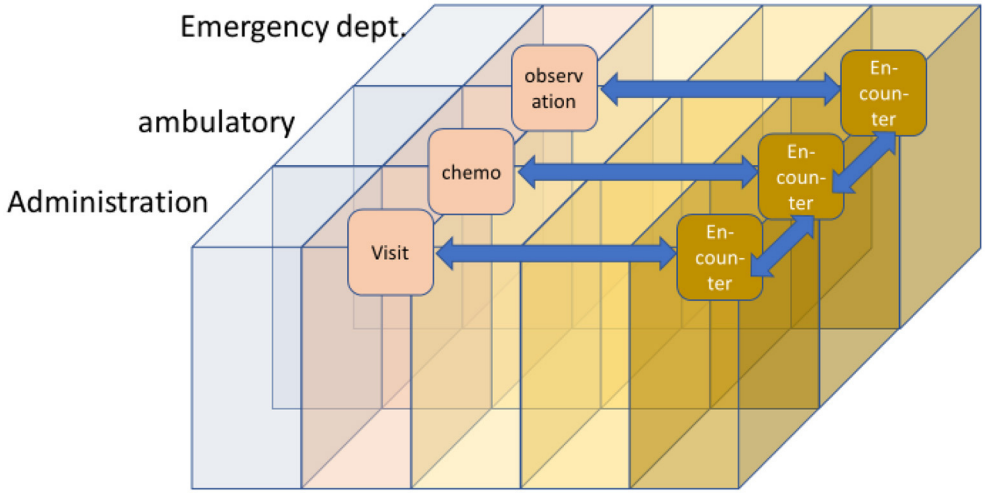

FIGURE 19
Example representation of data using the FHIR encounter resource.

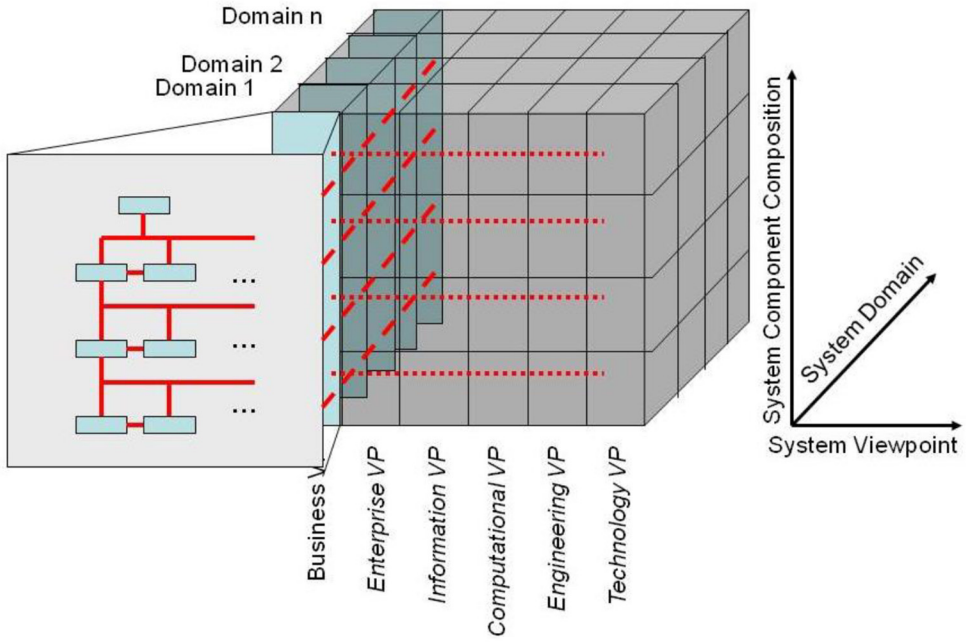

FIGURE 20
The GCM model and framework.

with generic granularity levels and the system's development process according to the ISO 10746 RM-ODP (18). Using the domain ontologies, all components must be represented and interrelated in the real-world business view, and thereafter transformed into the different viewpoints (ICT models). This must be done at the same granularity level for both the interrelation of components within any viewpoint and the transformation between them (represented by the red lines in Figure 20). Details can be found in (32).

ISO/TC 215 Health Informatics as well as the related European SDO CEN/TC 251 Health Informatics have declared the deployment of ISO 23903 mandatory for any project or specification addressing multiple domains with different knowledge spaces and ontologies to represent them. That

way, the correct development of new solutions as well as the integration of, or interoperability between, existing specifications can be easily performed and the correctness guaranteed. Meanwhile, ISO 23903 has been successfully used in standards specifying clinical models, presenting architectural approaches, managing concept mapping, and many more.

Summary

The paper demonstrated that multiple aspects must be considered when designing and implementing information systems. ISO 23903 is a good basis to support the alignment of different kinds of requirements. Furthermore, it enables the mapping between different domains, different specifications and products. Therefore, it provides an universal model and framework for advanced interoperability and integration between systems and any kind of principals such as organizations, persons, devices, applications and objects. Not all of the requirements to be incorporated are controlled by just one party. This paper should have made clear that following good modeling principles acc. to ISO 23903 is a mandatory demand that challenges all participants in the system design and development process.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

FO planed and designed the paper and authored its major part. BB authored Section 14 and contributed to all the other sections.

Conflict of interest

Author FO was employed by IT-Consultant in Healthcare.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Challenges and solutions for transforming health ecosystems in low- and middle-income countries through artificial intelligence

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Background: Recent studies demonstrate the potential of Artificial Intelligence to support diagnosis, mortality assessment, and clinical decisions in low-and-middle-income countries (LMICs). However, explicit evidence of strategies to overcome the particular challenges for transformed health systems in these countries does not exist.

Objective: The present study undertakes a review of research on the current status of artificial intelligence (AI) to identify requirements, gaps, challenges, and possible strategies to strengthen the large, complex, and heterogeneous health systems in LMICs.

Design: After introducing the general challenges developing countries face, the methodology of systematic reviews and the meta-analyses extension for scoping reviews (PRISMA-ScR) is introduced according to the preferred reporting items. Scopus and Web of Science databases were used to identify papers published between 2011–2022, from which we selected 151 eligible publications. Moreover, a narrative review was conducted to analyze the evidence in the literature about explicit evidence of strategies to overcome particular AI challenges in LMICs.

Results: The analysis of results was divided into two groups: primary studies, which include experimental studies or case studies using or deploying a specific AI solution (n = 129), and secondary studies, including opinion papers, systematic reviews, and papers with strategies or guidelines (n = 22). For both study groups, a descriptive statistical analysis was performed describing their technological contribution, data used, health context, and type of health interventions. For the secondary studies group, an in-deep narrative review was performed, identifying a set of 40 challenges gathered in eight different categories: data quality, context awareness; regulation and legal frameworks; education and change resistance; financial resources;

methodology; infrastructure and connectivity; and scalability. A total of 89 recommendations (at least one per challenge) were identified.

Conclusion: Research on applying AI and ML to healthcare interventions in LMICs is growing; however, apart from very well-described ML methods and algorithms, there are several challenges to be addressed to scale and mainstream experimental and pilot studies. The main challenges include improving the quality of existing data sources, training and modeling AI solutions based on contextual data; and implementing privacy, security, informed consent, ethical, liability, confidentiality, trust, equity, and accountability policies. Also, robust eHealth environments with trained stakeholders, methodological standards for data creation, research reporting, product certification, sustained investment in data sharing, infrastructures, and connectivity are necessary.

Systematic review registration: [https://rb.gy/frn2rz].

KEYWORDS

artificial intelligence, healthcare systems, low-and-middle income countries, scoping review, implementation challenges

Introduction

Information and Communication Technologies (ICT), in particular artificial intelligence (AI), is transforming health services, research, and public health in many countries (1). In its WITFOR Vilnius Declaration from 2003 already, the International Federation for Information Processing (IFIP) World Information Technology Forum (WITFOR), supported by the UNESCO, described the challenges and solutions in the context of impacts resulting from information and communication technologies as follows:

- **Bridging** the digital divide between rich and poor in the world; urban and rural societies; men and women; and different generations
- **Ensuring** the freedom of expression enshrined in Article 19 of the universal declaration of human rights and other such instruments
- **Reducing** poverty through the use of education and Information and Communications Technology (ICT)
- **Facilitating** the social integration of excluded segments of societies
- **Respecting** linguistic and cultural diversity
- **Fostering** the creation of public domains with full respect for intellectual property rights
- **Supporting** communities in fighting illiteracy
- **Encouraging** e-governance and e-democracy initiatives
- **Improving** the quality of life through effective health service systems
- **Protecting** the local and global environment for future generations.

In low-and-middle-income countries (LMICs), the use of these technologies can help to close the gaps in healthcare, especially in underserved regions that lack healthcare specialists, as well as improve public health surveillance (2). In addition, the United Nations has estimated that different digital health technologies, including AI, can help countries achieve the Sustainable Development Goals and reach the universal health services coverage goal (3). The WITFOR Vilnius Health Commission highlighted the inclusion of IT strategies in health care to target the major health problems in LMICs, such as HIV/AIDS, TB, Malaria, and mother and child health. LMICs should therefore prioritize Health Information Systems, using multiple sources of aggregated and anonymized data from different related sectors in society, aiming at strengthening health management and primary health care delivery, including a basic hospital structure (4). Integration within and between healthcare establishments requires consistent specification of data sets and terminology. Future health information systems should optimally use Free and Open Source Software, models, and component specifications characterized by scalability and flexibility through a component-based architecture enabling the free combination of relevant services allowing for

incremental development; portability separating logical and technological specifications, and a fine-grained architecture to manage complexity. Furthermore, sustainable systems must be based on: training and institutional development enabling local adaptation, maintenance, and use; leadership of health professionals and other domain experts in systems development; and must focus on the local use of information for action (5).

Autonomous systems and artificial intelligence significantly transform health and social care ecosystems (6). This paper especially addresses artificial intelligence for transformed health systems in low- and middle-income countries–frequently still called developing countries.

Rationale

Artificial intelligence (AI) has permeated all spheres of the development of scientific, social, and cultural knowledge of humanity. One accepted definition of AI is the capability of computers to mimic human cognition, becoming able to learn, reason, understand, adapt, self-regulate and interact with the environment (7, 8). In addition, some experts propose that artificial intelligence manifests itself through appropriately obtaining its goals; second, flexibility to change; third, learning from experience; fourth, making appropriate decisions (9, 10).

Artificial intelligence has changed how we communicate and interact with our environment. It can also improve and strengthen essential areas for the survival of humankind, such as food, transportation, education, and health. In particular, the health sector has experienced growth in AI research. The processes of promoting healthy habits, prevention, diagnosis, and treatment of diseases have been transformed to improve the effectiveness of these processes. Furthermore, the early detection of health threats from the environment or human activity, such as COVID-19, has benefited from AI development and deployment (11, 12).

Formal research differentiating the challenges and comparing the level of AI development between higher-income settings and LMICs was not found. However, the World Health Organization (WHO) highlights the importance of implementing technologies to guarantee universal access to health care and improve the living conditions of communities around all member countries (13). Particularly AI has the potential to improve patient care, diagnoses, and treatment and improve public health efficiency of health systems in high, medium, and low-income countries (14). Moreover, a recommendation on digital health adoption from the Organization for Economic Cooperation and Development (OECD), an international organization created to promote the economic health of members countries which are mainly high-income countries, claim the urgent need to develop policy to regulate ICT use, improve structures, and invest in human and institutional capacity. Those are the core challenges identified in this scoping review.

Low-and-middle-income countries are communities that do not have affordable and accessible healthcare services. Therefore, the potential for AI to help close the gaps in healthcare provision is clear. According to (15), in 2019, around 60% of the world's population lacked access to even essential healthcare. Also, (16, 17) declared that 8.4 million lives had been lost each year and $1.6 trillion in productivity in LMICs where poor health care quality is provided. Moreover, there are significant challenges surrounding AI implementation for healthcare in LMICs, as recently described by WHO in their guidance on Ethics and Governance of Artificial Intelligence for Health (14). One concrete example is digitizing medical and health records. Such records have the primary input of AI, which is the demographic and clinical data (10, 18). In addition, incorporating the results of the decision-making support systems into the processes in the health facilities reduces the workload of health workers (19, 20). Other critical challenges are ethical and regulatory issues. Special considerations regarding informed consent, security, privacy, trust, liability, confidentiality, equity, and accountability policies must be taken.

However, paradoxically, another significant challenge to effectively implementing AI in LMICs for healthcare comes from the vast and extensive development and deployment of AI in High-Income Countries (HICs). Since data used in the production of AI systems are highly linked to the context of use, implementing such systems in LMICs can result in contextual bias. According to (15), contextual bias means the development of predictive AI models trained with data not reflecting the real context of the use of the algorithms, which can be considered a threat to the promise of AI to foster healthcare democratization of health services in LMICs because the models trained with the wrong data, cannot be used to build decision support tools for primary healthcare practitioners, that way overcoming the shortage of specialized health care professionals. Moreover, the fact that ML models are created in HICs can drive inequality, concentrating wealth, resources, and decision-making power in the hands of a few countries, companies, or citizens (21).

Last but not least, AI-based models must be trained and deployed on a well-developed legal and regulatory framework tailored to the public health systems needs of LMICs. It would allow a careful adoption of these technologies and a positive impact on healthcare systems by addressing the biological and demographic differences of the population. Otherwise, AI could reinforce and exacerbate health and socioeconomic disparities (22). The process of managing AI should not be limited to solving health problems individually; implementing AI should be visualized as an object of transformation in LMICs' health systems (8).

Objectives

With the above in mind, this review aims to collect, identify and analyze the gaps and challenges of implementing AI in the healthcare systems of LMICs and provide possible solutions to strengthen health systems and overcome the challenges. There is a set of 40 challenges gathered in eight different domains that affect the stakeholders in the healthcare system.

The paper is organized according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist (23).

Methods

Protocol and registration

The protocol for this scoping review was drafted according to a pre-defined objective: to identify and analyze gaps, challenges, and possible solutions and strategies to strengthen health systems in LMICs through the proper development of AI. Within the protocol, there were detailed criteria to search and include/exclude sources of evidence and explain the search approach in the selected databases with a proper justification for choices. Once this was clear to reviewers, there was a consensus on extracting the data. The protocol provided the plan for the study selection process, including resolving disagreements between reviewers and the draft charting table for data extraction with accompanying explanations. The protocol was developed following the JBI Reviewer's Manual (24) and was finally revised on November 3rd, 2021. The protocol can be found in the URL: https://rb.gy/frn2rz.

Eligibility criteria

For studies to be included in this scoping review, they only needed to describe an AI solution or focus on discussing the gaps and challenges of developing AI for health systems in LMICs. We did not want to discard relevant contributions assessing their methodological robustness. Therefore, any study that could be classified as a research contribution according to the Equator (Enhancing the QUAlity and Transparency Of health Research) Network for which reporting guidelines exist (e.g., Observational studies, Systematic reviews, Diagnostic/prognostic studies, Case reports, Clinical practice guidelines, Qualitative research, Quality improvement studies, Economic evaluations). Peer-reviewed journal papers were included if they were published between 2011 and 2022, written in English or Spanish, and developed an AI application for specific health purposes (communicable diseases, maternal and newborn health, or cancer, among others), especially in LMICs. Studies with datasets were included and classified according to the data origin. Review articles, meta-analyses, and opinion papers were also included because they were considered relevant to the narrative review section. Moreover, the paper was included if any strategy or guideline for properly implementing AI was presented. Articles were excluded if they did not meet the mentioned criteria or were study or review protocols.

Information sources

Scopus and Web of Science (WoS) databases were used to perform the search to identify potentially relevant documents. Although PubMed supports searching and retrieving biomedical and life sciences literature, Scopus covers all journals in PubMed. The search strategy was drafted considering the review question and objective defined in the protocol. The terms for the search strings were (i) artificial intelligence and its synonyms or contained concepts (e.g., machine learning or data science), and (ii) the concept of low and middle-income countries and their synonyms (low-resource settings). Further refinement of the search strategy was made through team discussion. The studies were searched in the databases on November 8th, 2021. The final search results were exported into Bibliometrix (25), a tool for bibliometric analysis, where duplicates were removed.

Two complementary information sources were consulted for the data extraction process and classification of documents. First, the WHO health topic classification (26) was used to classify the health purpose approach in the included studies. The World Bank Country and Lending Groups Classification (27) was also used to obtain more information on the data and contributions origin since the study's objective was focused on LMICs.

Search

Description of the search strings used in Scopus and WoS and their results, are shown in **Table 1**. The strings were refined through two discussion rounds. Finally, the search was performed without any restrictions on the database (except for the year limitation established as eligibility criteria). Refining the search string allowed us to obtain wider results from Scopus and more restricted figures from WoS, as shown in **Table 1**.

Selection of sources of evidence

The reviewers screened 331 papers after removing duplicates. The screening process consisted of evaluating each publication by title and abstract; if the documents met the eligibility criteria, contributions, author's affiliations, and datasets used were considered. Finally, the identified relevant

TABLE 1 Information on string search.

ID	String search	Scopus	WoS
1	TITLE-ABS-KEY [("artificial intelligence" OR "machine learning" OR "deep learning") AND (lmic OR " low-resource settings" OR "low- and middle-income")]	285	
	[TS = (artificial intelligence OR machine learning OR deep learning)] AND TS = (lmic OR low-resource settings OR low- and middle-income)		230
2	TITLE-ABS-KEY [("artificial intelligence" OR AI OR "machine learning" OR "deep learning" OR "data analytics" OR "data science") AND (lmic OR "low-resource settings" OR "low- and middle-income")]	**311**	
	TS = ("artificial intelligence" OR AI OR "machine learning" OR "deep learning" OR "data science" OR "data analytics") AND TS = (lmic OR "low-resource settings" OR "low- and middle-income")		**161**

studies were classified according to the aim provided in the abstract's paper.

The eligibility of papers depended on the type of study identified. For this scoping review, sources of evidence were divided into two groups to facilitate the analysis of the results. The first group included experimental or case studies (those describing a specific AI solution); the second group comprised strategy or guidelines papers, opinion papers, or secondary studies like systematic reviews.

After identifying the type of study, a score from 1 to 4 was given to each paper according to the relevance of contributions from the study. Classification criteria for the primary studies group were:

- Score 1: Studies only describing a model-based solution (i.e., machine/deep learning model or natural language processing) or dataset building for a health context not located in LMICs.
- Score 2: Studies describing a data science solution (i.e., machine/deep learning or natural language processing implementations from feature extraction until deployment) or a model-based solution within a device for a health context not located in LMICs.
- Score 3: Studies only describe a model-based solution (i.e., machine/deep learning model or natural language processing) or dataset building for a health context in LMICs.
- Score 4: Studies describing a data science solution (i.e., machine/deep learning implementation from feature extraction until deployment) or a model-based solution with a device for a health context located in LMICs.

Classification criteria for the secondary studies group were:

- Score 1: Papers not describing any challenge (e.g., requirements, gaps, limitations, or barriers) nor proposing any solution (e.g., strategy, framework, initiative, policy, recommendation, or guideline) for AI use or implementation in LMICs.
- Score 2: Papers describing challenges (e.g., requirements, gaps, limitations, or barriers); however, no solution was proposed (e.g., strategy, framework, initiative, policy, recommendation, or guideline) for AI use or implementation in LMICs.
- Score 3: Papers proposing one or more solutions (e.g., strategy, framework, initiative, policy, or guideline) for AI use or implementation in LMICs, but restricted to any research context in health (tuberculosis, child and adolescent health, cancer, etc.).
- Score 4: Papers proposing one or more solutions (e.g., strategy, framework, initiative, policy, recommendation, or guideline) for AI use or implementation in LMICs, not restricted to any specific research context in health.

Disagreements on study selection and data extraction were solved by consensus and discussion with other reviewers when needed.

Data charting process

Data from eligible studies were charted using a data abstraction template designed for this review. In this template, there was detailed information on the types of research, the research contexts related to the applications in health and applications of AI, the origin of the studies (classified by country and by income), and the origin of the data used in the studies. The template structure (**Table 2**) is intended for having an overview of the trends and information sets within the topic at hand, which is the development of AI in LMICs for healthcare.

Data items

Data was extracted from information only available in the abstract. In addition, details were recorded on the template regarding the research type (e.g., experimental studies, systematic reviews, strategies or guidelines, opinion papers, case reports, study protocols, clinical practice guidelines, and qualitative research); research context on AI applications (e.g., Data-based diagnosis, AI model for image-based diagnosis, AI model for data-based diagnosis, AI model

for image-based mortality assessment, AI model for data-based mortality assessment, AI model for data-based treatment, AI application for LMICs, AI model for clinical decision support, mHealth for LMICs); research context in health (e.g., digital health, tuberculosis, child and adolescent health, cancer, and maternal and newborn health, among others), AI-driven health interventions (20) (e.g., diagnosis, mortality risk assessment, treatment, clinical decision support), study's origin (e.g., low-income economies, lower-middle-income economies, upper-middle-income economies, high-income economies), ethical aspects (i.e., it is mentioned or not), data set (i.e., there is, there is not, there is and it is from LMICs).

Synthesis of results

According to the two groups of papers organized for this scoping review, there are two complementary methods of summarizing the information found. For the primary studies group, a trend analysis was performed where information on the most used AI technology and the health context that was the most approached is presented. For the secondary studies group, a trend analysis was also performed on some features extracted along with an in-deep review of the papers having strategies for a narrative summary of the gaps, challenges, solution frameworks, initiatives, and strategies implementable for AI.

Results

Selection of sources of evidence

After removing duplicates, 331 papers were screened by title and abstract. 79 articles were excluded based on this information, and data was extracted from the remaining 252 papers to assess their eligibility. From data extraction results, two groups of papers were identified from the type of study: one group with primary studies [see the effects in the variables of interest when introducing any intervention (28)] and the other group with opinion papers, systematic reviews, papers with strategies or guidelines, under the name of secondary studies. From the first group, 44 articles were excluded for the following reasons: 17 presented solutions based on models not addressed to LMICs, and 27 presented advanced solutions not directed to LMICs. From the second group, 56 papers were excluded: 9 were study protocols, and 47 papers did not report information on gaps, challenges, or solutions for AI implementation for healthcare in LMICs (**Figure 1**). Finally, the remaining 151 studies were considered eligible for this scoping review.

From now on, the description of the results is divided into the two papers groups found. The description of the primary studies group aims to describe the trends of the solutions that exist and involve the development of AI for health care and where research efforts are directed, especially in the context of LMICs. For the description of the papers belonging to the secondary studies group, a narrative summary of the findings regarding gaps and challenges for implementing AI in LMICs and their resulting solutions is provided.

Characteristics of source evidence

Primary studies

In this first subsection, the trends in AI implementations in LMICs for healthcare are described, based on four aspects: the technological contribution, the data, the health context, and the interventions driven by AI for health.

