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Ecosystems-centered health and care innovation

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Ecosystems-centered health and care innovation

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Editorial: Ecosystems-centered health and care innovation

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Editorial on the Research Topic
Ecosystems-centered health and care innovation

Introduction

The rapid evolution of healthcare technologies has reshaped the way services are delivered, regulated, and perceived by stakeholders. From semantic interoperability in electronic health records to cloud-based regulatory platforms and precision medicine, these innovations aim to optimize outcomes for patients and providers alike. However, they also present challenges—ranging from ethical dilemmas to implementation barriers—that must be addressed to realize their full potential.

This editorial integrates findings from ten influential studies that explore various facets of healthcare innovation, offering a comprehensive view of the advancements and challenges in the field. These studies reflect the dynamic interplay of technology, ethics, policy, and patient-centric design in creating resilient and sustainable healthcare systems.

Semantic interoperability and data integration

The work of Bossenko et al. emphasizes the foundational role of semantic interoperability in enabling efficient healthcare delivery and secondary data use. Tools developed for transforming health data formats, such as the transition from CDA to FHIR in Estonia, exemplify the potential of reusable, domain-expert-friendly solutions to address interoperability challenges. Similarly, Bregonzio et al.'s work on FAIRification and data fusion within distributed analytics platforms highlights the importance of creating scalable, reusable, and interoperable data infrastructures. Together, these contributions underline the significance of harmonized data frameworks in driving global healthcare innovation.

Ethical considerations in precision medicine

Ahmed et al. systematic review examines ethical concerns surrounding precision medicine, emphasizing the patient perspective. Key themes include privacy, economic impacts, informed consent, and the risk of discrimination. Addressing these ethical

issues requires proactive patient education, research, and policy reforms to build trust and mitigate risks. These findings complement the recommendations by Kurihara et al., who advocates for a data-driven, participant-centered approach in research ethics, reinforcing the value of dynamic consent, and open science practices in fostering inclusivity and transparency.

Regulatory and ecosystemic approaches

Khalil et al.'s exploration of cloud-based regulatory platforms underscores their potential to revolutionize drug development by expediting the review process and enhancing global accessibility. However, realizing this potential requires concerted policy efforts and technological readiness. Sturmberg et al.'s critique of reductionist research methodologies highlights the need for ecosystemic approaches to clinical decision-making, emphasizing the integration of complex, multi-level health determinants.

Innovative solutions for aging and dementia care

Figueiredo et al.'s work on Living Labs showcases the value of end-user engagement in designing dementia care solutions. By addressing challenges such as sustainability and scalability, her proposed guidelines aim to maximize the impact of these collaborative innovation methods. Carriazo et al.'s analysis of the Andalusian digital health strategies further illustrates the power of Quadruple Helix collaboration in driving health improvements through ecosystemic approaches.

The European Health Data Space and global health implications

Laleci Erturkmen et al. and Katehakis et al. focus on the European Health Data Space (EHDS) initiative and the smartHEALTH European Digital Innovation Hub, respectively. Their work underscores the importance of harmonized data standards and interdisciplinary collaboration in advancing precision medicine and AI-driven healthcare services. These initiatives highlight the potential of unified data ecosystems to enhance global clinical research and improve patient outcomes.

Conclusion

The synthesis of these studies reveals a shared vision for the future of healthcare: one that leverages technology and innovation to improve patient outcomes, empower stakeholders, and address ethical and systemic challenges. Achieving this vision requires a collaborative, interdisciplinary approach, integrating the principles of semantic interoperability, precision medicine, and ecosystemic innovation. By prioritizing ethical considerations and fostering global partnerships, the healthcare community can ensure a sustainable and equitable future for all.

Author contributions

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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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Patients' perspectives related to ethical issues and risks in precision medicine: a systematic review

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Background: Precision medicine is growing due to technological advancements including next generation sequencing techniques and artificial intelligence. However, with the application of precision medicine many ethical and potential risks may emerge. Although, its benefits and potential harms are relevantly known to professional societies and practitioners, patients' attitudes toward these potential ethical risks are not well-known. The aim of this systematic review was to focus on patients' perspective on ethics and risks that may rise with the application of precision medicine.

Methods: A systematic search was conducted on 4/1/2023 in the database of PubMed, for the period 1/1/2012 to 4/1/2023 identifying 914 articles. After initial screening, only 50 articles were found to be relevant. From these 50 articles, 24 articles were included in this systematic review, 2 articles were excluded as not in English language, 1 was a review, and 23 articles did not include enough relevant qualitative data regarding our research question to be included. All full texts were evaluated following PRISMA guidelines for reporting systematic reviews following the Joanna Briggs Institute criteria.

Results: There were eight main themes emerging from the point of view of the patients regarding ethical concerns and risks of precision medicine: privacy and security of patient data, economic impact on the patients, possible harms of precision medicine including psychosocial harms, risk for discrimination of certain groups, risks in the process of acquiring informed consent, mistrust in the provider and in medical research, issues with the diagnostic accuracy of precision medicine and changes in the doctor-patient relationship.

Conclusion: Ethical issues and potential risks are important for patients in relation to the applications of precision medicine and need to be addressed with patient education, dedicated research and official policies. Further research is needed for validation of the results and awareness of these findings can guide clinicians to understand and address patients concerns in clinical praxis.

KEYWORDS

patients' perspective, patients' attitude, ethics, precision medicine, personalized medicine

Introduction

Precision medicine, often used interchangeably with the term personalized medicine, is a recently introduced approach to medical care, aiming to provide individualized treatment to patients based on their unique characteristics, including their genes, environment, and lifestyle. This approach has the potential to revolutionize healthcare, with implications across a wide range of medical specialties using different tools including bioinformatics, big data analysis and artificial intelligence/machine learning.

Precision medicine has clinical applications in different medical fields and specialties. Oncology is on the frontier of precision medicine leading to the development of targeted therapies that can selectively kill cancer cells based on their genetic/molecular aberrations (1). In Cardiology, precision medicine has the potential to improve risk stratification and identify patients who are at high risk of developing cardiovascular disease and apply to reduce their risk (2). Even in Psychiatry, precision medicine has the potential to improve the diagnosis and treatment of mental illnesses. For example, in the treatment of depression, genetic testing can identify patients who are likely to respond to specific antidepressants thus reducing the risk of side effects and improving treatment outcomes (3).

Despite the rapid advances, and the obvious prospect of immediate and future applicability of precision medicine in day to day care, important ethical and social issues should be carefully considered and ultimately addressed, to ensure that the benefits of this approach are equitably distributed and that patient rights are protected (4).

Several matters relating to ethical issues and risks in precision medicine are widely known. To start with, concerns have been raised regarding the privacy and security of big data including genetic data, particularly in the context of commercial genetic testing services (5). Commercial genetic testing companies collect large amounts of genetic information from individuals, which can include not only information about an individual's own personal and health data but also information about their relatives. The possibility of this data being misused or mishandled may be significant, with unprecedented consequences for the involved individuals.

In addition, precision medicine has increasing costs, as it often involves advanced diagnostic tests and targeted therapies (5). Thus, some patients may worry about the cost of these treatments and whether they will be covered by insurance. The cost concerns are related also to the risk for unequal access to precision medicine, particularly for marginalized communities who may not have access to genetic testing or targeted therapies. In those cases, the cost of precision medicine may disproportionately affect those who are already disadvantaged, which will lead of widening the gap between less economically developed countries and more economically developed countries. Moreover, the issue of unequal access to precision medicine is not limited to the developing world. Within developed countries, there are also disparities in healthcare access based on factors such as race, ethnicity, and socio-economic status. This means that even if precision medicine becomes more widely available, certain groups may still be left behind (6).

Other ethical issues include challenges in the informed consent process, the potential for stigmatization or discrimination based on genetic information as well as psychological impact and anxiety due to incidental findings (7).

It is important to point out that although the perspectives of patients on precision medicine might overlap with those of doctors, there might be important differences in priorities, concerns, and levels of understanding (7). Understanding the patient's perspective is crucial for ensuring that precision medicine is implemented in an ethical and responsible way and will provide guidance to healthcare professionals and policymakers to address these potential risks and ethical considerations. Although there are studies in specific populations and stakeholders' opinions (7), to our knowledge, there is no systematic review on the patients' perspectives on risks and ethical issues on the implementation of personalization of medicine.

Therefore, the aim of this systematic review was to provide a comprehensive overview and analysis of the perspectives of patients regarding ethical and related issues in precision medicine. This is the first systematic review to focus only on the patients' perspectives in this area.

Materials and methods

This systematic review was based on the Preferred Reporting Items for Systematic reviews and Meta-Analysis statement (PRISMA) guidelines (8).

Data sources and searches

The search of the medical literature was conducted in PubMed and was restricted to the last 10 years, including the timeline of 1/1/2012 to 1/1/2023. The research timeframe was chosen considering that although precision medicine applications were evident before, precision medicine expanded greatly in knowledge and applications in the last several years. In addition, previously, different terms were used to describe individualization of therapy, and in the last 10 years, the conceptualization of precision medicine became clearer with the preferred term shifting from personalized medicine to precision medicine (9). Published articles from, January 1st 2012 to January 1st 2023, were collected using a standard search strategy Search query: (((((((quantitative study) OR qualitative study) OR participant observation) OR focus group) OR interview) OR survey) OR questionnaire) OR patients perspective) AND ((((precision medicine[Title]) OR personalized medicine[Title]) OR personalized medicine[Title]) OR genomic medicine[Title])).

Study selection

Inclusion criteria included published articles examining the attitudes or views or perspectives of patients toward precision medicine, articles examining patients' and at the same time the

public's perspective and articles investigating parents' perspective regarding their children on precision medicine. Exclusion criteria included articles investigating the perspectives or views of the public without the participation of patients. Only articles in the English language were included. Further restrictions were applied to the selected articles based the sections of the PRISMA 2009 checklist (10). However, no further exclusion criteria regarding the sample size, ethnicity, age, and gender were applied.

Data extraction, quality assessment, and analysis

A systematic search was conducted exclusively in the PubMed database, resulting in the identification of 914 articles based on the search query. Four ($n = 4$) articles were excluded as duplicates, resulting in 910 articles for further screening. The search query included the terms "Personalized medicine" to ensure comprehensive coverage of precision medicine-related literature since it is often used interchangeably. However, this broad search approach led to the inclusion of numerous irrelevant articles with "Personalized medicine" in their titles, after carefully screening of the titles and abstracts. The abstracts of the 910 articles, were screened for relevance by two independent authors. The screening of the abstracts, after application of inclusion and exclusion criteria, resulted in only fifty ($n = 50$) eligible articles to be further assessed in full text. Subsequently, two ($n = 2$) articles were excluded as they were not written in English and one ($n = 1$) article was identified as a review article (7), thus was excluded. However, all the references of the identified review article were also checked for eligibility. Full texts of the fifty articles underwent a subsequent quality assessment and assessment by two independent authors. From those fifty articles, only twenty-four ($n = 24$) were included in the analysis due to the availability of sufficient data on the topic. Articles that solely presented public opinion, expert opinion or lacked information on the risks or potential harms of precision medicine were excluded. The twenty-three excluded articles ($n = 23$) were evaluated as being out of the scope of this systematic review, since they did not include a sufficient quantitative or qualitative report of the participants on the subject. Finally, bias assessment of the individual studies was performed using the Joanna Briggs Institute (JBI) critical appraisal tool for analytical cross sectional, case control and case report studies, where applicable (11). Studies with fewer than five positive scores were excluded. The assessment is presented as Supplementary material. Thus, finally, 24 studies that report on the patients' perspectives regarding possible ethical concerns of precision medicine were included. Figure 1 shows the flowchart describing the inclusion/exclusion process. After study selection, the following data were extracted from full-text articles: eligibility criteria, study source and year, study design, country, sample size, age, gender and disease type.

All included studies were thematically analyzed for identifying themes related to ethical concerns and risks in precision medicine. The thematic analysis was performed on the relevant patients' opinion/perspectives regarding our question's topic. Data were retrieved from each study and classified through thematic analysis first in subthemes and subsequently into the different themes.

Results

Studies characteristics

The overall population sample size of the studies ($n = 24$) was 7,082 participants. These included 6,101 patients and 981 parents of patients. The majority of the studies included, were conducted in the USA ($n = 17$), while the other studies were conducted in Canada, England, Western Switzerland, France, Jordan, and Australia. The patients had been treated under diverse specialties such as Oncology, Rheumatology, Nephrology, Gastroenterology, Pulmonology and Primary Care, and had received a variety of services including genetic testing and pharmacogenetic. From the 24 studies, there were 7 studies of Primary Care patients, 5 studies of Oncology patients, 2 studies of Gastroenterology patients, 2 studies of Rheumatology patients, 1 study of Pulmonology and finally 1 study of Nephrology patients. Studies included are presented in Table 1.

Patients' perspectives on ethics and potential risks regarding precision medicine

Through thematic analysis of the included studies, several ethical concerns and potential risks were identified and classified into eight main categories: privacy and security, economic impact, discrimination, informed consent, diagnostic accuracy, harms of precision medicine, mistrust in research and finally doctor-patient relationship. For detailed presentation of the themes per study please see Table 2.

The most common theme identified was privacy and data security. Patients from a total of sixteen ($n = 16$) studies expressed worries regarding data security, confidentiality, reidentification, data management flow, data invasion by unauthorized parties (5, 12, 14–17, 20, 22, 23, 26, 28, 29, 31–33).

The second most common theme was the economic impact from the application of precision medicine, either the cost of the services of precision medicine or its impact by losing insurability. The economic impact was expressed in twelve ($n = 12$) studies, with six ($n = 6$) studies reporting on the cost of precision medicine (6, 13, 18, 20, 22, 30) and four ($n = 4$) studies reporting on the patients' concerns on losing illegibility for insurability (5, 13, 18, 27). In two studies, patients expressed their concern regarding the insurance coverage of tests of precision medicine (5, 23) whereas in two ($n = 2$) studies they reported their willingness to pay out of their own pocket for precision medicine applications (15, 21). Lastly, one (1) study in particular shows patients worry regarding the loss of their job due to precision medicine (27).

The third most common theme identified in nine ($n = 9$) studies was the possible harms of precision medicine including four ($n = 4$) studies reporting anxiety (16, 21, 22, 32), three ($n = 3$) studies reporting possible psychosocial harm (13, 27, 28), one study ($n = 1$) reported the risk of unexpected paternity, and not taking care of yourself due to your genes (16), as well as the risk of extra burden due to extra testing; and finally one (n=1) study expressed a fear of human cloning (31).

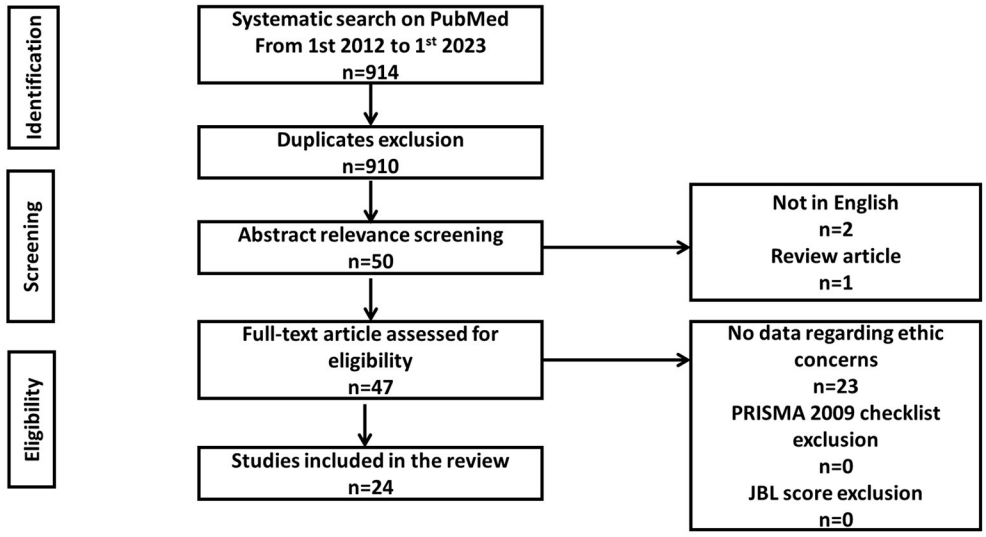

FIGURE 1
Flowchart for the exclusion criteria of the peer/reviewed papers.

In five ($n = 5$) studies, patients reported concerns regarding discrimination due to their ethnic background (5, 6, 13, 16, 33). In particular, it was expressed that these concerns emerged from the historical mistreatment of certain races by medical professionals (33).

Another theme emerging from four ($n = 4$) studies was the concern regarding the process of informed consent and the usage of their data including their genetic information without the patients' consent (6, 14, 17, 26).

Furthermore, patients' confidence in their healthcare provider and trust in biomedical and medical research were significant factors that caused concern. This theme of mistrust in research was identified in four studies with the references (19, 20, 26, 33).

The seventh identified theme in three studies ($n = 3$) were the patients' concerns regarding the diagnostic accuracy of precision medicine. An example is recently developed tests such as next generation sequencing (13, 15, 17), while in one ($n = 1$) study, patients reported concerns about trusting and putting faith in the technology used (22).

Finally, there were concerns of the patients regarding the development of precision medicine leading to an impact on the doctor-patient relationship as they may rely more on the technology rather than on person follow ups (24).

Perspectives of precision medicine among parents of patients

Among the studies three ($n = 3$) of the studies included reported on the parents' perspective ($n = 981$). The themes identified in these studies include concerns regarding economic impact of precision medicine such as cost of the tests of precision medicine (22, 30), re-identification and privacy risks for their children (31), the fear of losing their role in decision making as a result of using precision medicine tools with concerns regarding the quality and their faith in technology (22).

Risk/benefits relationships of Precision Medicine approaches

Information on patients' perspectives on risk/benefits relationships of Precision Medicine approaches was lacking from the great majority of the studies included, and was only mentioned in three studies stating that from the patients' perspectives potential benefits overweigh the possible risks (5, 25, 33).

Discussion

In this systematic review, we investigated the patients' perspectives toward the ethical issues and risks of precision medicine after screening 914 journal articles and finally including 24 articles. To our knowledge, this is the first systematic review that examines the perspectives of patients, identifying very few articles explicitly investigating the patients views toward the potential risks of precision medicine. The results of this review extend the current understanding of the application of precision medicine and the perspectives of patients regarding ethics and potential risks.

The most common theme identified was the patients' concern regarding privacy, confidentiality and security. Not surprisingly, privacy breach concerns were expressed between several different ethnic groups even though we live in an era where most of our life information is available online. While concerns regarding the security and privacy of the personal data were the most common, it should be taken into consideration that this could represent a bias due to the increasing attention on privacy issues, due to increased public awareness on the privacy of genetic data in particular, and the lack of extensive exploration of other ethical risks that precision

TABLE 1 Studies included on patients' perspectives ($n = 7,082$) related to ethical issues and risks in precision medicine.

Studies	Study type	Sample type and size	Participants age	Type of patients	Type of PM	Country
Hassan et al. (12)	Qualitative	16 patients	16–18 & +18	Patients of the sheffield genetics service	Genomic medicine services	England
Gray et al. (13)	Qualitative	111 patients	32–86	Lung, breast, colorectal cancer	Somatic genetic testing	USA
Kraft et al. (14)	Qualitative	122 patients	20–95	Multiple specialty group practice	Not specified	USA
Issa et al. (15)	Quantitative	300 patients	18+	Breast and colorectal cancer	genomic diagnostics	USA
Woodbury et al. (16)	Qualitative	21 patients	Adult patients	Primary care	Not specified	USA
Beans et al. (17)	Qualitative	21 patients	Adult patients	Primary care	Not specified	USA
Ruel-Gagné et al. (18)	Quantitative	277 patients	50–65	Rheumatoid arthritis	Not specified	Canada
Chakravarthy et al. (19)	Quantitative	3847 patients	Adults	Academic medical centers, community-based hospitals, traditional outpatient clinics and federally qualified health centers	Not specified	USA
Williams et al. (20)	Quantitative	252 patients	Mean age 51.47	Primary care	Not specified	USA
Subasri et al. (21)	Qualitative	18 patients	35–84	Inflammatory bowel disease, gastrointestinal-related cancers	Pharmacogenomics,	USA
Sisk et al. (22)	Mixed method approach	804 parents of patients	Mean age 38.9	Pediatric Healthcare	Artificial Intelligence	USA
Schroll et al. (23)	Quantitative survey	252 patients	>21	Lung, Breast, Ovarian, Prostate, Bladder cancer	Not specified	USA
Puryear et al. (5)	Mixed method approach	100 patients	18+	Primary care	Not specified	USA
Perlman et al. (5)	Qualitative	34 patients	≥18	Syringe exchange program & HIV clinic	Genetic Testing and Genomic Medicine	USA
Boyer et al. (24)	Mixed method approach	10 patients	35–70	Primary care	Not specified	western Switzerland
Choukour et al. (25)	Qualitative	12 patients	average age 39.3	IBD patients	Not specified	France
Knoppers et al. (26)	Qualitative	22 patients	Adult patients	Cystic fibrosis	Not specified	Canada
Khdair et al. (27)	Quantitative	254 patients	18–70	Food and drug allergy. Hay-fever, asthma, eczema or urticaria. T1D, SLE, RA, MS, Psoriasis and Hashimoto	Not specified	Jordan
Hyams et al. (28)	Mixed-methods approach	17 patients	Mean 71.5 cases+69.7 control	Cancer	Genetic	USA
Cooke Bailey et al. (29)	Quantitative	103 patients	average 61.45	Chronic kidney disease	Not specified	USA
De Abreu Lourenco et al. (30)	Quantitative	130 parents of patients	25–74	Childhood cancer survivors	genomic medicine	Australian
Norstad et al. (31)	Mixed-methods approach	pediatric $n = 32$ and prenatal families $n = 15$	not indicated	Neurocognitive presentations or multiple congenital anomalies and pregnant women with undiagnosed fetal anomalies	exosome sequencing	USA
Lee et al. (14)	Qualitative	122 patients	20–95	Primary care	Not specified	USA
Diaz et al. (6)	Quantitative	190 patients	≥18 years	Primary care	Not specified	USA

TABLE 2 Identified Themes and subthemes of ethical issues and risks in precision medicine.

Theme	Subthemes	Studies
Privacy and security	Confidentiality	4, 5, 8, 10, 12, 13, 14, 17, 19, 22, 23
	Data sharing	1, 14, 20
	Management flow	1, 3, 5, 13, 14, 22
	Data security	1, 5, 11, 14
Economic impact	Cost	2, 6, 8, 10, 21, 24
	Loss of insurability	2, 6, 12, 18
	Loss of job	18
	Willingness to pay	4, 9
	Insurance coverage	11, 12
Discrimination		2, 3, 5, 12, 24
Informed consent		14, 17, 23, 24
Diagnostic accuracy	Accuracy of new developed tests	2, 4, 14
	Faith in technology	10
Harms of PM	Psychosocial harm	2, 18, 19
	Unexpected paternity	5
	Not taking care of yourself knowing your gene	5
	Human cloning	23
	Anxiety	8, 12, 14, 16
Mistrust in research	Trust in Provider	8
	Trust in Biomedical research	3, 7
	Trust in medical research	17
Doctor patient relationship		15

Hassan et al. (12); Gray et al. (13); Kraft et al. (14); Issa et al. (15); Woodbury et al. (16); Ruel-Gagné et al. (18); Chakravarthy et al. (19); Williams et al. (20); Subasri et al. (21); Sisk et al. (22); Schroll et al. (23); Puryear et al. (5); Beans et al. (17); Perlman et al. (5); Boyer et al. (24); Choukour et al. (25); Knoppers et al. (26); Khdair et al. (27); Hyams et al. (28); Hyams et al. (28); De Abreu Lourenco et al. (30); Norstad et al. (31); Lee et al. (14); Diaz et al. (6).

medicine introduces (34). As precision medicine involves many types of data beyond genetic, privacy and confidentiality present an immense challenge and a major point of concern. In particular, personal data can be potentially used for commercial exploitation, as well as used as evidence against eligibility for insurance coverage or employment. Furthermore, patients that reported substance abuse, expressed concerns that their data could be potentially used to retract unsolved crimes and hence were reluctant to participate in precision medicine research programs (32). Interestingly, one of the studies demonstrated that the younger individuals are not so much concerned about privacy breach of their data but they were concerned about data accessibility (12). Finally, our study found that a portion of the patients are in favor of sharing their genomic data in a wider range but, as previously mentioned, this could be a subject of potential participation bias (12, 17, 29).

The second most common concern expressed by the patients was the economic impact of precision medicine which included the actual cost of the medical treatments and implications on insurance. The actual cost of the medical tests and its coverage by insurance companies as well as the loss of insurability due to having a genetic condition is a justified worry, which has led to the implementation of a new Law in the US called GINA which stands for Genetic Information Nondiscrimination Act (35). Other implications of the economic impact include insurance eligibility that might be jeopardized by findings of precision medicine and their ability to get employed (5, 13, 18, 27).

The theme regarding the possible harms of precision medicine included psychosocial harms and the need for genetic counseling. In particular, the potential increase in the number of diagnostic scans performed, can have a detrimental psychological impact on a patient that is already in distress where in extreme cases this psychological distress may lead to poorer prognosis (36). Research has shown that patients who undergo genetic testing and receive results indicating an increased risk for certain diseases may experience psychological distress and anxiety (34). This distress can have a negative impact on the patients' quality of life, as well as their ability to adhere to treatment and engage in healthy behaviors (35). Other more specific concerns include unexpected paternity and human cloning (14, 16). Finally, worrying about possible harms of precision medicine including "not taking care of yourself" while knowing your genes, is an issue that could improve through education. Especially regarding multifactorial diseases that can be influenced by genetics, epigenetics, environmental and lifestyle factors.

It is also essential to address concerns about unequal access to precision medicine and to ensure that patients from all backgrounds have access to these innovative treatments. From the patients' perspectives, concerns were raised regarding racial discrimination and the fear that their genes can be used against them. In particular, certain ethnic groups expressed mistrust that originated from historical evidence including the 1932 so called Tuskegee Syphilis Study which was a study that violated basic principles of bioethics that are autonomy, non-maleficence and injustice (33, 37).