As shown in **Figure 2**, from the 129 primary studies selected for this scoping review, 104 papers presented an AI model as the main technical contribution. Eighteen studies demonstrated an AI model plus its implementation in a technical platform (e.g., mobile, wearable platform). In four papers, the AI model was complemented by a framework, and the framework (without describing a model) was presented in only one contribution. Finally, the creation of a dataset was the contribution of two studies. From those studies presenting an AI model, 89 papers used machine learning (ML) models, 33 papers used deep learning (DL) models, and four papers used natural language processing (NLP) (**Figure 3**).

There are five types of platforms in the papers (**Table 3**). The most implemented are mobile applications in 10 papers, followed by wearables in four. Lastly, portable ultrasounds were developed in two papers, a web application and an enforcement system.

Regarding the data used in the papers, two aspects were considered for the trend overview. The first aspect is the data type (**Table 4**). Clinical records data is the most used type, with 22% of the papers. Then, almost 40% of the documents used images, specifically radiology images (19% of the papers) and satellite images (7% of the papers). The remaining types of data are physiological signals (6% of the papers); demographic, biological, epidemiological, and laboratory data (each one, 5% of the papers); surveys (i.e., data that was acquired from large national or international efforts) with 4% of the papers; geographical data, text corpus, movement signals, and sounds (each one, 2% of the papers); and only one paper used videos as data source.

For the second aspect is the size of the dataset used in these primary studies. **Figure 4** shows that most of the studies (51 papers) used small datasets, i.e., less than 1,000 instances. 44 papers deployed datasets that had between 1,000 and 9,999 instances, and 34 papers used large datasets with more than 10,000 instances.

The health topic addressed is the third aspect, when analyzing the trends in the studies found in this scoping review. In **Table 5**, there is the paper count for each health

TABLE 2 Description of data charting for individual sources of evidence.

Item	Description and options	Primary studies example	Secondary studies example
Title	Paper's title	Deep Learning Assistance for Tuberculosis Diagnosis with Chest Radiography in Low-Resource Setting	Artificial Intelligence in Health Care Laying the Foundation for Responsible Sustainable and Inclusive Innovation in Low and Middle Income Countries
Authors	List the paper's authors and affiliations	Nijiati et al. (36)	Alami et al. (8)
Year	Publication year obtained from metadata	2021	2020
Type of study	According to the aim of the paper, classification of the studies is according to: Experimental studies, systematic reviews, strategies or guidelines, opinion papers, case reports, study protocols, clinical practice guidelines, and qualitative research.	Experimental studies	Strategies or guidelines
Technical (AI) contribution	Essential contribution of the paper, can be classified according to: Data-based diagnosis, AI model for image-based diagnosis, AI model for data-based diagnosis, AI model for image-based mortality assessment, AI model for data-based mortality assessment, AI model for data-based treatment.	AI model for image-based diagnosis	AI for LMIC
Health topic	Purpose of the contribution to human health describe by topic and category; e.g., digital health, tuberculosis, child and adolescent health, cancer, and maternal and newborn health	Tuberculosis Communicable diseases	Digital health Health systems
Summary	Describe the abstract highlighting the components of interest for the research.	In a rural area of China, the authors have a dataset of X-ray images for the detection of tuberculosis. Using a DL model, the authors find an increase in detection accuracy when using the model to assist clinicians.	They propose a five-block guide for developing and implementing AI-based healthcare technologies for LMICs. They discuss the benefits, risks, and challenges of AI-based health, and from this, they draw guidance.
AI-driven health intervention	Select the type of intervention that is being used for the health topic among diagnosis, mortality risk assessment, treatment, clinical decision support, health policy	Diagnosis	Health policy
Study's origin	Name of the country and income classification	China Upper-middle-income economies	Canadá High-income economies
Score	Assign a score according to what is found in the abstract	3	4
Notes	Important information that needs to be taken into account	It is simple experimentation	They mentioned strategies

topic (31 topics) and each category of health topics (eight categories). For example, the most recurrent health topic is "maternal and newborn health," with 16 papers approaching it. This topic corresponds to the most recurrent category, "life-course approach," with 34 papers. The second and third places of the topics are "cancer" and "child and adolescent health," respectively.

Finally, the health interventions driven by AI mostly focused on diagnosing different diseases and conditions. In 66 papers, the authors addressed in their solution this intervention. Next, the AI solution considered in the paper was used for general purposes (29 papers), for example, age estimation and population density or distribution. The remaining interventions were mortality assessment with 18 papers, clinical decision support with 12 papers, and treatment with 4 papers (**Figure 5**).

From this data, different methods for diagnosis were implemented in the primary studies, precisely (i) the construction of datasets for diagnosis (i.e., data-based diagnosis) with two papers, (ii) the modeling of data (such as clinical or laboratory data) for diagnosis with 26 papers, and (iii) the modeling of images for diagnosis with 38 papers. Also, the information source for mortality assessment to build the model was based on images (2 papers) and clinical data (16 papers). Information on both approaches is presented in **Figure 6**.

Since the scope of the primary studies explored should be within the context of LMICs, results on the origin and affiliations of the authors of the papers were obtained as well.

Although the chosen papers use datasets from LMICs, the results show that many authors and affiliations belong to countries qualified as HICs. For example, in **Figure 7**, the USA leads the count with 64 papers that have authors affiliated with its universities and research centers, followed by the United Kingdom (UK) with 25 articles. Both countries are of course classified as HICs.

Secondary studies

This second subsection presents some highlights about the secondary studies group. First, **Table 6** shows the

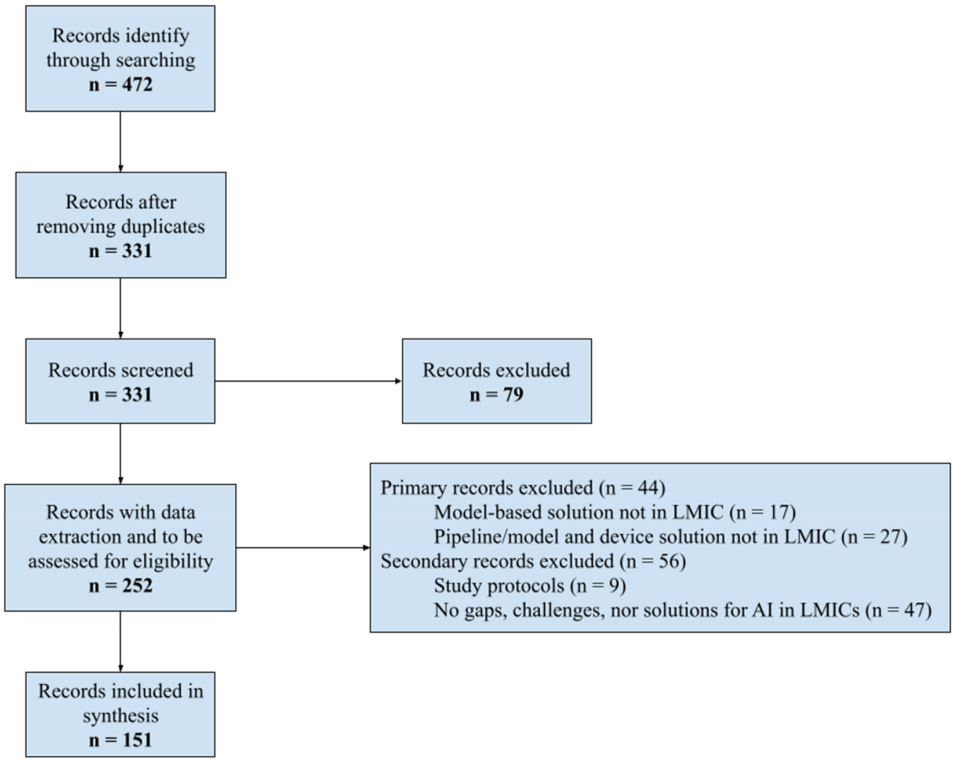

FIGURE 1
Flowchart of the study selection process.

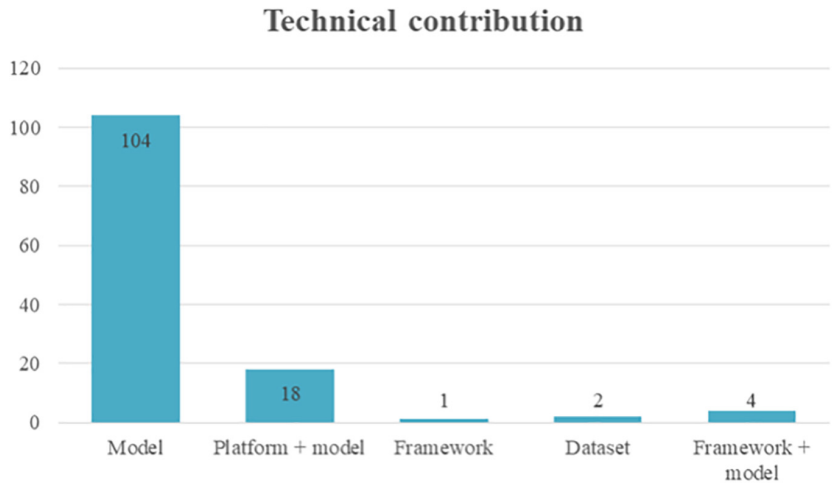

FIGURE 2
Distribution of the technical contributions.

distribution of the health topics; it has different results from the primary studies group. For example, the most common health topic was "Digital health", defined by the WHO as an umbrella term encompassing e-health interventions for strengthening health systems toward universal healthcare coverage.

From the list of countries obtained, 54% correspond to HICs, and only 3% correspond to Low-Income Countries (LICs). The remaining distribution is for Upper-Middle-Income Countries (Upper-MICs), with 17% of affiliations, and Lower-Middle-Income Countries (Lower-MICs), with 26% (Figure 8).

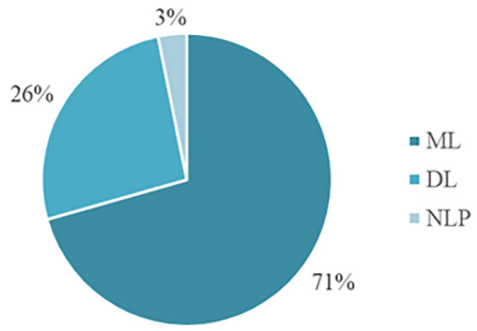

FIGURE 3
Distribution of the models.

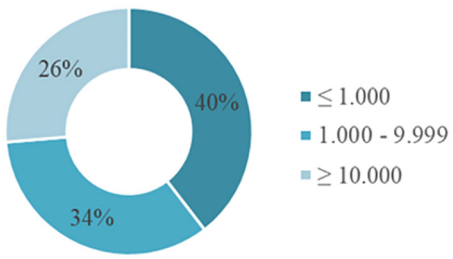

FIGURE 4
Distribution of the size of the datasets in the studies.

Figure 9 shows the type of research within this group of papers. Ten papers were found to have strategies or guidelines in the context of AI implementation policies in LMICs. Nine were opinion papers or editorial papers, and three were systematic reviews with important conclusions.

Secondary studies established a score for eligibility (explained in the Methods section), as presented in Figure 10.

TABLE 3 Distribution of the platforms used.

Type of platform	
Mobile application	10
Wearable	4
Portable ultrasound	2
Web application	1
Enforcement system	1

TABLE 4 Data found in the papers.

Type of data	
Clinical records data	28
Radiology images	24
Images	18
Satellite images	9
Physiological signals	8
Demographic data	7
Biological data	7
Epidemiological data	6
Laboratory data	6
Surveys	5
Geographical data	3
Text corpus	3
Movement signals	2
Sounds	2
Videos	1

Six papers were scored for only having challenges, five papers for presenting challenges and solutions for a specific problem or context, and 11 papers received a four-point score for proposing general solutions and contributing greatly to this scoping review.

As with the primary studies, for the group of secondary studies, information on the countries and affiliations of the authors of the reviewed works were extracted, obtaining a similar result. In Figure 11, the complete list of countries is found, and again USA and UK lead the count.

Similarly, the countries that belong to the HICs classification present the majority of results, in this group, with 85% of the papers. The remaining is divided into Upper-MICs with 4% and Lower-MICs with 11% of the papers (Figure 12).

Synthesis of individual results

For the description of the papers belonging to the secondary studies group, a narrative summary of the findings regarding gaps and challenges for implementing AI in LMICs and their resulting solutions is provided.

Dimensions and challenges

Forty different challenges were identified in the analyzed studies. They were grouped into eight categories: Data Quality, Context awareness; Regulation and Legal Frameworks; Education and Change Resistance; Financial Resources; Methodology; Infrastructure and connectivity; and Scalability. Each one of the challenges is detailed in Table 7.

Solutions to challenges

Based on the recommendations presented in the studies analyzed, including some reflections of the authors of this scoping review, eighty nine possible solutions to the challenges are identified. The solutions are shown in Figures 13–17, according to each of the eight dimensions.

TABLE 5 Paper distribution according to health topic and category for primary studies.

Category	Health topic	Papers per topic	Papers per category
Life-course approach	Maternal and newborn health	16	34
	Child and adolescent health	13	
	Healthy aging	3	
	Disability and rehabilitation	2	
Non-communicable diseases	Cancer	15	31
	Mental health	5	
	Cardiovascular diseases	4	
	Diabetes	4	
	Chronic respiratory diseases	3	
Communicable diseases	Tuberculosis	12	20
	Vector-borne and parasitic diseases	3	
	HIV/AIDS	2	
	Others	2	
	Hepatitis	1	
Disease prevention	Violence and injuries	6	12
	Vaccines and immunization	3	
	Nutrition	1	
	Physical activity	1	
	Other	1	
Health systems	Digital health	6	10
	Blood safety	1	
	Health services delivery	1	
	Health technologies and medicines	1	
	Primary health care	1	
Environment and health	Urban health	4	10
	Transport and health	3	
	Climate change	1	
	Housing and health	1	
	Water and sanitation	1	
Health emergencies	COVID-19 outbreak	7	7
Health determinants	Social determinants	5	5

Discussion

Summary of evidence

Primary studies

- Technical contribution

The standing-out contribution is Al models. The solutions are still incipient since it is not yet possible to determine if the models can be generalized regardless of the context. The models should be generalizable from the data science and artificial intelligence perspectives; nevertheless, there are problems, such as model discrimination for special or unprecedented cases. Eventually, implementing the models developed around healthcare can help streamline clinical care by properly monitoring the regular process of a defined treatment. However, human medical intervention remains essential for cases where the model cannot accurately classify or predict.

Given that implementation of good models is still in experimentation, it is clear why ML models, whether for data or images, are the most used. On the other hand, DL-based models are less common because two primary features are needed to develop them: having a large image bank, for example, those used in diagnosis (X-rays), and having a high computational capacity since the implementation of neural networks demands a lot of resources from the device or the cloud that runs the model.

Regarding the generation of platforms and models, the second contribution by the number of papers, it is noteworthy that mobile devices' solutions are widely implemented in LMICs contexts. In such contexts, the device penetration is high where the access to healthcare in different facilities is shallow or none (29).

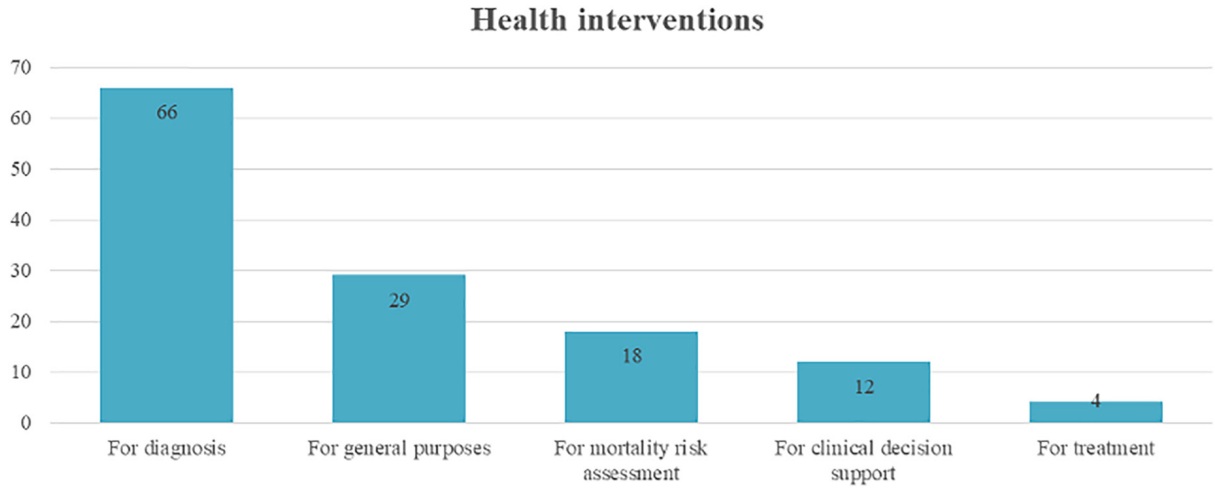

FIGURE 5
Papers using different health interventions.

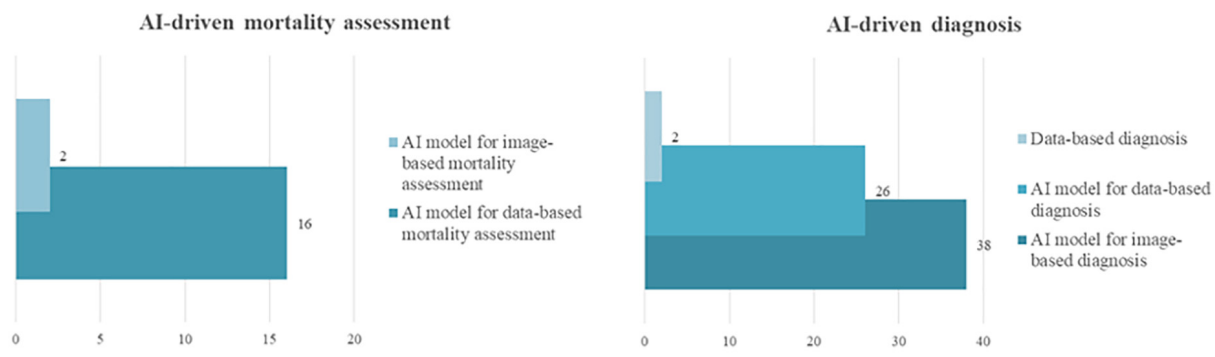

FIGURE 6
AI-driven approaches to health interventions.

- Data

Clinical data and radiology images are the most commonly used data types in experimental studies, which makes sense from a clinical and healthcare point of view: these data are the closest to representing medical knowledge for the diagnosis and consequent treatment giving certain conditions in a patient's health.

It is interesting to note that images are one type of data. Most of these correspond to photos taken with mobile devices, consistent with developing models and platforms based on this technology. On the other hand, physiological signals can be considered real-time indicators of a person's current state and help avoid bias or subjectivity in the information provided by a patient. Although they have this advantage, their processing is complex and depends on the type of device to collect the signal.

The type of data from surveys draws attention to the effort needed to obtain such data, both nationally and internationally, since collection requires logistical efforts and high economic capacity.

The distribution in the data quantity used in the selected experimental studies makes sense since verification of a model function is necessary to have contextualized data. This is an extra effort for the researchers; it is not easy to carry out in specific LMICs contexts in many cases. Those papers using large amounts of data do so because of their availability and not having to perform the collection work.

- Health context

The category with the most references is "life-course approach," which includes "maternal and newborn health" and "child and adolescent health." In the context of LMICs, women's pregnancy suffers from inequalities in care, especially in rural and marginalized areas. The physical and psychological effects of this lack of care lead to the deterioration of the newborn's and

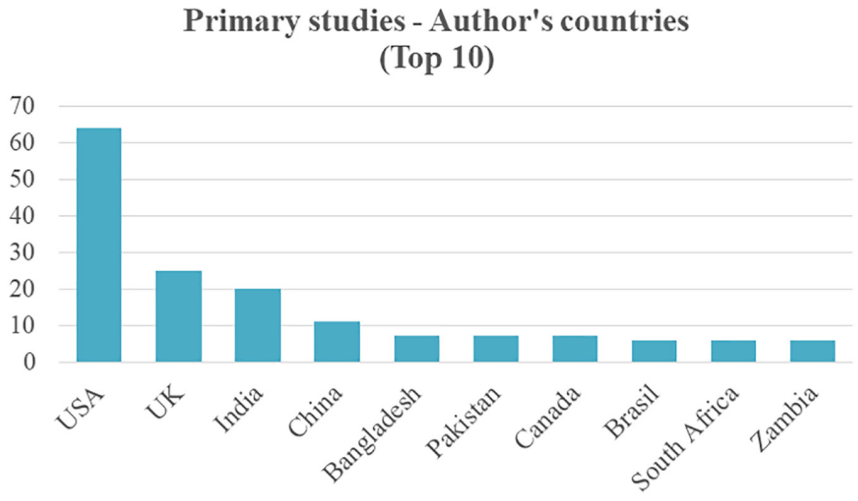

FIGURE 7
Top 10 of the author's countries and affiliations.

TABLE 6 Paper distribution according to health topic and category for secondary studies.

Category	Health topic	Papers per topic	Papers per category
Health systems	Digital health	14	15
	Health systems financing	1	
Environment and health	Social inequalities in environment and health	3	3
Communicable diseases	Vector-borne and parasitic diseases	1	2
	Others	1	
Health emergencies	COVID-19 outbreak	1	1
Non-communicable diseases	Mental health	1	1

her mother's health. In addition, in LMICs, there are high rates of child malnutrition, which has, consequently, effects on the health of children and adolescents and, therefore, uncertainty in the future development of these countries.

The following categories correspond to non-communicable and communicable diseases. These groups include chronic diseases such as cardiovascular diseases, cancer, chronic respiratory disorders, and diabetes. These diseases are highly addressed in experimental studies and are according to the data available from organizations such as the WHO about their prevalence in LMICs.

Cancer, for example, with a high prevalence in LMICs, presents many developments and implementations as researchers seek tools to generate an early diagnosis of the disease and, therefore, a greater probability of treatment success. Developments to preserve people's mental health are also highlighted, especially with the global context of COVID-19 and the isolation measures taken to counteract the contagion's negative effects. These measures have a huge impact on mental health (30).

Although the incidence of tuberculosis has been falling in recent years, it is still one of the leading causes of death globally (31). As a result, many efforts around early detection are being made to decrease its prevalence, especially in LMICs contexts, where funding for detection and treatment is far below what is needed (32).

- AI-driven health interventions

Experimental studies' primary purpose is to diagnose diseases, especially early and accurate diagnosis. Another purpose is the mortality assessment, mostly to avoid newborn deaths, which has a high rate in LMICs (33). Finally, clinical decision support systems are an important target for implementation; developing these systems can reduce hospitalization times, optimize treatment, and reduce work stress for health professionals (34).

- Country of affiliation

When extracting the affiliation data of the authors of experimental studies and contrasting them against the country's classification to which the research and development institutions belong, it was interesting to see

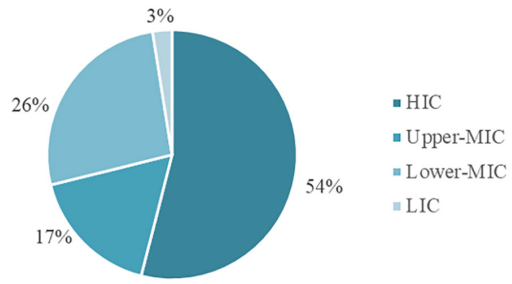

FIGURE 8
Distribution of author's countries according to income classification.

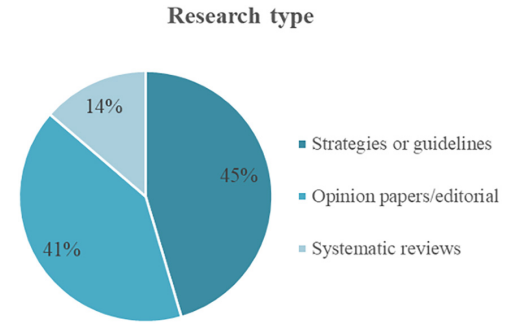

FIGURE 9
Distribution of the research type within the solution studies.

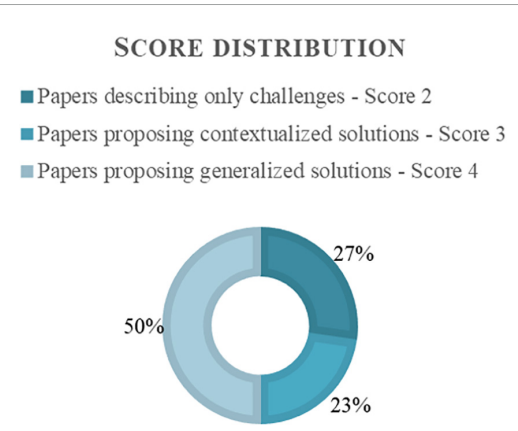

FIGURE 10
Distribution of the score within the solution studies.

that the developments of experimental studies are conceived mostly from HIC. However, the datasets were collected in LMICs contexts. A researcher's purpose is to impact the environment by detecting problems and proposing solutions driven by the characteristics of the context. Economic resources are decisive in the construction of solutions. For this reason, establishing relations between institutions is convenient to equate global efforts in this type of research to eradicate different personal and public health conditions.

Secondary studies

- Data Quality challenges

Data quality encompasses many aspects of data, from intrinsic to extrinsic. Accuracy is the correct representation of the health-related concepts considering the local LMICs context. Therefore, AI algorithms should be trained and evaluated using local data. Electronic Health Records (EHR) data and data registries are the preferred data source. Also, collecting data from primary healthcare workers improves the quality of data sources. Low-cost technologies such as sensors, phone applications, and public health surveillance data from non-traditional sources also improve data availability and diversity. Consistency, completeness, credibility, and currentness are other attributes that avoid the deployment of Garbage in, Garbage out (GIGO) algorithms. Maintaining quality data implies implementing robust data preparation to manage and prevent bias and cleaning processes engaging data scientists and multidisciplinary teams with knowledge and experience in the healthcare domain. Training different stakeholders, another domain explained below, is also important to improve data quality because it implies understanding the data sources and their context. The governance process includes data quality policies to provide certified datasets by independent and trusted local and international organizations. Quality improvement implies using clear and standardized metrics for data quality as proposed by several international standards and initiatives in software engineering. Co-design AI solutions with users, physicians, patients, and clinical managers contribute to improving data quality. Recommendations include implementing mechanisms to share health-related data and promoting the creation, use, and deployment of open-source databases such as MIMIC-III, a critical care database.

- Context-awareness challenges

Contextual awareness means that AI models and solutions must be validated using data from the local context in LMICs. A common gap mentioned in the literature is that most AI models used in LMICs are typically trained with HICs data with different demographic characteristics and contexts. Context awareness also implies an appropriate emphasis on application scenarios, policies, and disease priorities to prevent bias and promote model generalizability and explainability. Actions addressing contextual awareness challenges include local stakeholders' participation in data collection, regulatory decisions, technology development, and validation. Creating strategic partnerships between clinical practice, academia, and

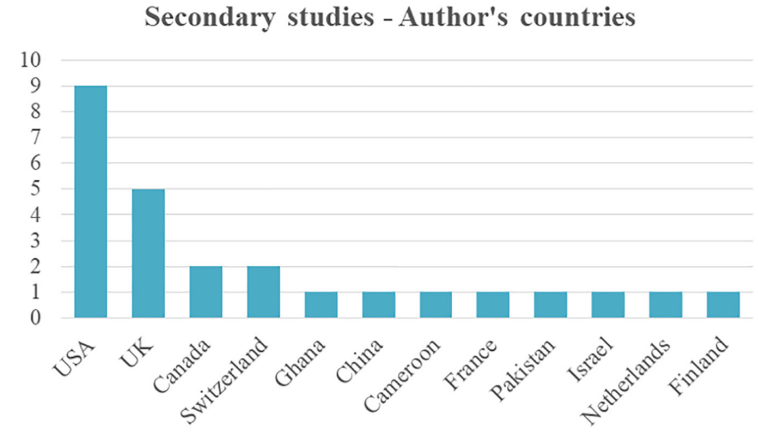

FIGURE 11
Top of the author's countries and affiliations.

industry is foremost important. Also, AI Interventions should be planned to consider the burden of disease in the local context. To manage and prevent bias, AI/ML systems must be transparent about the algorithms used and ethical aspects of managing and preventing bias. In this direction, to favor explainability, transparent models are preferred if the obtained performance is acceptable. In the case of using black-box models, it is suggested deploying explainability approaches such as Local Interpretable Model-Agnostic Explanations (LIME), SHAP (SHapley Additive exPlanations), Anchors, Counterfactual methods, among others. Data diversity is a very important factor in improving generalizability. ML techniques, such as regularization methods, make the models simpler.

- Challenges in the regulation and the provision of legal frameworks

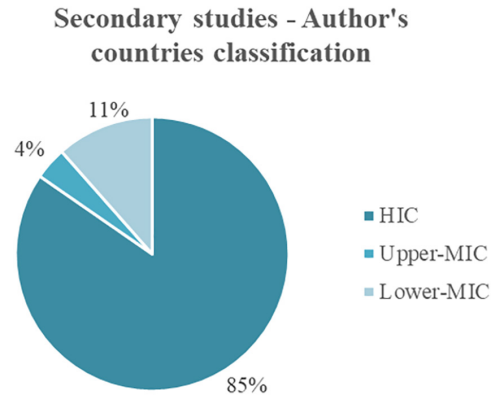

FIGURE 12
Distribution of author's countries according to income classification.

Local regulation and legal frameworks, strategies, and policies are fundamental to successfully deploying AI/ML solutions. The regulation includes the provision of privacy, security, informed consent, ethics, liability, confidentiality, trust, equity, and accountability policies. In addition, local governance and leadership are necessary to promote and execute national AI strategies included within digital health strategies at country, regional, and local levels. Recommendations to overcome security, privacy, safety, trust, and ethical issues include making mandatory before funding any intervention, the approval by ethical committees of informed consent, and clinical protocols.

Also, conformance of local policies to international regulation, scalable and composable access control and authentication mechanisms, anonymized or pseudonymized data, and mandatory privacy audits are necessary. ML policies and legal frameworks should protect individuals against unethical behaviors. In addition to ethical regulations and legal frameworks, which are the responsibility of governments, end-users, healthcare providers, and AI developers, share responsibility for managing ethics. Liability is a challenge for healthcare organizations, especially healthcare providers using AI-based solutions. Therefore, explainable ML models have to be provided. For example, data of certain patient groups in LMICs are frequently not present in local databases, caused by existing inequalities in the provision of health care services and low health insurance coverage. Inequality is also present when AI interventions take care mainly of the diagnosis but not the treatment and follow-up of patients. Trust in AI tools can be improved by training and educating healthcare professionals and involving end-users in developing AI technologies applying Human-Computing Interaction (HCI) approaches. Moreover, AI developers must be trained in accountability, privacy, and ethics.

- Education and change resistance challenge

TABLE 7 Set of challenges identified by domain with the respective description.

Challenges		Description
Data Quality	Accuracy	Accuracy means the degree to which data correctly represent a concept in a specific context (37). Therefore, AI algorithms should be trained and evaluated using local data.
	Consistency	Measures the coherence of data concerning the same or other data sources in a specific context of use (37). Accuracy, consistency, completeness, credibility, and currentness are other attributes that avoid deploying GIGO algorithms (Garbage in, Garbage out) in LMICs.
	Credibility	Determines how true and believable data is by users in a specific context of use (37). It is an essential attribute, especially in LMICs contexts, where many healthcare professionals are reluctant to use AI/ML technologies.
	Availability	is a measure of the capability of data to be retrieved by authorized users (humans or applications) in a specific period or context (37). The availability of quality data for training and evaluation is a frequently mentioned gap in LMICs.
	Diversity	Data diversity guarantees that data provides enough information to train AI/ML models. It maximizes the learning process, so ML models are fitted to the data. A common challenge mentioned in the literature data AI models are typically trained with HICs data, with different demographic characteristics, diseases, and contexts.
	Openness	This means that data is available to anyone for free, including permission for re-use and redistribution (38).
Context-awareness	Contextual applicability	AI models and solutions must be validated before deployment using data acquired from the local context in LMICs.
	Diseases priorities	AI interventions should be planned to consider the burden of disease in the local context.
	Appropriateness	It is the matching between a machine learning model and the target population. It encompasses deciding the application scenarios, policies, and liability, among others, in the local context (22).
	Bias (demographic, economic, racial)	It is defined as a systematic error that causes to favor one outcome over another. In terms of algorithms, bias is caused by an undesired dependence on a specific data attribute in the data, e.g., gender, race, or religion (22). In addition, (15) introduces the concept of contextual bias, in which the systematic error is caused by AI algorithms created in HICs and deployed in LMICs where the health contexts are different, e.g., differences in health risks, treatment, demographics, economy, etc.
	Fairness	Unlike bias, a mathematical construct, fairness is a socially defined concept in which the impact of an AI model in decision-making processes is assessed against a set of legal or ethical principles, which are often contextually dependent, e.g., it depends on the local government and culture.
	Generalizability	Defined as an attribute of ML models to determine how well it's trained to classify or predict new data correctly. Generalizability is relevant in LMIC due to data, infrastructure, and knowledge limitations to build new local models.
	Explainability	It is the level of understanding of how the system produced a specific result (39).
Education and change resistance	Training different stakeholders	The lack of training and understanding of AI technologies by different stakeholders (decision-makers, developers, health professionals, citizens, patients, communities, etc.) is a limitation in LMICs. Different stakeholders are involved in AI policies, regulations, research, design, implementation, and deployment.
	Insufficient motivation	Healthcare professionals and patients know that AI technologies have surpassed the human capacity to accomplish some administrative and clinical workflows. However, there is still a lack of motivation to use these tools, especially because of the unsolved ethical and regulatory concerns and the perceived risks of using AI applications in healthcare. Also, healthcare staff and front-line workers in LMICs still do not benefit from collecting and aggregating more and more data.
	Change resistance	Despite the inevitable advent of AI technologies, there is still a fear that AI will replace the work of healthcare professionals and staff.
Methodology	Reporting and methodological standards	Reporting and methodological standards are required for AI health interventions in LMICs. It includes standardized methods and indicators to evaluate the added value of AI interventions over current standards of care.
	Human-centered design	Human-centered design (HCD) is an approach to designing and developing interactive products, services, and experiences, driven by the user. AI systems need to involve different stakeholders to guarantee success. However, HCD is a practice that is not frequently used in AI solutions.
	Certification	Regulation and certification processes are necessary to promote the advance and large-scale deployment of AI/ML technologies. Also, to guarantee patient safety and effectiveness.
Regulation and legal frameworks	Informed consent	A typical healthcare scenario means an agreement between a patient and the healthcare provider about a medical condition and the options for treatment. Informed consent when AI/ML technologies are used in healthcare scenarios implies that patients are informed about this fact.
	Privacy	In the context of health, data management is defined as the right of a person to maintain their private life, avoiding any illegal gathering and use of their data (40). Therefore, AI/ML algorithms and solutions should respect health data privacy, supported by proper patient consent.

(Continued)

TABLE 7 (Continued)

Challenges		Description
	Ethical issues	An ethical issue is a behavior that is not in accordance with accepted principles of right or good conduct in data management and the decision-making process in healthcare. ML policies and legal frameworks should protect individuals against unethical behaviors.
	Data security	Information security protects against unauthorized access, use, disclosure, modification, or destruction of information (40). Therefore, from a technical perspective, AI/ML-based solutions or eHealth infrastructures should protect users against these problems.
	Liability	It is a current obligation acquired by an organization due to events that occurred in the past (41). Liability is a challenge for healthcare organizations, especially healthcare providers using AI-based solutions, because of the unexplainably of algorithms (black-box algorithms) and lack of unclear policy and legal frameworks in LMICs.
	Under-representation	Data on certain patient groups in LMIC are frequently not present in local databases due to the inequalities in providing health care services or health insurance coverage. Therefore, the above contribute to systematic biases causing non-representative conclusions (12).
	Confidentiality	It is a guarantee that data is not made available or disclosed to unauthorized actors (42).
	Trust	In the interaction between two actors, one actor assumes that the other actor will behave exactly as the first actor expects (42). A challenge in LMICs is the fear of patients' and practitioners' trust in the decisions or advice made by AI/ML systems.
	Accountability	The accountability of an AI/ML system is the guarantee that the actions performed by that system are traceable (43). Therefore, accountability is critical in "black box" ML models.
	Equity	Low socioeconomic populations have less access to healthcare. Therefore, databases and registries have less data on these minority populations, causing inequalities.
	Governance	Data governance requires a systematic process to guarantee data quality (Consistency, Credibility, Availability, Diversity, and Openness). Policies and processes for data governance and data ownership are limited in LMICs.
	De-identification	De-identification is the process of removing identifying data of a subject, eliminating the possibility of recognizing that subject in a specific context (44). De-identification is a challenge because many LMICs have different definitions of personal information. Moreover, when common characteristics aggregate de-identified data, there is a risk of identifying personal information (45).
Financial resources	Health system priorities	Decisions on allocating resources for Digital Health programs, particularly AI technology, are not frequently made, prioritizing local needs and the burden of diseases. However, the decisions in LMICs are sometimes made considering data availability and donors' funding priorities.
	Sustained funding	A lack of sustained funding restricts the development and adopting of digital health technology LMICs.
Infrastructure and connectivity	Poor connectivity	Despite big advances in connectivity, especially mobile networks, there are still many rural areas in LMICs where connectivity is an issue. Especially broadband connections.
	Electronic Health Record Systems/ Patient Registers	Integrated Electronic Health Record systems (EHR) are a challenge that still needs to be solved, especially in rural areas and countries where the health system is fragmented. Also, secure access to EHR data is problematic because of the lack of interoperability infrastructures and data-sharing policies. Patient registries are generally more complete than EHR systems, but due to their complexity for data processing, needed infrastructure and maintenance cost are scarcer in LMICs.
	Computer capacity	Increased computer and storage capability is one factor that has boosted AI solutions. However, access to high-performance infrastructures is costly, especially for LMICs, where providers are typically unavailable in the country.
	Interoperability–Data aggregation	International standards for interoperability and controlled vocabularies and terminologies are in place. However, the implementation of interoperability solutions in LMICs, connected to the implementation of robust integrated EHR systems, lags behind current developments in HICs.
Scalability	Scalable solutions	Scalable AI/ML solutions can increase their functionalities, responding to contextual demands. Therefore, scalable solutions are essential for widespread health intervention and support dynamic and diverse health contexts in LMICs.
	Cost-effectiveness	Digital health interventions, particularly AI-based interventions, must demonstrate cost-effectiveness, especially in LMICs where resources are scarce.
	Continuous impact evaluation	Health outcomes of AI interventions have to be continuously measured. This is complex and costly, especially in LMICs, considering the deficient infrastructures, digitalization, research agendas, and development environments.

Limitations in training and education of different stakeholders (decision-makers, developers, health professionals, citizens, patients, and communities) prevent the understanding, use, policy-making, research, and innovation of AI technologies in LMICs. Potential solutions include capacity building through professional bodies and societies, training and

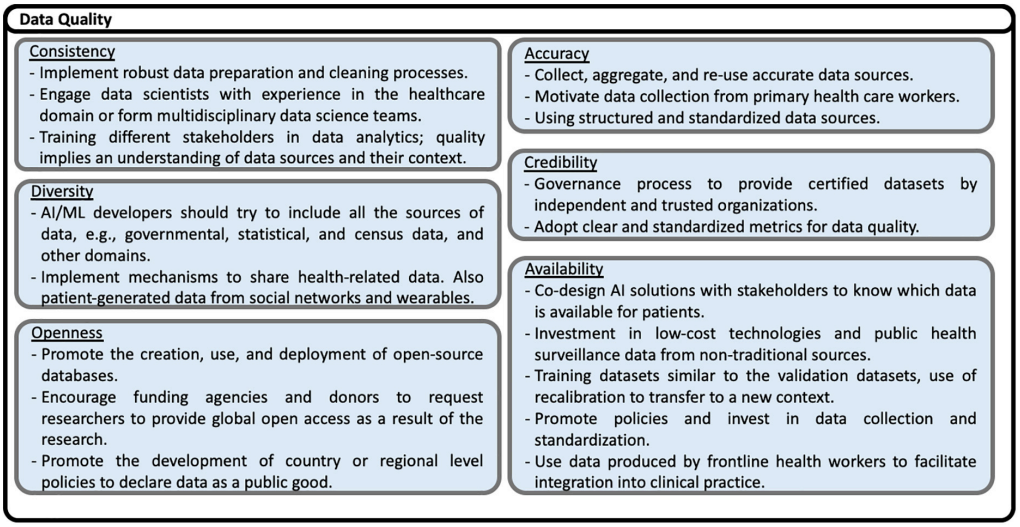

FIGURE 13
Solutions to challenges for Data Quality.

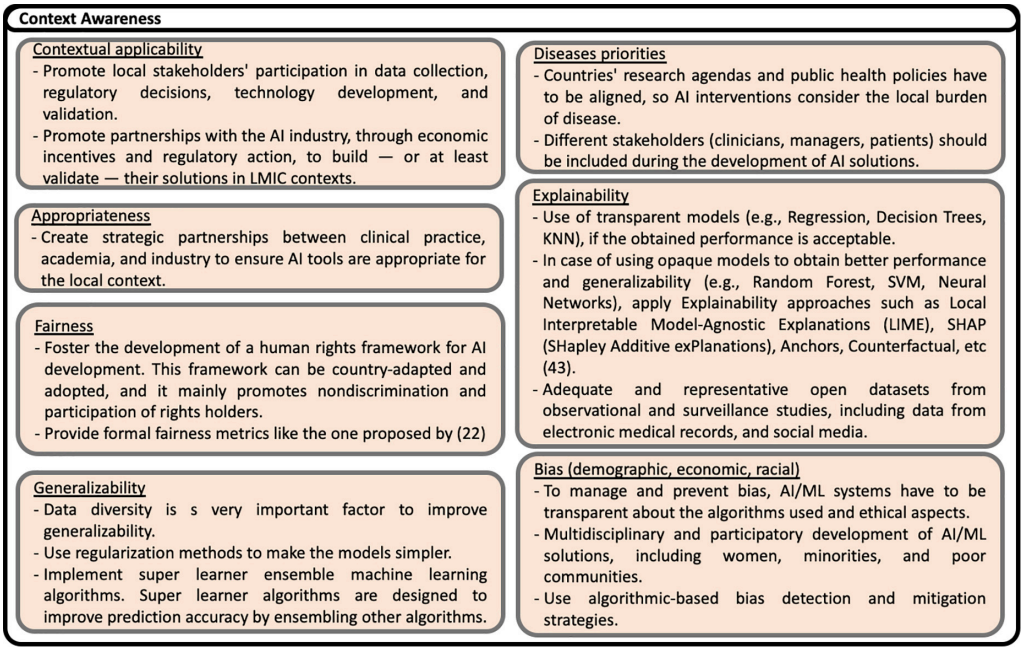

FIGURE 14
Solutions to Context-awareness challenges (22, 43).

retention to prevent brain-drain of local expertise, and cooperation agreements with HICs to train and educate stakeholders. In addition, insufficient motivation to use AI/ML tools is a major concern, especially because of the unsolved ethical and regulatory concerns and the perceived risks of using AI applications in healthcare. One alternative is providing economic incentives to create and use AI solutions in clinical practice. Also, the innovative implementation of business models around data collection and aggregation, which, ethically managed, could be an alternative incentive for building AI solutions. Another critical aspect is change resistance, mainly due to the fear that AI will replace the work of healthcare professionals and staff. Training and education of clinicians about the benefits and limits of artificial intelligence and machine learning, and more recently, hackathons and datathons

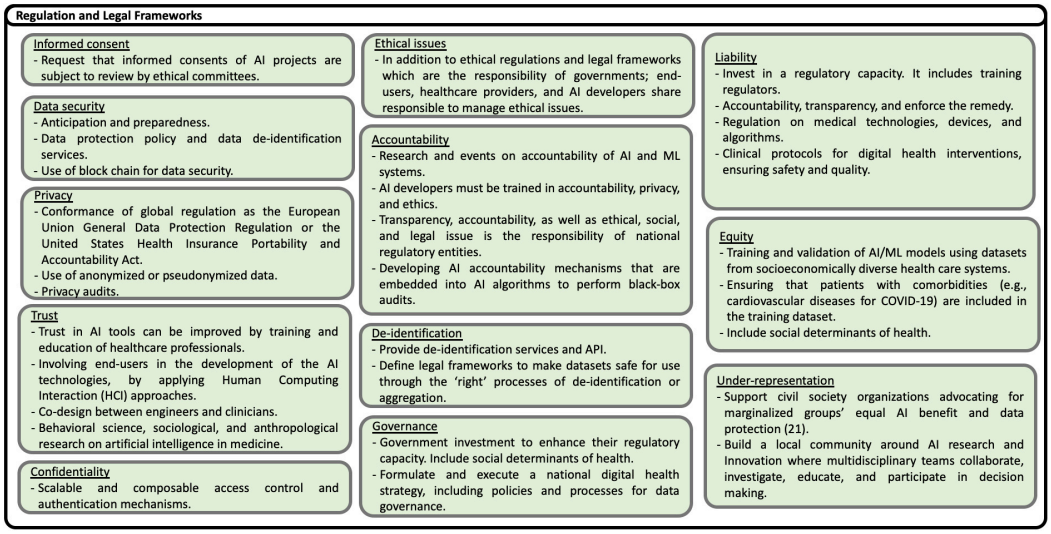

FIGURE 15
Solutions to Regulation and Legal Frameworks challenges (21).