There are several aspects regarding the patients' concerns on the process of informed consent. Firstly, patients expressed their worry about sharing their genetic information, through the usage of biospecimens especially genes and DNA, and possible future uses without their consent (6). In fact, hesitation on participating in genetic testing was evident, when the purpose of the genetic study was not clear, especially when patients were not fully informed of future uses without their consent (32). In addition, clear communication and the use of simple language on the consent form is important especially in clinical trials (26). However, patients' views can also vary, as some patients did not acknowledge the need of a different consent for their biospecimen for future research (14). Thus, the process of informed consent with clear communication following ethical guidelines, is critical to ensure that participants fully understand and consent to their involvement in research (36, 37).

Important concerns regarding trust in research were identified, especially when considering the origin of the studies and the ethnic

background of the patients. In a study from Canada, patients showed trust to the researcher, with no hesitation to participate (26), in contrast to a study from the USA, in which Latinos showed mistrust in research mainly due to the unfamiliarity to the healthcare system (14). Similarly, other studies reported this diversity regarding trust in research influenced by the ethnic background of the patient (21, 38).

Concerns on diagnostic accuracy of newly developed genetic testing methods such as full genome sequencing were reported (11, 23). It seems that participants acknowledge the large quantity of possible uncertain results can lead to psychological distress and anxiety in patients, and a loss of trust in the medical system (17). In fact, a previous study supports these concerns, demonstrating how direct-to-consumer testing may be misleading when it comes to testing for familial hypercholesterolemia (39).

The implementation of precision medicine besides requiring the efficient collection and secure storage of huge amounts of data, also requires technological evolvement by means of Artificial Intelligence (AI) algorithms to process them. Regarding this technological evolvement, the patients' attitude is largely negative due to the fact that it could potentially deteriorate patient-doctor relationships as medical experts may rely more on the algorithms to predict outcomes in an effort to increase efficiency at the cost of their expertise.

Regarding, the unique group, including parents of patients (they were considered in the study as they are considered as a proxy for decision making on their children), concerns were expressed that these algorithms might have a negative effect on their decision making regarding their children's health and that this could eventually result in confusion and conflicts with medical experts. In contrast, their faith in technology was viewed as a positive attitude expressing their openness regarding AI.

It is important to mention that although a full analysis on risk/benefit relationships of precision medicine was not possible due to lack of data from the great majority of the original studies, the few studies reporting such data, supported the view that potential benefits overweigh the possible risks.

This study has many strengths. First, to our knowledge, it is the first systematic review that examines the perspectives of patients on ethics and potential risks related to the use of precision medicine. Second, the use of broad initial search criteria resulting in 914 possible articles, ensures that all the relevant literature was screened for inclusion. Moreover, the use of PRISMA guidelines for conducting a systematic review and the fact that all the steps of this study were made by two independent reviewers, reduces errors and possible biases. Some limitations of the present study should also be mentioned. First, the literature search was conducted in PubMed and in the English language only, thus possible bias cannot be excluded. Indeed, two publications, not written in English, were excluded. Also, the timeframe of the study, from 2012-−2023, although covering the years when applications in precision medicine expanded greatly, might have resulted in missing very early studies prior to the time period.

Finally, due to the limited qualitative data in the studies, the selection bias for the patients' perspective may be possible. Thus, although the thematic analysis in this review reached saturation, additional themes within the studies might have been neglected. In addition, in thematic saturation, when an observation does not contribute new themes, does not preclude a future observation from contributing new themes, thus further research might illuminate new aspects. Especially, as some themes were derived from a small number of studies, the present results should be interpreted with caution. Given the heterogeneity of the studies' design, a meta-analysis was not attainable. There was a great variation in the methodology applied in different studies including interviews, focus groups, questionnaires and surveys in different patient populations and settings. A bias toward patients from developed countries, especially USA was evident. Another issue is the fact that the majority of the included patients was recruited from primary care and secondly from specialized units including those suffering from rheumatological diseases and cancer. Thus, differences regarding the therapeutic area cannot be excluded and replication of the results is warranted. The lack of extensive standardized questionnaires and insufficient exploration of the patients' experience toward this rapidly evolving field, poses a potential risk of alienating medical experts and the public.

In conclusion, this study identified the main themes that emerge from the point of view of the patients regarding ethical issues and risks of precision medicine. These results give guidance on further actions that are needed to address these concerns. These include patient education and transparency on privacy issues, data protection and legal and economic concerns. Policies regarding insurability should also be a priority. In addition, issues on the effectiveness of precision medicine applications should be explained in detail to build trust and acquire the patients' informed consent. Educating patients about precision medicine is important to ensure that they are aware of the potential benefits and risks of genetic testing and targeted therapies. The implementation of a comprehensive educational program with written and online resources, incorporating both support groups and healthcare professionals taking into consideration the diverse backgrounds of the patients would be beneficial in the active involvement in precision medicine. Through empowerment, patients acquire knowledge and understanding about precision medicine, and they can consequently make informed decisions about their healthcare and advocate for their own interests. Psychological support should be offered when appropriate and physicians should be trained for clear patient communication to avoid miscommunication especially regarding complex tests, genetic counseling and precision medicine applications. Moreover, it is important to remind everyone involved, that the patient doctor relationship remains the cornerstone of practicing medicine and should not be compromised. Finally, more research is needed to identify present and forthcoming ethical issues and potential risks that may emerge from the implementation of precision medicine. Replication studies across diverse populations are necessary to assess the generalizability and consistency of findings.

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

LA participated in study design, data collection, and data analysis and drafted the manuscript. ACo participated in in study design and data analysis and data interpretation. ACh participated in study design, data analysis, interpretation of data, writing the manuscript and he was also the supervisor of LA, from which this manuscript was produced. All authors have read and approved the final manuscript.

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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1215663/full#supplementary-material

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Walking the talk in digital transformation of regulatory review

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Cloud-based regulatory platforms have the potential to substantially transform how regulatory submissions are developed, transmitted, and reviewed across the full life cycle of drug development. The benefits of cloud-based submission and review include accelerating critical therapies to patients in need globally and efficiency gains for both drug developers and regulators. The key challenge is turning the theoretical promise of cloud-based regulatory platforms into reality to further the application of technology in the regulatory processes. In this publication we outline regulatory policy journeys needed to effect the changes in the external environment that would allow for use of a cloud-based technology, discuss the prerequisites to successfully navigate the policy journeys, and elaborate on future possibilities when adoption of cloud-based regulatory technologies is achieved.

KEYWORDS

cloud, submission and approval, digital transformation and big data, dossier and approval process, structured content, health authorities, data exchange, regulatory review models

1. Introduction

Cloud-based regulatory platforms have the potential to substantially transform how regulatory submissions are developed, transmitted, and reviewed across the full life cycle of drug development. The benefits of cloud-based submission and review include accelerating critical therapies to patients in need globally and efficiency gains for both drug developers and regulators (1, 2).

A growing number of regulators have recognized the role that cloud-based approaches can have in their technology plans. These include the FDA Technology and Data Modernization Action Plan (3) and elements related to informatics in the sixth reauthorization of the Prescription Drug User Fee Act (PDUFA VII), as well as the European Union cloud strategy (4). These strategies seek to modernize digital infrastructure to support the respective regulatory networks and create efficiencies in the review process. In addition, regulators have been working to update current review paradigms. In the US the Split Real Time Application Review pilot program (5) allows for a more staged approach to provision of data. Likewise in the EU the draft General Pharmaceutical legislation currently offers the promise of a phased review (6). These constructs do not require a cloud-based platform but could be considerably enhanced by a cloud platform in future.

The key challenge is turning the theoretical promise of cloud-based regulatory platforms into reality, building on the foundation of existing tools – such as CTD and eCTD – to further the application of technology in the regulatory processes.

While the ultimate vision is to provide technology-assisted data analytics and decision-making across the full range of biopharmaceutical product research and development, as well as the pain points associated with post-approval activities (7), we are not recommending any changes to standards of review or the important public health responsibilities that regulators carry out to ensure the safety, efficacy, and quality of medical products.

In this publication we outline regulatory policy journeys needed to effect the changes in the external environment that would allow for use of a cloud-based technology, discuss the prerequisites to successfully navigate the policy journeys, and elaborate on future possibilities when adoption of cloud-based regulatory technologies is achieved.

We describe here the progression along the regulatory policy journeys by describing potential initial cloud-based capabilities and two proofs of concept (POC) from Accumulus Synergy (8),[1] a developer of one such regulatory solution. The proposed cloud platform aims to facilitate a more dynamic and collaborative review model, which could ultimately support iterative upload of data and dialogue with regulators to improve speed, transparency, and efficiency in the regulatory review and approval process.

Figure 1 Illustrates the concepts of information flow between submission process participants as the foundation of future state ways of working.

2. Regulatory policy journeys

Regulatory policy focuses on evolving the external regulatory environment to support and adopt advances in science, technology, and drug development. A regulatory policy roadmap to articulate the cloud platform vision can be expressed as three major journeys progressing over a multi-year horizon as described in Table 1.

2.1. Journey 1: collaboration *via* cooperative relationships

Cloud-based technology could facilitate scaling of increasing multi-directional collaboration.

Collaboration between regulators is not new. Regulators are already working together on collaborative review processes to promote alignment on identification and resolution of review issues relating to clinical benefit/risk assessments such as FDA's Project Orbis (9, 10), and to manage their available application review resources more efficiently through work-sharing models such as the Access Consortium (11), or reliance mechanisms such as ZaZiBoNa (12). Benefits to regulators include sharing insights, optimizing resources across multiple organizations, and accelerating therapies that meet approval standards to their patient constituents.

Consolidating the interactions between drug developers and health authorities in a single cloud environment would create a single source of up-to-date referenceable truth for the exchange of information, data, and all aspects of the dialogue including information requests, post market requirements and commitments, and tracking of audit findings. However, this is not something that will be achieved in the short-term across multiple regulators. It still requires a sustained effort on harmonization and convergence of regulatory requirements around the world. A cloud platform removes storage constraints, but care is needed to ensure that this does not inadvertently allow a proliferation of non-value-added administrative documents and bespoke national requirements that do not inform the science of the regulatory review.

Scaling collaboration between multiple regulators or between regulators and drug developers would enable progress along our second proposed regulatory policy journey, efficiency.

2.2. Journey 2: efficiency

All regulators and drug developers are challenged by resource constraints including increasing size and complexity of drug development portfolios, the extraordinary scientific advances in recent years which require evolving data generation and review approaches such as FDA's accelerated approval pathways (13), and continued increase in post-marketing workload demands (7). Biopharma companies also face challenges as they seek to reduce the time it takes to bring products to patients more efficiently (14).

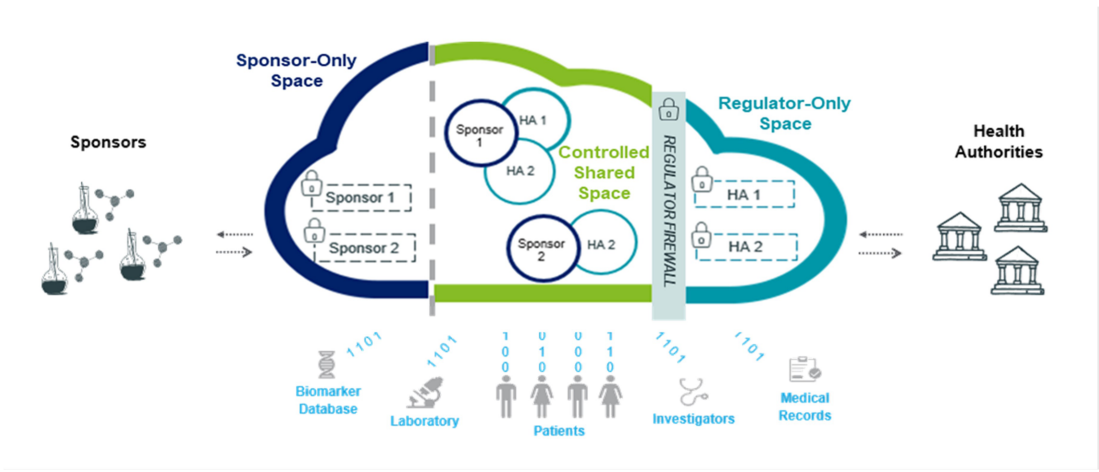
Cloud-based technology platforms offer the ability to realize several efficiencies in regulatory processes, leveraging workflows and optimizing efficiency to benefit public health. Cloud-based solutions will enable greater efficiency of review by providing the opportunity to evolve the dynamics of how review is managed and conducted, for example by allowing automation of routine administrative tasks and freeing up reviewer time for more impactful scientific work (15). Within biopharma companies, cloud-based work coupled with structured content, automation, artificial intelligence such as natural language processing, and machine learning could augment work currently performed by people, including authoring, data analysis, project management, and data/file management (16). All of these proposed changes to ways of working require policy-driven evolution of processes for both regulators and biopharma.

2.3. Journey 3: evidence generation, insights, and trends

Historically, randomized controlled clinical trials (RCT) have been the "gold standard" for generating evidence to support biopharma product approvals. While RCT remains the bedrock of risk–benefit decisions, biopharma and regulators are increasingly

1 Accumulus Synergy Inc. was formed in 2020 as a non-profit trade association advocating for digital transformation and regulatory harmonization. The company is developing a data exchange platform to enable enhanced collaboration and efficiency between life sciences organizations and health authorities worldwide. It has secured sponsorship from 12 leading biopharmas including Amgen, Astellas, AstraZeneca, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Pfizer, Roche/Genentech, Sanofi, and Takeda.

Cloud Submission Platform Concept



A cloud submission platform could be split into three workspace areas. These include the following dedicated workspace areas:

1. Drug Developer Space: drug developers can work with robust privacy and data security protections. Drug developers will be able to share information with collaborators in the biopharma-only space to facilitate co-development approaches (e.g., co-development, umbrella protocols, licensing agreements).
2. Shared Developer-Regulator Space: shared space where drug developers and regulators can communicate in a controlled environment. This space will enable more efficient exchange of questions and answers on review via the platform, but access rules will be robust and companies will not be able to access regulator authored assessment documents unless the regulator releases them.
3. Regulatory-Only Space: regulator-only area where they can review and interpret the data as a single regulator, as well as exchange information and collaborate securely with other regulators.

The platform should be governed by appropriate permission structures and security to ensure protections of regulators' work, and company data confidentiality while meeting countries' privacy laws. It should also ensure anti-trust protections in line with traditional co-development efforts between companies.

FIGURE 1
Cloud submission platform concept.

looking to leverage alternative and scientifically sound sources of clinical data including real world evidence (RWE) sourced from patient registries and electronic health records (17). RWE is becoming more widespread in use, although challenges remain such as heterogeneity, lack of standardization of terms and the large volumes of data. The need for standardization of terminology and heterogeneity of data is not something which will be solved *via* a cloud platform and requires action by appropriate bodies such as ICH. However, a cloud platform is a better storage solution for large volumes of data than today's submission paradigm.

Clinical trials are also increasingly becoming more digital both in terms of using digital tools to capture the data, (e.g., biosensors/wearables) and by decentralized approaches where the patients participate remotely rather than traveling to study sites (18). Cloud-based regulatory platforms could offer the possibility to house both data from traditional RCTs as well as data from new sources and technologies, allowing potential for integration and analysis across various data types. As observed in the efficiency journey, coupling expanded and unified data sets with artificial intelligence, machine learning, and automation could enable discovery of new trends and

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TABLE 1 Policy journey from-to shifts.

Current state	Future state
Journey 1: collaboration via cooperative relationships	
• Tendency for siloed individual country submissions by drug developers, in successive waves of priority	• Cloud technology facilitates ease of collaboration between regulators leading to greater use of reliance and work-sharing and hence more simultaneous submissions, reviews and approvals, based on common global submission content
Journey 2: efficiency	
• Manually intensive PDF document-constrained submissions with resource intensive re-transcription of data hampering trend analysis	• Structured data submissions that are both human and machine-readable allowing use of technology for assisted or automated confirmatory re-analysis by regulators
• Dialogue with biopharma sponsors generally only at discrete regulator review milestones based on touch points; little to no use of modernized technology assisted regulator reviews	• Evolution towards more continuous/iterative data upload and dialogue during review and enriched decision-making
	• Continuous data upload with real-time analysis and response
Journey 3: evidence generation, insights, and trends	
• Conventional clinical trial data as the primary evidence base with some use of novel sources of evidence	• Source-agnostic cloud-platform allows for bringing together diverse types of evidence, (RWD, data from wearables, etc.) alongside traditional sources. Potential new data insights and trends could be unlocked via analysis across unified data pool
• Knowledge management is manual, resource intensive and cumbersome resulting in data being used once for a submission and the ability to uncover new insights from data being limited and constrained	• More agile knowledge management allowing new insights from data to be uncovered with potential benefits to patients

insights in appropriate contexts (19). This could be particularly beneficial to regulators when they are examining trends that occur across products from multiple companies.

Evidence generation is evolving, and the use of technology must keep pace in order for data from new sources generation such as biomarkers, digital health tools, medical records, wearables to enhance traditional methods of evidence generation and provide valuable insights that otherwise would not be available. Cloud-based technologies will be necessary to ingest, standardize, exchange, and ultimately analyze the data coming from these new sources.

The journeys, which are over-lapping and interrelated, are a helpful way to envisage the future for regulatory submissions.

3. Pre-requisites for progressing the cloud-based regulatory submission and review

To unlock the benefits of cloud-based regulatory submission and review, there are several key policy areas that must be addressed, to create a hospitable operating environment for such cloud platforms, and to help industry navigate across the three journeys described above. These include the establishment of high quality and interoperable data standards, and policies that address data sharing, data privacy, and data security. All these policy areas require broad stakeholder engagement to achieve global scale and ultimately maximum patient benefit (2).

3.1. Regulatory harmonization of technical content requirements

Continued and sustained efforts to harmonize technical requirements for regulatory submissions *via* the International Council for Harmonization (ICH) are critical as this helps drive towards common global data requirements (20). Harmonization is a crucial enabler for reliance and work-sharing. Harmonized requirements together with the availability of secure cloud-based platforms can catalyze further collaboration between regulators and enable more patients to benefit from therapies in a timely fashion.

3.2. High quality data standards, interoperability, privacy and security

High quality data standards and interoperability are a necessary pre-cursor to support collaboration, streamlined data exchange, and other data driven advancements. Currently, data standards vary widely across regions with some countries only starting to implement digitalization while others have significantly matured their digital health infrastructures. ISO Identification of Medicinal Products (IDMP) specifies standard definitions for the identification and description of medicinal products for human use (21). This will help facilitate the reliable exchange of product information together with data exchange standards such as HL7's Fast Healthcare Interoperability Resources (FHIR) (22). Both will be critical to the success of any cloud-based platform by harmonizing data standards to ensure interoperability across different geographic regions. It is also essential to ensure that appropriate healthcare data policies are in place that will enable consistent high quality and secure data standards across regions (23).

Interoperability is a necessity for efficient data exchange and a foundational element to any regulator collaboration.[2] Increasing collaborative reviews, reliance, and work sharing (1) amongst regulators yields efficiency benefits to all participants and serves to reduce global drug approval lag.

Similar to data standardization and interoperability acting as the precursors to the technical exchange of data, policies governing data sharing, data privacy, and data security will also need development

2 Draft *CF* Reg. Data policy paper.

and harmonization to address the ethical, political, and patient concerns that could emerge from cloud-based collaboration (24). Policies will be required to address cybersecurity, antitrust/anti-competitive, intellectual property, and other issues (25). Policies and compliance enforcement will also be required to ensure protection of patients and their data (26).

As policies evolve and cascade, existing data infrastructure and agreements between stakeholders for data exchange will need to be re-assessed to ensure that they are fit for purpose.

Regulatory cloud platforms should be designed and built to meet all applicable regional and global privacy laws and implement appropriate safeguards to ensure that all data is protected.

3.3. Broad stakeholder engagement

Transitioning the ecosystem to cloud-based platforms is a complex and ambitious endeavor that will require a phased approach to deliver early and focused solutions that can be expanded to achieve the larger potential over an extended time horizon. Successful adoption of cloud-based platforms will ultimately require close partnership, collaboration, and alignment across a large and diverse set of stakeholders [e.g., regulators, drug developers, technology developers, Clinical Research Organizations (CROs)], trade associations, standards organizations (2).

4. Cloud platform capabilities

4.1. Cloud enabled regulatory collaboration

To realize the vision of cloud-based submission and review, fundamental platform capabilities are required. Two such capabilities – Data Exchange and Submission Review and Collaboration – are key components of the Cloud Platform Concept and detailed below with descriptions of how they relate to the previously outlined policy journey.

4.1.1. Submission review and collaboration

Submission review and collaboration can be developed as a core set of platform capabilities to enable more efficient and secure collaboration between biopharma sponsors, biopharma sponsors and health authorities, or between health authorities. The overall intent is to eliminate traditional document exchange across separate platforms by promoting submission and review in the shared spaces. Working in the shared spaces will reduce unnecessary data handling and transmission while promoting close to real-time exchange of feedback and information.

4.1.2. Data exchange

Cloud-based data exchange capabilities would support a codified, structured, standardized model to streamline data exchange, analysis, and interoperability. The exchange of structured and standardized information between drug developers and regulators could allow drug developers to move away from the current narrative heavy unstructured content and PDF format (Portable Document Format) to transmission of structured source data contained in regulatory filings. A fully digital/cloud-based environment would also require standardization of clinical trial terminology (CDISC) and use of visualization in regulatory review. The platform will need to be able to accommodate this and to also offer regulators tooling to quickly search across the increasing the volume and complexity of the submitted data so that additional data is useful not burdensome.

A more evolved user interface for regulators and drug developers could unite text, graphical data, and source data components into a "single pane of glass" to enhance submission, review, and post-authorization change management *via* optimized data replication, search, and assessment capabilities (27). Such a capability could leverage the latest standards including HL7's and sit atop a FHIR platform providing a standard for exchanging information across healthcare applications.

Data Exchange capabilities would support submissions that use different data types across the entire drug development lifecycle including pre-clinical, clinical (product safety and efficacy) and chemistry manufacturing and controls (product quality) data as well as evolving to allow for real-time submission and approval as seen in FDA's pilot, Real-Time Oncology Review or enabling extensions of shelf-life with incrementally new stability data.

4.2. Accumulus Synergy proofs of concept: project Orbis and labeling negotiations

Accumulus Synergy is developing a data exchange platform that aims to enable enhanced collaboration and efficiency between life science organizations and global health authorities (8).

Accumulus Synergy will aim to allow regulators and drug developers to road test its cloud platform *via* initial proofs of concept (POCs) and build subsequent learnings into future offerings. The initial offerings are limited in scale and scope to establish proof of concept. Accumulus has identified near-term focus areas for its initial use cases:

1. Project Orbis
2. Labeling negotiations

4.2.1. Project Orbis

Accumulus Synergy is developing a collaboration platform for use in Project Orbis (10), a submission review program initiated by FDA's Oncology Center of Excellence for concurrent submission review of oncology products among several global health authorities.

Accumulus Synergy's platform features include:

- Regulatory project creation and management
- Invitation management (GSP [Global Submission Plan] new eForm)
- Document parsing to enable collaboration (AAid [Assessment Aid])
- Novel content editor leveraging structured content for enhanced collaboration
- Project meetings, milestones, and artifact management
- Information request management (regulator questions) and library.

The configurable nature of its cloud capabilities built to support Project Orbis can be re-purposed for other types of collaboration,

work-sharing and reliance programs such as ICMRA pilots, ACCESS Consortium, all in support of regulatory harmonization and convergence, worldwide. Remote and hybrid inspections are another tangible example for cloud-based collaboration and opportunity for HAs to adopt Good Reliance Practices (GRelP) (28). The benefits to regulators include sharing insights, optimizing resources across multiple organizations, and accelerating reviews of therapies to their patient constituents.

4.2.2. Labeling negotiations

Labeling negotiations during the marketing application review process showcase the versatility of the Accumulus Synergy platform, applying the collaboration features from its Project Orbis support product to critical regulatory content shared between drug developers and regulators.

Labeling negotiation will leverage previously developed features and functionality:

- Project creation (new project type)
- Document parsing
- Accumulus Synergy's novel document editor for real time collaboration between the biopharma and a given regulator's comments, track changes, suggesting edits etc.
- Real time Q and A.

This POC is focused initially on the FDA, but all regulators conduct labeling negotiations with drug developers, so this could be a valuable to additional regulators in the future.

5. Discussion

The last decade of digital transformation has driven improvements across industries and across the globe. Digital transformation takes on many familiar forms including cloud-based application access, cloud-based storage, streamlined workflows, improved user experiences, artificial intelligence, and machine learning assisted work.

While stakeholders in the drug development industry have been able to leverage aspects of digital transformation in various parts of the drug development lifecycle, the regulatory framework governing the exchange of information between drug developers and regulators has not fully assimilated technologies available today. This may be due to the complexity of re-imagining the paradigm and the siloed nature of previous attempts (29). At the same time, collaboration between global regulators is growing and reached new levels during the Covid-19 pandemic (30), but this was manual, resource-intensive, and took place on platforms where there were limitations on the types and size of files that could be exchanged. Cloud-based platform capabilities can transform the nature of regulatory data and information exchange. Broad stakeholder engagement to evolve regulatory policies and enable the assimilation of current technologies into today's regulatory framework could generate substantial benefits for regulators, drug developers, and patients.

The pace of industry evolution will be set by the collective and joint efforts of leading health authorities, drug developers, trade associations, and technology developers. Accumulus Synergy has emerged in response to the need to bring these parties together to address the regulatory framework. With its nonprofit status and focus on global citizens, it is uniquely positioned to develop technologies that can help bridge the needs of drug developers and global regulators. The Accumulus Synergy Platform will aim to validate the cloud and digital transformation hypothesis by first enhancing regulator collaboration mechanisms and then expanding into the exchange of data and information. Over time the aspiration is for the platform to cover all data and information to support regulatory submissions across the drug development lifecycle.