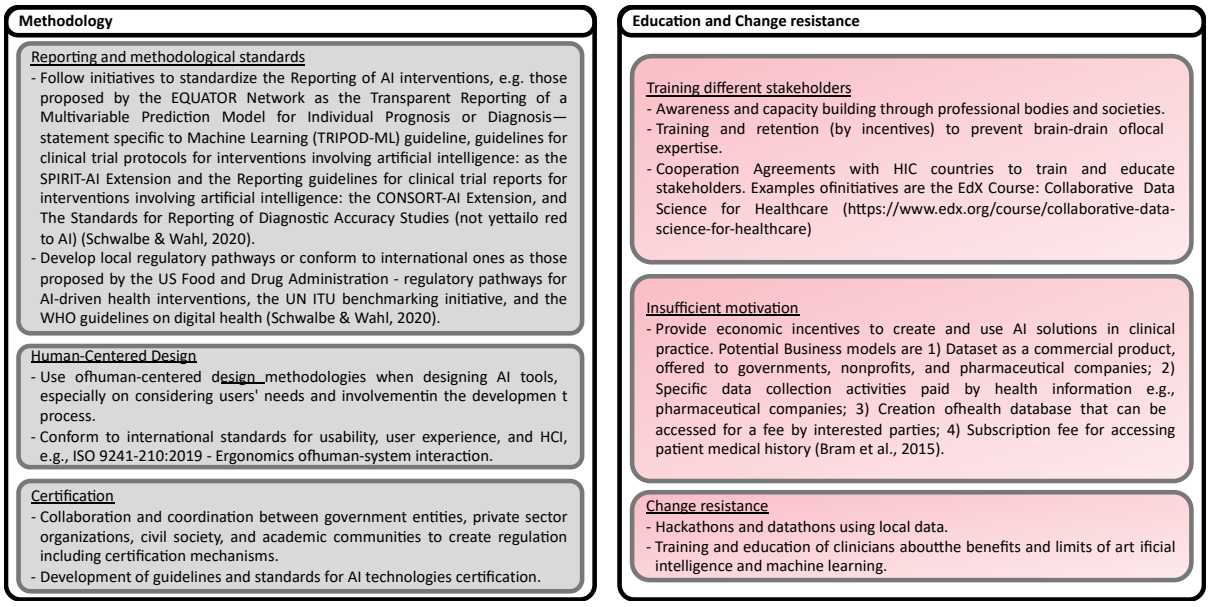

FIGURE 16
Solutions to Methodological and Education challenges (18, 20).

events using local data, have been demonstrated to be effective actions.

- Methodological challenges

Solutions to methodological challenges covered reporting and methodological standards, the Human-Centered Design (HCD) of solutions, and the adoption of certification mechanisms. Reporting and methodological standards are required for AI health interventions in LMICs to evaluate AI interventions' impact and added value over current standards of care. Several initiatives are being developed, becoming the standard de fact approaches for reporting AI interventions. One example is the EQUATOR Network, which has proposed guidelines for reporting interventions involving artificial intelligence. In the same

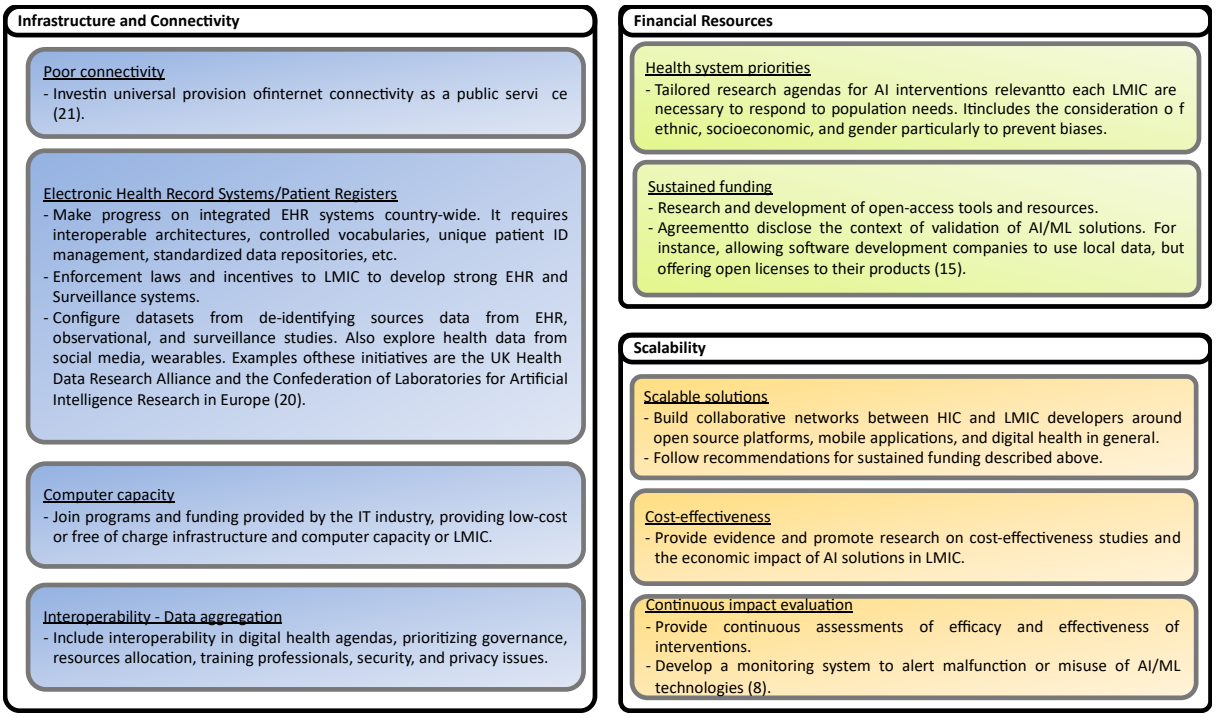

FIGURE 17
Solutions to Infrastructure and connectivity, Financial Resourced, and Scalability challenges (8, 15, 20, 21).

direction, the United Nations (UN), the International Telecommunication Union (ITU), and the WHO are proposing guidelines on digital health interventions involving AI technologies. To prevent bias and guarantee accuracy, diversity, and trust, AI systems need to be contextually aware and involve different stakeholders in all stages of development. Methodologies to support these challenges are HCD approaches. Multidisciplinary work requires collaboration and coordination between government entities, private sector organizations, civil society, and academic communities. Furthermore, certification processes are necessary to promote the advance and large-scale deployment of AI/ML technologies. Also, to guarantee patient safety and effectiveness.

- Data infrastructure and connectivity challenges

The increased use of mobile networks has improved connectivity in LMICs. However, many rural areas in LMICs countries lack continuous Internet access. Investment in the universal provision of internet connectivity is a priority. Regarding data infrastructures, the availability of electronic health records and secure access to EHR data is still an unsolved problem in many countries and regions. Therefore, governments, healthcare providers, professional associations, and other actors should promote the construction of national eHealth infrastructures, including interoperability platforms, the adoption of international vocabularies, terminologies, and ontologies, and the implementation of unique patient ID management systems and standardized data repositories. In countries where infrastructure and connectivity do not progress as desired, enforcement laws, on the one hand, but incentives to develop strong EHR and surveillance systems are possible alternatives. On the other hand, the demand for computing capacity and storage capability increases. Join programs and funding provided by the IT industry, providing low-cost or free-of-charge infrastructure and computer capacity to LMICs is a viable alternative.

- Financial Resources allocation challenges

The allocation of adequate and sustained financial resources is one of the challenges frequently mentioned in LMICs for implementing digital technologies in general. In many LMICs, Digital health and AI/ML technologies are not a priority, or the decision on the allocation of scarce resources is not frequently made, prioritizing local needs and the burden of diseases but considering data availability and donors' funding priorities. Potential solutions to overcome these challenges are establishing national research

and innovation agendas for AI interventions responding to population needs. It includes the consideration of ethnicity, socioeconomic, and gender, particularly to prevent biases. In addition, research and development of open-access tools and resources could foster AI interventions' experimentation, mainstreaming, and scale-up. One alternative in the agreement with international and local software development enterprises is to offer open licensing and free training of their products.

- Scalability challenges

Scalable solutions are important for extending AI-based health interventions and supporting the dynamic and diverse health contexts in LMICs. To be scalable, AI-based interventions demonstrate cost-effectiveness, health system efficacy, and economic impacts. Building collaborative networks between HICs and LMICs developers around open-source platforms, mobile applications, and digital health is promising. Health outcomes of AI interventions have to be continuously measured. This is complex and costly, especially in LMICs, considering the inadequate infrastructures, digitalization, research agendas, and development environments. Another strategy identified is to develop monitoring systems to report malfunction or misuse of AI/ML technologies.

The above recommendations provide a framework to be considered by health IT project at different levels, from pilot to national health information systems. However, the selection of the most relevant challenges depends on the maturity level of each project and especially on the context of the use of digital health solutions.

Limitations

One of the strengths of this scoping review is the strict adherence to the recommendations provided by the PRISMA extension for scoping reviews. In addition, PRISMA provides detailed descriptions for conducting scoping reviews systematically, allowing readers to assess the adequacy of the sources used, thus ensuring the reliability of the findings. It also allows for repeatability and updating of the review.

This scoping review has some limitations. First, reviewing the papers was made between two reviewers; even though this guarantees a less biased process, disagreements were solved between the reviewers and not by a third party. Second, the reviewing process took longer than expected due to the data extraction and charting. It probably could lead to outdated source data; this scoping review was a big undertaking, and results are only up to date as of December 2021. However, we presume that the results are not likely to be outdated soon if the tendency of LMICs researchers to produce just a few studies of AI use and application in healthcare does not change. Third, the scientific quality of the studies included in the review was not assessed. Many studies included have design limitations. However, including, for example, only randomized controlled trials would have extremely limited the number of studies to analyze.

Conclusion

This scoping and narrative review systematically characterized current AI healthcare implementations in LMICs, describing their technological contribution, data used, health context, and type of health interventions. It was found that most studies proposed experimental machine learning models followed by Deep Learning based models. However, few studies deployed the models, and those deploying them implemented them mainly on mobile platforms. Regarding data sources characterization, clinical records data and radiology images are the most commonly used data types in experimental studies. Most images correspond to photos taken with mobile devices. Most datasets are small due to the high cost of collecting local data. Bigger datasets correspond to international projects or organizations collecting data in LMICs or using open data such as satellite images or surveys.

Regarding the health context of AI applications, most interventions addressed maternal, newborn, and child and adolescent health. The second most common interventions were cancer, mental health, and cardiovascular diseases in the group of non-communicable diseases. Finally, tuberculosis, COVID-19, vector-borne and parasitic diseases, and HIV; accounted for the group of infectious diseases. Studies addressing violence and injuries were also prevalent. Regarding the type of intervention, the primary purpose of the experimental studies was the diagnosis of diseases, followed by mortality assessment.

This review study adds to the current literature a detailed description of gaps, challenges, and possible solutions for AI deployment in the healthcare systems of LMICs. Research on applying AI and ML to healthcare interventions in LMICs is growing; however, apart from very well-described ML methods and algorithms, several issues need to be addressed to scale and mainstream experimental and pilot studies. Those challenges include improving the quality of existing data sources, training and modeling AI solutions based on contextual data; and implementing privacy, security, informed consent, ethics, liability, confidentiality, trust, equity, and accountability policies. Also, potentiating widespread AI solutions in LMICs requires a robust environment with trained stakeholders, methodological standards for data creation, research results reporting, and product certification.

A very important lesson learned regarding the design and management in translational health ecosystems is the need to advance from a data focus to a concept and knowledge focus, i.e., replacing data sharing by knowledge sharing. This holds for all aspects and sections presented in this paper. In that context, we refer once more to the introductory paper of this Special Issue (1) or to (35).

Data availability statement

The data sources used in this study are available in Scopus and Web of Science Databases. Further inquiries can be directed to the corresponding author.

Author contributions

DL and CR-O conceived and designed the study, collected data, did the data analysis, and drafted the manuscript. BB addressed the general challenges LMICs face in their IT strategies for health. All authors revised, reviewed, and approved the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Linguistic and ontological challenges of multiple domains contributing to transformed health ecosystems

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This paper provides an overview of current linguistic and ontological challenges which have to be met in order to provide full support to the transformation of health ecosystems in order to meet precision medicine (5PM) standards. It highlights both standardization and interoperability aspects regarding formal, controlled representations of clinical and research data, requirements for smart support to produce and encode content in a way that humans and machines can understand and process it. Starting from the current text-centered communication practices in healthcare and biomedical research, it addresses the state of the art in information extraction using natural language processing (NLP). An important aspect of the language-centered perspective of managing health data is the integration of heterogeneous data sources, employing different natural languages and different terminologies. This is where biomedical ontologies, in the sense of formal, interchangeable representations of types of domain entities come into play. The paper discusses the state of the art of biomedical ontologies, addresses their importance for standardization and interoperability and sheds light to current misconceptions and shortcomings. Finally, the paper points out next steps and possible synergies of both the field of NLP and the area of Applied Ontology and Semantic Web to foster data interoperability for 5PM.

KEYWORDS

natural language processing, electronic health records, precision medicine, biomedical semantics, formal ontologies, terminologies

1. Background

Managing healthcare transformation towards personalized, preventive, predictive, and participative precision medicine (5 PM) is the background of a series of contributions for a broad audience [see the introductory paper to this Special Issue (1)], among which this paper highlights the role of language, semantics and standards for 5 PM. It intends to support the understanding of crucial notions in a field known as Biomedical Semantics.

5 PM considers individual health conditions, genetic and genomic dispositions in personal, social, occupational, environmental and behavioral contexts. The goal is to transform health and social care by fully understanding disease mechanisms and by turning health and social care from reactive to proactive. The current healthcare system transformations aiming at 5 PM

medicine are supported by a broad range of technologies, with data-centered approaches playing a crucial role. Other than with clinical trials, quality data are intended not only to be collected and analyzed for a specific purpose but during the whole care process within a health ecosystem, i.e., a network of all relevant interconnected entities ranging from patients and carers to diagnostic and care processes targeting clinical conditions, pathogens, devices and being reflected by an ever-increasing amount of data.

The implementation of 5 PM involves multiple domains and disciplines with their specific objectives and perspectives, using a broad range of methodologies, educational backgrounds, skills and experiences as well as a broad range of resources. The technologies to be deployed range from wearable and implantable micro- and nanotechnologies, biomolecular analytical techniques such as the family of OMICS technologies, up to super- and quantum-computing and big data analytics. Many of these technologies only unfold their potential if rooted in semantic resources like terminologies, ontologies and information models as core requirements for data standardization and interoperability.

The challenge is not only to understand the world of sciences and practices contributing to 5 PM, but also to formally and consistently represent it, i.e., of multidisciplinary and dynamic systems in variable context. Thus, mapping and harmonization data and processes among the different disciplines, methodologies, perspectives, intentions, languages, etc. must be supported. This is bound to the advancement of communication and cooperation between the business actors from data to concept and knowledge levels, in order to provide high-quality integration and interoperability between and within health ecosystems. Consequently, knowledge representation (KR) and knowledge management (KM) are crucial for the transformation of health and social care.

KR and KM happen at three levels: (a) the epistemological level of domain-specific modeling; (b) the notation level of formalization and domain representation; (c) the processing level of implementations. The different levels are represented by languages of different abstraction and processability.

Like specialized dictionaries provide words that constitute textual expressions in a certain field of interest, domain ontologies provide the building blocks for the construction of knowledge in that domain, in order to support representation and communication. For enabling interoperability between different stakeholder perspectives as well as logical deduction and machine processing, we have to advance ontologies to become a repository of representational units for precise descriptions of classes of domain entities in logic-based languages (2). In order to bridge to the way humans communicate, in a variety of natural languages and domain-specific sublanguages, the entities of meaning, as collected and defined within ontologies, must be linked to collections of natural language terms, i.e., domain vocabularies. More information on the health and social care transformation and the challenges to properly model the systems can be found in (1, 3, 4).

For representing health and social care ecosystems, we have deployed a system-theoretical, architecture-centric, ontology-based, policy-driven approach standardized in ISO 23903:2021 *Interoperability and Integration Reference Architecture – Model and Framework* (5), Figure 1. This standard introduces a top-level architectural model for any multi-domain system, formally representing its components, functions, and interrelations by a cube-shaped model with the three dimensions, *viz.* (a) domains representing specific aspects and perspectives of the system, forming domain-specific sub-systems; (b) generic granularity levels of the system's elements enabling the composition/decomposition of the system; (c) the viewpoints within its development process. The latter one extends the views defined in ISO/IEC 10746 *Open Distributed Processing – Reference Model* (6–8) *Enterprise, Information, Computational, Engineering and Technology* by the ISO 23903 *Business View*. This view is represented by the domain ontologies harmonized through foundational ontologies (9) aka upper-level ontologies, the different ISO/IEC 10746 views are represented through additional ontologies and specifications of the information technology domain. The former ones include BFO, GFO, UFO, DOLCE, and others, some of them also referred to by the ISO/IEC 21838 Top Level Ontologies (9, 10). The latter ones range from the *Business Process Modeling Language* (BPML) for the Enterprise View through the *Universal Modeling Language* (UML) for the *Information View* and the *Computational View* up to programming languages for the *Engineering View*. As described before, the languages thereby move towards higher expressivity, but more constrained grammars. Capturing knowledge in ontologies enables the understanding of facts and relations by both humans and machines. Thereby, structured and semi-structured knowledge can be represented in different styles at different levels of formalization (2). Figure 2 represents the knowledge types addressed in the ecosystem ICT solution development process. Taking these knowledge types into consideration can provide rigorous design decisions for knowledge representation and reasoning solutions using ontologies (section 6.1. Linguistic opportunities).

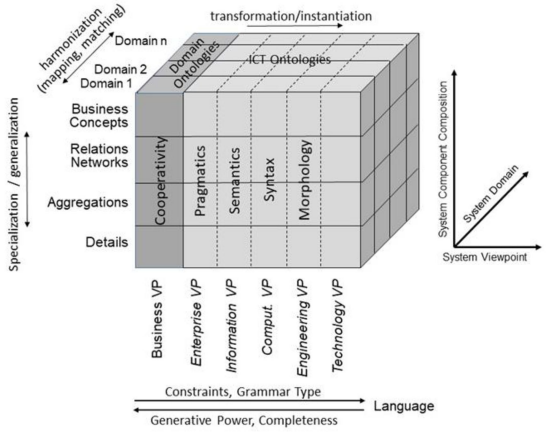

FIGURE 1
Transformed health and social care ecosystem according to ISO 23903 in a representational focus.

2. Introduction

A great challenge of 5 PM is to master the tradeoff between (i) the need to constitute clinical cohorts that are large enough for high evidence on the effectiveness of interventions and (ii) the need to account for the individual character of health and disease, which demands personalized decisions for those patients that cannot be considered instances of well-studied large cohorts.

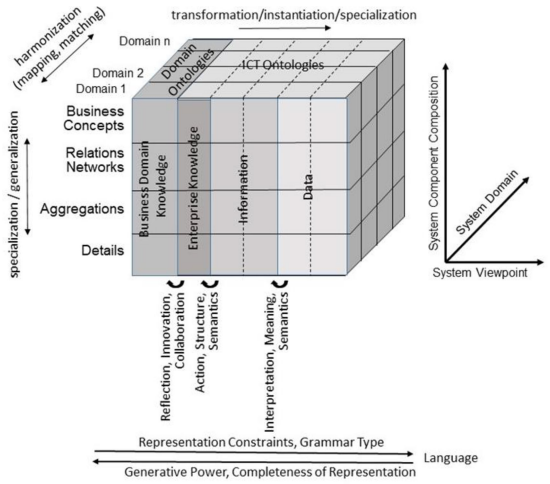

FIGURE 2
Transformed health and social care ecosystem acc. to ISO 23903 regarding the knowledge types in the ICT solution development process (after (11), changed).

The key to address this problem is data. The more reliable health data are available, the better personalized decisions can be responsibly made on a scientific basis, and the better are data from routine care suited for retrospective investigations. This requires a thorough understanding of (i) what biomedical data are, (ii) which different kinds of data need to be distinguished, and (iii) how data relate to the reality of facts and hypotheses in the domains of biomedical research and personalized healthcare.

We understand by biomedical data all those signals used to support human and machine communication and reasoning about entities (including actors and processes) in the biomedical domain, and which are processed using modeling and programming languages. We have to consider the whole range between structured data (codes, numbers), primarily for machine processing and unstructured data (text, images), mainly for processing by humans.

The way computers deal with data is different from how people do. This raises issues regarding data quality, completeness, processing workflows and interoperability. Data quality is affected not only by measurement inaccuracies, but also by human errors in data handling. Humans also account for the completeness of data collection and registration, but also of the outcome of data retrieval. The fact that the growing amount of biomedical data has far exceeded the limits of human cognition makes automatic data processing indispensable for responsible medical practice. Additionally, different professionals in health care encode data in different ways, using different structures and different languages. This makes data interoperability a major goal which has been largely unfulfilled to date.

Clinical data requires some language to be encoded, with a given vocabulary, syntax, a more or less apparent semantics, embedded into overly diverse and often only implicit pragmatic contexts. This is true for languages used by machines as well as for natural (i.e., human) languages. The following example will demonstrate this.

A hospital laboratory machine plots a set of attributes, values and unit triples (like "Hb; 14; g/dl") into a tabular structure. Similarly, a clinician inserts codes from a coding system (e.g., ICD-10) into an electronic health record (EHR) together with textual descriptions into a predefined table. In another setting, the clinicians write free-text reports, using the local natural language with its rules and domain-specific terms. In all these cases, not all semantics and contexts are obvious. E.g., the lab machine output does not explain the sampling and analysis techniques. The table with the ICD-10 codes, even correctly filled, may leave open whether the codes refer to diagnostic hypotheses at admission or to clinical evidence at the discharge of a patient. And in the doctor's report, crucial background information about the patient may be missing because the writer assumes it as known to the reader.

For a long time it has been daily practice for clinicians to supply structured information *via* forms and tables suited to machine processing, e.g., for billing, disease reporting and quality assurance, often redundantly and therefore unwillingly, which explains biases and errors (12). Nevertheless, textual content prevails in EHRs. It is created in various ways. Medical dictation and subsequent transcription by typists play a major role, although text is increasingly entered by medical staff themselves. Spoken language recognition systems are gaining acceptance due to enhancements of trained neural language models (13), which can be adapted to the domain and personalized to their users. No matter how human language is produced, the result is not error-free, particularly when created under time pressure. Several kinds of errors occur, such as typos, grammar violations, other deviations of writing rules such as colloquialisms, ambiguous terms, and undefined short-hand expressions like acronyms are deeply rooted in clinical documentation culture. For a long time, computers had completely failed to reliably extract meaning from this kind of technical language. However, during the last decades, the picture has been changing. The advances in web translation engines like DeepL or Google Translate, and more recently dialogue systems like ChatGPT, have impressively demonstrated how information technology is improving its ability to process human language in a robust manner.

Yet there are largely different flavors of human language as used in the biomedical field. Clinicians use their language and dialect in an *ad-hoc* manner, researchers publish in English, and only the latter one's texts are aligned with editorial principles before being published. In EHRs, narrative content can be completely unstructured or exhibit several degrees of structure, from document templates up to database tables.

Textual entries come in different degrees of standardization, from a completely unconstrained use of strings of characters over local term collections until shared dictionaries, linked to internationally compatible coding systems like ICD-10 or SNOMED CT. The most sophisticated ones are those that are rooted in some ontological basis, which provides standardized descriptions in logic defining and describing the referents of language entities, i.e., the concrete types of things, e.g., that hepatitis is an inflammation of the liver, that the eye is a sensory organ or that the sigmoid is part of the colon.

In this paper, we will provide an overview of current linguistic and ontological challenges which have to be met to provide a full support of transforming health ecosystems in order to meet precision medicine standards. We will particularly highlight standardization and interoperability aspects regarding formal, controlled representations of clinical and research data, but we will on the other hand consider the users' point of view. Clinicians require smart support to produce and encode content in a way that machines as well as humans with

different backgrounds and contexts can sustainably and reliably understand and process.

The requirement of interoperability and reusability has been formulated for research data by the FAIR (Findable, Accessible, Interoperable, Reusable) data stewardship desiderata (14). We reinforce these principles and advocate their use for all data in the field, which particularly includes routine data in EHRs, a scenario originally not in the focus of FAIR.

To this end, we discuss different formalisms to encode data and knowledge in biomedicine. We hypothesize that precision medicine, requires precision formalisms, such as KR languages with mathematical precision and computable semantics. This desideratum is challenged by a clinical documentation culture, in which narratives are the main carrier of information.

3. The perspective of human language

3.1. The characteristics of clinical and scholarly language

The crafting of a human language expression regarding its representation of reality principally depends on our innate capability to use a set of symbols and rules. It adjusts to the degree of precision needed by the data exchange use case as well as the background knowledge and thematic scope of the communication partners.

> E.g., the expression [i] "MCP, pale, cld, 90/45, 130/min" is precise enough to describe a life-threatening shock situation when uttered by a clinician in an emergency scenario. Clinicians prefer brevity of information-rich messages over redundancy (cf. the following expression [ii]), as long as the recipient of the message can be expected to fill the gaps, here added in italics:
>
> "*Minimally conscious patient with a* pale *face*, cold *skin*, *and an arterial blood pressure measured with a sphygmomanometer on the upper arm resulting in a systolic value of* 90 *mmHg and a diastolic value of* 45 *mmHg, with a pulse rate, measured digitally over a peripheral artery (normally at the wrist), of* 130 beats per minute *on average*."
>
> The message would even be understood when introducing some noise, such as typing errors and other mistakes like in expression [iii]: "MCP, palle, cld, 90/455, 130/s" (*sic*!).

The correct, unambiguous and precise expression [ii] would, in contrast, not be preferred by the (human) recipient of this information, as perceived wordy and redundant. Similarly, a structured representation (Table 1) would take more time to read than [i]. The shared knowledge of the situational context (in this example the primary assessment of vital signs in an emergency situation), opens a mental map, which already contains the parameters and requires only the values to be added, such as interpreting the frequency value 130/min as heart rate even if the attribute pulse rate' is not given.

In contrast, an automated decision support system would not tolerate any missing parameter, and a wrong unit of measurement could cause considerable harm. The tendency to brevity, the acceptance of noise and the reliance on contextual information to fill gaps and correct errors is characteristic for oral communication, as well as in SMS or social networks posts. Clinical language, equally produced in a hurry, prioritizing content over form, resembles more to the language of WhatsApp messages and tweets than to scholarly publications (15). Table 2 gives an overview of typical characteristics of clinical language.

TABLE 1 Tabular representation of the short clinical text "MCP, pale, cold, 90/45, 130/min."

Emergency case – first assessment	
Consciousness	Minimal
Skin color/face	Pale
Skin temperature	Cold
Systolic arterial pressure (arm) in mmHg	90
Diastolic arterial pressure (arm) in mmHg	45
Pulse rate (beats per minute)	130

Published texts, in contrast, are carefully copy-edited and follow guidelines, which, e.g., prevent the use of unorthodox spelling or undefined acronyms. The reader of a scientific paper would not be left in the dark, whether "MCP" means "Monocalcium Phosphate", "Metacarpophalangeal," "Medical College of Pennsylvania" or, like in our example, "Minimally conscious patient".

The observation that clinical narratives are often characterized by complete freedom in text design, forms a contrast with the enormous amount of effort invested in vocabulary normalization over decades (16). To name just a few, ICD-10 (17) is a worldwide standard for encoding medical conditions. Phenotype data can be coded by MedDRA (18) or the Human Phenotype Ontology (19), LOINC (20) is used as a controlled vocabulary for laboratory and other observational characteristics, ATC (21) and RXNorm (22) describe drugs and drug products, and SNOMED CT (23), an ontology-based terminology, claims to provide codes for the whole range of EHR content. For scholarly publications, the controlled MeSH vocabulary (24) is used for abstracting the key topics a scientific paper is about. Medical terminology systems are heterogeneous and overlapping. The UMLS (Unified Medical Language System) (25), maintained by the US National Library of Medicine, is a long-lasting effort of the biomedical informatics community to collect and to map medical terms from over a hundred terminology systems, thus facilitating interoperation, biomedical language processing and retrieval.

Although clinical terminology systems are often referred to by the term "controlled vocabulary" (CV), this does not imply that they play a significant role for controlling the terms used when producing clinical or scholarly narratives. Their main purposes are the support of structured data entry into forms such as for health statistics, quality assurance, reporting, and billing, the semantic annotation of article content in literature databases and the standardization of clinical data sets for research, e.g., within the Medical Outcomes Partnership (OMOP) Common Data Model (26).

Most terminology systems are primarily models of human language. They organize words and cohesive multiword sequences, normally referred to as "domain terms" or "terminological units." These units are connected by semantic relations such as synonymy and hyponymy. From a class of domain terms, normally one, typically self-explaining term is flagged as the preferred term. Its meaning is further explained by textual elucidations. Semantic

TABLE 2 Sublanguage characteristics in clinical narratives.

Phenomenon	Example	Elucidation
Telegram style	"left PICA stroke, presented to ED after fall"	Incomplete sentences, sketchy style
Colloquialisms	"pothole sign", "snorkel"	Milieu-specific sub-languages
Ad-hoc abbreviations	"infiltr"	Truncation ("infiltrated mucosa")
Ambiguous short forms	"RTA"	"Road traffic accident", "Renal-tubular acidosis"
Short forms of regional or local scope	"LDS Hospital" "St. p."	"Latter-Day-Saints Hospital" "Status post" = "History of"
Conventionalized Latin abbreviations	"V mors can dig V dext"	"Vulnus morsum canis digiti quinti dextri" = "dig bite in the right 5th finger" (common in some European languages)
Spelling errors, typos	"Astra-Seneca," "Hipotireose"	accidental or systematic (e.g., 2nd language speakers)
Spelling variants	"Esophagus", "Oesophagus"	e.g. American vs. British English
Single noun compounds	"Ibuprofenintoxikation"	Non-lexicalized long words (in languages such as German, Swedish)
Anaphora	(i) "adenoCa rect pN + MX G2 (…). tumor excised *in toto*" (ii) "no blood in stomach (…). mult mucosal erosions"	Understanding requires reference to surrounding text, (i) "Tumor" coreferential to adenocarcinoma described in left context (ii) "mucosal erosions" refined to "erosions of gastric mucosa"
Negations	"No evidence of pneumonia" "Pulmones: nihil," "metastasenfrei"	non-standard, jargon-like
Epistemic (uncertain, speculative) contexts	"susp MI, DD lung embolism"	suspected diagnosis, differential diagnosis
Temporal contexts	"h/o Covid-19" "Streptokokkenangina 06/16"	"history of" coarse grained dates (mm/yy)
Other contexts	(i) "father: pancreas ca" (ii) "refrained from resuscitation"	(i) family history (ii) plans not executed

relations in informal terminology systems, however, rely more on context-dependent human judgment than on crisp, objective criteria. E.g., the fact that "Animal" is a hypernym of "Human" may be trivial for a biologist, but debatable for a jurist. For a chemist "alcohol" is clearly a hypernym of "ethanol," whereas a general practitioner uses them as synonyms. The meaning of "fear," "anxiety" and "worry" has no clear boundaries, so that whether they are considered synonyms is much dependent on individual judgment and situational context.

3.2. The processing of biomedical language by computers

For decades, natural language processing (NLP) has been seen as an important and relevant application area of artificial intelligence, particularly because it bears the promise to bridge between humans and machines. Only in the last decade, however, NLP technology has reached enough maturity to play an ever-increasing role in application software, which determines ever larger parts of our everyday life, particularly in mobile applications.

When applying NLP technology to clinical narratives or scholarly publications, the main focus is on text mining, by use of different information extraction (IE) methods (27). IE systems analyze text structure and content in order to fill pre-structured information templates. An example is the processing of a pathology report in order to populate records of a tumor registry (28). This task of distilling structured data from unstructured text serves many purposes. Applied to clinical text, structured extracts can be used for all the documentation and annotation purposes as addressed in the previous section.

The complexity of the extracted information ranges from simple binary variables such as *Smoker* (yes/no), to parameters with numerical values for a parameter like *Oxygen Saturation* (e.g., 98%) to codes from a terminology system with up to hundreds of thousands of possible values. Their standardized meaning, is then often further contextualized by information models such as HL7-FHIR (29, 30), which provide information templates that represent the context in which the codes have to be interpreted, e.g., the role a disease code plays within a diagnostic expression. Instantiated FHIR resources specify, e.g., the time of a diagnosis and whether it refers to a current health problem, a resolved one, one in the patient's family, or a hypothesis raised by a clinician.

Text mining analyzes and normalizes linguistic units of different granularity. The largest unit is the document. Documents can be distinguished by types (e.g., discharge summary, radiology report, progress note) as well as subdivided into sections. Sections can also be assigned a type, e.g., *Diagnosis*, *Evolution*, *Laboratory*, *Medication* etc. in clinical documents or *Introduction*, *Methods*, *Results* etc. in scholarly publications. Within sections, sentence-spanning phenomena such as anaphors (see Table 2) or semantic relations need to be identified for a complete understanding, e.g., to link the mention of a procedure with the mention of an anatomical structure. Sentences are decomposed into smaller units (chunks) using shallow parsing, supported by the analysis of parts of speech (POS), i.e., the identification of word classes such as *Noun*, *Verb*, *Adjective* etc. Within chunks, text

passages that can be mapped to a controlled term are finally identified by matching against a domain vocabulary, such as constituted by or linked to one of the mentioned terminology systems. Such passages can be short (e.g., "cough"), but also complex, such as "non-intensive COVID-19 infection with positive vaccination status." At this level, two NLP tasks must be distinguished. First, the identification and delineation of a text passage to which a specific semantic type like *Disease*, *Symptom*, *Medication*, *Proper Name*, *Institution* can be ascribed. This is known as *Named Entity Recognition*. Second, the mapping of the identified candidate to the target vocabulary, which is known as *Named Entity Normalization, Entity Linking* or *Concept Mapping* (31–33). Pioneering systems for the English medical language are cTAKES (34), MetaMap (35) and MedKAT/P (36). In these systems, text content is automatically matched against terms in terminology systems and tagged with their codes.

Many use cases require connecting text passages, after normalization, to a temporal context. Clinical texts often do not report on facts chronologically, and time differences between important events of a patient history, e.g., between the first diagnosis of a tumor and its recurrence after therapy, are of prime interest. Standards like TimeML (37) have been proposed, as well as algorithms for the identification of time events, e.g., HeidelTime (38). The evaluation of temporal relations and putting events into context has also been addressed by the 2012 i2b2 Challenge on evaluating temporal relations in clinical text (39). Equally important is the identification of the negation context of a text passage, where NegEx (40, 41) has been optimized to different domains and languages (42–44), but the generalizability of the approaches is still missing (45).

The described analysis steps are implemented in classical text mining systems as software known as automated annotators or taggers. A common framework is Apache UIMA (46). Individual text analysis modules communicate in a processing pipeline by enriching a complex data structure, which incrementally adds information to the text under scrutiny. This information is represented by typed, access-optimized feature structures, which assign types and properties to a span of characters corresponding to text passages. Component repositories like DKPro (47) based on uimaFIT (48) support a flexible composition of use case specific building blocks for NLP systems, which implement specific functionalities in the chain. Important Python based NLP frameworks which have to be mentioned in this scope are spaCy (49) and Spark NLP (50).

A major paradigm shift has occurred in NLP during the last decade, driven by the unprecedented rise of artificial neural networks (ANNs) for machine learning, known as Deep Learning. Although the principles of ANNs have been formulated about 80 years ago, only now their combination with powerful computer architectures, big amounts of data, and innovative algorithms has unveiled their potential. Their popularity has been supported by practical program libraries such as KERAS, TensorFlow, PyTorch, and HuggingFace (51–53).

Deep learning approaches have largely replaced "shallow" machine learning methods in recent years, especially because features that are productive for learning success no longer require time-consuming feature engineering (54). Revolutionary for natural language processing are embeddings, which are computed semantic representations of text passages in vector spaces of medium dimension (e.g., 300), learnt from textual data. The embedding-based vector representation can be used for example to identify related term-candidates by applying different distant metrics like the cosine-similarity within this n-dimensional space. More recent architectures, particularly BERT (55) and GPT (56) can provide so-called contextualized embeddings (57), in contrast to first non-contextualized approaches like Word2Vec (58), GloVe (59) and fastText (60). For a given linguistic unit, these can incorporate the relevance of preceding units to their vector representation and thus distinguish between homonyms (e.g., "delivery" in "drug delivery mechanisms" from "normal labor and delivery"). For many of the model-based extraction tasks, Deep Learning, specifically the use of transformer-based architectures is now standard, and in some cases specific tasks no longer rely on the interaction of pipeline elements, but can be handled with an independently trained model, also known as end-to-end processing.

Training neural networks with sufficiently large amounts of data is "expensive" in terms of hardware requirements and processing time. This is specifically true when it comes to the generation of language models, which are usually downstreamed in a second step to a specific problem domain like named entity recognition or document classification, often referred to as transfer learning (61). Just some openly available language models exist for the clinical domain (62) which can be leveraged adequately for this kind of model-based problem adaption.

Nevertheless, traditional, "low-tech" rule-based approaches still find their application, particularly where scarceness of training data meets in-depth expert knowledge about the domain. Training models only on publicly available data is by far not enough to reach a good quality, particularly when it comes to entity normalization and disambiguation, and even more for languages other than English (63). This is particularly important for clinical narratives, because contrary to scholarly publications, most clinical texts, from a global perspective, are written in languages other than English.

It should not be forgotten that speech recognition technology, nowadays mostly implemented as recurrent neural networks like LSTMs (13) is becoming increasingly popular. A randomized study from 2015 showed an increase in productivity by physicians using this technology (64). In the meantime, speech recognition software has been shown to be faster and more accurate than typing, but the acceptance by clinicians still leaves a lot to be desired (65).

4. Ontological perspective

4.1. The need for semantic integration of health data

For the most part, medical research and medical standards of care are driven by international scientific and professional communities. Researchers and practitioners with different linguistic and cultural backgrounds have little problems when discussing medical issues, as long as a certain level of command of English and the knowledge of English medical terminology is guaranteed. Thus, experts from Baltimore, Bamako, Beijing, Berlin, Bogotá and Brisbane can get together to discuss issues of state-of-the-art clinical diagnosis and therapy. The picture changes already when we want to automatically integrate data from two hospitals in the same city: All kinds of major problems will arise, and harmonization of data from their respective EHRs requires human labor to an often-prohibitive extent. Similar challenges arise whenever we attempt to bridge

between EHR data and content of scholarly publications and databases.

The main desideratum is semantic interoperability. The role ontologies and other semantic standards can play in fostering or creating semantic interoperability of heterogeneous clinical and scholarly data to fulfill the pHealth requirements will be discussed in the following section.

4.2. Ontologies as a special type of terminology systems

Ontologies have been important resources in computer science for decades, accompanied by a variety of tools and representational languages. Unfortunately, the way how they were conceived and defined, as well as the purposes for which they have been built, has shown great variation. We have introduced the notion of a terminology system in the previous section, and often the term "ontology" is also used to refer to them. We consider this view to be of little use. Instead, we introduce the clear bipartition, highlighting "ontologies" as "formal ontologies" (66–69), contrasting them with the large number of terminology systems that are not based on formal semantics, such as ICD, ICF, MeSH, MedDRA, but also the UMLS Metathesaurus.

Formal ontologies are "precise mathematical formulations" (70), or more concretely, logic-based definitions and elucidations of the types of entities of a domain and the way they are related. This requires a computer-interpretable language, which typically distinguishes between individuals, classes and properties. The main purposes of ontologies are (i) to support knowledge representation and reasoning and (ii) to foster interoperability by standardized descriptions. One example is the automatic assignment of a class to individuals based on a computer-interpretable, axiomatic specification of the inclusion criteria for the class. In Utecht et al. (71) demonstrated that an ontology-based system can categorize potential drug–drug interaction (PDDI) evidence items into different types of evidence items based on the answers to a small set of questions. They tested RDF/OWL data representing such questions for 30 evidence items and showed that automatic inference was able to determine the proper evidence type category from a list of approximately 40 categories based on this small number of simpler questions. This is a proof-of-concept for a decision support infrastructure that frees the evidence evaluator from mastering relatively complex written evidence type definitions and allows for ontology-driven decision support.

The fact that natural language plays only a secondary role in formal ontologies is not a contradiction to what we wrote in the previous sections. The main difference is that the types of entities characteristic for a domain is the starting point when building an ontology, and not the meaning of domain terms in a particular natural language in the first place. In no way this should detract from the importance of domain language dictionaries. But the concerns are strictly divided: the ontological standardization of domain entities on the one hand, and on the other hand the anchoring of domain terminologies in several natural languages and dialects. This means, in practice, that synonyms and term variants in different languages are then linked to ontology IDs. At least one preferred term, often referred to as "label" is needed in order to make the ontology understandable by humans. Enriching it by additional terms is often done by the ontology builders themselves. Here, the ontology also fulfills the role of a dictionary.

Standardization has been an important issue regarding the formal languages employed by ontologies. Based on description logics (72), promoted by the W3C, the declarative Ontology Web Language OWL has become widely accepted. OWL is devised to verify the consistency of a set of logic-based axioms from which implicit knowledge can be made explicit by so-called description logics reasoners (73).

Equally, by the W3C, the Simple Knowledge Organization System SKOS (74) has been promoted as a representation of systems that informally structure a domain by its terminology. SKOS' main objective is to enable easy publication and use of vocabularies as linked data. Both OWL and SKOS are part of the Semantic Web family of standards built upon RDF and RDFS, both are used with data represented in the universal Resource Description Framework (RDF) of the Semantic web (75, 76). The abstract syntax of RDF – which does not enforce any strict semantic interpretation, has at its center the representation of data as triples, i.e., statements consisting of subject, predicate and object (75). The simple, very small structure can be linked together using International Resource Identifiers (IRIs) for each entity in the domain of discourse (75), thus enabling the creation of complex knowledge graphs.

The following example may illustrate the difference between the two languages. In SKOS, the triple < "Homo sapiens"; skos:broader; "Living organism" > expresses that the meaning of the expression "Living organism" is conceived as broader than the expression "Homo sapiens." In OWL, the triple < "Homo sapiens"; owl:subclassOf; "Living organism" > has the status of an axiom. It means that the class of all individuals of the type "Homo sapiens" is included in the class of all individuals of the type "Living organism." Whereas in SKOS, the relata are human language expressions like words and terms, in OWL "Homo sapiens" and "Living organism" are no more than human-readable class labels that make the ontology human-readable. The exact meaning of the classes requires further definitions of these types. According to these definitions, the axiom could be questioned by the fact that the class labeled as "Homo sapiens," according to how it is defined, may also include dead persons. As SKOS has no formal semantics, it is at the discretion of the users to approve the statement < "Homo sapiens"; skos:broader; "Living organism" > as largely appropriate, despite boundary cases like the abovementioned one.

Thus, RDF-based Semantic Web standards constitute a framework that equally accounts for ontologies as carefully constructed cornerstones, for informal knowledge organization systems as bridges to human language, and the breadth of knowledge representation built upon it.

4.3. Standardization aspect of ontologies

Whereas computer science has always had a functional look on ontologies – an ontology is as good as it supports a given use case and its particular world view, life sciences have put much more emphasis on the interoperability aspect of ontologies. For instance, the Open Biological and Biomedical (OBO) Foundry (77) established a set of principles (78), ontologies have to comply with: orthogonality, open access, instantiated in a language that allows computer-interpretability, and use of common, shared identifiers (79). Over the last years, the

OBO Foundry community has worked to improve those principles and increase compliance for the OBO Foundry to become a key resource towards making biomedical data Findable, Accessible, Interoperable, and Reusable (FAIR) (80).

Orthogonality means that each ontology has its scope limited to entities of clearly defined types and scopes. It points to a framework of shared fundamental categories: chemical entities and roles such as in ChEBI, anatomical entities in the FMA, cell components, biological processes in the biological process and molecular "function" (activity) in the Gene ontology. Other examples are qualities in the human phenotype ontologies, locations in the environment ontology. All this points to high-level types of a common "upper level" (9), which is the focus of interest of the Foundational Ontology/Applied Ontology community. Foundational upper-level types, properties and related axioms (e.g., that a process is located in some space or that an immaterial entity cannot have material entities as parts) strongly constrain the modeling freedom of the ontology engineer, for the benefit of interoperability.

In the domain of life science, BFO (81, 82), the Basic Formal Ontology has found the widest acceptance. Figure 3 demonstrates its upper level.

The fact that BFO 2020 has become an ISO standard (10) sheds light on a new view on ontologies, namely the standardization (83) of entities in the field of science. In engineering it has always been obvious that a narrative description of an artifact would not be sufficient for producing interoperable industry-standard products. Only exact technical specifications guarantee the smooth interaction of technical components like plugs and sockets. The argument in favor of biomedical ontologies is that like bits and pieces of industrial artifacts require adherence to mathematically precise standards to be exchangeable and interoperable, entities of interest for precision-oriented science and health care require the same accuracy in terms of ontological definition and delineation. Such entities of interest range from biomolecules and pathways over body parts, disease processes, quantities and qualities, pathogens, medical devices up to all kinds of interventions and complex business processes in 5 PM contexts.

Apart from BFO, standardization has also been an issue in biomedical terminologies, particular in the case of SNOMED CT (84), which set off as an international terminology for EHRs, but which then increasingly adopted principles of formal ontology and logic, so that it can now be seen as clinical ontology of high coverage and granularity.

4.4. Assessing biomedical ontologies

However, not all healthcare and life sciences ontology developers share the view that ontologies should be interoperability standards. Up until now, numerous project-specific ontologies have been built without any interoperability or standardization interest. They are maintained for the duration of a certain project and are then abandoned. They do not refer to foundational ontologies, nor do they re-use content from other domain ontologies. Such resources amount to many hundreds, which can be inspected *via* BioPortal (85), a collection of ontologies and ontology-like representations, regardless of their formal rigor and maintenance status.