5.1. Where are we heading?

An organization such as Accumulus Synergy is needed to generate the activation energy the biopharma industry needs to rally its multiple stakeholders around the possibilities of cloud-based submissions and evolving regulatory frameworks. Such momentum will inspire several trajectories that could be further imagined and explored at the option of regulators and innovators:

1. Expansion within and beyond biopharma to other life sciences sectors
2. Technology Aided and Real-Time Decision Making
3. Expanded Global Collaboration.

5.1.1. Expansion within and beyond biopharma

Once the model of partnership, innovation, and collaboration to shift into cloud-based submissions has been set initially within biopharma, rapid expansion will be needed to support the needs of small and medium sized entities, device and diagnostic providers, and generics. A broader market will also emerge for technology entrants beyond Accumulus Synergy to continuously expand options and improve the industry. The model can scale to support the full remit of health regulators.

5.1.2. Technology aided and real-time decision making

Data standards, interoperability, and security advancements will pave the way for increased use of advanced data analytics, machine learning and artificial intelligence within the regulatory framework (29). Equipping regulators with both data and tools to analyze data rapidly and efficiently at scale could lead to shifts in how their work is performed. Risk-based machine supported, or even automated decision models, will emerge to support regulators with their vast review and decision-making workload.

Additionally, data can be transmitted as it is generated and correspondingly consumed and assimilated into decision models allowing for real-time analysis and decision making versus the current batch model where all the submission data is submitted together after the last component is finalized.

5.1.3. Expanded global collaboration

Increasing the opportunities for technology assisted collaboration creates greater transparency in review and decision making. It will lead to continuous learning, improvement, and innovation within each health authority, and possibly sharing of practices. Levels of collaboration could be achieved where both work and decisions are shared, and greater levels of reliance and possibly convergence could be achieved, bringing the greatest acceleration value to patients as more global citizens could benefit from concurrent decisions around therapeutic safety, efficacy, and quality.

6. Conclusion

Re-designing the paradigm from a document centric mindset to a data centric approach is a bold, transformative, multi-year endeavor and will ultimately touch all aspects of research, development and life cycle management. Journeying towards this will unlock efficiencies not yet available to drug developers and regulatory authorities. There are many practical aspects of this new paradigm to be worked out which are beyond the scope of this short paper. We call drug developers, regulators, trade associations and other key stakeholders to work together in supporting harmonized efforts towards the development of cloud-based technologies that will drive greater industry productivity, acceleration, and patient benefit.

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

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

Conflict of interest

RK was employed by Scimitar Inc. JM was employed by Pfizer Inc. AG was employed by GlaxoSmithKline. LA was employed by Sanofi. FB was employed by F. Hoffmann-La Roche Ltd. GB-R was employed by Amgen, Inc.

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Declaration of Helsinki: ethical norm in pursuit of common global goals

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The World Medical Association's Declaration of Helsinki is in the process of being revised. The following amendments are recommended to be incorporated in pursuit of the common goal of promoting health for all. 1. Data-driven research that facilitates broad informed consent and dynamic consent, assuring participant's rights, and the sharing of individual participant data (IPD) and research results to promote open science and generate social value. 2. Risk minimisation in a placebo-controlled study and post-trial access to the best-proven interventions for all who need them. 3. A future-oriented research framework for co-creation with all the relevant stakeholders.

KEYWORDS

Declaration of Helsinki, data-driven research, placebo, post-trial access, stakeholder involvement, health for all

1 Introduction

The Declaration of Helsinki (DoH) of the World Medical Association (WMA) (1), first adopted in 1964, is the world's most widely recognised ethical principle for medical research involving humans. The WMA began the process of revising the DoH in April 2022, from the last version dated 2013. Research involving humans is a core activity in the development of medicines. For this reason, the authors have discussed the ideal function of the ethical norm of research involving humans, considering our global experience of the COVID-19 pandemic and other disasters, including war situations. The DoH is a fundamental ethical norm, not guidance for specific changing situations. However, as described below, the drastic changes in both global society and the scientific environment over the past decade have posed an acute challenge to this fundamental norm.

2 Ethics in data-driven research

2.1 The Declaration of Taipei and broad informed consent

The WMA's first declaration on health databases in 2002 was triggered by the nationwide genome biobank planned in Iceland around the time of the completion of the human genome draught sequence. It was revised in 2016 as the Declaration of Taipei (DoT) (2) on health databases and biobanks. However, the latest version of the DoH does not mention the DoT. Recently, the secondary use of real-world data (RWD) from clinical practise or data generated from research has been widely accepted, particularly with the rapid development of artificial intelligence. RWD are also used as external controls (3) to compare new intervention with natural history of disease rather than conducting placebo-controlled trials. Furthermore, the COVID-19 pandemic has raised an acute demand for data-driven public policy, not limited to health policy. Meanwhile, the European Union's General Data Protection Regulation (4) and the proposed regulations of the European Health Data Space (5) seek to increase the potential for secondary use of personal data within a strengthened governance framework whilst guaranteeing individuals' rights to control their data and increasing data portability. In such an environment, clarification of the link between the DoH and the DoT is essential (6, 7). The DoT is not limited to the protection of privacy and data security. It sets out a governance framework including the management of incidental findings, intellectual property rights, and material transfer agreements, which must be explained to the individuals who consent to the multipurpose use of their data. Such a type of consent is called "broad informed consent" in the guidelines of the Council for International Organisations of Medical Sciences (CIOMS) (8), as opposed to both orthodox informed consent for use with an explicit purpose and traditional broad blanket consent. This concept of broad informed consent can enhance the common understanding of the emerging environment of data-driven research amongst researchers, research ethics committees, research participants, and society at large.

2.2 Rights to know/not to know and dynamic consent

The DoH guarantees research participants the right to know "*the general outcome and results of the study*". However, it does not guarantee research participants the "right to know or not to know" (9) both incidental findings and study target outcomes, depending on the level of scientific validity, clinical significance, and actionability. These rights are endorsed in the CIOMS guidelines (8) and incorporated into some regional guidance (10). On the other hand, the International Conference on Harmonisation's Good Clinical Practise (ICH-GCP) (11–13) does not assure these rights. Therefore, in pharmacogenomics studies and other clinical trials to develop therapeutics with biomarkers, including those for infectious diseases, the ethical responsibility of the physician investigator to inform study participants of clinically significant results generated by biomarkers without marketing authorization may become difficult. For this reason, these rights should be aligned and recognised within authoritative international norms such as the DoH.

Research participants should also be guaranteed the right to be informed about the secondary use of their data and the possible consequences, as well as the right to withdraw their consent to further use of their data. Consent that guarantees such rights is called "dynamic consent" (14, 15). Mechanisms to ensure dynamic consent can be achieved through an improved data management structure, as it requires informing individuals about secondary use projects, using advanced information technology tools, and terminating the use of data from individuals who have withdrawn amongst a large number of data subsets. Management and handling of broad informed consent and dynamic consent should be described both in the protocols and informed consent forms and evaluated by research ethics committees. The approach for informing participants on using their data for secondary studies should be carefully described.

2.3 Individual participant data sharing and result registration for open science with social value

Registration of "individual participant data (IPD) sharing plan" (16) and "results" of a clinical trial in a public database (17) have become regulatory requirements in various countries (18) but are not explicitly mentioned in the DoH. In the United States (19) and the European Union (20), open science has been promoted by ensuring public access to peer-reviewed papers and their supporting data from publicly funded research. As data from research involving humans is recognised as a public good (21), it should be reaffirmed as an ethical obligation of researchers to disclose not only the research results but also the IPD sharing plan in public databases.

There is also an urgent need to ensure the quality of data-driven research whilst guaranteeing the right of individuals to control their own data. The CIOMS guidelines define "social value" not just "scientific value" as the ethical justification for research. The mechanism to ensure scientific integrity, including responsible data management, to generate social value, using personal data with/without explicit consent but gaining social consensus, must be established. For this reason, "social value" should be defined in the DoH as a requirement for any type of research.

3 Placebo control and post-trial access

3.1 Risk minimization in placebo control

Controversy over the DoH article on the placebo-controlled trial has spanned approximately 30 years and, unfortunately, has led to unsuccessful attempts to develop pragmatic guidelines. The DoH should restore the original pursuit of ideals as the ethical duty of physicians (22–24). In 1975, it was clearly stated that the interests of research participants must prevail over the interests of science and that every patient in research should be assured of the best-proven method (25). Thus, since 1975, it has been recommended that a new intervention be compared with a proven intervention. This is based on the Declaration of Geneva (26) and the International Code of Medical Ethics (27), which clarify the duty of physicians to patients. The justification for a comparative study has been recognised as "clinical equipoise" (28) or "uncertainty" (29) between the arms being compared.

This ethical norm is not "deceptive" (30–32), because it is independent of the statistical methodology used, with the intention to reject the null hypothesis of a significant difference in efficacy. The DoH's current notion of the risk threshold, "no increase in serious or irreversible harm" in the control group, is not consistent with the policy of risk minimisation that applies to all types of research, not just comparative trials.

3.2 Post-trial access for all

The debate on placebo control raised a norm in the 2000 version of the DoH regarding the right of trial participants to post-trial access to interventions proven to be effective. This was to avoid injustice and exploitation of the host community of a placebo trial in low- and middle-income countries (LMICs), which may not have access to a high-priced intervention that has been shown to be effective (33, 34). In subsequent revisions, it also came to be a pragmatic guideline requiring to describe a plan for post-trial access in the study protocol and informed consent form. Approximately two decades later, our unprecedented experience with the COVID-19 pandemic led to a significant shift in practise. Governments, in cooperation with companies and other stakeholders, made maximum efforts to provide vaccines proven to be effective to those who needed them around the world. The post-trial access, achieved for COVID-19 vaccines due to the solidarity and collaboration amongst stakeholders in the global community represents progress, although not a universal success. Bilateral negotiations between companies and governments in high-income countries have neutralised the ideal of equitable vaccine distribution set out by COVAX (35). Some initiatives of technology transfer and capacity development have been sought in the pursuit of common global goals (36, 37), to overcome inequity and injustice in the right to health (38). "Post-trial access for all" should not be seen as idealism. It should be clearly recognised as the international principle and ethical obligation of the government, sponsors, researchers, and relevant stakeholders, including health technology assessment bodies, in support of the global availability of the best-proven interventions and access for all those who need them.

3.3 Obligation of care

Other unprecedented situations of clinical trials in war/conflict, as well as natural disasters, highlighted the needs of patients seeking access to investigational intervention (39, 40). Sponsors, investigators, and regulators (41–43), undertook joint efforts to continue or start investigational treatment for patients with acute needs, and developed procedures for adherence to GCP under disruptive circumstances, including the cases of emigrations. Access is not only the issue of post-trial but also the issue of patients' right to health and the obligation of care of the physician (8). Research is now an integral part of the health system and people's lives (44). This is the same in both normal and emergency settings. We should also assure hospitals and other points of care, as well as patients, that they must be protected under neutrality principles (45) during conflicts. We have to find agreed-upon solutions for acute conflicting values in the name of "justice." Post-trial access must be rephrased and recognised as a human rights norm, superseding any inequity, injustice, or inhumanity.

4 Future-oriented framework for co-creation

4.1 Interdisciplinary study team and patient public involvement

The DoH has been the model for more than half a century with its paternalistic nature to clarify an individual physician's obligation to an individual patient (46). Meanwhile, authors participate in the Ethics Working Group (EWG) of the International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP). IFAPP was founded in 1975 as a Federation of National Member Associations, composed mainly of physicians engaged in the development of medicines. In 2018, taking into account the multidisciplinary collaboration of different expertise needed, IFAPP updated its Code of Ethics to a new Ethics Framework (47) that clarifies the shared responsibility of different experts involved in all aspects of medicine lifecycle management.

In the current decade, greater involvement of patients, the public, and bioethicists has been needed, taking into account not only normal but also catastrophic situations. For this reason, we strongly endorse the norm of shared responsibility amongst interdisciplinary teams, along with the promotion of patient and public involvement (PPI) (14). PPI activities should be evaluated to ensure that they adequately protect and do not unduly influence patients or the public. It is worth noting that our comments for the revision of the DoH have been constructed through extensive communication with and learning from patient and public positioning groups or individuals. For example, in Japan, patients and citizens, who have been well emancipated through a systematic educational programme (48), have expressed their own opinions on the DoH (15) with the aspiration for social value in research, ensuring the dignity and rights of research participants.

4.2 Diversity in study participants, and in ethical review

In addition, we need principles of inclusiveness that apply to vulnerable populations, providing them equitable access to promising investigational interventions within a robust framework of risk and benefit assessment and avoiding "therapeutic misconception" (misunderstanding of research as therapy). The diversity of participants in clinical trials is also essential to ensuring the generalisability of trial results (48, 49). Inclusiveness and diversity are also needed in the membership of research ethics committees to assess the values and perspectives of these various study participants and emerging new scientific methodologies, such as decentralised clinical trials, adaptive designs, and pragmatic trials, which may sometimes include cluster randomisation (50). Research Ethics Committee membership must be appointed in a fair and transparent manner.

The study evaluation system in these dynamic situations, including disaster settings, must incorporate strengthened situational adaptive nature and procedures. Innovative ethical review systems should be developed, such as generic protocol review during normal times and rapid expedited review in times of disaster; as well as reviewing the clinical use of unproven interventions with, e.g., Bayesian statistical methods to evaluate safety and efficacy according to the collection of case data. Such studies would require appropriate data quality and integrity oversight.

4.3 Research not limited to medical, as co-creation with study participants

Finally, to achieve the protection of research participants and research integrity in such an evolving environment, we need to recognise study participants as partners in co-creation (51). Various types of research, not only medical and health-related but also social, behavioural, educational, engineering, environmental, and space development, have become subject to ethical principles. This suggests the need to change the key terminologies from "medical research involving human subjects" to "research involving humans (or human participants)".

5 Conclusion

The DoH, a living document (52), has continued to uphold its nature as a code of ethics for a physician conducting research, with the utmost respect for the dignity and human rights of an individual research participant. It reminds us that the physician–patient relationship, whilst it exists within the context of a dynamic community and global society, continues to be paramount. The altruism of participants could be fulfilled by knowing that the results of the research contribute to people with common sufferings worldwide. The ethical principles of research involving humans must be in pursuit of the common goal of promoting the health and wellbeing of every member of our global community. For this reason, we recommend the following to be incorporated in the next revision of the DoH:

- Data-driven research that facilitates broad informed consent, dynamic consent, and data sharing for open science generating social value.
- A plan to minimise the risk for placebo-controlled studies, and post-trial access to best-proven interventions for all who need them.
- Future-oriented research framework for co-creation amongst interdisciplinary teams, patients and the public, research ethics committees, and all other relevant stakeholders.

Author contributions

CK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. SK-F: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. SB: Writing – original draft, Writing – review & editing. AC: Writing – original draft, Writing – review & editing. YN: Writing – original draft, Writing – review & editing. SN: Writing – original draft, Writing – review & editing. JS: Writing – original draft, Writing – review & editing. KM: Project administration, Supervision, Writing – original draft, Writing – review & editing. VB: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

JS is an owner and executive consultant of PPH plus GmbH & Co. KG. AC is employed by Pfizer Healthcare Ireland. VB is president of IFAPP.

SK-F declares that he serves as Associate Editor in Frontiers in Medicine and Frontiers in Pharmacology, and CK serves as a reviewer of Frontiers in Pharmacology. This had no impact on the peer review process and the final decision.

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The need for a change in medical research thinking. Eco-systemic research frames are better suited to explore patterned disease behaviors

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Many practicing physicians struggle to properly evaluate clinical research studies – they either simply do not know them, regard the reported findings as 'truth' since they were reported in a 'reputable' journal and blindly implement these interventions, or they disregard them as having little pragmatic impact or relevance to their daily clinical work. Three aspects for the latter are highlighted: study populations rarely reflect their practice population, the absolute average benefits on specific outcomes in most controlled studies, while statistically significant, are so small that they are pragmatically irrelevant, and overall mortality between the intervention and control groups are unaffected. These observations underscore the need to rethink our research approaches in the clinical context – moving from the predominant reductionist to an eco-systemic research approach will lead to knowledge better suited to clinical decision-making for an individual patient as it takes into account the complex interplay of multi-level variables that impact health outcomes in the real-world setting.

KEYWORDS

systems thinking, research design, philosophy of science, uncertainty, evidence-based medicine, complexity science, philosophy of medicine, complexity thinking

Scientific research traditions

The roots of modern research trace back to the late 17th century with the exploration of the innate (physical) world.

Newton's research establishing the laws of the innate physical world based on experiments and repeated measurement in the controlled setting of the laboratory. This approach is based on a number of assumptions with limitations in real world applications – firstly, to experiment in the laboratory setting removes all external context that otherwise would impact the experiment (the law of the free fall of an object holds true only in a vacuum); secondly, that one can exactly measure observations (though Gauss showed that repeated measurements always have an error that symmetrically distributes around the mean); and lastly, that repeating the same experiment at a later time in a different setting will result in exactly the same outcome.

About a century later, Goethe and Humboldt demonstrated that Newton's laws of the innate world of physics did not apply to the animate world of living beings. To understand and predict their behavior required the simultaneous understanding of their environmental context (1). Furthermore, Pareto observed another important phaenomenon of the animate world, namely that it has a consistent distribution pattern that follows an 80/20 split – now known as the Pareto or inverse power law distribution (2). These observations marked the recognition of the interconnectedness and interdependence inherent in biological systems.

Humboldt is regarded as the founder of systems sciences – the sciences of interconnectedness and interdependence within mechanical and biological systems. In general terms, such systems consist of at least two parts where

- the whole cannot be divided into independent parts,
- each part affects the behavior of the other, and
- the way each part affects the behavior of the system depends on what at least one other part is doing (3).

Biological systems have the added characteristic of being adaptive, i.e., the behavior of one part can change the behavior of all other parts. Over time such changes lead to emergent – marginally stable – system states [homeokinetics (4)] which, in the medical context, we associate with particular diseases and disease severities (Figure 1 – top).

Mechanistic vs. eco-systemic research questions

There is a basic difference between physical and biological/social research questions. Physics is concerned with explaining cause-and-effect relationships in the innate world whereas biological/social sciences focus on understanding the emergent structural and behavioral phenomena in nature. While physics rightly focuses on researching *mechanisms* through a reductionist research paradigm, biological/social sciences should adopt an eco-systemic approach to understand the ways living beings '*behave*' and constantly *adapt* at all scales of organization within their changing environments. Biological/social sciences should not only concern themselves with the structure and dynamics of 'biological/social systems', but more importantly with finding *meaning* or *making sense* of those eco-systemic interactions (5, 6).

Medicine is not a science, it is a praxis (7). Clinicians use those scientific results that as good as possible apply to the individual. Given the endless biological/social variability between individuals and their highly variable living environments, they can never deliver perfectly predictable outcomes. Despite these variabilities, our interventions almost always result in one of a number of limited (i.e., not infinite) familiar patterns of outcomes.

The early successes of medicine arose mainly from the insights of reductionist research that explained the 'simple' cause-and-effect mechanisms of then common and life-shortening infectious diseases. However, 21st century medicine mostly struggles with chronic and complex diseases whose successful management demands a systemic understanding of the 'complex' interactions amongst the multiple variables from across the different scales of organization.

Put pragmatically, studying the effect of a defined antibiotic on a defined bacterium, an antihypertensive on blood pressure changes, or an antidepressant on a change in mood/anxiety scores in the laboratory would rightly be best done using the reductionist cause-and-effect research approach. However, many of these findings produced in the highly controlled laboratory environment are not reproduced in 'real world' clinical trial settings.

Clinically relevant questions necessitate systemic research approaches focused on patient relevant outcomes like:

- Does a new antibiotic work safely in people, and if so, what is the right dose for a particular person?
- Does lowering blood pressure prevent heart attacks or strokes, and if so, how much blood pressure reduction for an individual patient reduces his/her *absolute* risk of an event?
- Which type/combination of therapy/ies is best to recover from trauma or loss, and how does that vary amongst people from different social/ethnic backgrounds?
- Whom does a particular population-based prevention intervention benefit, and what are the issues that make it fail in others?

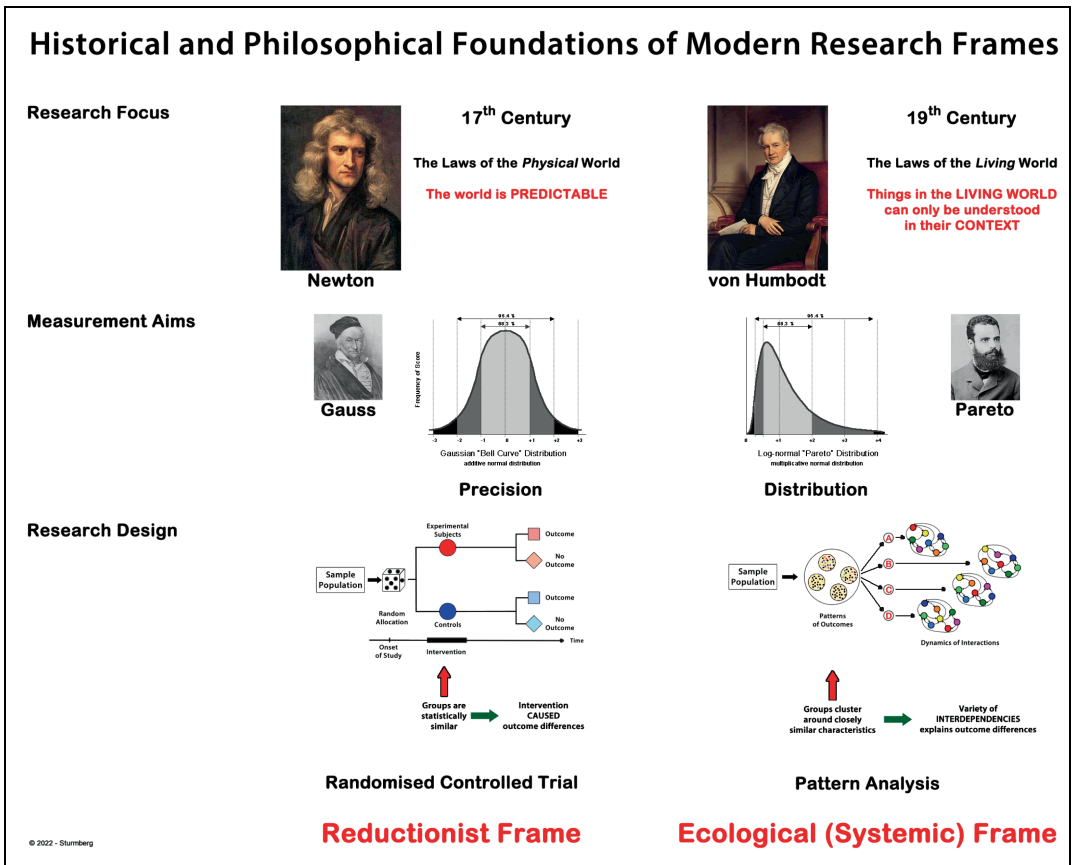
In the laboratory setting, research typically focuses narrowly on one-to-one relationships in the absence of any other contextual constraints (8). What may work well in the deliberately chosen context-free laboratory setting does not necessarily also work as a clinical intervention in diverse clinical settings. By their very nature clinical events are caused by a multitude of interacting factors. Clinical interventions cause one-to-many interactions simultaneously affecting physiological, environmental as well as sense-making/coping systems. Put succinctly, one-to-many relationships cannot be studied by 'squeezing' them into 'sanitized' one-to-one methodologies (8).

The bottom section of Figure 1 - bottom provides contrasting examples of research questions that either focus on mechanistic cause-and-effect problems or seek to gain insights and understandings of the complex interconnected and interdependent one-to-many cause-and-effect dynamics impacting people's health.

Finding the cause vs. understanding heterogenous outcomes

Researching a cause-and-effect problem like determing whether 'a new antibiotic kills a bacterium *in vitro*' falls within the Newtonian research paradigm. It requires repeating the same experiment to determine the reliability of observations.

In contrast research to understand observable differences, i.e., patterns, related to a particular phaenomenon [e.g., blood sugar dynamics in insulin-dependent diabetics (29), or experiencing significant diabetes symptoms despite adequate blood sugar control (30)] requires a different approach. Patterns emerge depending on the interactions and combinations of several contributing variables. Pattern analysis techniques like cluster (31) or network (32) analysis can identify which combinations and interactions lead to each of the observed outcomes of interest, and may guide further research in understanding their 'causal pathways.' Figure 1 contrasts the differences between the two frames, and Figure 2 illustrates how cluster analysis techniques can inform the management of coronary artery disease (33).



QUESTION / DOMAIN	**Questions** that can be answered by a *reductionist* research design to explain ***cause-and-effect*** relationships	**Questions** require an *eco-systemic* approach to gain knowledge and understanding about ***observed patterns***
Medical device therapies	Can an occluded coronary artery be quickly reopened by a stent in the situation of a myocardial infarction to prevent or mitigate the consequences of acute ischemia? [9, 10]	Does stenting of atherosclerotic lesions in coronary arteries prevent future myocardial infarctions or early death due to cardiovascular causes? [11-14]
Psychological Therapies	Which therapies have a greater effect on different forms of psychopathology? [15-18]	Which biopsychosocial or ecological processes are involved in the emergence of psychological distress or psychopathological signs/symptoms?[18-20] How could psychological well-being be conceptualized? [21]
Pharmacotherapy	Which drug best lowers LDL-cholesterol? What dose of a statin will achieve a cholesterol level? [22]	How do the pharmacological interactions between various inherited or co-expressed factors explain this variance in clinically observed patient outcomes? [23, 24]
Surgical Interventions	Does arthroscopic partial meniscectomy in the elderly improve longer term pain control?	How can we best influence the complex interplay of various factors contributing to the pain experience in elderly patients with osteoarthritic knee pain? [25]
Population Health	How effective is once-weekly semaglutide in reducing weight in adolescents? [26]	How does the media's reporting on obesity, nutrition and physical activity influence obesity levels? [27] Do community interventions improve sustained smoking cessation rates? [28]

FIGURE 1
Comparison of the reductionist and eco-systemic research frames. Note, that the reductionist approach aims to establish clear and repeatable cause-and-effect relationships, whereas the eco-systemic approach aims to gain insight into the dynamics that result in patterned outcomes. Understanding what "caused" an observed pattern (looking backwards) will allow clinicians to use the "pattern specific" interventions best suited to this patient (looking forward). The table provides research questions that can be best answered within each research frame (the selected references only relate to the nature of research questions rather than the differences in research methodology).