A critical analysis is therefore appropriate. When reviewing the ontologies created in recent years, we see, on the one hand, increasing acceptance of good practice design principles, at least where there are enough resources for ontology curation, such as in SNOMED CT and some of the OBO Foundry ontologies. On the other hand, despite all research and education in the field of Applied Ontology, numerous ontologies continue being constructed idiosyncratically, for specific use cases only, and without concern for interoperability. Such ontologies often ignore the strict requirements of logic, do not use machine reasoning and do not subscribe to any upper-level ontology. They often contain workarounds with the purpose to represent what ontologies are not meant to express, namely fuzzy, context-dependent or probabilistic representations. The fact that the use of the logic of OWL is restricted to axioms that are universally true, is often not taken into account in all its consequences. Even people with sufficient training in ontology are not aware of the fundamental differences

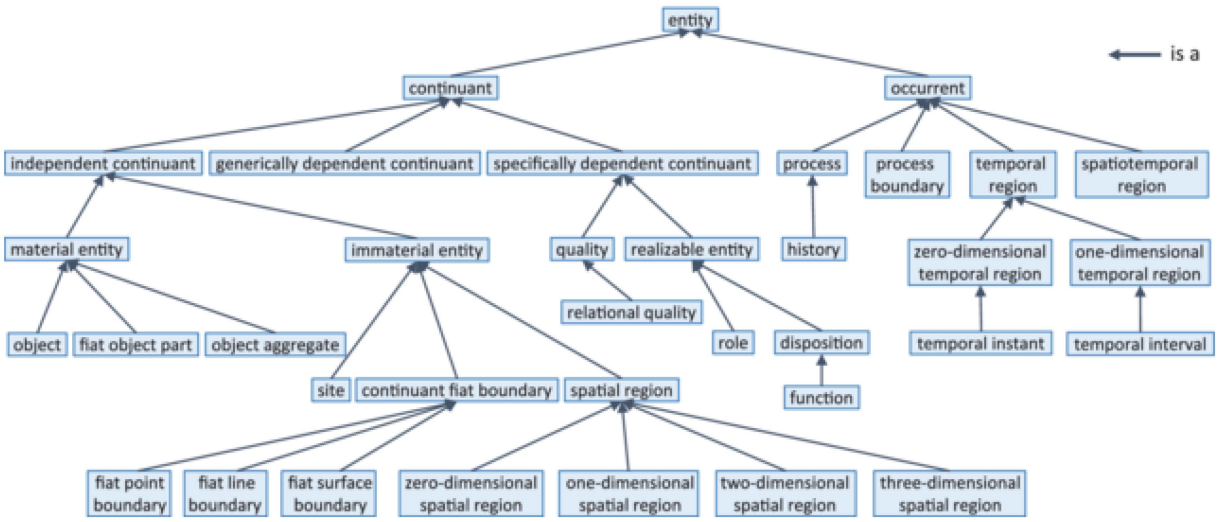

FIGURE 3
BFO-2020 taxonomy (according to ISO 21838-2 (10)).

between the statement "tobacco causes lung cancer" and the statement "tobacco contains nicotine." Only the latter one can be properly expressed by OWL, because tobacco always contains nicotine. The former one, in contrast, makes a probabilistic statement about populations, regarding a non-accidental co-occurrence between smokers and people with lung cancer, which does not preclude smokers without cancer and lung cancer patients that never smoked.

Another pitfall is improper or ambiguous labeling. Bioportal currently displays 58 ontologies with a class labeled "heart," although the heart of an adult fly, a mouse embryo or a human heart transplant do not have much in common. Absurd mappings derive from the matching of labels, e.g., of "cold" to "chronic obstructive lung disease" (for which the acronym "COLD" is used). Even good ontologies often do not have a good labeling discipline, because the language expressions used as labels have different meanings in different communities. In other cases, ontologies like the Gene Ontology (GO) do not have more than one label per class, which leads to the practice to refer to GO classes as "GO terms," which is confusing for anybody with a terminology of a linguistics background.

Finally, a complicating factor when constructing ontologies is the continuous nature of many natural kinds (86). Instances of hearts, brains and muscles – be it from mice, humans or flies – do not have sharp boundaries that delineate them from the neighboring anatomical structures, such as an engine in a vehicle. Heart surgeons would consider the pericardial sac and parts of the great vessels as part of the heart – as they transplant it together with the heart proper – opposed to anatomists, who share an ontogenetic (embryological) perspective. All these subtleties are seldomly made explicit in ontologies, so that the risk that re-using ontological content created in a different context produces unwanted effects, is considerable. After all, considering those human-made and therefore imperfect ontologies comes back to the problem we have with natural language as a means to encode information and knowledge, viz. the need to consider context and the acceptance of having fuzzy, partly conflicting, partly ambiguous representations.

5. Integration of ontologies and natural language for 5PM

We now move to discuss the interface between ontologies and natural language technologies, with the goal to support formal, unambiguous and canonical representations of structured and unstructured data in the field of 5 PM, encompassing research data as well as real-world data from EHRs.

5.1. Canonic representations of narrative content

It is unrealistic that non-standardized and low-structured narrative data, currently prevailing in EHRs (87, 88) will be replaced at some point by completely structured and standardized documentation, as little as it is likely that future scholars will publish all their data according to the FAIR criteria. Human language will probably never lose its function in clinical and scholarly communication and documentation, due to its capability to describe facts and events in a flexible and granular way, just to the degree that it is understood by clinicians or researchers that share the same or similar contexts. The challenge is therefore that heterogeneous data of all kinds is analyzed and semantically interpreted in a way that leads to maximally standardized and interoperable representations. This is why semantic standards with a big, international user community, e.g., SNOMED CT, LOINC, and FHIR should be preferred as target representations in biomedical data normalization workflows.

5.2. The resource problem

The performance of NLP systems depends crucially on the available resources. These include terminology systems and corpora, as well as language models derived from the latter. For the clinical language, there is a great need to catch up here, due to the lack of models tailored to clinical language, as well as natural languages other than English (62). So does the UMLS aggregate an impressive variety of terminology systems, but mainly in English, thus limiting terminology support for other languages. SNOMED CT has been translated and is being maintained in several languages, incurring high costs and efforts, and results lag behind, particularly for smaller languages. In addition, the existence of a translation does not necessarily mean that it is suitable for NLP applications. Terminology systems tend to be normative in nature, so that terms are ideally unambiguous and self-explanatory. This often does not reflect clinical language use. E.g., in a corpus of 30,000 cardiology physician letters from an Austrian hospital (89), the authors did not find the word "Elektrokardiogram" a single time – contrasting with thousands of occurrences of the acronym "EKG." For "liver metastases," the term "sekundär malign levertumör" (secondary malign levertumör) is found in the overall Swedish translation of SNOMED CT, for which not a single use can be found in the entire web, while the clinically common "levermetastaser" has over 200,000 Google hits, but is missing in the Swedish SNOMED version. The EU project ASSESS-CT (90) propagated the creation of so-called interface terminologies, collections of technical terms that primarily represent the language used in the clinic. Examples for interface terminologies are the German ICD-10 alphabet (91) or the Austrian interface terminology for SNOMED CT (92). Corpora, i.e., text collections are essential for training NLP systems as well as for their evaluation, for example in shared tasks, which are scientific competitions like i2b2/n2c2 or the ShARe/CLEF eHealth and SemEval challenges (93), partly re-using narratives from the most prominent clinical language resource MIMIC (94). The more such open resources exist for a language group, the better synergies can be exploited by developers of NLP systems. For example, a large part of the quality of the Google translator is due to the simple fact that Google has direct access to gigantic amounts of multilingual texts.

Clinical researchers can only dream of this. Clinical content is highly confidential, so that only reliably anonymized data can be considered for the training of NLP systems. Anonymization means marking names of persons and institutions (95) in order to remove the direct reference to persons and institutions, an absolute requirement for clinical texts to be processed for purposes other than patient care and by persons other than those directly caring. What content is relevant for de-identification – PHI (protected health information) – is often not specified, so that many countries apply the HIPAA safe harbor criteria (96), developed in the USA. However, concerns regarding the release of anonymized clinical text samples are still enormous. As an example, the

completely manually anonymized German-language annotated clinical corpus BRONCO could only be released after it was divided into randomly arranged individual sentences, the coherence of which could demonstrably not be restored (97). Other ways of providing open clinical corpora include the creation of completely synthetic texts using machine learning (98). Access in a controlled setting for the use case specific adaptation of clinical NLP systems is indispensable for any reasonable use of narrative data in combination with enhanced standardized and interoperable clinical phenotype representations into a transformed health ecosystem.

5.3. Manual annotation as a fundamental task

Annotated corpora, i.e., text collections that were manually enriched by labels that describe the text according to its syntactic and semantic features, is not only an enormously resource-intensive effort, but also of utmost importance for entity normalization and semantic relation detection, but also text classification, sentiment analysis, question-answering and other tasks. Models trained with annotated corpora enable machines to understand the meaning of language in clinical narratives, and allow for more accurate analysis of medical data, particularly in P5 medicine settings.

Semantic annotations should be guided by the same interoperability resources and using the same interoperability standards as expected for the target representation of clinical content. Only under these circumstances, consistency in annotation can be reached, and principled annotation guidelines can be formulated (99). Such annotation guidelines have to bridge between shared representations of the portion of reality the texts are about (health care scenarios for EHR content, lab procedures, clinical research paradigms, scientific methodology and argument when it is about scholarly content) on the one hand, and the text surface on the other hand. This means to link text passages to the ontology classes they denote (or to abstractions thereof, such as upper-level categories like *Body Part*), which requires a deep knowledge of the underlying ontology as well as familiarity with the domain, particularly in the case of ambiguous text passages such as acronyms. Entity normalization, i.e., the linkage of words and text passages to ontology identifiers such as SNOMED CT or LOINC codes is only the first step. Equally important is their linkage to contextual or temporal modifiers, in order to represent the entirety of a statement, e.g., whether a diagnosis is confirmed, suspected or negated, when an examination was done or when a recurrence of a disease occurred. Finally, annotations often need to be linked by relations, such as procedures or observations with the related anatomical sites, operations with devices or infections with pathogens, but also sequences of events by their temporal order and possibly causation. The relations used for annotation should be consistent with the underlying standards, such as *Finding site* in SNOMED CT or *verificationStatus* in FHIR. For assessing the quality of the manual annotations, the inter-rater agreement between annotators is very often measured *via* Cohen's kappa, Fleiss kappa or F1 value (100, 101). The higher the value, the higher the agreement of two human annotators for a specific annotation task. An excellent overview of manual annotation tools is given by Neves and Ševa (102).

5.4. Pervasiveness of semantic technology in health informatics

This section is primarily concerned with the interplay between health standards, terminology systems like classifications and terminologies, as well as semantic web technologies. This is an important aspect of health data infrastructures and, in order to understand ontology-related challenges to creating transformed health ecosystems, these categories need to be considered.

At this time, there is wide-spread agreement that semantic data harmonization and integration are necessary to move forward biomedical research on a number of key areas in the field (103–106). The recent COVID-19 pandemic showcased the importance of fast and reliable data and knowledge management to support COVID-19 (107, 108) research. This research is crucial to reign in the spread of COVID-19 and effectively improve patient outcomes. While this trend is certainly welcome and hopefully is the first step into deeper involvement of the biomedical informatics community in research regarding semantic technology, there is still much work to do in order to reach the pervasiveness of semantic technology in health informatics for the benefit of P5 medicine.

In a recent systematic literature review on semantic interoperability in health record standards (104), de Mello et al. proposed a five-category taxonomy for research in that area: (1) Health standards (e.g., OpenEHR, HL7, DICOM), (2) Classification and Terminologies (e.g., ICD, LOINC, SNOMED CT, MeSH), (3) Semantic Web (e.g., OWL, RDF, SPARQL, SKOS), (4) Storage (e.g., Multi-model, Semantic Web based, graph database), (5) Evaluation (e.g., Usability, Functional test) (104). The authors of the review concede that many of the research papers included fit in more than one category, which means that the classes in this taxonomy are clearly not mutually exclusive (104). For instance, both the ontology SNOMED CT and the language OWL are considered standards. The review also found that the use of ontologies and other Semantic Web technologies (SWTs) is motivated by the possibility to create logical inferences and rules from them. This finding leads to the core of the difference between an SWT-based approach to semantic data integration and harmonization and the use of the other categories (104).

The fact that biomedical researchers chose SWTs due to the ability to create new data points or run more inclusive queries using logical inference is a highly relevant point. One example for such an inference used in querying data is if a biobank stores a specimen labeled "cerebellum" and the biobank uses an anatomy ontology to specify that every cerebellum is a part of some brain, a biobank user can retrieve that specimen when running a query over all specimens of the brain or its parts, rather than running multiple strings (brain, cerebellum etc., possibly also including all synonyms) in one or multiple queries. The fact that the cerebellum is part of the brain is explicitly stated as part of the knowledge system and not externalized in the mind of some database employees. An example for a new data point created based on automatic inference is if a study has the information that the pediatric patient Jane Doe lives with their parent John Doe and the system also has the information that John Doe is a smoker, a knowledge management system containing a computer-interpretable definition of a smoking household as a household that has at least one smoker as a member, the system automatically infer that Jane Doe is living in a smoking household. Beyond these use cases, the use of ontologies and other SWTs also allows automatic

sorting of individual entities in categories that have computer-interpretable definitions, as (71) demonstrate.

One application of SWT is Knowledge Representation and Reasoning (KRR) (109), a core area of Artificial Intelligence (110, 111). KRR provides the basis for "representing, maintaining, and manipulating knowledge about an application domain" (111), such as medicine. According to Lakemeyer and Nebel (111) the core elements to meet that aim are explicitness and declarativeness. Explicitness means that the knowledge needs to be stored in a knowledge base along with formal representations describing it in an unambiguous way, and declarativeness means the "meaning of the representation can be specified without reference to how the knowledge is applied procedurally, implying some sort of logical methodology behind it" (111). It is clear that this specification of knowledge representation is largely about the way that the meaning, or semantics, of the knowledge is specified. It is implicit in the Lakemeyer's and Nebel's specification that the call for explicitness entails the requirement for the knowledge to be represented in a computer-interpretable language. The motivation to add reasoning as a crucial component to knowledge representation is, according to Brachman and Levesque (110), that this allows to infer new, often actionable knowledge, such as a potential adverse reaction to a drug inferred from previous drug reactions. In sum, when talking about the area of KRR, the semantics of knowledge rests on the formalization of the knowledge in a computer-interpretable language, the coding of unambiguous representation of its meaning in a way that does not refer to its operationalization. Keeping this in mind, highlights a number of obvious gaps in how the biomedical informatics community uses the term "semantics."

In 2018, Brochhausen et al. pointed out, that there might be a disconnect regarding the use of the terms "semantic" or "semantics" in biomedical informatics: terminology systems, often in combination with Common Data Models (CDMs) are implemented to provide semantics and foster semantic integration and researchers using those resources and claim their data is semantically integrated and computer-interpretable (112). None of the systems assessed in their study exhibited any features that amount to semantics, in the sense of the KRR community. Most of the tools featured human-interpretable definitions. To help address that communicative gap, Brochhausen et al. proposed the term computable semantics (112), which basically applies to the specification of semantics in a KRR context. They proposed to use a sorting task to assess whether a computer understands the data as a low hurdle measure to test for the existence of semantics.

But if this communicative gap exists, what is meant when biomedical informatics papers talk about semantics or semantic interoperability. The multitude of interpretations of the terms "semantic," "semantics," or "semantic interoperability" warrants a systematic review, which is out of scope for this paper. However, we want to highlight some possible interpretations and how they compare or relate to the SWT approach using ontologies.

One traditional perspective is that achieving semantic interoperability relies on and can be achieved by the use of standardized terminologies or controlled vocabularies. In 2016, Seerainer and Sabutsch affirm: "Semantic interoperability within a nationwide electronic patient record, entailing the interconnection of highly diverse organizations with various IT systems, can only be achieved by providing standardized terminologies" (113) . Their paper (113) describes the development of a national terminology system to share EHR data in Austria. To achieve these, multiple terminologies are loaded onto a terminology server, partially translated, and made available for users along with a manual on how to implement and use the terminologies (113). It is obvious that an approach like this is very different from what Brochhausen et al. call computable semantics. While the standardized terminology restricts the number of terms used, the interpretation of what those terms mean is not achieved, in fact not even guided by the computer. The interpretation of the allowable terms and values is completely externalized to human agents using them. The manuals and textual definition might provide some insight into what the intended meanings are, but ultimately, there is no guarantee that the terms and values are interpreted in the same way from one user to the next and from one clinical site to the next. The inherent problem of interpreting terms from terminologies and vocabularies has been highlighted by three studies in the past, which show that inter- and intra-coder equivalence in coding medical material with SNOMED CT did not surpass 58% (90, 114, 115). It is important to note that those findings predate substantial changes in SNOMED CT, which moved it to be more like an ontology (116), while currently considerable parts of it lack both formal and textual definitions.

We have mentioned above the role that the interplay between informal terminology systems and ontologies plays for semantic integration in conjecture with ontologies (104). In creating that interplay, researchers and developers frequently rely on mapping one or more terminological resources with one or more ontologies.

6. Future opportunities

6.1. Linguistic opportunities

The use of NLP for processing clinical routine data has long been seen as a rather academic topic, which may be useful to solve well-delineated problems, but whose implementation within robust IT environments was still a long way away and not safe enough for clinical decision support. Whereas in the 20th century AI and NLP was characterized by unrealistic promises and several drawbacks, the universal AI boom of the last 10 years has brought intelligent applications including "understanding" of human language within user reach.

But the question of how these developments can be translated into real improvements of health care and health management is not ultimately answered, in particular, how can they be harnessed for events with high and urgent information and action needs, such as pandemics? A recent review (117) of approximately 150 NLP studies on COVID-19 focused on the extraction of information from published texts and identified the need for using clinical documents as a source as largely unmet.

Success criteria for the application of NLP in electronic patient records are crucial, for example user-friendly NLP platforms that implement current technology, which are extensible and customizable *via* open interfaces, and enable high quality text recognition, thus creating trust in their use and enabling automation of medical documentation processes. The performance of clinical NLP systems should be easily proven *via* benchmarks and shared tasks within the process of the adaptation to the application domain. This has to be done with a consistent and continuous application-oriented

development of semantic standards, in particular ontologies such as SNOMED CT and information models such as HL7-FHIR, with specific consideration of the output of clinical NLP systems. This goes along with easy access to terminology resources, corpora and language models optimized for the clinical language. Modern hospital IT should therefore support computationally intensive AI processes, such as with GPU computers, and therefore enables easy integration and adaptation of NLP systems specifically but support multimodal approaches in general by combining, e.g., OMICS, image and textual resources widening the patient's digital pheno- and genotype scope. Qualitatively adapted NLP systems, at its best, adapted to an entire target domain (118), can therefore be seen as one part in a holistic P5 medicine approach. The domain-adapted resources should not be locked in this setting, but legal and regulatory frameworks should facilitate the use and reuse of medical data to train artificial intelligence across institutions, as well as the sharing of domain-adapted NLP models.

6.2. Ontology-related opportunities

Over the last few years, we see a growing interest in using ontologies and SWTs. While there is still a communication and knowledge gap regarding computable semantics, ontologies get increasingly used. We have pointed out the two major repositories for biomedical ontologies, the BioPortal (85) and the OBO Foundry (79, 80). Having repositories making biomedical ontologies available which are typically focused on a specific domain or use case, raises the question of how expanding the coverage of those repositories, the individual classes and relations can be orchestrated and organized. As mentioned above, the strategy of the BioPortal and the OBO Foundry are quite different: the BioPortal is an open repository that allows developers to upload their ontology, then provide tools for users to identify the right ontology for their project. The OBO Foundry's approach from its very beginning has been more coordinated. This is not only true regarding the principles submitted ontologies need to follow, but also the evolution towards more rigorous inclusion criteria (79, 80). Figure 3 shows the initial conception of OBO Foundry coverage regarding biological and biomedical domains and the axes the coverage was supposed to expand along. However, as the OBO Foundry grew, there have been an increasing number of ontologies added that cut across some of the axes shown in Figure 3. This meant that the orthogonality of the ontologies in the OBO Foundry was a work in progress in the initial years (119), but lately, independent analysis demonstrated the positive impact of OBO Foundry principles on the quality measure of OBO Foundry ontologies (120). Yet there are important biomedical ontologies growing independent of the OBO Foundry and uncoordinated with shared foundational ontologies. In the first place, this is the case with SNOMED CT as a resource that requires licensing, which contradicts the OBO Foundry principles. For the future, it is an important issue to ensure that the resources required for clinical interoperability are freely available to all participants as so-called knowledge commons. Since the development and maintenance of high quality semantic resources require considerable efforts, a strategy for sustainable evolution still has to be developed.

However, increasing unification of the existing ontologies in the OBO Foundry and principled expansion of its coverage might require further development and assessment of methodologies to guide ontology design decisions and representational strategies. The publication of ISO 23903 (5) *Interoperability and integration reference architecture—Model and framework*, marks one new opportunity to provide rigorous guidance for orchestrated ontology development. Brochhausen et al. have recently demonstrated the use of the reference architecture model and framework to analyze ontological representation and modeling for clinical data and other data relevant to biobanking for orthopedic trauma care (121). Viewing the data and specimen management as the business case represented in the *Business View* as defined by the GCM, necessary changes from the perspective of local EHR systems become obvious and can be handled on a principled basis. The local EHRs are likely to enforce one patient identifier (ID) per patient. The business case of integrating data from multiple healthcare providers requires transition to allowing multiple patient IDs per patient to accommodate sampling regarding tumor progression happening in multiple providers (121, 122) . This is modeled by progressing through the *Enterprise View*, allowing multiple IDs into *the Business View* (Figure 2), which provides ways to query for patients across multiple patient IDs. The result is the ontology design decision which allows a one-to-many relationship between patients and IDs. This certainly could have been done based on *ad hoc* decision, but the principled approach, if used consistently, will allow increased rigor on ontology design decisions.

They showed that the reference architecture assisted in the resolution of representational design decisions and provided a rigorous way of managing such representation questions. Additional research is needed to test the usefulness of ISO 23903 for this purpose and alternative methods for rigorous methods of ontology design need to be developed and evaluated.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MK and SS wrote the sections on NLP. MB and CZ contributed to the section on ontologies, supported by SS. BB wrote the background section and contributed to the overall design of the article, as well as to Section 6 **Future opportunities**. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The ethical challenges of personalized digital health

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Personalized digital health systems (pHealth) bring together in sharp juxtaposition very different yet hopefully complementary moral principles in the shared objectives of optimizing health care and the health status of individual citizens while maximizing the application of robust clinical evidence through harnessing powerful and often complex modern data-handling technologies. Principles brought together include respecting the confidentiality of the patient–clinician relationship, the need for controlled information sharing in teamwork and shared care, benefitting from healthcare knowledge obtained from real-world population-level outcomes, and the recognition of different cultures and care settings. This paper outlines the clinical process as enhanced through digital health, reports on the examination of the new issues raised by the computerization of health data, outlines initiatives and policies to balance the harnessing of innovation with control of adverse effects, and emphasizes the importance of the context of use and citizen and user acceptance. The importance of addressing ethical issues throughout the life cycle of design, provision, and use of a pHealth system is explained, and a variety of situation-relevant frameworks are presented to enable a philosophy of responsible innovation, matching the best use of enabling technology with the creation of a culture and context of trustworthiness.