How to measure clinically relevant outcomes?

Clinically meaningful eco-systemic outcome measures can only be direct measures of endpoints such as hospitalizations, mortality or quality-of-life, resulting in so called '*patient-oriented evidence that matters*' (POEM) (34). Clinical research frequently relies on indirect ('*surrogate*') outcome measures in the form of 'biomarkers' like laboratory measures and radiological quantifications that are assumed to indicate 'clinically meaningful' outcomes (34) or a combination of very different clinical ('*composite*') outcomes that tend to overstate benefits (35) (in this context one should consider Goodhart's law[1]). However, even though biomarkers may align with pathophysiology of disease, they often fail to reliably predict effects on a clinically meaningful endpoint. For example, clinical trials of lowering the biomarker LDL has had at best tenuous impact on overall survival (36). Even more difficult to define are meaningful outcome measures for psychological/psychotherapeutic interventions – symptom reduction/remission, while common outcome measures, are highly subjective (37) with patients taking what they think and feel most relevant for their lives (38). And finally, the magnitude of an outcome is sensitive to the characteristics of the study population – while an intervention may have only a small benefit at a community level it may result in more people benefiting than the same intervention targeting a high risk cohort (39).

Hence, the *question* we really need to answer is: which patient in which context will *most likely* benefit from an intervention in a subjective and objective way?

Implications

Research, regardless of its methodology and rigor, provides additional data rather than information or knowledge (40). Statistics indicate the probability that – at the population level – these data *correlate* with particular population observations. However, statistical correlation does not equate to *causation*. Statistical correlation can only infer a potential causal relationship with a certain probability, and only if the relationship is based on a strong pathophysiologic rationale (41, 42). Hence, it is the researcher's responsibility to provide critical *contextual interpretation* of new data to justify their integration to existing understandings. As clinicians we must consider the new understandings in relation to their applicability at the individual/population level, but most importantly, in their unique contexts. And finally, research cannot relieve us from the task of making decisions and being responsible for them.

Knowing the '*study patient*'

It is critical to appreciate that there is no 'prototypical' patient who can guide clinical practice. The randomized controlled trial provides crude information about the outcome differences of the '*average* patient' in a study cohort receiving an active versus a placebo intervention. Observed differences, even when statistically significant, generally only have a very small pragmatic (or absolute) benefit. An intervention that helps 1 in 2 *average* patients (NNT = 2) is 50% effective and 50% ineffective, one that helps 1 in 20 (NNT = 20) is 5% effective and 95% ineffective, one that helps 1 in 100 (NNT = 100) is 1% effective and 99% ineffective, one that helps 1 in 200 (NNT = 200) is 0.5% effective and 99.5% ineffective, and so forth (43). Put differently, even so-called 'good medical interventions' are – pragmatically speaking – ineffective for most patients, and the one benefiting is not identifiable from the data. The same applies to harms which often are not expressed in clearly understandable and comparable terms. Of note, in many cases the increase in intensity of an intervention does not improve outcomes but results in increasing harms, e.g., the so called 'J' curve in treating hypertension (44, 45) or the use of non-steroidal anti-inflammatories in acute and chronic pain (46).

Whose interests matter most?

Research, like other societal activities, is shaped by the philosophical (47, 48), political and industry doctrines and vested interests of its time – consider, e.g., Mbeki's stance on HIV (49), or the regulation of embryonic stem cell research (50–52); or industries' influence on research agenda setting (53), financing, conducting and interpreting research (54), or influencing which type of evidence should be prioritized for policy-making (55).

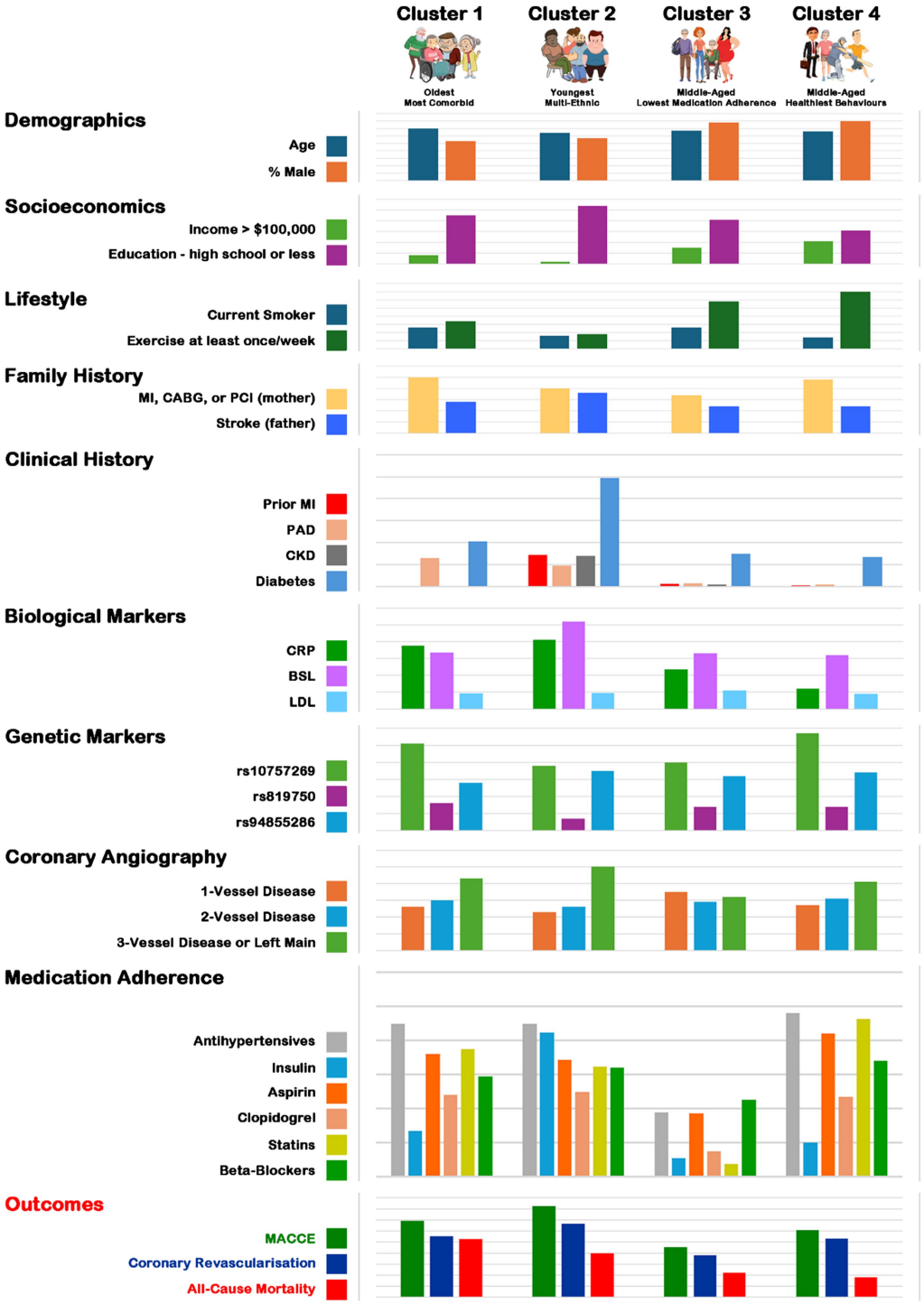
The reductionist understanding that the '*statistically significant*' *dichotomous* outcome difference in a randomized controlled trial implies a 'mechanistic' cause-and-effect relationship remains widely, but incorrectly, regarded as providing sufficient evidence to promulgate particular pharmaceutical or biomedical interventions to an affected patient population. This misunderstanding suits industry interests well (56). The typical large-scale multi-national industry funded studies only demonstrate small though statistically significant effects, often limited to surrogate or composite outcomes, which are promoted as seemingly benefiting (the misuse of *relative benefit*) a large number of people (euphemistically referred to as 'customers'). The rising trend of accelerated drug approval based on surrogate outcome improvements is of great concern given that more than half of approved drugs do not report confirmatory trial outcomes within the required timeframe causing patient harm and high costs despite uncertain clinical benefit (57, 58).

These observations highlight the significant conflict of commercial versus patient-benefit interest of pharmaceutical/device-maker companies (59) – they have nothing to gain from identifying the small group of patients who will ultimately benefit from a given medication/device (60, 61). Further, applying data from relatively healthy, homogeneous backgrounds to vulnerable patient groups not studied in the trials is fraught. The prevailing focus on biomedical intervention research distracts us to appreciate that greater health improvements are more often achieved by strengthening services that address the social and inequality issues within societies (62, 63).

Can precision-medicine result in better global health?

The precision-medicine movement has recognized the failings of population-based intervention studies and

1 When a measure becomes a target, it ceases to be a good measure.



Redrawn from Data of 1329 Participants (total of 155 Variables) by:
Flores AM et al. Unsupervised Learning for Automated Detection of Coronary Artery Disease Subgroups. Journal of the American Heart Association. 2021;10(23):e021976. doi:10.1161/JAHA.121.021976

BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CRP, C-reactive protein; LDL, low-density lipoprotein; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention

MACCE, composite of myocardial infarction, stroke, coronary and/or peripheral revascularisation

FIGURE 2
Patterns associated with cardiovascular disease outcomes (33). The comparisons should be read across the domains as well as columns. A few notable observations should be highlighted (some are well-known): education and income are associated with better outcomes; a diagnosis of diabetes is associated with greater coronary artery disease burden; CRP levels are high in the oldest multi-morbid and diabetes effected multi-ethnic cluster, while LDL levels are remarkably similar across the 4 clusters; 3-vessel disease is age and co-morbidity burden associated; medication

(Continued)

FIGURE 2 (Continued)

adherence appears to have little impact on disease severity and both, composite and all-cause mortality outcomes. Composite cardiovascular and all-cause mortality outcomes are associated with age and co-morbidities, whereas medication neglect and positive health behaviors have paradoxical associations with composite cardiovascular but no all-cause mortality associations. The difference in coronary revascularization in the latter two clusters may indicate provider bias – non-adherence to medical protocols makes those less deserving, while the health-conscious behavior ones overly deserving of interventions. Redrawn from data of 1329 participants (total of 155 variables) by: Flores et al. (33). BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CRP, C-reactive protein; LDL, low-density lipoprotein; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; MACCE, composite of myocardial infarction, stroke, coronary and/or peripheral revascularization.

aims to discover more specific interventions at the genome/transcriptome/proteome levels. These are expected to be highly predictable to deliver the desired outcome at the patient level (64, 65). Precision-medicine has demonstrated marked improvements in the treatment of certain cancers and improved pharmacotherapy (e.g., warfarin), but has failed to improve interventions and outcomes for common and multimorbid conditions (66, 67).

The promises of precision-medicine may be more wishful thinking than reality (65, 68, 69). Even changes at the physiological level have systemic effects beyond the correction of a specific genomic, transcriptomic or proteomic abnormality. Furthermore, the simplistic understanding that any such 'precision' therapy will have a specific target in human biology is fraught and ignores known physiology and pharmacology. Any drug must overcome basic absorption, distribution and metabolism problems even before it comes close to effectively targeting the cell machinery. Additionally, drug effectiveness changes with variability in cell biology, genetic makeup, genomic expression, and change in cell presentation over time (70). Latest at the metabolomic level will we see divergent systemic behavior and less predictable outcomes. Despite these fundamental reservations, an approach to collate the outcomes of individually targeted precision-medicine interventions has the potential to identify community-wide response patterns, an approach that aligns with the eco-systemic research frame.

The way forward

In conclusion, achieving more predictable medical interventions requires a more comprehensive understanding of which systemic variables, and which contexts, lead to the variety of our observable outcome patterns. Recent systems-focused research has demonstrated improvements in diabetes management (71), the drug treatment of hypertension (72), understanding the treatment of depression (73) and the treatment of brain tumors (74) but is, at this stage, a notable exception in clinical research. More systems-focused studies would significantly contribute to the knowledge required to define which outcome pattern a patient – and especially those with multiple morbidities – most likely will belong to. Understanding the underlying bio-medical, social, emotional and interpersonal features (75) underpinning outcome patterns would then enable us to offer the *most likely* treatment to remedy the issue of concern.

Learning to cope with uncertainty

One of the challenges to achieving this goal is our psychological need for certainty in clinical decision-making under always uncertain circumstances. The mental frame of evidence-based medicine as outlined by Sackett et al. remains widely seen as the best possible solution – "*integrating clinical expertise with the best available external evidence from systematic* [meaning clinically relevant] *research*" (76) in clinical decision-making for this particular patient. However, the best available evidence remains insufficient, which is something that patients and doctors alike should be painfully aware of, but neither are comfortable to acknowledge in a fully open and transparent way. Unwittingly, they collude, in Richard Smith's words, in a "*bogus contract*" (77).

Medical education, industry and the media all reinforce the socialization of medicine's unquestionable grandeur. Collectively we rid ourselves of the discomforts of uncertainty by using the mental trick of "'*causal inference*' *as a tool … to determine a cause by observing an effect*" (78). We fail to see the circularity in the argument – an '*observed effect*' suddenly is the new cause for '*another* observed effect' and so forth (79). Having, what seems to be, a rational argument allows us to confidently justify the widespread use of therapeutic approaches of limited to minimal effectiveness.

Embracing the inherent complexities

While this discourse outlines the philosophical and methodological underpinnings of medical research thinking, it calls for pragmatically considering the inherent complexities facing medical research and practice. From a science perspective, studying biological/social systems with their nonlinear distribution patterns requires different methodological research approaches. From a professional perspective, medical interventions are system-wide interventions, and their impacts always need to be considered across the molecular to environmental scales. From a practitioner perspective, even the most appropriate and most diligent research trial will always only give an *approximate* answer, and it ultimately at best reduces some degree of a clinician's uncertainty when having to make decisions in the context of the patient in front of them (80). And from a societal perspective, it challenges the usefulness of medical guidelines as much as the listing and/or public reimbursing of many drugs and medical interventions, like the suppression of ventricular ectopic beats with fleconide (81), the mortality benefits of colorectal cancer screening (82, 83), the

effectiveness of molnupiravir on hospitalization or death (84), or knee arthrospcopy for degenerative osteoarthritis (85).

Concluding thoughts

In summary, the reductionist medical research of the late 19th/early 20th century undoubtedly has lead to great benefits in understanding and treating the predominant infectious diseases of the time. However, it failed to achieve the same benefits in relation to the now predominant chronic and multimorbidid conditions affecting our patients. These problems are systemic in nature, i.e., they are the result of interconnected and interdependent activities spanning from the gene to the societal level. From a pragmatic perspective, we need to firstly shift our way of thinking toward an eco-systemic frame, and secondly, need to further develop the as yet embryonic eco-systemic research tools to find those solutions that allow us to offer the *most likely* beneficious approaches to each of our patients. And lastly, there is an urgent need to re-orientate our undergraduate medical courses to develop critical analytic thinking, and to teach our post graduate specialty trainees a wide range of research methodologies beyond the RCT.

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

JS: Writing – review & editing, Writing – original draft, Visualization, Resources, Conceptualization. JM: Writing – review & editing, Writing – original draft, Conceptualization. FT: Writing – review & editing, Writing – original draft, Conceptualization. TK: Writing – review & editing, Writing – original draft, Conceptualization.

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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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A comprehensive analysis of digital health-focused Living Labs: innovative approaches to dementia

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The increasing prevalence of dementia demands innovative solutions; however, existing technological products often lack tailored support for individuals living with this condition. The Living Lab approach, as a collaborative innovation method, holds promise in addressing this issue by actively involving end-users in the design and development of solutions adapted to their needs. Despite this potential, the approach still faces challenges due to its lack of recognition as a research methodology and its absence of tailored guidelines, particularly in dementia care, prompting inquiries into its effectiveness. This narrative review aims to fill this gap by identifying and analysing digital health Living Labs focusing on dementia solutions. Additionally, it proposes guidelines for enhancing their operations, ensuring sustainability, scalability, and greater impact on dementia care. Fifteen Living Labs were identified and analyzed. Based on trends, best practices, and literature, the guidelines emphasize user engagement, interdisciplinary collaboration, technological infrastructure, regulatory compliance, transparent innovation processes, impact measurement, sustainability, scalability, dissemination, and financial management. Implementing these guidelines can enhance the effectiveness and long-term impact of Living Labs in dementia care, fostering new collaborations globally.

KEYWORDS

Living Labs, open innovation, digital health, dementia, innovation ecosystems

1 Introduction

Among the challenges associated with the ageing population, dementia presents an increasingly pressing societal issue. Being one of the most prevalent neurodegenerative diseases with no cure currently available, dementia ranks at the top among the leading causes of disability and dependency among older people worldwide (1). In 2020 the global number of people living with dementia was estimated at over 55 million and it is expected to reach 139 million by 2050 (2). The caregiving burden is predominantly shouldered by informal carers, typically family members and friends of those living with dementia. As the prevalence of dementia continues to rise without effective treatment, and the cost of dementia care increases, the urgent need for alternative solutions becomes more apparent. This leads to a growing reliance on innovative technologies or services to provide new responses to those affected by dementia (3, 4).

In recent years, research on using technology for dementia has gained more attention. The main areas of technological development include diagnosis, assessment and monitoring, maintenance of function, leisure activities, and caregiving and management (5). Digital health strategies for people with dementia or cognitive impairment are diverse, including Artificial Intelligence (AI), Big Data platforms, and telemedicine for monitoring cognitive functions; Extended Reality – Virtual Reality (VR), Augmented Reality (AR) and Mixed Reality (MR) – for education, training, and treatment; and robots and smart home technologies to enhance daily activities and social skills (6).

Although various methods and approaches for designing technology exist, a considerable number of products currently available on the market are not tailored to meet the needs of persons living with dementia (7). Given this high rate of failure, it became imperative to actively involve end-users in co-creation processes, increasing relevance and attention directed toward the Living Lab approach (8, 9). Involving and engaging individuals living with dementia in these processes poses significant challenges due to their impaired cognitive abilities. Nevertheless, excluding them will cause difficulty in implementation in real-life scenarios and will probably decrease the hypothesis of success and acceptance of such solutions (10).

Although there is not a widely recognized definition of a Living Lab, this concept is centred on two main ideas: the real-life experimentation environment and the active involvement of users in the innovation process (11, 12). Operating across diverse contexts, Living Labs serve as dynamic spaces for testing, validating, developing, and co-creating throughout the entire design and commercialization process. They function as collective hubs for innovation, offering valuable insights, serving as testbeds for pioneering products, services, systems, and solutions, and helping to create a sense of community across the development process (11). Living Labs are a collaboration between multiple stakeholders. Four key groups of stakeholders are responsible for the successful implementation and development of a Living Lab: governmental bodies, industry, academic institutions, and end-users (quadruple helix approach) (13).

Recently, these collaborations have been transformed and innovation has been accelerated due to the emergence of Smart Cities, the Internet of Things (IoT), AI, ER, and Big Data paradigms, among others. These technological advancements have not only facilitated rapid access to innovation but also enabled transitions toward greater sustainability. Moreover, they have significantly enhanced the exchange of data and knowledge, serving as drivers for policy development and the scale-up of initiatives (14).

Since 2015, there has been a substantial increase in publications focusing on Living Labs. In the field of dementia, the total number is lower but the tendency to increase since 2015 is also found. Currently, there is a large number of actively functioning Living Labs on a global scale, with a particularly pronounced prevalence in European regions (12, 15). This approach has been frequently applied to the development of health devices, addressing mostly issues associated with vulnerable groups, such as older people and age-related diseases (16).

Publications addressing the diverse needs and expectations of people living with dementia, along with corresponding solutions, have emerged in the last few years but remained notably limited (17). A scoping review conducted in 2021 investigated Living Labs studies that focused on cognitive impairment and dementia-related solutions. The Living Labs identified were dedicated to enhancing the health, quality of life, independent living, home care, and safety of older adults with cognitive disorders or dementia. Additionally, they aimed to provide support for professional and family caregivers while alleviating their burdens (17). In the context of dementia Living Labs, technological products or services that support people to live independently and well at home, such as assistive technology, are the most common (18).

Despite the potential of the Living Lab approach and the successful development of products, services and solutions (19, 20), this methodology still faces several challenges. One significant issue is that Living Labs are usually unrecognized as a research methodology and, consequently, lack the credibility required for securing traditional research funding (21). Additionally, there is a lack of tailored and specific guidelines for Living Labs, particularly in the field of dementia.

To address the gap in research focusing on the distinct features and practices of Living Labs dedicated to dementia, and to meet the societal need for tailored digital health technologies for individuals affected by this condition, this narrative review aimed to identify and analyze the characteristics of digital health Living Labs with solutions for dementia. Thus, to answer the question "**What are the main characteristics of digital health Living Labs focused on dementia?**," Living Labs with this focus were screened and analyzed. Insights into their collaborative ecosystems, user engagement approaches, technological infrastructure, regulatory compliance, innovation processes, impact on healthcare outcomes, and strategies for funding and resource management were collected. The findings of this research contributed to the formulation of a comprehensive set of guidelines intended to inform about the operation and development of future Living Labs in the field. By optimising the effectiveness and impact of forthcoming Living Labs, this initiative strives to enhance approaches to develop digital health technology tailored to dementia care.

In 2015, an attempt to propose a Living Lab protocol for evaluating interventions in the context of dementia was already undertaken, albeit limited to three study cases featuring specific interventions and a restricted participant pool. The main findings from this study underscore the importance of actively involving relevant stakeholders from the inception of the process. Moreover, it stated that the industry stakeholders' needs should be aligned with the Living Lab's needs to gather usable insights for their interventions (22). Another study explored academic-practice partnerships of the Living Lab approach to dementia care and concluded that researchers should take the

initiative in shaping collaborations and providing opportunities for stakeholder engagement (23). Recent research delved into the operational aspects of Living Labs incorporating real products from Small and Medium-sized Enterprises (SMEs) in the everyday living environment of individuals living with dementia. The study emphasized the need for diverse stakeholder compositions and expertise. Furthermore, Living Lab researchers were identified as pivotal connectors and buffers between individuals living with dementia and SMEs, facilitating the adoption of technological products (18). It also highlighted that the implications of living with dementia need to be acknowledged and respected by care professionals, researchers and companies which may imply the adaptation of the technology, methodologies, or evaluation process, requiring time, flexibility, patience and commitment by all of the institutions involved (18).

2 Materials and methods

The process of selecting Living Labs involved the application of multiple screening methods. Initially, four electronic databases (PubMed, Web of Science, Scopus, EBSCOhost) were searched to identify articles referencing Living Labs specifically dedicated to dementia and/or cognitive impairment. It is important to note that, because dementia is typically diagnosed when cognitive impairment becomes severe enough to affect social or occupational functioning (24), the study included Living Labs focused on dementia, cognitive impairment, and both.

The search strings and outcomes are detailed in the Supplementary Table S1. Following the removal of duplicates and non-English written articles, a pool of 57 full-text articles was screened for Living Labs focused on digital health, with solutions on dementia and/or cognitive impairment. From these databases, 23 articles mentioned established Living Labs and 7 Living Labs were identified with the desired focus.

Complementary to this, a search of the most established global Living Labs network was undertaken to identify other Living Labs with the intended focus, the European Network of Living Labs (ENoLL). ENoLL was chosen due to its international presence and extensive network (25). The search was performed in February 2024. From this screening method, 5 additional Living Labs with the intended focus were retrieved.

Furthermore, web searches were conducted to uncover additional relevant Living Labs. This retrieved 3 additional Living Labs. A total of 15 Living Labs were analyzed. Information about these Living Labs was gathered from their official websites and relevant scientific publications, including original research articles, reports, and case studies.

In the analysis of these Living Labs, each Living Lab was analyzed considering the following aspects: (1) type of living lab, (2) collaborative ecosystem, (3) user-centric approach, (4) technological infrastructure, (5) regulatory and ethical compliance, (6) innovation processes and methodologies, (7) impact and success metrics, (8) sustainability and scalability, (9) knowledge sharing and dissemination, (10) funding and resource management. These aspects were chosen based on ENoLL evaluation criteria for Living Labs eligibility (26).

Regarding the type of Living Lab, three distinct types were considered: research-driven Living Lab, Living testbed, and Living Lab as a service. To clarify, a research-driven Living Lab is characterized by a primary focus on scientific investigation and experimentation. This type of Living Lab prioritises academic research and collaboration with research institutions. Their primary goal is to generate new knowledge and advance scientific understanding. Living testbeds are environments specifically designed for the practical testing and validation of technologies, solutions or innovations. These testbeds aim to replicate real-world conditions to assess the feasibility, performance, and functionality of new concepts. Living Lab as a service refers to a model where organizations offer Living Lab facilities and expertise as a service to external entities, such as businesses, startups, or government agencies. This approach allows external partners to leverage the infrastructure, resources, and knowledge of an established Living Lab without having to develop and maintain their own. It is pertinent to note that certain Living Labs may fall into more than one of these designated categories (27).

Then, collaborative ecosystems were assessed aiming to explore whether Living Labs led collaborative initiatives and projects with other entities such as universities, industry, healthcare providers, government agencies and others.

Concerning the user-centric approach, the focus shifted to examining the integration of end-users in co-creating and evaluating digital health solutions, along with exploring the methods and tools employed to gather feedback and ideas from these users. In this context, it is essential to distinguish between two key concepts: co-creation and co-design. Co-creation involves a collaborative approach to creative problem-solving that engages diverse stakeholders throughout all stages of an initiative, encompassing problem identification, solution generation, implementation, and evaluation. On the other hand, co-design is a subset of co-creation, specifically emphasising the active collaboration among stakeholders in designing solutions tailored to a pre-defined problem (28).

Turning to technological infrastructure, the analysis centred on studying the availability of the necessary infrastructure for testing and validating digital health products. This also encompassed an examination of the integration of emerging technologies such as AI, IoT, VR, wearables, etc. in testing processes.

Subsequently, regulatory and ethical compliance was considered, particularly focusing on the adherence to frameworks related to health, digital health, and data protection and security in the healthcare field.

Concerning innovation processes and methodologies, the analysis encompassed the transparency and structure of the innovation process (prototyping, testing, and scaling up). This also involved evaluating the utilization of design thinking, agile methodologies, or other relevant approaches.

The impact and success metrics of Living Labs were analyzed with a focus on their demonstration of improving healthcare outcomes, efficiency, and patient experiences, accompanied by clear success metrics and evidence of achieved results.

This was followed by exploring the sustainability and scalability plans and initiatives of the Living Labs, which included strategies for integrating successful solutions into health systems.

In terms of knowledge sharing and dissemination, emphasis was placed on the efforts of Living Labs to share knowledge, best practices, and lessons learned with the wider community through dissemination activities.

Lastly, funding and resource management were considered, exploring budgetary allocations, funding sources, as well as the effective utilization and management of resources to sustain the operations and objectives of Living Labs.

3 Results

The data collection methodology allowed the identification of 15 Living Labs (Table 1). The majority of the Living Labs selected were European ($n = 11$): France ($n = 4$), England ($n = 2$), Spain ($n = 2$), Germany ($n = 1$), Scotland ($n = 1$) and Sweden ($n = 1$). Living Labs from Canada ($n = 2$), Australia ($n = 1$), and the United States of America ($n = 1$) were also included.

Among the 15 identified Living Labs, the primary research focus centred around leveraging digital technologies to improve/benefit: quality of life, well-being, dignity, cognition, autonomy, independent living, accessibility, social innovation, solutions focused on diagnosis, and the healthcare of people with dementia. Additionally, several Living Labs had solutions to reduce the burden on families, informal and professional caregivers and other health professionals of people living with dementia (Table 1).

The products tested/developed included assistive technologies (e.g., remote monitoring systems and context-aware applications), environmental assistance "smart homes" by intelligent appliances and furniture (e.g., kitchen appliances, refrigerator and bed), intuitive user interfaces (e.g., TV and voice control), health monitoring technologies (e.g., apps), digital diagnostics and phenotyping, digital therapeutics and clinical implementation (e.g., sensing technology to assess behavioral and psychological symptoms and to monitor treatment response in people with dementia).

The characteristics of each Living Lab were collected, and the main findings are presented in Table 2. The main categories of the Living Labs studied were research-driven Living Lab ($n = 12$), Living testbed ($n = 9$) and Living Lab as a service ($n = 3$).

Regarding the collaborative ecosystem, the majority of the Living Labs analyzed are known to carry out or are carrying out partnerships with different entities ($n = 12$), including industry, startups, SMEs or larger companies, R&D organizations or centres, universities, healthcare providers and civic sectors and associations, building projects and various collaborative initiatives. However, only a small number ($n = 2$) reported having partnerships with policy-makers and representatives of ethical committees. For example, the LUSAGE Gerontechnology Living Lab demonstrated a comprehensive engagement across a wide spectrum of stakeholders, including in their network, policy-makers, health insurers, representatives of ethical committees and other relevant stakeholders (29). It's important to acknowledge that available information was limited in this field for the remaining Living Labs, preventing definitive conclusions regarding their partnership structure.

Based on the available information, within the selected Living Labs, most have included co-creation with the end-users ($n = 6$), others include co-design and user testing ($n = 3$), only co-design ($n = 2$), or only user testing ($n = 1$). Interestingly, the DIDEC Living Lab follows a co-learn, co-design and co-effectuate pathway (20). For the co-creation and co-design and to gather feedback and insights from users, several strategies were reported, including focus groups, interviews, direct observations, surveys, questionnaires (e.g., pre-and post-intervention), workshops, meetings or sessions, mapping and strategic foresight.

Concerning technological infrastructure, a significant number reported having the necessary mechanisms to guarantee effective testing and adequate validation of the results of their products, services or interventions ($n = 9$). Some had fully equipped simulated real environments. For instance, the Bremen Ambient Assisted Living Lab (BAALL) features all standard living areas—bedroom, bathroom, dressing area, living and dining room, kitchenette, and home office—within a 60 m2 apartment, suitable for accommodating two people on a trial basis (30). Similarly, the LUSAGE Gerontechnology Living Lab boasts a versatile architectural layout that can be tailored to conduct *in-situ* observations, mimicking a home-like setting, according to the requirements of each project. This setup offers a controlled environment for studying user interactions with technological devices via non-intrusive methods such as an eye tracker, different types of sensors, and an audio and video recording system (29). Interestingly, the StrathLab uses VR to model 'real-world' environments such as pharmacies, or various spaces within a household (31). Alternatively, one Living Lab identified relied on external institutions for assessments in real-life conditions, for instance, hospital departments, day-care centres or residential establishments for dependent older adults. Related to this, some Living Labs reported integrating emerging technologies in testing processes ($n = 6$), using mostly different types of wearables and sensors, but also, AI, RV and AR.

Regarding regulatory and ethical compliance, as well as data protection and security, there was limited information accessible online. Only two Living Labs explicitly state compliance with regulatory frameworks and ethical guidelines. The Living Lab at Liverpool John Moores University emphasized the importance of ethical considerations, ensuring that individuals deemed too vulnerable or lacking capacity should be identified and should not participate. As part of their methodology, they also provide individuals living with dementia the option to have another person present during interviews, whether it be their informal caregiver or formal carer, as a supportive measure (21).

In terms of the innovation process carried out and the methodologies applied, some of the selected Living Labs lacked publicly available information about their innovation process. Nevertheless, many exhibit transparent and structured innovation processes, including ideation, prototyping, testing and scaling up, primarily employing problem-solving methodologies ($n = 10$). Based on the information available, the most predominant is design thinking, i.e., human-centred design to tackle problem-solving needs; only a small number of Living Labs utilize agile methodology, i.e., an iterative and incremental process that is beneficial in uncertain contexts (32).

In terms of impact and success metrics of the selected Living Labs, the majority demonstrate their impact on improving healthcare outcomes, efficiency, or patient experiences ($n = 10$). This is evidenced through the sharing of success stories, the introduction of products and interventions in the market and the publication of scientific articles, case studies or reports. However, fewer have clear and available success metrics and evidence of achieved outcomes ($n = 6$).

Concerning sustainability and scalability, the absence of information prevented a detailed analysis of the Living Labs' plans, initiatives, or strategies in this domain. Only one Living Lab

TABLE 1 Identified Living focused on digital health, with solutions for dementia and/or cognitive impairment (n = 15), along with their corresponding countries, as well as a brief overview outlining the purpose and objectives of each Living Lab.

Living Lab	Country	General description and objectives of the Living Lab
LUSAGE Gerontechnology Living Lab	France	The LUSAGE Gerontechnology Living Lab specialises in designing and providing assistive technology for older adults, focusing on enhancing their autonomy and quality of life, particularly those living with cognitive impairment (e.g., Mild Cognitive impairment, Alzheimer's disease and related dementias), and supporting their informal and formal caregivers.
Bremen Ambient Assisted Living Lab (BAALL)	Germany	At the BAALL, new ambient assisted living technology is tested for usability in a 60 m^2 apartment designed for two people. This apartment includes standard living areas and follows the design-for-all principle. This Living Lab anticipates the scenarios that may arise from age-related physical or cognitive impairments and plans to compensate for them using technological assistance.
The Living Lab at Liverpool John Moores (LJMU)	England	The LJMU collaborates with people living with dementia to develop innovative solutions for their daily challenges. The team works with the business sector, academia, and service providers, focusing on co-creating memory-enabling technologies for the health and social care of people living with dementia.
Laval-ROSA Transilab	Canada	The Laval-ROSA Transilab uses Living Lab and learning health system approaches. It aims to improve care transitions between different settings - Family Medicine Groups, home care, and community services -, ultimately improving the care of people living with dementia and their caregivers.
Médéric Alzheimer Foundation Living Lab	France	The Médéric Alzheimer Foundation Living Lab develops and evaluates products, services, and interventions for people living with dementia, involving them throughout the process. It aims to enhance the integration and quality of life for older adults with Alzheimer's and related illnesses. Its main focus is assessing the impact of psychosocial interventions, such as cognitive stimulation through technology use, art therapy, music therapy, and reminiscence, on the quality of life for those living with Alzheimer's disease.
DOMUS (Laboratoire de Domotique et informatique Mobile à l'Université de Sherbrooke)	Canada	The DOMUS features a versatile infrastructure for designing, implementing, and evaluating cognitive orthotics (assistive technology) that supports various activities of daily living (ADLs), to help people with cognitive impairments - Alzheimer's disease, mental retardation, schizophrenia, or traumatic brain injury – to live independently. DOMUS operates three Living Lab variants: a smart apartment for short-term studies; a housing unit enabling long-term studies in a technology-rich real house; and mobile setups for long-term studies in older adults' homes.
Swinburne Living Lab	Australia	The Swinburne Living Lab aims to increase the quality of life and independence of vulnerable user groups, including older adults, individuals living with dementia, those with disabilities and culturally diverse groups. This Living Lab plays a key role in the development of Assistive Robots for the future of healthcare. Their goal is to create innovative solutions that are easily embraced by users because they fit with their actual needs.
MINDLab	Spain	The MINDLab aims to enhance social healthcare and promote independent living among older individuals and those facing autonomy challenges, such as people living with dementia, through innovative solutions. This Living Lab focuses on older adult's home settings. Its activities range from assessment of needs and co-design to implementation in simulated Living Lab environments and real home pilots, with a thorough analysis of usability challenges. Companies have the opportunity to test their technology in real environments.
Idea	Spain	The Idea Living Lab aims to improve the quality of life of older people, including individuals with cognitive impairments. It provides services and products in the field of care and digitalization. The Idea Living Lab also provides services to public administrations, private entities, and technology companies, including gerontological consulting, research partnerships, product viability analysis, co-design and testing of ICT products.
Pasteur Innovative Living Lab of Nice	France	The Pasteur Innovative Living Lab of Nice fosters the emergence and growth of digital technologies in the domain of homecare and independent living. This Living Lab is equipped with a model apartment that is designed as a showcase and a testing platform for technologies supporting independent living and autonomy.
Lab4Living	England	The Lab4Living aims to address real-world issues that impact health and well-being, developing products, services and interventions that promote dignity and enhance quality of life. Established to promote user-driven innovation through co-creation, Lab4Living focuses on various projects, with a particular emphasis on researching ageing and age-related diseases such as dementia.

(Continued)

TABLE 1 (Continued)

Living Lab	Country	General description and objectives of the Living Lab
StrathLab	Scotland	The StrathLab aims to translate health and care innovation into equitable and accessible care for all. Its focus is on improving socially inclusive and sustainable care at home through technology. StrathLab is connected to a set of networks such as Carer and Dementia Networks. StrathLab has innovation facilities including VR labs and simulations of real-world environments.
The Technology and Aging Lab at McLean Hospital	United States	The Technology and Aging Lab at McLean Hospital provides an environment for optimising treatments and providing support for patient-centred research initiatives. This Living Lab researches the influence of digital tools on psychiatric care throughout life, with a special emphasis on older adults and individuals living with dementia and their caregivers. The investigations cover digital diagnosis tools, technology-enhanced therapies, and the incorporation of technology into patient care processes.
Living Lab Vieillissement et Vulnérabilités (LL2V)	France	The LL2V is focused on testing, evaluating, researching, and developing prevention and support solutions for common vulnerabilities in older adults, including cognitive impairment. Its projects involve the creation of digital solutions such as innovative VR entertainment and the development of Integrated Technology Assistance for daily living, among others.
Digital Innovation for Dementia Care (DIDEC)	Sweden	The DIDEC aims to enhance innovation, competitiveness, and growth among SMEs focusing on technology for dementia care. It aims to achieve this through enhanced methodologies for collaborative and challenge-driven innovation within dementia care. The initiative utilizes a dedicated testbed for its activities.

has available information about this. As a result, it is not feasible to examine how these entities aim to integrate successful solutions into conventional healthcare systems or their broader sustainability and scalability efforts. It is also important to highlight that some of them exhibit lower maturity or are relatively recent, with a temporal scope constrained within the bounds of specific research projects. The only exception is the Laval-ROSA Transilab which has clear plans for sustainability, beyond the planned project funding. For instance, they intend to employ a research agent to facilitate coordination and foster internal sustainability (33). Additionally, this Living Lab also aims to support the learning transfer from Transilab to other health organizations (33).

Regarding sharing and dissemination, almost all the Living Labs reported efforts to share knowledge, best practices and lessons learned with the broader community ($n = 14$). Additionally, half of the Living Labs analyzed are members of ENoLL ($n = 7$). ENoLL, a global network of open Living Labs, plays a crucial role in this dissemination by fostering a dynamic, multi-layered innovation ecosystem that facilitates cooperation and synergy among its members and external stakeholders (25). Besides ENoLL, the Swinburne Living Lab is also a member of the Australian Living Lab Innovation Network (ALLiN) (34). Furthermore, the dissemination of knowledge by some of the identified Living Labs is promoted through the publication of editorials, literature reviews, case studies, book reports and other scientific articles, training, workshops, congresses, webinars, newsletters and/or posters (20, 21, 29, 30, 33, 35–38).

Finally, regarding financing and resource management, the larger part of the Living Labs provides limited or no information on this aspect. From our analysis, only four Living Labs have some information about financial support. For the majority, project funds are described as the main source of budgetary support. The importance of financial support was particularly stressed by the LUSAGE Gerontechnology Living Lab which underscored the need for a sustainable business model. This model should address key issues such as defining roles for private (such as banks and insurance companies) and public stakeholders, recognizing the value of innovative solutions, and establishing legal and political frameworks for sustainability strategies (29).

4 Discussion

Many digital health solutions for dementia do not meet the specific needs, expectations and capabilities of individuals (39). This highlights the importance of creating customized technology and the need for the Living Lab approach, which involves end-users in the development process through a collaborative multidisciplinary network. While this approach is gaining increased interest from researchers and policymakers as a "practical innovation ecosystem," there remains a significant gap in understanding its operation and resultant outcomes, prompting inquiries into its effectiveness (40).

With this in mind, the present study focuses on examining Living Labs that utilize digital solutions for individuals living with dementia or cognitive impairment. It aims to analyze their main characteristics to ultimately develop guidelines and highlight best practices for future initiatives in this area, and potentially aid in harmonising procedures regarding the operation of Living Labs in the field of dementia. To achieve this, 15 Living Labs were identified and analyzed, and several aspects came into consideration.

It is important to note that ENoLL already has a list of 20 indicators of the success of the performance of a Living Lab that can be seen as guidelines to follow. These indicators are based on the following areas: active user involvement, multi-method approach, multi-stakeholder participation, orchestration, real-life setting, and co-creation (26). There are other tools, similar to this one, that have been developed mostly in European projects [e.g., SISCODE Self-assessment questionnaire by Schmittinger et al. (41, 42) but are still in the testing phase or are not easily accessible due to scattered publications (41–43). Although these indicators are critical, they are

TABLE 2 Characteristics of the selected Living Labs ($n = 15$).

Criteria for evaluating Living Labs	Living Labs ($n = 15$)
Type of Living Lab	
Classification or categorization of Living Labs.	• Research-driven Living Lab ($n = 12$) • Living testbed ($n = 9$) • Living lab as a service ($n = 3$) • Information not available ($n = 1$)
Collaborative ecosystems	
Partnerships with different entities.	• Yes ($n = 12$) • Information not available ($n = 3$)
Collaborative initiatives and projects.	• Yes ($n = 12$) • Information not available ($n = 3$)
User-centric approach	
Integration of end-users in the co-creation and evaluation of digital health solutions.	• Co-creation ($n = 6$) • Co-design and user testing ($n = 3$) • Only co-design ($n = 2$) • Only user testing ($n = 1$) • Co-learn, co-design and co-effectuate ($n = 1$) • Information not available ($n = 2$)
Methods and tools for gathering user feedback and insights.	• Yes ($n = 12$) • Information not available ($n = 3$)
Technological infrastructure	
Availability of necessary technology infrastructure for testing and validating digital health products.	• Yes ($n = 9$) • Information not available ($n = 6$)
Integration of emerging technologies (e.g., AI, IoT, wearables) in the testing process.	• Yes ($n = 6$) • Information not available ($n = 9$)
Regulatory and ethical compliance	
Adherence to regulatory frameworks and ethical guidelines related to healthcare and digital health.	• Yes ($n = 2$) • Information not available ($n = 13$)
Data privacy and security	
Robust data privacy and security measures to protect sensitive health-related data.	• Yes ($n = 0$) • Information not available ($n = 15$)
Innovation process and methodologies	
Transparent and structured innovation process, including ideation, prototyping, testing, and scaling.	• Yes ($n = 10$) • Information not available ($n = 5$)
Impact and success metrics	
Demonstrated impact on improving healthcare outcomes, efficiency, or patient experiences.	• Yes ($n = 10$) • Information not available ($n = 5$)
Clear success metrics and evidence of achieved outcomes.	• Yes ($n = 6$) • Information not available ($n = 9$)
Sustainability and scalability	
Plans for sustainability and scalability of the Living Lab and its initiatives.	• Yes ($n = 1$) • Information not available ($n = 14$)
Strategies for integrating successful solutions into mainstream healthcare systems.	• Yes ($n = 1$) • Information not available ($n = 14$)
Knowledge sharing and dissemination	
Efforts to share knowledge, best practices, and lessons learned with the broader community.	• Yes ($n = 14$) • Information not available ($n = 1$)
Funding and resource management	
Adequate funding sources and efficient management of financial resources.	• Yes ($n = 4$) • Information not available ($n = 11$)
Allocation of resources for research, development, and operations.	• Information not available ($n = 15$)

general and lack the specificity needed for the operation and development of digital health Living Labs in dementia care.

The main focus of the Living Labs identified was to improve the quality of life and health of people living with dementia. However, it is worth mentioning that certain Living Labs prioritised the needs and designed solutions that targeted not only people with dementia but also individuals in their ecosystems, including caregivers, family members, and health professionals. Given the escalating demand for family caregivers due to the ageing population and the growing prevalence of dementia, there is a pressing need for tools that alleviate their burdens (physical, psychological and financial). These caregivers, who are predominantly older individuals themselves, require assistance and support in managing their caregiving responsibilities, enhancing their understanding (e.g., disease, care tasks, legal issues), and accessing healthcare services (44). Moreover, there is a noticeable willingness among caregivers to adopt new technologies to aid in their caregiving tasks (44).

Interdisciplinary collaboration also emerged as a crucial aspect of the selected Living Labs, promoting cooperation among researchers, healthcare professionals, technology experts, designers and people living with dementia to leverage diverse perspectives and expertise in solution development (18). However, it is fundamental to cultivate strategic partnerships with policymakers and ethical committees to ensure the sustainability of Living Lab initiatives. Ensuring long-term engagement with users and stakeholders is highlighted as essential, emphasising continuous feedback gathering, impact assessment, and adaptation to evolving user needs (29).

A significant hurdle faced by Living Labs in this field stems from the recognition that unique challenges arise in the process of co-creating products, services, and practices with people living with dementia. Communicating with designers and articulating their thoughts in a traditional co-design setting proves to be challenging for people with dementia (45). However, this design-driven approach to Living Labs has already proven effective in improving the value proposition of an innovative technological solution in the context of dementia care (46).

Within the studied Living Labs, most included co-creation with the end-users, while others included co-design and/or user testing. In this setup, users may either be seen as passive subjects to be observed or can actively participate as equal co-creators, offering valuable insights into the development of sustainable products and services. It is essential to emphasize that within a Living Lab approach, users should be regarded as partners in the innovation process, rather than just subjects of study (47). The selected Living Labs used different strategies to gather feedback and co-create with their end-users, such as focus groups, interviews, surveys, workshops, and strategic foresight exercises. While there is no standard practice in the literature, common methods for involving people with dementia in all phases of development include interviews and observations (48).

It is important to note that these approaches differ in the nature and intensity of the relationship between designers and users. A systematic review of involving people living with dementia in developing supportive technologies highlighted a lack of specific knowledge about the research methods and materials required to actively engage these individuals throughout the development process. It suggests that successful co-design with people living with dementia may not yet exist or is unpublished. The review found that the people involved were typically in mild to moderate stages of the condition. In all the studies reviewed, the initial idea for the technology or service had already been formed before including people with dementia. None of the articles measured whether the participants felt like equal partners in the process (48).

Co-creation with people with dementia can require multiple moments of explaining and repeating instructions, methodologies may need to be adapted to improve accessibility and timeframes may need extending (18). It is important to highlight that, although core symptoms such as reduced retrospective and abstract thinking, the course of dementia can vary, both between and within individuals, in an unpredictable way (48, 49). This is reflected in how they interact with and adopt technology (50). Therefore, designers and researchers should focus on the individual's current abilities when using or testing technology (50). Despite these challenges, individuals living with dementia often exhibit a sense of purpose and curiosity toward testing new products, which fosters their willingness to participate in such initiatives (18). Additionally, support from informal and formal caregivers can enhance the ability of people living with dementia to use the technology (50). Usually, caregivers also play a vital role in explaining and stimulating the use of technologies, which implies that the caregivers also need to embrace the technological product or service and see the value it adds to their daily care practice (51).

The selected Living Labs exhibit some gaps and weaknesses that may impede their overall effectiveness and long-term impact. One significant limitation is the lack of transparent communication channels and overall information about the Living Lab, which may hinder openness toward new partners, collaborations, investors and public visibility and interaction. This also extends to critical information about regulatory frameworks, ethical guidelines, data privacy and security measures, funding sources, and efficient financial management for research, development, and operations.

The lack of solutions to integrate the existing healthcare system may also hinder adoption and interoperability. A recent review showed that the Living Lab approach contributes to the successful implementation of innovations in healthcare. It also reported that for this successful implementation, it is necessary six factors: early involvement of end-users, appropriate timing, effective leadership, openness to change, sense of ownership and organizational support (52).

Additionally, some of the Living Labs have a short-term duration, confined to the duration of specific research projects, which raises concerns about sustainability. The ability to continue project activities after the project concludes is jeopardized, potentially limiting the lasting impact these initiatives could have. Consequently, valuable effort, expertise, and knowledge acquired during these projects are at risk of being lost. Additionally, Living Labs frequently exhibit localized and small-scale scopes, presenting difficulties in achieving scalability. To attract larger-scale innovative enterprises, Living Labs must collaborate at national and international levels, overcoming this scalability challenge (53).

Another issue is that several of the identified Living Labs do not seem to undertake project evaluations or assess their impact. This lack of systematic evaluation hampers the progress of Living Labs, as it becomes challenging to learn from experiences and enhance future endeavors (54). Although Living Labs are beginning to pay attention to sharing their outcomes and benefits, only a few have focused on evaluating or measuring their performance (12).

Finally, the lack of a higher number of published articles or other dissemination activities restricts the broader accessibility of valuable insights and best practices in this field. Addressing these gaps is crucial for fostering the growth, sustainability, and impact of a Living

Lab. In fact, questions about the effectiveness and outcomes of Living Lab initiatives are partly owed to the paucity of published evidence and insufficient reports of performance evaluations (40).

4.1 Guidelines for digital health Living Labs focused on dementia

Drawing from trends, best practices, and limitations observed in the analyzed Living Labs in this narrative review, as well as insights from existing literature discussed above, a comprehensive set of guidelines is proposed for Living Labs employing digital solutions for individuals living with dementia or cognitive impairment. These guidelines encompass 10 pivotal areas (Table 3).

These pivotal areas include the establishment of collaborative ecosystems, promoting interdisciplinary engagement among dementia researchers, healthcare practitioners, technologists, and caregivers. Additionally, a user-centric approach, where individuals living with dementia are engaged throughout all stages of innovation, is prioritized and tailored to the specific cognitive and functional intricacies of these individuals. Ensuring a robust technological infrastructure is essential, finely tuned to address the unique needs and challenges inherent in dementia care. Adhering to regulatory and ethical standards is emphasized to safeguard the integrity and privacy of sensitive health data. Transparent innovation processes are advocated, requiring clear documentation of methodologies and decisions throughout the innovation lifecycle. Moreover, the guidelines stress the importance of demonstrating impact through measurable success metrics, as well as planning for sustainability and scalability, and facilitating knowledge sharing and dissemination. Efficient financial and resource management is highlighted, alongside the implementation of continuous monitoring and improvement mechanisms, allowing for iterative refinement and adaptation of strategies in response to evolving technological landscapes and user needs within the dementia care paradigm.

TABLE 3 Guidelines proposed for the operation and development of digital health Living Labs focused on dementia.