KEYWORDS

ethics, personalized health, trust, consent, connectivity, evidence, evaluation, policy

1. Introduction – long-standing and new challenges accentuated by digitized personal health

1.1. Transformative methods bring related challenges

The personalization of healthcare is a foundational principle from the earliest code of medical ethics. Now, after two centuries of primarily static paper-based recording and communication methods, electronic digitized technologies for data capture, processing, and communication open radical new opportunities to enable the personalization of care and the harmonization of contributing professional components, but this unprecedented opportunity brings concurrent new challenges in the need to blend foundational principles with the maximization of new benefits.

Digitization in healthcare is an aggregation of the newest technologies throwing up its own challenges within data management and healthcare delivery. Ongoing organizational, methodological, and technological advancements lead to a complex transformation of health

and social care toward personalized, participative, preventive, predictive, and precision medicine (characterized as 5P medicine) (1). Such 5P medicine ecosystems are highly complex, dynamic, multidisciplinary, context-sensitive, knowledge-driven, and policy-controlled. The ecosystem is structurally and functionally characterized by its components representing specific aspects of the system, their functions, and relationships as well as the interaction of the system with its environment. The challenge is to define all impacting domains and to formally represent the related knowledge for the concrete use case of each specific business system. To ensure quality, consistency, and trust, the ISO 23903:2021 interoperability and integration reference architecture – model and framework (2) should be used. Policies that should control the behavior of 5P medicine business systems during their design and deployment include legal constraints, procedural requirements, and security and privacy concerns, all being focused on the goal of individual expectations and wishes of patients and the related practice decisions of professionals. All these should be underpinned and guided by ethical principles. The paper will address the ethical domain in this holistic context.

1.2. Personal yet informed – two key healthcare dichotomies spanning the millennia

The mission of pHealth brings together across three millennia old and new challenges of trust, risk, and ethics related to healthcare delivery. The key to the success of pHealth is the effective use of medical and personal data, which is an ethically sensitive issue even at the simplest level, and particularly so when using technological tools which in their details (and controls) are unfamiliar to many of those served. It juxtaposes four challenging concepts – the use of information embedded in the confidential patient-clinician dialogue; the use of extended personal case history to give a full longitudinal picture; sharing with co-creators of care to enable smooth holistic service delivery; and, the utilization of composite medical knowledge distilled from population-level personal health outcomes.

The Hippocratic Oath of *circa* 400 BC is firmly grounded on the health professional's interaction with the individual regardless of their status, but at the same time also emphasizes the practitioner's dependence on their teacher (and thus on antecedent knowledge) and on the importance of deferring to the superior technical skills of others (3). Two millennia later, in 1623, Donne emphasized that "No man is an island … because I am involved in mankind…" (using "man" in the historic representation of "person") (4). Nowhere is this more true than in medicine and healthcare where medical knowledge can only be built up by the creation of insight from the epidemiology and treatment outcomes of a wide population – but the delivery of that care should be personalized and confidential, yet it is often shared within a virtual team.

For optimal and ethical health care delivery, the health professional should not work outside personal knowledge (and related locus of practice) but at the same time should competently access and utilize the full body of relevant health evidence in the specific illness or practice field. Moreover, this knowledge should be applied in a way moderated to match the personal presentation and characteristics of the subject of care. From this arises an essential need, identified from Hippocrates onward, to exploit cumulative health knowledge and relate it through the treating clinician back to the situation of the presenting individual – a daunting task unless well supported by the methods and resources of the day.

1.3. The computer as a powerful enabler

Computing – the rapid processing of standardized data items and presentation of calculated results – brought a new and powerful tool to address this challenge. In the mid-20th century, the power of computers was starting to be developed for healthcare purposes, and interest blossomed as the potential nature and scale of use became apparent.

In 1977, an influential paper considering the emerging opportunities and issues for informatics application in medicine focused on decision-making in medicine and opened with the following sentence (5):

> *Medicine is a discipline of judgment and action. At each moment of his professional life, the physician must suggest decisions and actions to his patient. In order to do this, he must gather some pertinent information and extract in the most logical and the surest way arguments allowing him to achieve his objectives.*

Apart from the archaic male personalization, this neatly sums up the computational task for clinical practice, and, thus, in modern terms, the safe delivery of personalized medicine. The paper mapped the healthcare decision processes and the related information dependencies, and this can be updated to the modern context of pHealth as shown in Figure 1, which indicates that it is the combination of the patient's views and physical presentation and the knowledge gleaned from the electronic record and from emergent medical knowledge that the clinician analyzes in order to create a proposed course of action; this is then shared with the patient and the process is iterated as necessary.

The task for 21st-century pHealth is to accommodate the latest person-centric concepts and to ensure that all the components and the whole process meet ethical requirements. Within this, using computational support is very different from submitting to technological domination – the computer must be used responsibly and ethically as a controlled tool. As such, the art of medicine remains, with the clinician and the patient working together to engage responsibly designed technological tools in the interest of balancing competing interests, making fine judgments, and ensuring consistency of delivery.

1.4. Social responsibility and ethics in science and technology

Fortunately, the need to carefully define the role of technology within medical decision-making was recognized at a relatively early stage. Once the power of computers in health and healthcare became clear, commentators began to identify the need for responsibility and ethics. By 1992, Durbin published an article on Social Responsibility in Science, Technology, and Medicine (6). Subsequently, Beckwith and Huang wrote, "If society is to remain in step with new technology, the scientific community needs to be better educated about the social and ethical implications of its research" (7). Questions on Ethics,

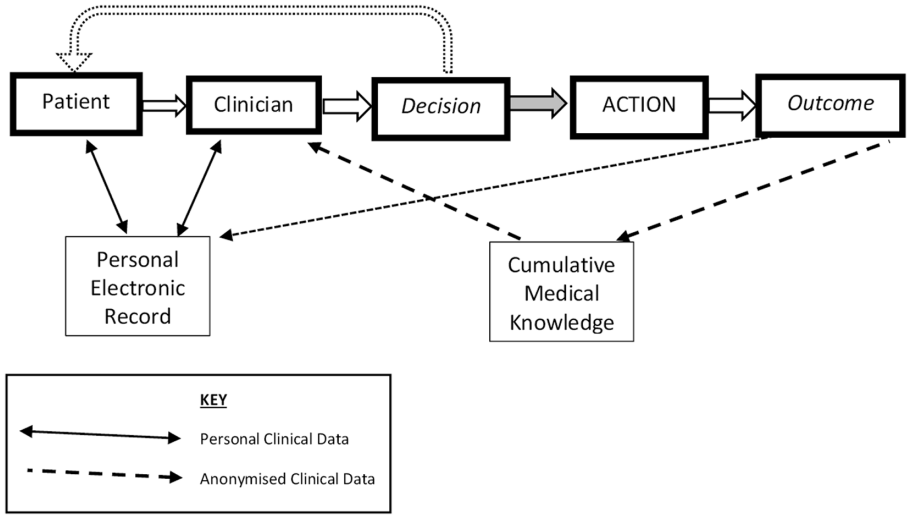

FIGURE 1
Types of personal data flow enabling decisions for evidenced Personalized Health. Developed from Grémy and Goldberg (5).

Computing and Medicine, and the informatics transformation of healthcare started to be explored (8). This issue has extended with the expansion of digital data gathering and communicating technologies to augment and extend the core computing function not least including the new opportunities but related bias and evidence risks of so-called Artificial Intelligence (AI) in health data analysis (9–11).

1.5. The expansion of 'patient' to 'connected service user'

The sociological context of patienthood has been steadily developed, linking again to no 'man' being an island (4). No person should live in isolation, with the corollary that a person's health condition is influenced by their immediate family and friends, as well as impacting them. In turn, those close contacts may be active in providing aspects of healthcare support; the 'Patient' in Figure 1 should be seen as a node interacting with formal and informal carers, necessitating authorized information flows, and finally, the patient and their close network should not be passive recipients of healthcare but should be involved in treatment and delivery decisions, allowing for preferences (12, 13). The World Health Organization has framed this in a Global Strategy on People-centered and Integrated Health Services (14). Thus, this special edition, and this paper, emphasizes the importance of "participative" alongside the other pHealth principles of the "5P" approach, namely, personalized, participative, preventive, predictive, and precision, while building on a recent framing of the ethical aspects (15, 16).

2. A holistic, design-based, and person-focused approach to ethics in pHealth

Based on an interdisciplinary architectural approach to pHealth (1) and the analysis of related trust aspects (17), this paper seeks to blend the ethical dimensions of healthcare principles and person-based values and expectations with new technology challenges. It also draws on the emerging understanding of Responsible Research and Innovation (RRI), which seeks to circumvent the false dichotomy between the ethics of research and the new ethical issues of changed roles, processes, and societal effects as innovation is rolled out (18–21). The claim is that the old and the new are mutually enabling if fundamental ethical principles are included as core design principles.

Moreover, it is both wrong and inefficient to treat ethical aspects as something to be applied retrospectively as a summative acceptance test – in order to be grounded and robust, and in order to avoid the need for post-build rectification, ethical principles need to be built into pHealth system development from the conception of objectives through to ensuring effective and equitable use in practice in line with Responsible Research and Innovation principles. Figure 2 shows how ethics need to be woven formatively through the life cycle of the endeavor.

Because pHealth embraces multiple contexts, it crosses several dimensions of ethics (15). These include the patient-practitioner interaction with medical ethics, the interaction of public health institutions embracing public health ethics, and the secondary use of data pertaining to the ethics of health research and the creation of accessible knowledge. Therefore, the ethical considerations on pHealth ecosystems could be required to navigate between and balance multiple considerations, and different frameworks and approaches have been described as Reflective Equilibrium (22), which has been shown to be applicable in modern health policy challenges (23).

This necessitates using a range of viewpoints and principles to initiate and support a normative discussion in order to reach a rational and defensible position as the issue progresses. Questions of technology interfacing with personalization are addressed in Section 3, while a review of the main principles, frameworks, and approaches to ethics which can be utilized is in Section 4.

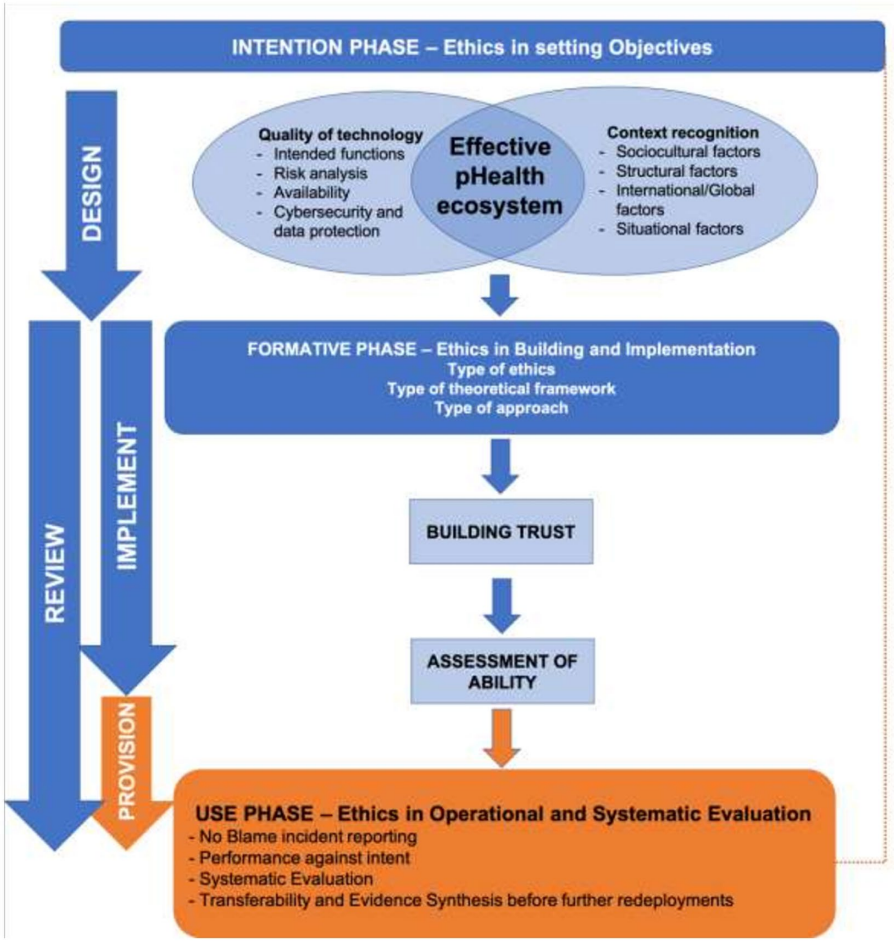

FIGURE 2
How Ethical Reflections should permeate pHealth Design and Application.

2.1. Ethical approaches applied throughout pHealth design and build

The three aspects of applying ethics in the system process are:

2.1.1. The intention phase (ethical objectives)

Whilst improved care delivery and clinical outcomes are often the initial trigger for pHealth and other health informatics initiatives, ethically, the core objectives when setting up any form of the health system should be equity of accessibility and acceptability. Inequity is often unintentionally built into health systems through hindrances which include practical access, differential health determinants, and restricted eligibility, and informatics systems can be postulated to ensure equity of advocacy (24). The utilization of data technology requires us to enquire as to how this tool might either enhance or impede our ethical intentions. For example, we might need to ask about the effect of any relevant digital divide in society, whereby many of those most in need of healthcare are less active with or do not trust digitally provided services (25).

Thus, the intention phase and the setting of objectives in a holistic and reflective mode provide a key opportunity to set any initial technical breakthrough or service efficiency objectives into a richer, balanced, and ethically underpinned holistic purpose. Included in this is moving away from concepts of 'disadvantage' and of 'hard-to-reach' patients toward equity of delivery and an acknowledgment of our past failures in underserving particular communities. User views and values should be incorporated, and any inherent difficulties or challenges should be addressed, and the risk of designing primarily for 'people like us' (26) and of building in new technological health inequities (27, 28) are, thereby, avoided. It is also important to manage expectations and avoid hyperbole from organizational or political sponsors with blinkered or institution-focused unrealistic aspirational goals.

2.1.2. The formative phase (implementation ethics)

To make things happen at a practical level, there is a need to build and develop trust into a shared and enduring state of systemic trustworthiness (29, 30). This must apply across the infrastructures required to support data capture, record linkage, and maintain confidentiality and data security, as well as practices such as biobanking, data extraction storage, and interrogation. To build trust and trustworthiness, it is important not only to have a technically well-developed system but also to understand what matters to the people whose participation is crucial and to involve them from an early stage (12). In a wider engineering design context, the concept of Value-Sensitive Design has been developed with this in mind (31).

From the technical viewpoint, developers should ground trustworthiness on "quality" based on international evidence, guidelines, and recommendations. Quality is a process that runs throughout the development process from the early design phase. However, the quality and functioning of the technology are also dependent on effective adoption, and, again, a deliberative approach related to the system and context is needed to identify and apply ethical values (32). Since the adoption and effective use largely depend on context recognition, both the quality of technology and context recognition contribute to the design phase to implement an effective pHealth digital system (Figure 2).

2.1.3. The use phase (provision of service ethics)

A strong moral claim would be that the only personalized medicine worth having is that which is genuinely available to every person based on an evidence base that reflects their lived experience and their biology and treats them equally according to need. This is in the context of the change in health care delivery model from ring-fenced individuals to connected citizens, with identified family members and informal carers. Ensuring that both professionals and patient and carer users have adequate levels of e-literacy (33) for their respective roles in the particular system context is a specific aspect of ensuring that implementation and use are ethical.

3. The intersection between technology and personalized health goals

Personalization is the action of designing a good or a benefit to meet someone's individual requirements. When offering personalized care, the system needs to serve all citizens equally according to their needs. The ethical requirement is to meet these needs optimally and safely while allaying any anxieties and fears, optimizing the use of societal resources, and minimizing adverse effects on their familial and personal social context. This sets the framework for deliberation on the design and implementation approaches taken and sharing the rationale and justification. Herein lies the social responsibility of the doctor and other health professionals, and the requirement that patients acknowledge some sense of solidarity with others whose interests also need to be taken into account.

Personalization in a medical or health context is reflected in the concept of personalized medicine (PM) which seeks to make healthcare smarter and more efficient by integrating information from different sources. It is understood as "tailor-made prevention, diagnosis, and treatment for individuals or groups of individuals, enabling healthier and more productive lives" (34). Further, "The goal of personalized medicine is to optimize medical care and outcomes for each individual, resulting in an unprecedented customization of patient care" (35). PM is based on describing interventions that apart from the clinical patient profile, seek "biological information and biomarkers on the level of molecular disease pathways, genetics, proteomics, and metabolomics" (33, 36, 37), which is both promising and challenging.

Personalized medicine generally aspires that treatment will be directed to those patients who are more likely to receive benefits or not be harmed (37). Individually tailored therapies will result in higher possibilities in the field of disease prevention, improvement of survival rate, and extension of health span (38). However, "integration of personalized medicine into the clinical workflow requires overcoming several barriers in education, accessibility, regulation, and reimbursement" (35). Nevertheless, personalized medicine is a core principle of health optimization; it should mean that delivery is optimized to the needs of the patient and their immediate care team, thus maximizing uptake and effectiveness and minimizing carer disruption (12, 39).

3.1. Technological considerations

There are three element contexts for a pHealth service system:

- **Component** (such as input or output device, sensor, etc.),
- **Construct** of the components into a delivery system, and
- **Context** of service into which it is placed (treatment patterns, permitted reimbursed actions, etc.)

pHealth digital systems should implement technologies able to serve the needs of personalized health, for instance, offering personalized services, collecting personal health information, informing patients with personalized content, and enhancing communication. This may lead to a simplistic view in which the pHealth digital system is at the intersection of mHealth (mobile applications for personalized services), Internet of Health Things (IoHT, for data collection and/or therapy delivery), and telemedicine (to enhance communication). However, while personalization refers to a single 'patient', the real-world application of personalized interventions creates a layer of complexity, as described in Figure 3.

The individual patient is always the starting point of the process, and mHealth apps, IoHT devices, and other software tools are used to collect personal health-related or environment-related data (activity, diet, habits, geo-localization, etc.) and support the patient in managing their health status (e.g., drug alerts, warnings, physical activity alerts, diet suggestions, etc.) This represents the overall "Virtual PHI repository" (17), in which personal data are not limited to those generated when the individual is a "patient" but also when she/he is still healthy. Clinical data in the electronic health record (EHR) are part of personal data managed within healthcare information systems. However, the defined challenges cannot be managed simplistically at the data level but have to consider the real-world business system, actors' perspectives, contexts, experiences, skills, methodologies, languages, etc. (Figure 3), so the formalization and representation of the concepts and knowledge as described in the introductory paper (1) as well as in ISO 23903 (2, 40) is required.

Telecommunication and connectivity allow the subject to connect to all the relevant actors in the healthcare pathway, including caregivers, families, healthcare professionals, and reference communities such as patient associations. The same connectivity can be used to share data in a bi-directional fashion from the EHR to and from the patient. However, there are other actors in the picture. Data collected can have several "secondary" uses spanning from governance decision-making (e.g., drug surveillance and diagnostic appropriateness), to research, and also to the use of anonymous data in large, big data ecosystems for the possible use of artificial intelligence, cognitive computing, and machine learning. In the long run, the data generated and collected within a pHealth system will be relevant not only at the personal but also at the population level, in the light of "precision public health" (1). This complexity allows the transition from the simple definition of a

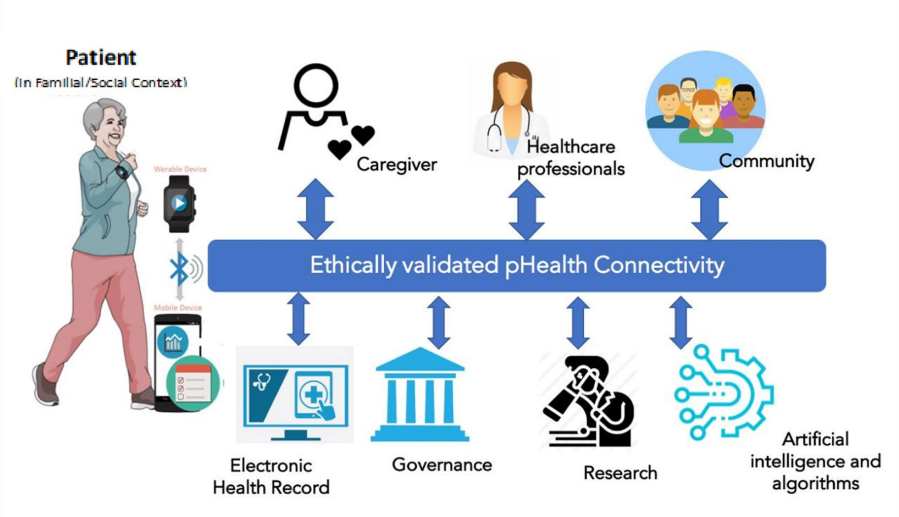

FIGURE 3
Actors, contexts, and technologies of a pHealth digital ecosystem.

pHealth digital system to a pHealth "ecosystem" (17), in which the common goal of all stakeholders is the patient. Solving this challenge requires the ontological representation of the business system and its domains involved, and this especially holds for policies and ethical challenges in transformed health ecosystems (41).

The broader ecosystem, with heterogeneous stakeholders, systems, services, technologies, and actors, generates ethical challenges that have to be considered as a set of "filters" to be applied to the data flow between the main actors and the pHealth digital ecosystem. Each activity and its data flow should be validated intrinsically when it is being set up. The new, pHealth-specific, ethical responsibilities are to ensure the appropriateness of each interconnection including relevance, necessity, consent, accuracy, and the ethical integrity of the whole system from the patient's viewpoint including what is shared and what is identifiable. To better understand this, the contexts in which the pHealth ecosystem acts need to be defined, and these are determined by the technical structure and the delivery processes it supports, as shown in Figure 3.

From the technical viewpoint, the core focus of ethics is ensuring quality in building pHealth digital systems and the necessity and controls of each component and interconnection. Given the complexity of the scenario (Figure 3), a pHealth digital system should consider several types of quality principles, including at least medical device quality (as defined, for instance, in the European Medical Device Regulation 2017/745 - EU MDR) (42), software quality [as defined, for instance, in the norms "Software as a Medical Device (SaMD): Key Definitions" (43) and "Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations"] (44), and data protection [General Data Protection Regulation EU 2016/679 (45) and Cybersecurity in Medical Devices: Quality System Considerations and Content FDA draft guidance 2022] (46).

As summarized in SaMD Possible Risk Categorization (44), after a system quality process is in place, it is reasonable to expect that:

- The system will perform its intended functions to meet its intended use, implying that the system responds to its requirements
- The system will be safe, so it will not create injury or damage to the users
- The system will provide a reasonable level of availability, reliability, and correct operation
- The system will be protected from cybersecurity intrusion and misuse and will ensure data protection.