Enhancing collaborative ecosystems	• Stress the necessity of fostering interdisciplinary collaboration among researchers, healthcare professionals, technology experts, designers, and caregivers to ensure holistic solution development. • Encourage strategic partnerships with policy-makers, ethical committees, advocacy organizations, and community groups to promote the sustainability and scalability of Living Lab initiatives.
Establishing a user-centric approach	• Integrate end-users, including people with dementia, caregivers, and healthcare professionals, in the co-creation process from the outset. This involvement should extend beyond mere consultation to active collaboration • Emphasize the importance of co-creation and co-design methodologies tailored to the unique needs and challenges faced by individuals living with dementia. These methodologies should accommodate various cognitive abilities and communication styles, facilitating active participation and meaningful engagement throughout all stages of innovation. • Advocate for the development of user-friendly and accessible communication channels and methodologies to facilitate the involvement of individuals with varying degrees of cognitive impairment. This may involve employing multiple modalities such as visual aids, simplified language, and interactive tools to facilitate understanding and engagement.
Technological infrastructure and emerging technologies	• Ensure the availability of well-equipped simulated environments for effective testing and validation of digital health products. • Advocate for adaptable and inclusive technological infrastructure to accommodate the diverse needs and preferences of individuals living with dementia • Embrace emerging technologies such as VR, AR, AI, IoT, wearables, and robotics in testing processes.
Regulatory and ethical compliance	• Stress the critical need for adherence to regulatory frameworks related to health and digital health and ethical guidelines, particularly regarding data privacy and security measures, to protect sensitive health-related data of individuals living with dementia. • Emphasize transparent communication of regulatory compliance measures and ethical considerations to stakeholders and the broader community to build trust and foster accountability.
Transparent innovation processes and methodologies	• Implement transparent and structured innovation processes, incorporating ideation, prototyping, testing, and scaling up. • Utilize design thinking and agile methodologies methods to enhance innovation processes. • Ensure inclusive decision-making by providing opportunities for stakeholders to contribute to the decision-making process and clearly outline how decisions are made. • Maintain accessible and well-documented records of the innovation processes and methodologies employed and make resources, protocols, and methodologies easily available to all involved parties.
Demonstrating impact and success metrics	• Establish clear success metrics for outcomes, efficiency (e.g., cost–benefit analysis, product/solution adoption rates), and patient experiences (e.g., user feedback and satisfaction). • Regularly assess and report the impact of Living Lab initiatives on improving the quality of life and/or health of people living with dementia.

(Continued)

TABLE 3 (Continued)

Sustainability and scalability planning	• Develop sustainability and scalability plans and initiatives, outlining strategies for integrating successful solutions into conventional healthcare systems. • Foster long-term partnerships and collaborations to ensure the continued success and growth of Living Lab initiatives. • Encourage Living Labs to develop long-term sustainability and scalability plans beyond the duration of specific research projects, leveraging strategic partnerships and diversified funding options. • Advocate for collaboration at national and international levels to overcome scalability challenges and attract larger-scale innovative enterprises, ensuring the broader adoption of successful solutions.
Knowledge sharing and dissemination	• Establish open and accessible communication channels to facilitate the sharing of knowledge among Living Lab stakeholders and the broader community. • Stress the importance of publishing articles and engaging in dissemination activities to increase the accessibility of valuable insights and best practices in the field. • Encourage active participation in collaborative networks and platforms to facilitate knowledge exchange and project partnerships, leveraging existing networks such as ENoLL and similar organizations.
Financial and resource management	• Highlight the necessity of transparent financial structures and efficient management of funding sources, addressing key issues such as defining roles for private and public stakeholders. • Advocate for diversified funding options and strategies to mitigate financial risks in innovation projects, ensuring the sustainability and longevity of Living Lab initiatives.
Continuous monitoring and improvement	• Implement a robust monitoring system to track the progress of Living Lab initiatives. • Regularly review and update the action plan based on the evolving technological, regulatory, and healthcare landscape, i.e., iterative evaluation. • Regularly benchmark and analyze outcomes against successful models to pinpoint areas for improvement and adapt Living Lab strategy in response to evolving goals, emerging trends, and the dynamic nature of innovation.

By addressing these areas, Living Labs can create a comprehensive environment for developing digital health solutions tailored to the specific needs of individuals living with dementia. These guidelines, designed to be actionable, empower Living Labs to tackle challenges and leverage best practices, fostering sustainable innovation through interdisciplinary collaboration, active end-user involvement, and strategic partnerships. Furthermore, they offer a framework for continuous improvement, ensuring adaptability to evolving technologies and user needs. By adhering to these guidelines, the Living Lab community can elevate the quality and impact of their initiatives, ultimately enhancing health outcomes and quality of life for people living with dementia. These guidelines provide practical recommendations for researchers, policymakers, and other stakeholders interested in advancing innovation in this field.

4.2 Limitations of the narrative review

This study has some limitations that need to be addressed. The process of selecting Living Labs may have introduced bias, as it relied on the publication of scientific articles and networks. This approach may have overlooked relevant Living Labs that are not mentioned in published scientific articles or belong to ENoLL, however, to overcome this, additional web searches were carried out. Additionally, the majority of the identified Living Labs were from European countries, with fewer from other regions. This geographic imbalance may limit the generalizability of the findings, as different regions may have unique healthcare systems, regulatory frameworks, and cultural factors influencing Living Lab operations. Finally, the analysis of Living Labs relied on publicly available information from official websites and scientific publications. However, the completeness and accuracy of this information may vary, leading to potential gaps or inaccuracies in the assessment of Living Lab characteristics and activities.

5 Conclusion

The rise of dementia within an ageing population demands innovative solutions, with Living Labs offering promising avenues for co-creating and testing interventions. In this study, 15 digital health Living Labs focused on dementia and/or cognitive impairment were examined and guidelines for the operation and development of these Living Labs were constructed. Key findings reveal the importance of user engagement and interdisciplinary collaboration. Challenges include integration in the healthcare system, communication gaps, limited scalability, and lack of systematic evaluation. These challenges underscore the need for a holistic approach to address the multifaceted issues hindering the effectiveness and long-term impact of Living Labs, an approach that holds promise as a practical innovation ecosystem. Proposed guidelines emphasize user-centric approaches for people living with dementia, specific collaborative ecosystems, technological infrastructure, regulatory compliance, transparent innovation processes, impact measurement, sustainability planning, knowledge sharing, financial management, and continuous improvement. Implementing these guidelines can enhance the effectiveness and long-term impact of Living Labs in dementia care. Moreover, the guidelines suggested have the potential to serve as a valuable resource for Living Labs, focusing on similar solutions, on a global level. This will pave the way for new and successful collaborations.

Author contributions

TF: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft. LM: Conceptualization, Data curation, Methodology, Visualization, Writing – review & editing. JoC: Conceptualization, Data curation, Methodology, Visualization, Writing – review & editing. DV: Conceptualization, Data curation, Methodology, Visualization, Writing – review & editing. SA: Conceptualization, Writing – review & editing. ND: Conceptualization, Writing – review & editing. MB: Conceptualization, Writing – review & editing. JF: Conceptualization, Writing – review & editing. MG: Conceptualization, Writing – review & editing. DF: Conceptualization, Writing – review & editing. AF: Conceptualization, Writing – review & editing. IF: Conceptualization, Writing – review & editing. JuC: Conceptualization, Writing – review & editing. MR: Conceptualization, Writing – review & editing. EC: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

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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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Supplementary material

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Advancing healthcare through data: the BETTER project's vision for distributed analytics

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Introduction: Data-driven medicine is essential for enhancing the accessibility and quality of the healthcare system. The availability of data plays a crucial role in achieving this goal.

Methods: We propose implementing a robust data infrastructure of FAIRification and data fusion for clinical, genomic, and imaging data. This will be embedded within the framework of a distributed analytics platform for healthcare data analysis, utilizing the Personal Health Train paradigm.

Results: This infrastructure will ensure the findability, accessibility, interoperability, and reusability of data, metadata, and results among multiple medical centers participating in the BETTER Horizon Europe project. The project focuses on studying rare diseases, such as intellectual disability and inherited retinal dystrophies.

Conclusion: The anticipated impacts will benefit a wide range of healthcare practitioners and potentially influence health policymakers.

KEYWORDS

data space, distributed analytics, FAIR principles, healthcare, rare diseases

1 Introduction

In recent years, data-driven medicine has gained increasing importance in terms of diagnosis, treatment, and research due to the exponential growth of healthcare data (1). The linkage of health data from various sources, including genomics, and analysis via innovative approaches based on Artificial Intelligence (AI) advanced the understanding of risk factors, causes, and development of optimal treatment in different disease areas; furthermore, it contributed to the development of a high-quality accessible health care system. However, medical study results often depend on the number of available patient data, crucially when it comes to rare diseases this dependency is accentuated. Typically, the more the data is available for the intended analysis or the scientific hypotheses, the more accurate the results are (1). Nevertheless, the reuse of patient data for medical research is often limited to data sets available at a single medical center. The most imminent reasons why medical data is not heavily shared for research across institutional borders rely on ethical, legal, and privacy aspects and rules. Correctly, data protection regulations prohibit data centralization for analysis purposes because of privacy risks like the accidental disclosure of personal data to third parties.

Therefore, in order to (i) enable health data sharing across national borders, (ii) fully comply with present General Data Protection Regulation (GDPR) privacy guidelines, and (iii) innovate by pushing research beyond the state of the art, this project proposes a robust decentralized infrastructure that will empower researchers, innovators, and healthcare professionals to exploit the full potential of larger sets of multi-source health data via

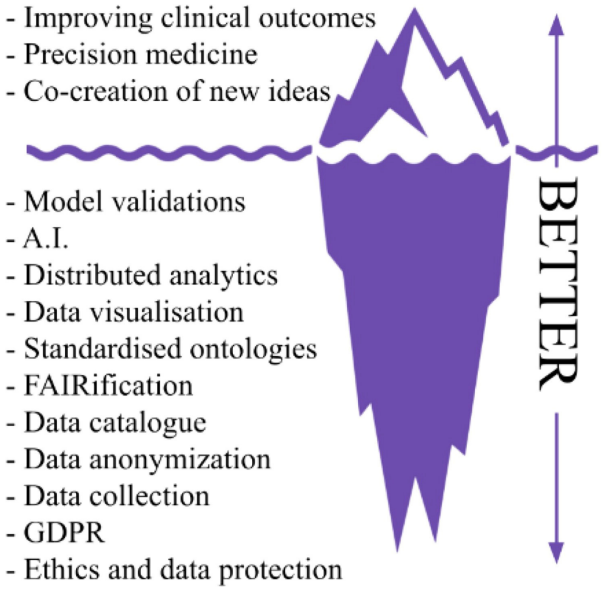

FIGURE 1
Iceberg representation of needed tasks to achieve precision medicine and innovation in real world scenarios, readapted from Subbiah (2).

tailored AI tools useful to compare, integrate, and analyze in a secure, cost-effective fashion; with the very final aim of supporting improvement of citizen's health outcomes.

In this paper, we present the Better rEal-world healThdaTa distributEd analytics Research platform (BETTER), a Horizon Europe Research and Innovation Action that has been conceptualized and designed as an interdisciplinary project consisting of 3 use cases all of which involve 6 medical centers located in the European Union and beyond, where sensitive patient data, including genomics, are made available and analyzed in a GDPR compliant mechanism via a Distributed Analytics (DA) paradigm called the Personal Health Train (PHT) (3).

The main principle of the PHT is that the analytical task is brought to the data provider (medical center) and the data instances remain in their original location. While many classic PHT approaches exist in the literature [see DataSHIELD (4) and WebDISCO (5)], for this project, two mature implementations of the PHT called PADME [Platform for Analytics and Distributed Machine Learning for Enterprises (6)] and Vantage6 [priVAcy preserviNg federaTed leArninG infrastructurE for Secure Insight eXchange (7)] will be fused and adopted as building blocks for the proposed BETTER platform. PADME has been developed by the Klinikum Der Universitaet Zu Koeln (UKK) and has already proven successful in several clinical use cases in Germany. Similarly, Maastricht University (UM) implemented and publicly released Vantage6 (8), a PHT paradigm successfully applied in many real-world healthcare use cases. UM showcased how to perform DA with horizontally (9) and vertically (10) partitioned data in different disease areas, namely oncology (9, 11–15), cardiovascular diseases (10, 16), diabetes type 2 (17), and neurodegenerative diseases. This work shows that federated learning in the healthcare domain is technically feasible, and shows a historical track record and knowledge of applying federated learning in the medical domain while knowing the challenges to scale and adoption, which are addressed in this project.

The clinical use cases we consider focus on evidence-based research on the following pathologies:

(1) Paediatric Intellectual Disability,
(2) Inherited Retinal Dystrophies, and
(3) Autism Spectrum Disorders.

Within those use cases innovative digital tools, technologies, and methods will be researched, developed, and validated in real-world scenarios. In this paper, our focus is on the catalyst role that distributed analytics can have in the field of e-health interventions, contributing to the transformation of the field of health services at an EU-wide level.

2 Building the research agenda

During the early design of our Research and Innovation Action, we came up with the need to define specific objectives and relate them to explicit measurable outcomes in order to help the development of the agenda and the workplan of the action. Below we present each of the three main BETTER research agenda constituents.

2.1 Overcome cross-border barriers to health data integration, access, FAIRification, and preprocessing

We aim to guide medical centers in collecting patient data following a common schema in order to promote interoperability and re-use of datasets in scope. This includes legal, ethical, and data protection authorizations, data documentation, cataloging, and mapping to well-established and therefore widely understood ontologies. Attention will be devoted to the FAIRification of the datasets used in the project. This means that the FAIR principles (18) (i.e., Findability, Accessibility, Interoperability, and Reusability) will be guaranteed in the results of the project. We will also focus on the integration of external sources such as, but not limited to, public health registries, European Health Data Space [EHDS, (19)], the 1+Million Genomes initiative [1+MG, (20)] and the European Open Science Cloud [EOSC, (21)].

Legal and ethical implications shall need to be duly considered and procedures for data access and re-use will be proposed. As a default preprocessing step data pseudonymization will be performed to mitigate the risk of personal data leak; this will be followed by data quality and integrity assessment. Finally, this objective enables the integration of a BETTER station at each medical center premises, validating the accesses to the relevant local datasets including genomics.

This first aim builds on the matured experience where cross-border health data integration has been demonstrated on a small scale. Novel concepts and approaches will be researched and developed to address BETTER integration of multiple data sources, interoperating with public health data repositories via BETTER,

data quality, and integrity assessment algorithm in a distributed fashion. A real-world large-scale data integration framework based on well-established ontologies will be demonstrated accounting for heterogeneous data sources including whole genome sequencing.

2.2 Deploy a distributed analytics framework for cross-border data processing and analysis

We plan to deploy, test, and utilize BETTER, a PHT-distributed analytics platform composed of stations hosted at each medical center's premises. Furthermore, a central service will be hosted by UKK in order to monitor and orchestrate activities. Importantly, this framework will support the development of analytics and AI tools via both Federated and Incremental Learning modalities; in line with GDPR data will not leave a single medical center. This framework will be exploited by researchers, data scientists, and software developers to securely build applications for analyzing multiple health datasets including genomics.

Access to cross-border healthcare data is indispensable for innovation; however—currently—it is time-consuming and difficult due to privacy and regulatory concerns (9). Furthermore, to effectively exploit multiple datasets via AI, a common schema and ontology should be applied. Here the ambition regards the deployment of BETTER, a privacy-by-design infrastructure, to all medical centers connecting FAIR data sources and allowing federated data analysis and machine learning. Crucially, patient data never leaves a medical center. To this end, the BETTER platform complements the implementation of EHDS2 (22) as it focuses on the integration of patient data including genomic and other clinical research data thus offering a reference architecture for future synergies between EHDS and 1+MG.

2.3 Development of distributed tools leveraging artificial intelligence capabilities

Within each use case, tailored tools are developed in order to properly answer clinical needs. Some of those will indeed exploit DA and AI to push data analysis boundaries going beyond the state of the art. Crucially, multiple data sources including genomics will be fused together aiming to better understand risk factors, causes, and development of the studied diseases. The tools will be developed using a co-creation methodology where medical end-users closely collaborate with researchers and technology providers enabling the emerging new concepts. Finally, trustworthy AI guidelines (23) will be followed throughout the development lifecycle, and particular attention will be devoted to the explainability of the developed tools.

Distributed algorithms iteratively analyze separate databases in order to learn without patient data being centralized (24). Within the healthcare sector, this subject is attracting a lot of attention and enabling important advances (25); furthermore, researchers are actively working on topics such as federated and incremental learning modalities, data and model parallelism, and ensembling techniques (26). This objective aims to research and apply novel computer vision, machine-, deep-, and reinforcement-learning techniques and apply them to health-related real-world data available in the use cases under study.

Apart from the above, there are other important aims that the project supports such as the ELSA (ethical, legal, and societal aspects) awareness in the AI lifecycle and aspects related to the planning, coordination, and implementation of the different medical use cases, on which we do not elaborate as they are not related to the core aspect of distributed analytics as a means to change our approach on real-world data integration.

3 The technology constituents

The BETTER project builds on the experience gained by UKK on PADME in deploying security-by-design PHT infrastructures in several real-world scenarios enabling medical centers to share and analyze multi-sources health data via a federated learning paradigm in a GDPR compliant mechanism. The importance of this result is also highlighted in a recently published Nature article (2) about the next generation of evidence-based medicine, the authors present an iceberg where evidence-based medicine represents only the tip of the iceberg, while the vast amount of different and heterogeneous data sources and processing tasks represent what lies underneath the surface. The author argues that "a deep synthesis and amalgamation of all available data is needed to achieve next-generation, deep evidence-based medicine". Figure 1 exploits the iceberg analogy to summarize the BETTER contributions.

In line with the emerging concept of the European Health Data Space, BETTER aspires to offer a lighthouse implementation of healthcare distributed analytics via a multidisciplinary framework based on PADME that supports better healthcare delivery, better research, innovation, and policy-making and, indeed enables medical centers to make full use of the potential offered by a safe and secure exchange, use and reuse of health data. Furthermore, three real-world use cases addressing different medical domains will be demonstrated and specific tools based on the latest technology and AI will be developed to address clinical needs in an innovative way, aiming to achieve results that go beyond the state of the art. BETTER will showcase a consistent, trustworthy and efficient set-up for the use of health data, including genomics, for clinical decision support.

The proposed platform will follow an inclusive, rich inter- and trans-disciplinary methodology, not only across scientific disciplines but also facilitating and promoting knowledge sharing between universities, Small and Medium Enterprises, and healthcare professionals. An Agile methodology will be adopted and a shared 'language' will be built to effectively close gaps between scientific knowledge, clinical needs, policy changes, and technological issues in a broader sense. Contrary to a waterfall model, ideas, prototypes, and discussions will constantly loop through the project's beneficiaries for early validation and fast development. Vitally, brainstorming, collaborative design, and scientific contamination will be promoted across use cases by actively engaging (calls, meetings, workshops, events, etc.) researchers, technology providers, healthcare professionals, and relevant stakeholders.

3.1 The overall BETTER platform

As per the PADME framework, BETTER relies on the concept of "bring-computation-to-data" via incremental and federated learning, which avoids unnecessary data moving across medical centers while exploiting much of the information encoded in such data (1). The intuition behind BETTER can be explained via a railway system analogy which includes *trains*, *stations*, and train *depots*. The train uses the network to visit different stations to transport, for example, several goods. By adapting this concept to BETTER, we can draw the following similarities:

- The *Train* encapsulates an **analytical task**, which is represented by the good in the analogy.
- The **data provider** takes over the role of a reachable *Station*, which can be accessed by the Train. Further, the Station executes the task, which processes the available data.
- The *Depot* is represented by our **central service** including procedures for Train orchestration, operational logic, business logic, data management, and discovery.

Thus, from a top-level perspective, the main infrastructure components are Trains, Stations, and Central Service; furthermore, additional modules are available for privacy and security enforcement. An overview of the whole BETTER platform system can be observed in Figure 2; the main constituents are detailed below.

3.1.1 Trains

A Train needs to encapsulate code to perform certain analytical tasks, which are executed at distributed data nodes (the Stations). As it performs its duty, a Train travels from one Station to another and executes commands on-site, utilizing the data available in each location. Thus, the result of the analysis is built incrementally and can be anything, based on the Train code. To achieve this result, the code of the train is encapsulated in an Open Container Initiative-compliant [see The Linux Foundation (27)] image where the code is encapsulated along with all the required dependencies, thus eliminating the need for Train developers to handle the diverse execution node environments. Moreover, in order to increase transparency, a Train stores metadata information about the data the code is accessing, the type and intent of the analysis and its creator. In order to enhance security, a Train must be instantiated exclusively from a Train Class that is stored within an App Store. The App Store is a repository of Train Classes; ahead of being published in the App Store each Train Class is examined by the community and/or by automatic procedures to detect malicious code in particular to prevent disclosure of Stations private data. During their lifecycle, trains can be in several states. First, a Train Class which passed security checks is created and stored in the App Store. When a researcher or an innovator wants to conduct a data study, they select a suitable train from the App Store, and a new instance of the Train is created. Subsequently, the Train moves to an idle state, waiting to be moved to a Station; after the transmission, the Train remains in the idle state at the Station and applies to achieve the permit to be executed. If the Station Administration grants the permission the Train changes its state to running. At this stage, two scenarios may happen:

(a) The Train execution is successful, and the Train is sent back to the Central Service to be routed to the next Station;
(b) The Train execution fails: in this case, the Train is however sent back to the Central Service for code analysis and debugging.

3.1.2 Stations

A Station is a node in the distributed architecture that holds confidential data and executes the code of the trains. In the most common scenario, a Station corresponds to an institution, hospital, or department. Each Station acts as an independent and autonomous unit. Each Station has two main components: (a) the data and (b) the software (i.e., the container executor). Stations receive trains to be executed; however the execution is not automatic by default but rather the Station administration has to grant permission and can reject the Train, for example, due to doubts about the data usage or a lack of capacity. Anyhow, Station administration can also configure that Trains with specific characteristics are automatically executed. When the execution of a Train terminates, the Station administrator checks the results of the Train. The train can be rejected if the results contain confidential data. In addition, every Station offers a visual interface that serves as a control panel for the Station administration to coordinate the Trains' execution cycle. To summarize, each Station has to:

(a) Manage the permission applications for controlling access to the confidential data stored within the institution;
(b) Execute the Trains producing the partial results in the context of incremental use of the federated analytical framework.

3.2 The BETTER central service

The Central Service component provides three types of services: (a) a metadata repository to allow data discovery; (b) management tools for Train creation, secure transmission to Stations, orchestration, monitoring, and debugging; and (c) a repository of pre-trained trains that can be directly used by healthcare professionals on their own data to get the results of an AI-based method that has been iteratively trained on data from various institutions. The metadata repository of the Central Service, for each health record datum (e.g., radiology image, genetic test) stores (a) information about its type, the format in which the information is encoded, and the protocol and technologies that have been used for its production; (b) anonymized patient-related data (of particular relevance for patient stratification and longitudinal studies); and (c) information on the location of the datum (i.e., the custodian Station where the datum resides). Notice that only metadata are reported, not the data itself, which is only stored at the corresponding Station. The metadata repository is constantly updated by means of federated queries to all the Stations affiliated with the distributed architecture. The data in the metadata repository are stored using terms from well-known and standard pipelines, in order to maximize the interoperability of data from different institutions. The Central Service also

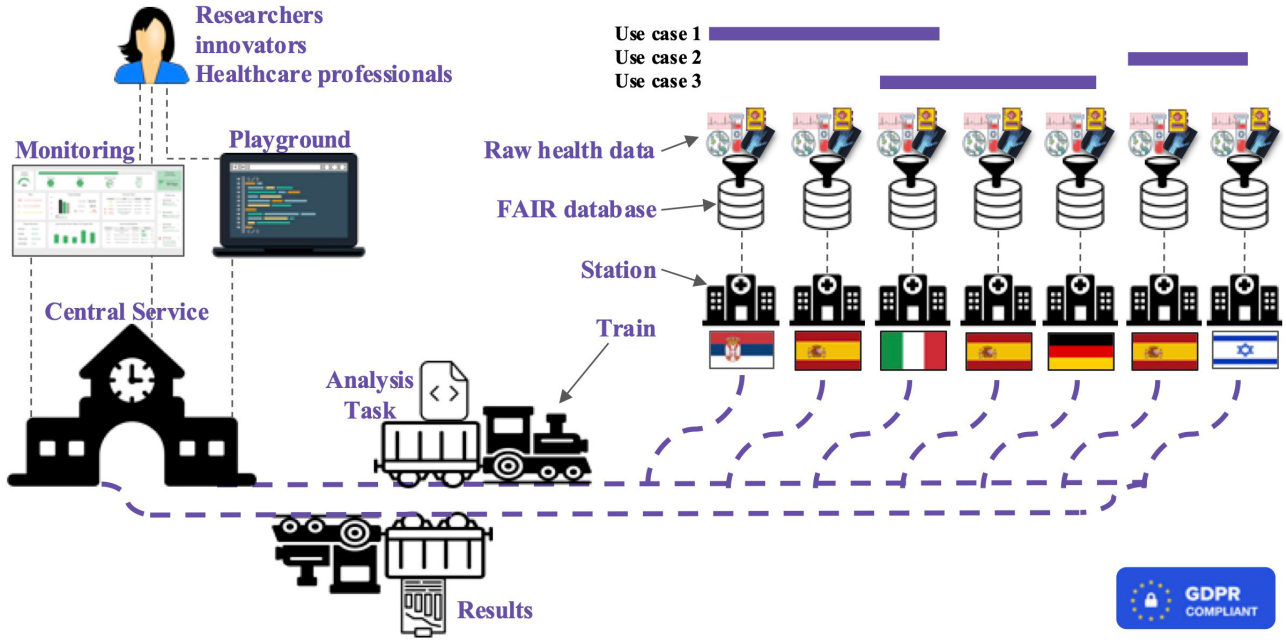

FIGURE 2
High-level representation of the BETTER platform where researchers, innovators, and healthcare professionals can run analysis and receive results exploring cross-boarders health data.

provides all the management tools to allow the creation of a Train by a scientist from a Train class in the App Store, the secure transmission to and from Stations, and the notification to the scientist.

Finally, Trains that have been executed on several Stations and have been analyzed both by each of the Station Administrators and by the involved partners to ensure that they do not disclose protected data, can be stored in a repository of pre-trained Trains. We envision such Trains to perform future complex AI-powered operations (e.g., evaluate the condition of a patient from a medical record); a healthcare professional can clone a pre-trained Train on their local environment and execute it on their local data to get predictions. In this way, both patients and healthcare professionals can benefit from AI-based solutions, without the need to design the analysis and train the model. Moreover, as the execution is local, no private data is disclosed.