3.2. Human context considerations

"The pHealth system covers the organization of people, institutions, and resources that deliver pHealth services meeting the health needs of individuals" (47). By definition, this takes pHealth into further ethical challenges, including the use and meaning of data on activities and relationships in addition to contextualizing personal biophysical and mental status data, as is considered below.

In the view of the WHO, ecosystem services are crucial for human well-being and health as they play an important role in the provision of basic services. "Changes in their flow affect livelihoods, income, local migration, and, on occasion, political conflict. The resultant impacts on economic and physical security, freedom, choice, and social relations have wide-ranging impacts on well-being and health" (48). Health initiatives should consider health determinants from outside and within the health system, meaning that contextual elements need to be considered when creating policies aiming to improve health (49). A key theme throughout this paper is the focus on the person, and populations, as the purpose for pHealth services but also as variable determinants of how services should be shaped, and thus meet ethical expectations.

4. The philosophy of personalization and the related ethical principles

4.1. Description of approaches to ethics

Ethics provide standards that underline our choices. It is concerned with "morality, deciding upon the right action and

making the right choices in situations which arise" (50). In the view of the World Health Organization "health ethics promote the consideration of values in the prioritization and justification of actions by health professionals, researchers, and policymakers that may impact the health and well-being of patients, families, and communities" (49). Its interdisciplinary scope includes a wide range of domains which include public health, health research, and clinical care (51).

Medical ethics refers to the interaction between the health practitioner and the patient in the scope of clinical care, and the most widely known approach as articulated by Beauchamp and Childress has four pillars - autonomy, no maleficence, beneficence, and justice (52, 53).

Public health ethics, by contrast, "apply to interactions between an agency or institution and a community or population" (53) and places in the center the principles such as population health maximization, interdependence, community trust, solidarity and reciprocity, autonomy, protection of the vulnerable, and justice (54–56).

Ethics of health research and innovation should be based on respect for persons, concern for individual well-being, and justice across the population (57). Espousing Responsible Research and Innovation (RRI) principles research in this field should address societal needs and challenges, engage a range of stakeholders to enable mutual learning, anticipate potential problems and assess alternatives, and provide guidance on ways to proceed (58).

"Health ethic frameworks provide for a systematic analysis and resolution of conflicts through the evidence-based application of general ethical principles, such as respect for personal autonomy, beneficence, justice, utility, and solidarity" (51). Such frameworks provide fundamental methods for ethical decision-making. At the simplest level, one can identify three potential theoretical frameworks which are based on different traditions of normative ethical theories:

The **consequentialist** framework represents a pragmatic approach; this places in the center potential directions of actions and considers those who will be directly and indirectly affected. The goal is to produce the most good.

A forward-looking ethical theory originating in the work of the 19th-century philosopher Jeremy Bentham, where moral actions are judged in terms of their consequences, and a good outcome is seen as one which promotes good and avoids harm most effectively for the greatest number (59).

The **Duty** framework reflects community rules and expectations; it centers its attention on the duties and obligations with the aim of performing the correct action.

A duty or deontological approach looks backward and bases moral evaluations on the extent to which an action conforms to duties and obligations. The moral agent is required to act in good conscience sometimes irrespective of the potential for bad consequences. This approach is epitomized by Immanuel Kant (60).

The **virtue** framework based on the identification of character traits defines ethical behavior as whatever a virtuous person would do in the situation to seek to develop similar virtues (61).

An approach where in a modern context the classical list of virtues is complemented by more contemporary interpretations including the possibility of specific professional virtues.

Ethical reflections should also govern the design, development, implementation, and use of health technology innovations. Recently, Vandemeulebroucke et al. (62) systematically identified several ethical approaches to Health Technology Innovation. Their inclusion here is not to say they are to be endorsed or promoted but rather to acknowledge their influence within the disciplines of bioethics and medical ethics.

The four **Principles of Biomedical Ethics**. As mentioned earlier, as formulated by Beauchamp and Childress (52), these comprise:

- "*Respect for autonomy*" which means supporting autonomous decisions but also in the choice of whether or not to use health technology innovations and share personal information (confidentiality),
- "*Beneficence*" relies on the fact that actions are good for others because they are good in themselves,
- "*Non-maleficence*" means avoiding harmful initiatives, and
- "*Justice*" is the guardian of fairness and equality.

A **Deliberative Democratic** approach puts at the center interaction, deliberation, and basic democratic principles. It is composed of three elements:

- *Wide Reflective Equilibrium (WRE)* whose main goal is "to produce insight into the moral principles and viewpoints that stakeholders use to make their moral judgment about Health Technology Innovations" (62).
- *Accountability for Reasonableness (A4R)* identifies four conditions that guarantee that WRE processes are deliberative democratic
    - publicity as a guardian of transparency,
    - relevance as the indicator of appropriateness and acceptability for the potential stakeholders to use Health Technology Innovations,
    - revisability which ensures that there are methods for improvement and corrections of the processes based on newly emerging evidence, and
    - enforcement which ensures that "all of the above criteria must be met during a WRE process" (62).
- *Interactive Technology Assessment (ITA)* iterating emergent results with the views of stakeholders to accommodate moral, ethical, or societal issues.

Religiously Inspired frameworks are the third group of ethical approaches identified by Vandemeulebroucke et al. (62), of which two specific ones are:

- *Personalist* approaches state that humans should be considered holistically as the reference value for ethical decisions, including those considered in Health Technology Innovations. This is expressed by four principles:
  - Defense of human physical life is characterized by the constant respect for human life at all levels of its existence
  - Safeguarding the therapeutic principle means ethical acceptance when all particular conditions are met
  - Freedom and responsibility refer to freedom of use and responsible use of HTI
  - Sociality and subsidiarity are based on mutual respect among users of HIT and societal "support to those who cannot meet their own needs without undermining the place of citizens' initiatives."
- *Islamic* approaches consist of five principles found in sacred sources such as the Quran, Sunnah of the Prophet, Ijtihad, and the Shariah:
  - Protection of faith
  - Protection of life
  - Protection of intellect
  - Protection of progeny
  - Protection of property

The eponymous **AREA** framework consists of four dimensions:

- Anticipate – a constant awareness of potential difficulties with the usage and application of HIT as well as preparedness to solve the potential problems with appropriate tools or strategies
- Reflect – the identification of challenges that arise from the usage of HIT in order to "identify in advance the motivations behind the products they develop or use and to identify the results they want to achieve."
- Engage – the involvement of all possible stakeholders whose actions are correlated with the HIT (and thus includes coproduction).
- Act – the active incorporation of the insights developed during the steps of Anticipation, Reflection, and Engagement.

The **Capabilities** approach puts human capabilities at the center. This approach developed by Nussbaum focuses on social justice and aims to show what it means for people to live a dignified life within a fair and just society (63). Dignity is considered within the context of everyday life at the family level, organization level, societal level, and national and global levels, with 10 components that can be summarized:

1. Life – being able to live meaningfully to the end of life.
2. Bodily health.
3. Bodily integrity (including freedom from assault or violence).
4. Senses – including imagination, thought, reason, and freedom of religious expression.
5. Emotions – to enable attachments to things and people.
6. Practical reason.
7. Affiliation – with and toward others and the social basis of self-respect.
8. Other species - concern and cohabitation for and with the world of nature.
9. Play - being able to laugh, play, and enjoy recreational activities.
10. Control over political and material environments.

These capabilities have been further considered and analyzed by several commentators with regard to assistive health technologies (64–66).

Care ethical approaches rely on the Care-Centered Framework which consists of five elements that might be used prospectively and retrospectively. There are five key elements that play a crucial role:

- The Context within which the innovation is used,
- Type of intervention for which the innovation was designed (e.g., treatment),
- Stakeholders who are playing the most significant role in the process of health policymaking,
- Type of health technology innovation which will be used, and
- Moral attitudes that are present in health policymaking.

Casuistic approaches claim that technological innovations in health can be assessed based on the context within which they will operate. They reject the concept of the universality of ethical frameworks. "How certain ethical principles and values were implemented in previous cases and contexts can at most indicate a certain direction for the evaluation of new HTIs" (62).

Eclectic approaches are combinations of the above-mentioned frameworks. Among them, there are two groups. The first one relies on ethical concepts extracted from various ethical theories; the second group draws from sociology and is mixed with ethical, bioethical, and philosophical elements.

This rich range of approaches gives the developer or policymaker the opportunity and the challenge of ensuring a balanced, open, and reasonable way forward in ensuring that pHealth developments have considered their ethical framework in a way relevant to their societal, healthcare, and infrastructure contexts. This is broadly analogous to the consideration of technical options as well where some contextual factors are already set, and the need is to design in the most effective and constructive way. Justification of optimum gains, proactively analyzing to ensure the avoidance of unintended adverse effects, and creating a positive outcome without collateral adverse effects is the prime duty of the policymakers and developers.

4.2. Practical assessment of ethics in pHealth

Ethics and ethical considerations branch from the identification of all the care delivery objectives and technical and contextual characteristics of the system. The health and well-being of the individual are the central focus of pHealth, with societal factors and optimum use of overall health system capabilities as related goals. As indicated throughout this paper, there is an ethical duty on developers, policymakers determining investment priorities and system

characteristics, and operational staff implementing systems and service delivery to consider in conjunction with professional and citizen users the ethical issues involved and achieve a balanced prioritization of principles in a defined and defensible way. These stakeholders should engage in a democratic process of conversation, exploration, explanation, adjustment, flexibility, and understanding of different points of view to clarify why and how they have come to their positions, which should enable a positive and unambiguous objective route forward, yet with sensitivity and flexibility to facilitate necessary later adjustments.

The assessment of the ethical implications of an ecosystem depends on using a reflective and informed balance of approaches (e.g., principles of biomedical ethics, deliberative democratic, religiously inspired, etc.); the selection of the most appropriate ones will largely depend on the identified contextual factors. However, both technical and contextual factors have to be taken into account. The approach based on the widely known "principles of biomedical ethics," if properly combined with the identified technological quality characteristics and the contextual factors, may be able to cover most of the views.

For example, the "respect of autonomy" is not ensured solely by the fact that the system works as intended, but it is crucial to consider other questions, including trust and usability – which are inter-related, and whether confidentiality and controlled sharing of key data meet the patient's wishes. Hence, the system might need to record the acceptance by the patient as to the care options underpinning pHealth actions, who are involved including informal carers, and who can see what information and who can contribute findings, as has been considered (67–71).

Another example relates to "non-maleficence": once a system is tested against any residual risk of harm to the patient and also in terms of cybersecurity and data protection, then it might be assumed that the system ensures the "non-maleficence" principle. However, other harms can arise if the perfectly functioning system yields the expected practical benefits to the patient, yet at the same time the patient now feels uncomfortable because the pathology now becomes evident – in effect, the patient feels stigmatized at the same time as being well-served practically.

5. Domains and contexts of personalized digital health

As pointed out by Blobel, "The pHealth system covers the organization of people, institutions, and resources that deliver pHealth services meeting the health needs of individuals" (47), while "The pHealth ecosystem describes the aforementioned system and the environment it interrelates with" (47). The WHO approach confirms the importance of health determinants from outside and within the health system (51). Understanding context is crucial to providing high-quality health services as it "reflects a set of characteristics and circumstances that consist of active and unique factors, within which the implementation is embedded" (49, 72), meaning that contextual elements need to be considered when creating and running pHealth systems and enabling policies, therefore recognition of contextual determinants is required while implementing Health Innovation Technologies to achieve pHealth. Contextual factors might be considered through the socio-cultural, structural (internal and external), international (extended to global), and situational factors as Leichter (73) proposed and Zdunek et al (49) modified. Contextual factors are also the starting point for key actions in the process of adaptation of digital solutions in health (Figure 2).

Socio-cultural factors relating to pHealth need to consider a wide array of issues. On the one side, societal attitudes toward digitalization have to be taken into account. These are influenced by various factors in historical and traditional views on health and well-being as well as healthcare. This is also related to tolerance and acceptance of newly emerging technologies and innovations in health in its broadest sense. The factor which will influence high or low levels of those elements is awareness. Knowledge about advantages and disadvantages related to pHealth might influence the development of an environment supportive of digital health. What is relevant here might include religion and its normative role in setting ethical and moral rules which define what is good and what is bad. The responsiveness to norms and values, which are grounded not only in religion but also in history and tradition, is expressed by the feasibility to adopt concepts of pHealth. Trust in new concepts, for instance, science, evidence, digital solutions, and policymakers will facilitate adaptation processes that enable digitalization by creating digital-friendly trends and fashions reflected in pro-digitalized lifestyles as a consequence of freedom of reasonable choice. E-literacy (33), trust in the safeguards within a proposed system, and belief in achievable benefits, as they apply at population, professional, and patient levels, will be strong factors.

Socio-cultural determinants in terms of pHealth include a wide array of factors, and societal attitudes towards digitalization have to be taken into account. They are influenced by

- History and traditional views on health issues
- Tolerance for and awareness of newly emerging technologies and innovation in health
- Religious aspects in terms of moral rules – defining what is good and what is bad
- Lifestyle – trends and fashions
- Level of freedom and independence, as well as the definition of freedom in the context of living
- Trust in science, evidence, policymakers, and digital solutions in health
- Family – relationships between family members, multigenerationality, and family carer involvement in the process of digitalized care/medicine
- Culture – norms, values, and symbols within the context of living
- Adaptation to change
- Fluent communication strategies
- Law
- Political ideology

Structural determinants (external)

- Political engagement and prioritization of digital health
- Policy preparedness for the introduction of newly emerging technologies and solutions
- The economic condition of the state and financial matters – reimbursement issues

Structural determinants (internal)

- Access to new technologies within the healthcare system
- Provision of health services and appropriate health infrastructure
- Skilled health workforce who will be able to design the process of implementation of new technologies
- Overall condition of the health care system and its preparedness for digitalization

International/global determinants of pHealth

- Connectivity
- Participation in the global institutional structures which are prompting new solutions in the scope of digital health and health innovations
- Culture of the use of evidence-based solutions emerging in other contexts
- Global evidence flow – exchange of information between agencies, structures, organizations, institutions, researchers, practitioners, and users
- Global long-standing processes such as environmental changes and climate change, which affect the paradigmatic shifts

Situational determinants of pHealth – unexpected events which can have their origin in:

- Global situational aspects – pandemic, war, etc.
- Behavioral situational aspects – failures of the digitalized health solutions which may discourage populations to use the innovation
- Procedural situational aspects – (un)favorable law
- Institutional situational aspects – initiatives performed at an institutional level, e.g., by regional organizations which might be facilitating or weakening the attitudes toward digital solutions.

These contextual factors may influence the values and approaches to ethical criteria, as analyzed in Section 4. In some situations, approaches may need to be modified to account for local belief systems, values, health system values, or technical infrastructures and priorities. In other cases, the strength of robustly designed digitization and personalization approaches may modify and improve some existing context restrictions.

Based on the recognition of the contextual factors, the trust level should be measured and assessed. Where it is observed that there is a high level of insecurity with the pHealth solutions, appropriate policies should be developed. The next stage is to access the population's ability and readiness for the introduction of pHealth mechanisms. At all stages, appropriate ethical frameworks should be taken into account. The frameworks should be chosen based on the importance of contextual determinants. Where religion, history, and tradition are of high importance, the religious-based frameworks might be of importance.

6. Ethics, evidence, monitoring, and evaluation

6.1. Making ethical service implementation decisions

To be ethical, pHealth systems must be grounded on empirical objective evidence since otherwise they would be aspirational or speculative as the patient care and the business investments would be unproven. The ethical imperative for evidence-based health informatics systems and decision-making has been clearly expressed (74, 75).

Unfortunately, the availability of objective evidence is less straightforward than it might be. A lot of information may come from vendors' or suppliers' promises rather than from independent evidence of proof in use. Secondly, pHealth is seldom a single system but rather a build-up of components to match local care delivery circumstances and informatics infrastructures. There is also frequently an aversion by policymakers and vendors to seeing their investments subjected to searching evaluation in case it leads to suggestions of sub-optimal products or poor policymaking (76).

The soundest decisions are made when each aspect is decided based on relevant objective evidence. However, pHealth is a progressive and fast-developing scientific and service domain, and therefore waiting for solely prior in-use evidence would create stasis. It is therefore essential to ensure ethical means are found for ensuring implementations are safe and ethical, while also enabling and encouraging carefully considered innovation and improvement.

Innovation in each of these in a service investment is not about research or experiment, where the outcomes are hypothesized but not proven, and for which research protocols, ethical approval, and participant consent are required. Rather, innovation is about delivering a service in a new and more modern way compared with systems based on already existing evidence. With such innovation and context changes come risks, which should be identified objectively and then managed ethically (77, 78).

In any national or local setting, there are likely to be new elements, which will cause 'known unknowns' within an overall grounded service development. These may be either new component technology, or they may be pHealth functioning seen to be effective elsewhere and which there is a valid desire to emulate. Without these innovative drives, no further progress would be made, yet these innovations create new assumptions and risks.

To seek to address this conundrum, there are policies and frameworks which can be applied where a form of acceptable, controlled, and grounded speculation is needed to justify innovation as being ethically sound even though it is beyond the foundation of past performance evidence. Notable among these is the Precautionary Principle, which has been espoused by the European Commission as a policy touchstone and provides safeguarding of the population by ensuring new risk is considered and appropriately mitigated; three other frameworks enable anticipatory objective formulations of expectations.

The **Precautionary Principle** of not letting new risks run unchecked has been very helpfully codified by the European Commission to apply to science-based innovation (79). Though sometimes erroneously portrayed as hampering innovation, this policy is intended to enable scientific progress without letting the population be exposed to unquantified risk. It requires risks of an as yet unvalidated innovation to be assessed and mitigated through controls based on six rules:

Controls should be

- proportional to the chosen level of protection
- non-discriminatory in their application
- consistent with similar measures already taken

- based on an examination of the potential benefits and costs of action or lack of action (including, where appropriate and feasible, an economic cost/benefit analysis)
- subject to review, in the light of new scientific data
- capable of assigning responsibility for producing more scientific evidence

Noteworthy is that this is part of a hierarchy of deepening evidence gathering, and the possible risk from the innovation must be weighed up alongside the cost of inaction on that innovation.

Then, of the three anticipatory methods:

Transferability relates to whether something which works in one health system or population setting will work identically in another. The components are not new, but the hypothesis that they will work in the same way in a different operational and service setting cannot be assumed, and indeed major challenges and risks may occur, ranging from data feeds to societal acceptance. The Population, Intervention, Environment, and Transfer (PIET) model shows how to assess these four domains (80).

Update Equivalence is whether updated components or different inter-relationships of components will operate as planned based on previous versions. This is a significant conundrum in many fields including pharmaceuticals, medical devices, and even aviation (81). Both the new material or component and its interaction both with its embedded system and with users must be objectively considered, planned benefits scrutinized, and possible unanticipated effects considered and either ruled out or guarded against.

Evidence Synthesis is the technique whereby evidence obtained in one setting is reviewed to identify the dependence on context and the influence of specific aspects, so as to enable a reasoned hypothesis of potential performance and outcomes in a new setting or with a new component (82).

6.2. Monitoring

No system, technology, or skilled team is likely to run exactly to expectations when first instigated. This makes it important to put in place monitoring arrangements, which may be close and frequent examination in the early days to identify any teething problems or failures to meet specifications or acceptance. Even when a system has run according to plan from the outset, it is important to continue regular monitoring as equipment or its use can deteriorate, staff start to work less rigorously, or new staff may not be trained to the initial standard. However, monitoring is not just about finding problems though this is important; monitoring may also find unexpected improvements, for instance, as staff becomes more proficient and users increasingly accept the innovations or other benefits such as better service outcomes.

Monitoring should relate to the three stages identified in Figure 2, namely, objectives, design, and use, while the area to be monitored should match the technology and interest areas of Figure 3. The metrics used should relate to the business plan and clinical protocols which should be at the core of any pHealth or other clinical system.

The Donabedian triptych of Structure, Process, and Outcome forms a useful framework (83, 84). The structure includes technical equipment, infrastructure, and allocated staff establishment, and monitoring will show if the intended pattern and levels continue to be present. The process will include the patient flow and key points of pHealth interactions, but it should also include equipment availability and response times, as well as whether responses were compromised by additional use or competing traffic. The outcome should include costs and numbers treated compared with the business plan, clinical outcomes against expectations, and user acceptance and satisfaction. Again, target values should have been set in the business and implementation plans.

6.3. Evaluation

While monitoring is focused on how the implementation is working in real life, Evaluation is a more holistic appraisal, often run by an expert third party (74, 75, 85). Evaluation requires systematically examining each aspect of the design and running of a system, and the International Medical Informatics Association has endorsed both a methodology (86) and a standard for reporting such studies (87), which itself has been accepted by the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) system (88). Conducting evaluation studies is important to underpin the claims of the technological support sector and provide the body of evidence needed for informed policymaking. Analyses have been carried out on the volume and focus of past evaluation studies (89, 90) and on the need for a systematic forward view (91). pHealth, as a newer and key informatics application area bringing personalization to patients through digital processes, needs to demonstrate its commitment to expanding its evidence base by means of evaluation studies so as to progress in this important discipline (92).

6.4. No blame reporting

Another key aspect of an ethical implementation is that any person using the system should be able to report any problem or apparent fault or error that they perceive. The obvious objective is to ensure that risks or faults are corrected and is similar in principle to reporting other areas of health care such as medication errors. While IT systems can indeed have faults that need reporting, which can include failure to display past results when relevant, correctly functioning informatics applications including pHealth can have aspects that users do not fully understand – either because they are not intuitive to users (clinical or lay) or because staff have not been adequately trained or do not have access to relevant documentation. This is particularly important with the inclusion of AI given its invisibility of origin and process. Thus, no-blame reporting is an effective means of identifying and rectifying these softer areas aspects of user-perceived or user-believed problems as well as technical problems, ensuring that systems are trusted and therefore optimally used.

7. Conclusion

Personalized digitally supported health is the ideal of health care philosophy and purpose but has ethical challenges along the way

caused by the concepts, novelty, and need for a wide range of new care delivery approaches to achieve effective personalization, while at the same time using varied and innovative technologies. The road to pHealth is paved with good intentions, but there are pitfalls on the route.

By its nature, pHealth has the potential to create suspicion and negativity if perceptions of black-box thinking, system determination of treatments and actions, and domination by impersonal technology are allowed to take hold. Therefore, to achieve their goal, pHealth system creators must engage with ethics at all stages of design, build, and operation in a number of ways – adherence to established ethical principles, openness and inclusivity with stakeholders, and concurrent review and evaluation; moreover, these must be related to societal and system contexts.

Taking a proactive open approach to ethical commitment and methodology is not only morally right but will be rewarded with an aura of trust and of person-centered philosophy which will strengthen the general appeal of pHealth.

The 5P medicine methodology and the related ISO 23903 standard are designed to address this. This paper has sought not only to argue the case but also to outline the range of methods available to be selected and used according to the service area, system type, and context of service delivery.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Author contributions

MR assembled the author team, facilitated virtual panel discussions, and acted as facilitator and integrating editor. All authors contributed material from their own dimension and expertise, equally responded to ongoing revisions, and agreed the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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