A web-based monitoring interface will ensure users with different roles access with respect to different content and functionalities within the BETTER platform. Researchers, innovators, and healthcare professionals will be able to perform analysis through the Central Service, as well as share results with other researchers and professionals to enhance cross-border collaboration in medical investigation. Moreover, policymaker user access will be also available with a high-level reporting view to easily see trends, and patterns and identify unexpected events. This will enable policymakers to identify problems and take data-driven corrective actions.

3.2.1 Monitoring component

The BETTER platform includes a Train metadata schema that provides detailed information about each Train, allowing Train requesters and Station administrators to access relevant data such as Train location and status. Each Station is also equipped with a metadata Processing Unit that collects and stores static metadata about the Station and dynamic Train execution information such as current state and processing unit usage. This dynamic data is converted to conform with the schema standard and transmitted to a global Train metadata repository located in the Central Service. The Station administrators can also apply customizable filters to the metadata stream, allowing them to maintain control over the outgoing processes through a web-based monitoring interface. If PADME is used, a reference to the available metadata schema is in the documentation (28).

3.2.2 Playground component

The research and development of AI-driven analysis on distributed health data today still represents a significant challenge due to the complexity and limited literature available. Based on experience, researchers and developers require time and practice to familiarize themselves with the infrastructure and overcome the initial complexity. To this end, BETTER provides a Playground component that allows exploration, test, and validation of analysis tasks. For instance, it allows for:

(1) Testing criteria including proper connection interface, matching schema, error-free analysis execution, and correct result storage structure.
(2) Validate connection interface: the DA algorithm must be able to connect to the data source properly. This means the configuration of the algorithm should match the data source's connection interface. All connection credentials (such as file path, hostname, port, and type of database) should be correct.

(3) Assess matching schema: the DA algorithm should be able to send correct queries to the data store and receive the corresponding results. Hence, the expected data schema of the analysis task should match the actual schema of the data source.
(4) Error-free execution: if the connection interface and matching schema are correct, the DA algorithm should execute without any errors. This means the program should terminate with exit code 0, indicating a successful program execution.
(5) Correct result storage: the analysis results should be stored in the correct location and format. The code should emit the results as a file or a processable bit string for transmission. An initial implementation of this component is available and documented on PADME [see Weber and Welten (29)].

3.2.3 Privacy and security enforcing components

The privacy and security components can be subdivided into two aspects: (1) components for user authentication and (2) permission management and components for secure transmission and lifecycle handling of Trains.

Regarding the first aspect, the access to the Central Service (that allows to request a train and to query the metadata repository) is controlled by an Identity and Access Management (IAM) component which manages user accounts and access authorization.

Regarding the second aspect, Trains' life cycle handling, as per PADME the architecture follows several design principles to protect sensitive data. One assumption is that the station admin, who is interacting with the Station software, is authorized to inspect and release potentially sensitive data, which has been generated in the context of the Train execution (e.g., a query result or model parameters). However, the admin's authority is limited and is only valid within the institutional borders. Therefore, the admin must not see the results of the preceding stations. The admin further should also be sensitized to the intrinsic activities of the executed Train and the files inside the Train, which will be released after the Train has left the institution. To meet these requirements, the Station software incorporates a mechanism to inspect the Train contents and visualize added, changed, or deleted files. In addition, in case the Train produces query results, the admin is able to audit the file contents themselves. The software detects the changes and only visualizes data, which is relevant to the current station by simultaneously hiding information from other stations.

For transmission, BETTER adopts a private-public key encryption policy; the assumption here is that the Central Service is considered trusted. The accomplishment of a secure transmission is made possible through the implementation of an encryption process that ensures no Train is stored in an unencrypted form and only the intended recipient has the ability to decrypt it. This strategy specifically employs the utilization of private and public keys for each involved entity, including the Train requester, Central Service, and Stations. First, the train requester instantiates a Train instance, which is encrypted by a symmetric key. This symmetric key is generated for each Train request ad hoc. In the second step, the symmetric key is encrypted by the public key of the first station. After the Train transmission, the Station reversely decrypts the Train, executes it, and re-encrypts it with the public key of the Central Service. This procedure is repeated for each Station in the route. At the end, the final Train including the encrypted aggregated results is stored in the Central Service encrypted such that only the requester is able to inspect the results.

3.3 Deployment at each medical center

The proposed platform requires that a dedicated hardware (server) is deployed within each medical center premises; this server actually implements the Station and ensures the availability of computational power. As per PADME, the integration of a new Station (medical center) in the BETTER ecosystem is done through an "Onboarding Service." The service includes registration to the BETTER Station Registry and setting up the Station Software. The Station Registry is a central service that allows users to onboard, register, and manage station information. It provides an overview of stations. A new station is registered by filling in the station data. The Station Registry also generates public/private keys and the .env file for each onboarded station. The Station Software can be configured by following the provided web browser-based wizard steps. Station Software is a local software component that is installed on the medical center site. Station software provides a graphical user interface as a management console to coordinate the Train execution cycle. The connection from Station Software to the medical data source that is kept in the medical center server should be configured by the Medical center IT department. As a reference, well-documented deployment instructions are available on PADME documentation (30).

4 Data aspects

Better integration and use of health-related real-world and research data, including genomics, for improved clinical outcomes, is gaining more importance in the last years. The context to this relates to the fact that researchers, healthcare professionals but also science entrepreneurs shall benefit from better linkage of health data from various sources, including genomics, based on harmonized approaches related to data structure, format, and quality. This shall be further useful as they will have access to advanced digital tools for the integration, management, and analysis of various health data re-used in a secure, cost-effective, and clinically meaningful way enabling the improvement of health outcomes. Below we present our approach toward data FAIRification and data fusion in the BETTER project.

4.1 Data FAIRification

4.1.1 Rationale

A solid infrastructure that is able to organize and share the needed information at the central level (thus enabling also pair-wise interchanges between the data providers' stations) is needed. As a fundamental approach for designing the metadata, the BETTER project will follow the DAMS proposal (1), which has introduced a foundational metadata schema to allow DA infrastructures to comply with FAIR principles (18). The DAMS schema comprises two categories of metadata: those related to Trains and those related

to Stations. Trains must be described by (1) *Business information* (e.g., the author of the Train algorithm); (2) *Technical information* (e.g., the data type the algorithm is processing); and (3) *Dynamic execution information* (e.g., the log output the Train is producing). In parallel, Stations must contain (1) *Business information* (e.g., the location of the data provider); (2) *Runtime environment information* (e.g., capabilities in terms of computational power); (3) *Data information* (e.g., size of a dataset or the data type provided by the station).

The choice of which attributes including within each entity dimension of the repository will be crucial for fulfilling the FAIR data principles requirements. In line with the DAMS approach, we plan on aligning our business information to the DataCite Metadata Schema (31), which assigns digital object identifiers to both trains and station assets and ensures that sufficient information is available for each of their components. The Friend of a Friend ontology (32) can be employed to express business information about social entities (such as the owners of trains and stations). The technical information of the train and the data information of the data provider will be aligned with the Software Ontology (33). The Data Catalog Vocabulary may be used to provide predefined attributes describing the semantics of data sets (34).

Differently, clinical data types and related metadata are typically specific to the context of use, leveraging the characteristics of the disease, of patients, and relevant parameters for the problem at hand. BETTER is prepared to address the data management problem with a general approach. As these data types are not covered in DAMS, their management will be inspired by extensive previous work in the field [conducted within the "Data-driven Genomic Computing" ERC AdG n. 693174 (35)]. More specifically, four directions in the agenda of BETTER will be followed to guarantee the scalability of semantic/syntactic standards of clinical data types:

1. We will ensure interoperability at the level of the same pathology by having the partners generate datasets that agree upon the same standards.
2. We will employ a data schema that captures the main properties of a generic clinical context, keeping a high abstraction level to encourage maximum interoperability [examples are the Genomic Conceptual Model (36) and the COVID-19 Host Genetics Initiative Data Dictionary (37)]. Typically, clinical data involve demographic (or static) information on the patient and longitudinal measurements related to medical encounters, treatment, or laboratory measurements.
3. We will use a key-value paradigm for information that is not shared among different pathologies and that is specific to a given use case, thus creating a very flexible and expressive data model that allows storing all relevant information without dealing with integration and interoperability at the storage level [see Masseroli et al. (38)].
4. We will perform semantic annotation by using, predominantly well-adopted terminologies such as NCIT (39), the International Statistical Classification of Diseases and Related Health Problems (ICD) at its most updated version [11th revision, (40)], and Logical Observation Identifiers Names and Codes [LOINC, (41)]. For other information, we will employ dedicated biomedical ontologies as we described in Bernasconi et al. (42), sourcing them from BioPortal (43) and Ontology Lookup Service (44). In this way, we will pursue complete semantic interoperability between the metadata associated with known ontology.

For genomic data, the BETTER project will initially acquire DNA and RNA sequencing data in both FASTQ and BAM formats. All submitted sequence data will be aligned using the latest human reference genome; variant and mutation calls will output VCF and MAF formats, whereas gene and miRNA expression quantification data will be kept in TSV format. Other genomic signals for tertiary data analysis will be homogenized according to guidelines of the Global Alliance for Genomics and Health (45).

4.1.2 Approach

As a first step, BETTER deals with datasets discovery at each medical center. Multiple focus groups will be organized with both technical and clinical stakeholders to understand in depth the available datasets, more specifically: (1) dataset characteristics and size (to support *findability*); (2) data types with their attributes and value ranges (useful to *interoperability and reusability*); (3) pathology-related interpretation (to assess *interoperability* aspects); (4) examples of data usage in real-world scenarios (to foster *reusability*). Dataset profiling activities will be conducted manually and with available tools (46). They will allow to measure the overall value of the data at hand, assessing typical data quality metrics such as coherence, completeness, as well as the heterogeneity of the attributes, which are possible feature candidates. For what regards genomic data, we will evaluate the possibility of re-running bioinformatic pipelines to homogenize the collected data among different centers.

Secondly, the project tackles datasets' pseudonymization. By default, data will be pseudonymized before joining the BETTER platform, which requires the implementation of modules for: (1) identifying personal data from images and text; (2) pseudonymization of reference ID to preserve leakage between same patient samples; (3) where applicable, defacing of face images.

Thirdly, we will develop a unified schema repository for medical centers' data and metadata integration. A unifying global model will be designed to accommodate all the data formats and their describing metadata, and serve as a reference for the next analysis steps.

Finally, we will deal with FAIRification of medical centers' datasets. We will research and develop dedicated preprocessing and ETL (Extract, Transform, and Load) processes to onboard health datasets from each medical center to BETTER (allowing the *accessibility* principle within the PHT framework); this task will achieve data FAIRification by scheduling transformation functions to adjust the initial content into appropriate destination formats (making it *findable* through appropriate metadata). Medical-center-specific data formats, protocols, and characteristics will be mapped to a standard schema, enabling *interoperability* and, eventually, distributed analytics–available for future *reuse* in other European-level infrastructures. Building on previous research of the projects' participants, user-friendly FAIRification instruments will be preferred, and re-using and enhancing existing open-source packages, such as University M (47), will be encouraged.

To achieve a completely interoperable format of the metadata repositories, we will provide their content in standardized formats such as Resource Description Format (RDF) or JavaScript Object Notation (JSON). These standards make it unnecessary to know the internal structural organization of a specific data provider in order to successfully execute a Station data retrieval query. Moreover, RDF/JSON data store approaches are sufficiently flexible to describe arbitrarily complex concepts without the need to redesign the providers' databases. Eventually, we will allow the metadata information to be queried through APIs internal to the project participants. Genomic, image, and clinical data, instead, as they will not be shared, will have to comply with specific data formats that will be indicated in the metadata schema. The proposed ecosystem will be designed so that it complies with any main data storage technology and, therefore, also with emerging standards like the Fast Healthcare Interoperability Resources (FHIR) (48).

4.1.3 State of the art

Implementing FAIR principles in the context of a big distributed platform is an effort that concerns multiple aspects. While the literature offers many contributions in the areas of FAIR principles interpretation (49, 50) FAIRness assessment (51–53), FAIR tooling (54), and FAIR service support (55, 56), here we restrict to reporting the few successful experiences that have build FAIR-compliant infrastructures in very specific and practical scenarios.

A preliminary effort of nine Dutch labs aimed to publicly share variant classifications (even if at the time the "FAIR" concept had not been developed yet) (57); the work was expanded 2 years later in the context of the "Rational Pharmacotherapy Program" (The Netherlands Organization for Health Research and Development), developing an instruction manual for FAIR genomic data in clinical care and research—this was based on an inventory of commonly used workflows and standards in the broader genome analysis (58). The same authors finally proposed a FAIR Genomes metadata schema, specifically focusing on promoting genomic data reuse in the Dutch healthcare ecosystem (59). Parallel efforts were devoted to analysis in distributed platforms for radiomics (60) and leukodystrophy (61). ETL processes that are compliant with FHIR were proposed in Peng et al. (62) and Van Damme et al. (63).

To the best of our knowledge, a large, coordinated European-level effort of FAIRification, such as the one proposed in BETTER – with the goal of enabling better distributed analytics—has not been achieved yet in a documented way. BETTER aims to describe all data in a standardized comprehensive manner, so as to process the data in the trains with the most current machine learning available models. Integral analyzes performed on secure systems will provide insight into disease for large cohorts of patients, with significant impact.

4.2 Data fusion

To gain the maximum from data, an important step is data fusion. Data fusion is the process of integrating multiple data sources to produce more consistent, accurate, and useful information than that provided by any single data source. Local data fusion consists of integrating data from multiple sources within a single institution (or Station). This type of data fusion is useful when the data sources are heterogeneous, such as genomic, clinical, and phenotypic data of the same patient. Using AI-based solutions to integrate data heterogeneous data enables the creation of complementary, cohesive, and more complete information, which leads to more accurate insights (64). Moreover, we plan to develop frameworks and methods to also allow us to integrate patients' data from wearable devices and smartphones. Distributed data fusion is the task of integrating data from multiple institutions (Stations). While local data fusion is well-established, distributed fusion is a fairly novel discipline and contains large potentials (65, 66). We envision two main applications for distributed data fusion: integration of homogeneous or heterogeneous data sources. The first aims at creating larger cohorts by combining data provided by independent institutions and removing potential biases due to different collection protocols or techniques. Examples are batch removal algorithms for genomic data (12) or image registration (67). Several methods based on AI exist to perform such tasks and are commonly used by the research community; the challenges for the BETTER architecture consist in designing and developing approaches to achieve the same results in a distributed context, where no data sharing is allowed. The second application can be used to combine several data modalities, each providing different viewpoints on a common phenomenon to solve inference and knowledge discovery tasks. The ambition is to fuse several dimensions including laboratory analysis, medical reports, drug therapy, imaging, genomics, socio-demographic, geographical, and medical questionnaires. To this aim, we also plan to investigate the availability and fuse publicly accessible data sources. In the context of the project, we will develop and implement AI-based solutions tailored to the clinical use cases, e.g., intended to perform analyzes on clusters of interest or compare different therapeutic regimens. Finally, we plan to adopt AI to generate several synthetic datasets, using generative AI and data augmentation approaches to be released to the community for developing medical AI-based solutions.

5 Conclusion

The BETTER project relies on the concept of "bringing computation to data" through incremental and federated learning. This approach avoids unnecessary data transfers between medical centers while effectively utilizing the encoded information within. The project builds upon the experience gained from previous initiatives like the PADME and Vantage6 projects, as well as from the health/genomic data integration expertise of the Data-driven Genomic Computing project.

Aligned with the European Health Data Space (EHDS), BETTER aims to empower EU medical centers and beyond to fully exploit the potential of securely exchanging, utilizing, and reusing health data, facilitated by robust data FAIRification.

Starting from the domains of intellectual disability, inherited retinal dystrophies, and autism spectrum disorders—with potential expansion to other diseases —the analytical tools

developed will enhance healthcare professionals' proficiency in cutting-edge digital technologies, data-driven decision support, health risk surveillance, and healthcare quality monitoring and management. These advancements are expected to positively impact health policymakers and innovators alike.

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

MB: Conceptualization, Funding acquisition, Project administration, Writing – original draft, Writing – review & editing. AB: Investigation, Writing – original draft, Writing – review & editing. PP: Investigation, Writing – original draft, Writing – review & editing.

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Conflict of interest

MB was employed by Datrix S.p.A.

The remaining 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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An assessment of the European Patient Summary for clinical research: a case study in cardiology

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Introduction: The European Health Data Space (EHDS) initiative was launched to create a unified framework for health data exchange across Europe. Central to this initiative is the European Electronic Health Record Exchange Format, designed to achieve interoperability of electronic health record data across Europe. Despite these advancements, the readiness of current guidelines and implementations, such as the European Patient Summary, to support secondary use in clinical research, particularly in cardiology, remains underexplored.

Methods: This study aims to evaluate the European Patient Summary guidelines and their implementations, specifically the HL7 FHIR International Patient Summary Implementation Guide, to determine their suitability for secondary use in clinical research. The focus is on identifying gaps and extensions needed to enhance the utility of the European Patient Summary for building artificial intelligence models in assisting heart failure management.

Results: We selected two European Union-funded research projects, DataTools4Heart and AI4HF, that aim to reuse electronic health record data to develop artificial intelligence models for personalized decision support services for heart failure patients. We analyzed their clinical use cases and the specific data items required, and we compared these with the current European Patient Summary guidelines and provided a detailed gap analysis indicating similarities and required extensions. In our gap analysis, we also compared the needs of DataTools4Heart and AI4HF with the HL7 FHIR International Patient Summary Implementation Guide to assess the extensions needed to support clinical research.

Discussion: The EHDS is a transformative initiative to establish a European health data ecosystem that supports healthcare delivery and clinical research. Our comparative analysis demonstrates that, with minor extensions, these guidelines have significant potential to facilitate access to electronic healthcare record data for the secondary use, particularly in training AI models. We advocate for the adoption of an International Patient Summary format as a semantically

interoperable core set of data elements, which will enhance global clinical research efforts and improve patient outcomes through precision medicine.

KEYWORDS

health ecosystem, secondary use of EHR data, clinical research, interoperability, common data model

1 Introduction

The COVID-19 pandemic has highlighted the critical importance of robust health data ecosystems and efficient data-sharing architectures. The demand for timely, accurate, and comprehensive health data storage and exchange became paramount as the world faced an unprecedented public health crisis. The pandemic exposed several weaknesses in existing health information systems, including fragmented data silos, a lack of interoperability, and inadequate data-sharing mechanisms. These challenges have highlighted the urgent need for interconnected health data systems that facilitate seamless data sharing across different platforms, regions, and sectors.

In response to these challenges, the European Council has recognized the urgency of enhancing health data ecosystems across Europe, leading to the emergence of the European Health Data Space (EHDS) initiative (1). This initiative is a pivotal step toward building a European Health Union. The EHDS aims to create a unified and secure environment for health data exchange, enabling seamless cross-border collaboration and improving healthcare delivery, research, and policymaking. The EHDS has two main purposes: (1) enabling the primary use of health data to support or provide direct individual healthcare delivery to ensure continuity of care for the patient and (2) facilitating the secondary use (or reuse) of health data. This secondary use can involve individual-level, personal and non-personal health data, and aggregated datasets—particularly those generated during healthcare provision—to support research, therapeutic and vaccine development, innovation, policy-making, and regulatory science.

Central to achieving the goals of the EHDS is the European Electronic Health Record Exchange Format (EEHRxF) (2). The EEHRxF, initially introduced in the European Commission recommendation of 2019, provides the technical specifications and guidelines necessary to achieve interoperability of electronic health record (EHR) data across Europe. The EEHRxF defines key datasets under key priority data categories, including patient summaries, electronic prescriptions/dispensations, laboratory measurements, medical imaging reports, and hospital discharge reports. The eHealth Network (eHN), established under Article 14 of Directive 2011/24/EU on the application of patients' rights in cross-border healthcare, is co-chaired by Member States' representatives, and the European Commission and provides guidance and recommendations to facilitate the cross-border exchange of health data within the European Union. The eHN has defined the European Patient Summary (EPS) guidelines (3) as an identifiable dataset of essential and understandable health information to ensure safe and secure healthcare. EPS is implemented in the eHealth Digital Service Infrastructure (eHDSI) using Health Level 7 (HL7) Clinical Document Architecture (CDA) within the scope of MyHealth@EU (4), one of the cornerstones of the EHDS to facilitate the cross-border exchange of health data within the European Union. An HL7 FHIR IPS IG for EPS is under development. The EPS will be aligned with ISO 27269: 2021 Health Informatics—International Patient Summary (5) to ensure compatibility whenever applicable. For the implementation of the upcoming guidelines (such as the Laboratory Report), eHN has chosen the HL7 Fast Healthcare Interoperability Resources (FHIR) standard (6). An HL7 FHIR-based implementation guide (IG) has also been provided for ISO 27269 International Patient Summary (IPS) specification (7). Systemized Nomenclature of Medicine (SNOMED) has made a free set of Systemized Nomenclature of Medicine-Clinical Terms (SNOMED CT) available as part of its Global Patient Set (GPS) to support the implementation of the IPS.

The provisionally approved Regulation on EHDS on 24 April 2024 by the European Parliament and the Council (8) will make the adoption of the EEHRxF mandatory for EHR systems operating in all Member States, and EHR systems will be CE marked. Consequently, funds from both the European Commission and Member States will be allocated to ensure the interoperability of EEHRxF-format data, including patient summaries, both within and between countries. This development presents a significant opportunity to enhance interoperability in health data exchange. Moreover, even if EEHRxF is explicitly mentioned only for the primary use of health data, it marks an important step toward enabling the secondary use of EHR data. The heterogeneity of data formats across health data silos has been a major barrier to the secondary use of EHR data, and the introduction of interoperable EHR systems is key to overcoming this challenge.

EHR data collected for primary care purposes are invaluable resources for clinical research (9–13). These records provide comprehensive, real-world insights into patient health, capturing a wide array of clinical variables. The rich datasets derived from EHR data enable researchers to design clinical studies while considering the standard of care when establishing eligibility criteria and facilitating patient recruitment, as well as conducting observational studies to identify patterns and uncover insights that can enhance patient care. Additionally, EHR data serve as a critical data source for training artificial intelligence (AI) models in predictive analytics, thereby improving the accuracy and efficacy of these models in forecasting health outcomes, personalizing treatment plans, and advancing precision medicine.

In the EHDS architecture, the secondary use of health data, including training data for AI model development, will be regulated and structured to protect privacy while fostering innovation. Through the EHDS, AI developers can access a catalog of available datasets, such as Electronic Health Records (EHRs), registries, biobanks, and other relevant health data repositories, by following a series of steps. First, the AI model developer must verify eligibility and register with an authorized institution, such as a Data Access Body or another governing authority within the EHDS. Afterward, the developer should submit a detailed application outlining the project's purpose, including how the data will be used, ensuring it aligns with permissible secondary uses. Following an ethical and legal review to confirm compliance with EU regulations, the developer can access the metadata catalog once the

secondary use application is approved. This catalog allows the browsing of metadata descriptions to identify suitable datasets for AI model training based on parameters such as population characteristics, health conditions, and clinical outcomes. Once the relevant dataset (s) are identified, the developer submits a formal access request, followed by the signing of a Data Sharing Agreement (DSA). Depending on the architecture (centralized or federated), access to de-identified data is granted either through a centralized platform or a federated system, where data remain with individual data holders but are accessible for processing. At this stage, agreeing on a common data model for secondary use becomes crucial. AI developers need a consistent data structure to efficiently process and prepare the data for model training, including tasks such as cleaning, normalizing, and extracting features. The adoption of a common data format, such as the European Patient Summary (EPS), would significantly facilitate this process. EHR systems already implementing EPS for primary use could easily share de-identified patient medical summaries as training data for AI models. This would allow AI developers to establish their data preparation and model validation pipelines with the assumption that a common data model is available in each EHDS Data Access Node. For EHRs that do not currently support EPS, data transformation pipelines (14, 15) can be employed to convert local formats into the EPS format.

While the adoption of a standardized format such as the EPS within the scope of the EHDS offers significant opportunities for clinical research, a comprehensive analysis of its practical value remains absent. In this study, we aim to assess the current EPS guidelines and their implementations to evaluate their readiness to meet the requirements of clinical research studies that specifically seek to reuse patient summaries. Given that the data requirements for clinical research are highly dependent on specific research questions, conducting a domain-independent study is challenging. We have decided to focus on the requirements of one of the vertical domains, clinical research studies in the cardiology domain, as an initial attempt to highlight the gaps. This analysis is intended to contribute to the ongoing European effort to establish the necessary infrastructure for enabling the secondary use of EHR data in the EHDS. By providing a gap analysis, we aim to identify how the existing IPS can be extended to maximize its utility for clinical research in cardiology.

2 Methods

For this assessment, we selected two ongoing EU-funded R&D projects—DataTools4Heart and AI4HF—that aim to reuse EHR data to develop AI algorithms for personalized decision support services for heart failure (HF) patients. These projects were selected because they collectively address a broad range of clinical research questions in cardiology, covering use cases across all stages of care delivery: primary, secondary, and tertiary care. We analyzed their clinical use cases and the specific data items required, and we compared these with the current EPS guidelines (3), which identify core data elements with some references to applicable standards. In our gap analysis, we also compared the needs of DataTools4Heart and AI4HF with the HL7 FHIR IPS Implementation Guide (7), which provides a directly implementable specification for patient summaries.

DataTools4Heart (DT4H) (16) is an R&D project funded by the European Union's Horizon Europe Framework under Grant Agreement No. 101057849. DT4H develops innovative tools to enable EHR data interoperability, quality, and reusability in cardiology while ensuring privacy, thereby improving collaboration between clinical centers. The DT4H toolbox will be exploited by the clinical partners to reuse existing, currently difficult-to-access EHR data in clinical research studies. The overarching aim of the DT4H project is to assess treatment, referral pathways, and prognosis of HF patients across different European countries using a privacy-enhancing federated learning approach based on real-world data. To investigate the different complicating factors of HF treatment, three clinical sub-studies for patients with an HF encounter have been proposed:

1 To investigate associations between chronic kidney disease and hyperkalemia and medication prescribed on discharge from a hospitalization for acute HF.
2 To develop a prognostic risk score for patients with acute HF presenting at the emergency department.
3 To investigate referral pathways in patients with HF who are referred from another healthcare facility for HF complaints.

AI4HF (Trustworthy Artificial Intelligence for Personalised Risk Assessment in Chronic Heart Failure, Grant No. 101080430) (17), is an innovative initiative that harnesses the power of artificial intelligence (AI) to provide personalized risk assessment and care plans for individuals living with HF. It utilizes advanced AI algorithms, global collaboration, and a patient-centered approach with the ultimate aim of improving healthcare outcomes. In the project, integrative and trustworthy AI models for tailoring the management of HF patients are co-designed, developed, evaluated, and exploited. The three sub-studies mentioned above are also studied in AI4HF, along with two additional HF-focused studies: (1) identification of novel electrocardiogram (ECG) and cardiology magnetic resonance (CMR)-based features to characterize HF patient subgroups, and (2) predicting major adverse cardiac events/end-stage heart failure outcome in patients with non-ischemic dilated cardiomyopathy.

As both projects utilize real-world EHR data to develop AI models specifically for HF patients, we have established a common data model (CDM) to improve data interoperability while addressing data heterogeneity across European regions and cardiology units. The proposed CDM has been implemented by utilizing the HL7 FHIR standard in terms of data model and data access Application Programming Interfaces (APIs). Following the HL7 FHIR profiling approach, analyzing the requirements of each use case, a set of HL7 FHIR profiles, code systems, and value sets was developed and published (18). The effort was initiated in the DT4H project and continued in the scope of the AI4HF project. In this context, the CDM was examined and extended to address the needs of AI4HF, and it was later renamed the Common Data Model for Heart Failure Research.

We have analyzed the EPS guideline core data element list as well as HL7 FHIR IPS IG (further referred to as IPS IG) and compared this with DT4H/AI4HF CDM to assess whether patient summaries provided in these formats can be readily utilized by DT4H and AI4HF to seamlessly extend the training and validation data sets in the context of both projects.

3 Results

In the following sections, we have summarized the result of the gap analysis between DT4H/AI4HF CDM, EPS guidelines, and HL7

FHIR IPS IG. We have presented our assessment by grouping the similarities and differences of core data elements under the main EPS sections.

3.1 Patient information

The patient profile in the DT4H/AI4HF CDM is quite similar to both the IPS IG patient profile and the EPS core data element list. It is possible to map required data elements, namely identifier, birthdate, gender, and address, directly to the IPS IG Patient Profile.

In the DT4H/AI4HF CDM, the "death date" is defined. This data element is not included within the EPS core data element list; however, it is available in the IPS IG Patient Profile. In the DT4H/AI4HF clinical use cases, the "cause of death" of a patient is an important element. The DT4H/AI4HF CDM represents this via a specific HL7 FHIR observation profile, where the primary condition for death is represented with an ICD-10 code. However, we could not locate this data element in either the EPS Core data element list or IPS IG.

Finally, in the DT4H/AI4HF CDM, the "ethnicity" of the patient is also needed to calculate the patient's cardiovascular (CVD) risk score and assess algorithmic fairness. Ethnicity is not explicitly included in the EPS core data element list or the IPS IG. The value set for this data element in the DT4H/AI4HF CDM is a limited set of SNOMED CT codes that have been selected to represent the following values: African, Asian, Caucasian, Hispanic, and Unknown.

3.2 Problem lists

The condition profile in the DT4H/AI4HF CDM maps to the IPS IG Problems and Past Illnesses sections. The core data elements identified in the EPS, i.e., "problem/diagnosis description," "onset date," and "end date" are also included in the DT4H/AI4HF CDM. The clinical status data element required in the DT4H/AI4HF CDM to express the status as active or resolved is represented as an optional element in the IPS IG. In the EPS core element list, medical problems are grouped as "resolved" and "ongoing" in different sections. In the DT4H/AI4HF CDM, we also have an optional "severity" element to express severity, which is also available in the IPS IG. This information is not included in the EPS guideline.

In the DT4H/AI4HF CDM, symptoms are represented with an observation profile, with a selected set of SNOMED CT codes as a value set to represent cardiology-related symptoms. In the EPS core data set or in the IPS IG, there is no specific data element reserved for symptoms; it is assumed that the symptoms are represented via a problem data element as well.

3.3 Medications

In the DT4H/AI4HF CDM, separate HL7 FHIR profiles have been created for medications administered within the hospital (medication administration) and medications taken by patients outside the hospital (medication statement). When compared to the EPS core data elements (including medication brand name, active ingredient, date of onset for treatment, dosage regimen, route of administration, and intended use), we see that most of the required attributes in the DT4H/AI4HF CDM are already covered. The only missing information in the EPS guideline is whether the medication relates to inpatient or outpatient medication administration. Finally, the "end date" of medications is not specified in the EPS. In the IPS IG, it is possible to utilize both medication administration and medication statement within the medications section, and both of them already cover these requirements.

3.4 Procedures

For representing procedures, the content of the DT4H/AI4HF CDM is slightly different than the EPS core data elements and IPS IG. The EPS and IPS IG Procedure profiles include limited data elements, such as procedure description/code, date, and body site, which are also included in the DT4H/AI4HF CDM. Along with these elements, CDM includes the "reason" to record indication, "status" to record whether the procedure is ongoing or completed, and "category" to record whether it is a diagnostic or surgical procedure. Additional optional elements are the "outcome" to record the success of the procedure and the "report," reference to any report resulting from the procedure.

3.5 Vital signs

The core data elements available in the DT4H/AI4HF CDM in the Vital Signs Profile are equivalent to the IPS IG Vital Signs Profile, including vital sign code, value, date, and units. In the EPS, vital signs are represented under the Results category as Observations, which includes the required data elements listed above. In the DT4H/AI4HF CDM, vital sign tests are specified with specific LOINC codes, including body height and weight, BMI, body surface area, systolic and diastolic blood pressure, heart rate, and oxygen saturation. These are covered by the Vital Signs value set of HL7 FHIR, which is utilized in the IPS IG.

3.6 Results

There is a good match between the EPS Core data element set results, the IPS IG Observation Results: laboratory/pathology profile, and the DT4H/AI4HF CDM Lab Result profile data elements. In the DT4H/AI4HF CDM, in addition to the Lab Result profile, we have three specific profiles to record an electrocardiogram (ECG), echocardiogram (ECHO), and magnetic resonance imaging (MRI) results as observation profiles where specific ECG, ECHO, and MRI parameters are represented as components with a well-defined value set. These details are not available in the EPS core data element set or IPS IG. However, it is possible to represent these with the Observation Results: radiology (IPS) profile.

3.7 Social history

In the DT4H/AI4HF CDM, there is a specific profile for recording Smoking Status, which overlaps with the Tobacco Use Profile of the

IPS IG. It also aligns with the Social History core data elements identified in the EPS.

3.8 Admission or discharge information or healthcare encounters

In the DT4H/AI4HF CDM, we require the list of patient encounters, and when possible, these data are referenced from the conditions, lab tests, and vital signs indicating the scope of these elements. It is also important to note admission and discharge dates. Encounter information is unavailable in the IPS IG and the EPS, although it is available in eHN Hospital Discharge Report (HDR) guidelines and ISO IPS.

In DT4H/AI4HF CDM within the Encounter Profile, we require basic data elements such as "start date," "end date," and "reason." In addition, we also need to record the classification of patient encounters (e.g., patient encounter, emergency visit) via the class attribute of the base FHIR Encounter resource. Finally, in the DT4H/AI4HF clinical use cases, it is required to know where a patient was admitted from (physician referral, transfer) and, if discharged, the organization to which the patient is discharged. The admission source is represented via the admission/admit source attribute with a value set including codes such as "from accident/emergency department, physician referral, transferred from another hospital, general practitioner referral." The location/organization to which the patient is discharged is represented via the admission/admit source attribute.

3.9 Allergies and intolerances

In the DT4H/AI4HF CDM, we have a specific profile for recording allergies and intolerances, which is very much aligned with the core data elements of the IPS IG and EPS. In the DT4H/AI4HF CDM, the "clinical status" attribute is required, while it is optional in the IPS IG.

3.10 Other elements required

In the DT4H/AI4HF clinical use cases, we need to know about the referral events in EHR to investigate referral pathways in patients with HF. Hence, in the DT4H/AI4HF CDM, we have a specific profile to record referral events, the HL7 FHIR Service Request Profile. The "Requester practitioner role," the "Performer practitioner role," and the "Reason" are important data elements in the DT4H/AI4HF CDM for the Referral Category.

In the DT4H/AI4HF clinical use cases, information about the patient's employment status, income level, and socio-economic status is required. The DT4H/AI4HF CDM represent these via specific HL7 FHIR Observation profiles. Similarly, in the DT4H/AI4HF clinical use cases, it is required to know the New York Heart Association (NYHA) (19) class of the patient. The DT4H/AI4HF CDM represents this via a specific HL7 FHIR Observation profile. The EPS core element set and IPS IG are represented under the Functional Status Category.

Finally, since CDM focuses on the clinical research studies in the cardiology domain, in the DT4H/AI4HF CDM, we have also identified an extensible value set to represent the codes for conditions as a selected set of ICD-10 codes, codes for the medications as a selected set of ATC codes. In the DT4H/AI4HF CDM Lab Result Profile, we have identified several lab tests required for cardiology studies with the identified LOINC codes and units. These value sets are available online in DT4H/AI4HF CDM (18).

4 Discussion

As summarized in Table 1, within the patient information, problem list, and procedures categories, the DT4H and AI4HF projects require additional data elements not included in the EPS Core data element list. Most of these additional elements can be represented in the HL7 FHIR IPS IG. However, among the extended elements, only the "cause of death" and "ethnicity" elements are not profiled in the IPS IG.

Two important missing data element categories are encounters and referrals. It is critical for DT4H/AI4HF research studies in the cardiology domain to collect information about admission and discharge data and referrals between healthcare services. Additionally, linking problems, lab tests, radiology results, and medications with corresponding encounters is essential for DT4H/AI4HF studies. Within encounter information, it is possible to express the admission source and discharge disposition, which, to a certain extent, can be utilized to understand referral pathways. Therefore, adding encounter information as a separate category within the EPS/IPS guidelines would significantly increase their value for clinical research. It should be noted that encounters are included in the eHN HDR guidelines and ISO IPS.

In the DT4H/AI4HF CDM, specialized value sets have been defined for problems (including diagnosis and symptoms), medications, lab tests, procedures, and vital signs. As depicted in Table 1, the defined preferred and extensible value sets in the IPS IG often cover these specialized value sets. However, these specialized value sets indicate a set of selected codes for ensuring interoperability and identifying the critical data that should be available for specific research studies.

We suggest that the extension of EPS with these elements, which have been identified as gaps in Table 1 and summarized in this section, would greatly increase the practical use of patient summaries as a potential source of data for clinical research studies. It should be noted that in this study, we have focused only on the particular needs of the cardiology domain, which is a limitation. Similar studies should be carried out in different vertical domains. EPS/IPS extensions can be coordinated as profiles focusing on the needs of specialized domains, such as cardiology, respiratory disease, and pediatrics. These domain-specific profiles are needed to ensure interoperability and data availability in patient summaries, enabling secondary use for clinical research.

It should be noted that studies have already been initiated to extend the European EHRxF to facilitate secondary use for clinical research. An important initiative in this respect is the xShare project (23), funded by the EU. It aims to expand the EHRxF to effectively share and use health data within the EHDS for continuity of care, public health, and clinical research. Studies have already been initiated to define an extended core data element set (IPS + R) that could streamline clinical research by directly leveraging standard healthcare data. Initial xShare activities have been focused on analyzing various IPS-related standards [i.e., ISO IPS (5), HL7 FHIR IG for IPS (7), EPS

TABLE 1 A summary of the DT4H/AI4HF extensions over EPS core data elements and availability of these extensions in HL7 FHIR IPS IG.

Data element category	DT4H/AI4HF extensions added over EPS core data element	Availability of these extensions in HL7 FHIR IPS IG
Patient information	The death date element is added (via the "deceased Date Time" element of the HL7 FHIR patient resource)	Included in the IPS patient profile
	A cause of death element is added (via a specific Observation Profile)	Not included
	Ethnicity is added (via an extension over the HL7 FHIR Patient resource)	Not included
Problem list	A severity element is added (via the HL7 FHIR Condition resource)	Included in the IPS Condition Profile
	Symptoms are represented via a specific Observation Profile (the problem data element in EPS)	Represented via IPS Condition Profile
	A specific value set is defined to identify critical symptoms for the cardiology domain	IPS Condition Profile defines a preferred value set (Value Set: Problems—IPS) as a subset of SNOMED CT codes
	A specific value set is defined to identify a critical diagnosis for the cardiology domain by selecting codes from ICD-10	
Medications	Medications administered within the hospital and medications taken by patients outside the hospital are represented separately (via Medication Administration Medication Statement profiles)	Possible to use both Medication Administration and Medication Statement within the Medications Section
	In EPS, it is proposed to use ISO IDMP identifiers and SPOR (Substances, Products, Organizations, Referential) reference implementation to code the data element of the medicinal product description In DT4H/AI4HF CDM, a specific value set is defined to identify critical medications for the cardiology domain by selecting codes from ATC	The IPS Medication Profile defines the preferred value set for coding medications by choosing a subset of SNOMED CT for the medicinal products. However, as an alternative, binding an ATC-based value set is also recommended
Procedures	A reason element is added (via the "reason" element of the HL7 FHIR Procedure resource)	It is not included in the IPS Procedure Profile, but it is possible to use the base HL7 FHIR Procedure profile within the Procedures section of IPS Composition, which includes these
	The status element is added (via the "status" element of HL7 FHIR Procedure resource)	
	A category element is added (via the HL7 FHIR Procedure resource)	
	An outcome element is added (via the HL7 FHIR Procedure resource)	
	A report element is added (via the report element of HL7 FHIR Procedure resource)	
	The procedure value set has been defined to identify critical procedures for cardiology domain DT4H/AI4HF use cases by selecting codes from ICD10-PCS	IPS Procedure Profile defines the preferred value set for coding procedures by choosing a subset of SNOMED CT
Vital signs	The vital signs value set has been established to identify critical vital sign tests relevant to DT4H/AI4HF use cases	Included
Results	A specific value set is defined to identify critical laboratory tests for the cardiology domain by selecting codes from LOINC	A specific extensible value set (Value Set: Results Laboratory/ Pathology Observation) has been defined in IPA IG by selecting a large set of LOINC codes under the Laboratory class
	Specific Observation profiles to record ECG, ECHO, and MRI results are defined where specific ECG, ECHO, and MRI parameters are included by specifying codes from SNOMED CT and LOINC where possible	These can be practically represented via the Observation Results: radiology (IPS) profile. This profile defines an extensible value set for coded radiology measurement observations by selecting codes from SNOMED CT, LOINC, and DICOM. The value sets specified do not directly cover the DT4H/AI4H CDM value set. However, as this value set is practically extensible, it is still possible to represent these data elements within IPS
Social history	None	—
Encounters	An Encounter Profile has been added	Not included in HL7 FHIR IPS. However, it is included in ISO IPS and eHN HDR guidelines
Allergies and intolerances	None	—
Referral	A referral profile has been added	Not included

(3), IHE IPS (20) and USCDI (21)] and comparing them with the CDISC CDASH core data elements for research and key data elements identified through IMI EHR4CR (10) and EHR2EDC, as well as key public health data elements (PHIRI) (22).

The gap analysis presented in this study is shared with the xShare consortium. When we have collaboratively compared our gap analysis, we already see many overlaps: In their ongoing studies, the xShare project has also identified Encounter as an important missing data element category, which is also in line with our findings from the gap analysis. Similar to our findings, patient death date is also identified through xShare analyses as a potential addition to core data elements. In addition, an identifier for clinical research patients is proposed as a "research subject identifier" to maintain patient privacy for clinical research and observational studies. Another gap identified by xShare for EPS is the need to indicate whether the medication is ongoing or stopped. Finally, the xShare project has identified an important potential additional information category, Adverse Events, which was not directly required in DT4H/AI4HF clinical studies but would be critical in other clinical studies.

The findings of the DT4H, AI4HF, and xShare projects reinforce the benefits for patients of not only ensuring that adequate data is readily available from healthcare for research and public health but also that there be an effort to harmonize or align across the various IPS and EPS standards/documents. The next step for xShare is to assign terminology for the core data element set so that healthcare data can be semantically interoperable. The DT4H/AI4HF CDM work has provided valuable input in that context. xShare is a collaborative that intentionally includes six standards development organizations (SDOs). The greatest benefit to patients is for these SDOs to collaborate and agree on a single standard for patient summary data. This is an important step in the road to the adoption of an international patient summary format as a semantically interoperable core set of data elements to enhance global clinical research efforts and improve patient outcomes through precision medicine.

5 Conclusion

The EHDS represents a transformative initiative to establish a European health data ecosystem, fostering collaboration, enhancing healthcare delivery, and enabling secondary use of EHR data. The EHDS is also pivotal for advancing clinical research studies to develop AI models for personalized healthcare. By providing a robust and standardized framework for the secure and efficient sharing of EHR data across Europe, the EHDS enables researchers to access real-world rich, diverse, and comprehensive data sets for training and validating AI models. This will not only enhance the accuracy and reliability of AI-driven insights but also accelerate the development of personalized therapies, ultimately improving patient outcomes and advancing the field of precision medicine. In this paper, we have conducted a comparative analysis of the EPS and one of its implementations, namely the HL7 FHIR IPS IG, evaluating its potential to be used as a standard to access EHR data for training AI models in two existing research projects. We have concluded that with few extensions, the EPS as a part of the EEHRxF has great potential to facilitate accessing EHR data for secondary use purposes in cardiology research studies. In addition, we encourage the generation and adoption of an EPS that incorporates the work of the various Standards Development Organizations (SDOs) that focus on healthcare and research standards towards a single definitive core set of patient summary information for healthcare that can be leveraged for research and public health. Given that clinical research and its associated standards are global, the EHDS will most benefit patients if core summary health data is standardized and semantically interoperable across borders.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://github.com/DataTools4Heart/common-data-model.

Author contributions

GL: Conceptualization, Formal analysis, Methodology, Writing – original draft. AS: Conceptualization, Methodology, Writing – original draft. TN: Conceptualization, Methodology, Writing – original draft. MB: Validation, Writing – review & editing. KL: Validation, Writing – review & editing. PG: Validation, Writing – review & editing. CC: Validation, Writing – review & editing. RF: Validation, Writing – review & editing. RB: Writing – review & editing, Validation. RK: Validation, Writing – review & editing.

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Conflict of interest

GL, AS, and TN were employed by SRDC Software Research & Development and Consultancy Corporation.

The remaining 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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The smartHEALTH European Digital Innovation Hub experiences and challenges for accelerating the transformation of public and private organizations within the innovation ecosystem

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Digital innovation can significantly enhance public health services, environmental sustainability, and social welfare. To this end, the European Digital Innovation Hub (EDIH) initiative was funded by the European Commission and national governments aiming to facilitate the digital transformation on various domains (including health) via the setup of relevant ecosystems consisting of academic institutions, research centres, start-ups, small and medium-sized enterprises, larger companies, public organizations, technology transfer offices, innovation clusters, and financial institutions. The ongoing goal of the EDIHs initiative is to bridge the gap between high-tech research taking place in universities and research centres and its deployment in real-world conditions by fostering innovation ecosystems. In this context, the smartHEALTH EDIH started its operation in Greece in 2023, offering technical consultation services to companies and public sector organizations to accelerate digitalization in precision medicine and innovative e-health services by utilizing key technologies such as artificial intelligence, high-performance computing, cybersecurity, and others. During its first 20 months of operation, over 50 prospective recipients have applied for consulting services, mainly seeking "test-before-invest" services. This paper aims to provide insights regarding the smartHEALTH initiative, preliminary outcomes and lessons learned during this first period of operation. To this end, this paper outlines smartHEALTH's approach to attracting recipients and providing expert guidance on utilizing state-of-the-art technologies for innovative services, product development, and process creation to accelerate digital transformation.

KEYWORDS

digital transformation, electronic health, artificial intelligence, cybersecurity, high-performance computing, innovation ecosystems in health and care, place-based innovation, precision medicine

1 Introduction

The advent of the digital era is undeniable. The world is experiencing the Fourth Industrial Revolution, also known as Industry 4.0, which involves the integration of intelligent machines and systems, transforming production processes to enhance efficiency. In the healthcare sector specifically, emerging technical paradigms can provide huge prospects driven by digitalization, artificial intelligence (AI), and fifth generation (5G) telecommunications (1). Recognizing the importance of building a digital society, and as digital technologies offer new ways to citizens to learn, entertain, work, explore, and achieve personal ambitions, the European Union (EU) has reacted. The envisaged digital world should be founded on European values, ensuring that no one is left behind and that everyone enjoys freedom, protection, and fairness. To achieve this, the EU has set a goal for a Digital Decade, aiming to equip all citizens with the skills needed to use everyday technology (2). The EU's Digital Decade provides a comprehensive framework that guides all actions related to digital space, ensuring that technology and innovation benefit everyone. In order to achieve the ambitious goals of the EU Digital Decade framework, the establishment of the Digital Compass was essential (3). The Digital Compass serves as a tool or guide that outlines specific goals and metrics for this transformation. It translates the ambitions of the Digital Decade into four key targets, known as the "four cardinal points," for 2030. These targets focus on: (i) *Digital skills*: Ensuring that 80% of adults have basic digital skills and that Europe has 20 million ICT (Information and Communications Technology) specialists; (ii) *Secure and sustainable digital infrastructure*: Expanding high-performance connectivity, including 5G across Europe, and establishing secure and efficient digital infrastructure such as cloud computing and edge computing; (iii) *Digital transformation of businesses*: Helping 75% of EU companies adopt cloud computing, big data, and AI technologies. Also, increasing the number of tech-based start-ups and promoting innovation, especially among small and medium-sized enterprises (SMEs); and (iv) *Digital public services*: Ensuring that key public services are available online for citizens (e.g., citizens' access to their electronic health records regardless of the country they are located to support cross-border healthcare services).

In line with the EU's vision for digital transformation by 2030, the European Health and Digital Executive Agency (HaDEA) plays a pivotal role (4). HaDEA is responsible for implementing digital and health-related initiatives like EU4Health and Digital Europe, ensuring these program meet the objectives of the Digital Decade. The EU4Health program, with a budget of €5.3 billion for 2021–2027, aims to enhance healthcare systems through digital innovation, which is crucial to achieving the broader goals of the Digital Decade (5). The Digital Europe Program, with an overall budget of over €7.9 billion, provides funding for technological advancements that support these initiatives, including healthcare technologies, digital skills, and cybersecurity (6). These initiatives, among others, send a clear message that public health and the development of relevant digital health services is a priority for the EU.

This is also supported by initiatives like the European Health Data Space (EHDS) regulation, which will be a key pillar of a strong European Health Union. In spring 2024, the European Parliament and the Council reached a political agreement on the Commission's proposal for the EHDS (7). The EHDS is expected to: (i) empower individuals to take control of their health data and facilitate the exchange of data for healthcare delivery across the EU (primary use of data); (ii) foster a genuine single market for electronic health record systems; and (iii) provide a consistent, trustworthy, and efficient system for reusing health data for research, innovation, policy-making, and regulatory activities (secondary use of data). The pressing need for the homogeneity and interoperability of European electronic health records is also highlighted by the Digital Decade 2024: eHealth Indicator Study (8). The main actions of the EHDS are organized in two pillars: (i) "Primary use" of healthcare data focusing on the ability of a European citizen to use his/her data across Europe, regardless of where these data are originally created/hosted to support cross-border healthcare services; and (ii) "Secondary use" of health data to support policy making and research for public health purposes.

Collaboration plays a key role in the success attained to date by networks of innovation ecosystems generated around entities known as European Digital Innovation Hubs (EDIHs), recently created following European Commission initiatives to boost the digitization of the European economic fabric (9). EDIHs are recognized as essential policy instruments designed to boost the digitalization of small and medium-sized enterprises (SMEs) and facilitate the transition to Industry 4.0 (10, 11). These hubs play a crucial role in fostering digital ecosystems across Europe, which consist of heterogeneous organizations spanning various economies, industries, and contexts. By offering a wide portfolio of supporting services, DIHs aim to enhance the digital capabilities of companies and drive innovation in regional economies (12). The Digital Europe Program supports the operation of European Digital Innovation Hubs (EDIHs) formed by strong collaboration between research and technology organizations (RTOs), universities, and representatives from the market such as innovative companies and business associations. The challenge of digital transformation is huge for companies in the EU. According to the Digital Decade targets set for 2030 the AI take-up is 11% of enterprises in 2023 against 75% of enterprises targeted for 2030 (13). EDIHs are expected to be a main actor boosting this process in the EU context (9, 14). Currently, there are 227 EDIHs of which 151 are funded directly by the Digital Europe Program. This Network of EDIHs is widely distributed across 85% of European regions, covering almost 90% of the EU's working population. The services provided by EDIHs to SMEs and public sector organizations encompass a broad spectrum of technologies and sectors showcasing diversity in strategies and designs. The hubs demonstrate strong competencies in key technologies like AI, cybersecurity, and high-performance computing (HPC) (15).

As far as Greece's population is concerned, this was 10,032,508 as of August 21, 2024 (16). The 2024 International Monetary Fund (IMF) figures show a gross domestic product (GDP) *per capita* of $23,966

(nominal) and $41,188 purchasing power parity (PPP) (17). Greece is recovering from a 10-year financial crisis and the COVID-19 pandemic, which heavily impacted its economy. Greece ranks 37th globally in the Global Innovation Index and is a "Moderate Innovator" (13). However, it ranks 25th out of 27 EU countries in the 2022 Digital Economy and Society Index (DESI) (18). Despite improvement, austerity measures still remain, and digital transformation is considered a key aspect which could facilitate businesses to be competitive, especially in the post-pandemic era.

The Digital Decade 2024 report highlights Greece's efforts to improve its digitalization, especially in e-health, which has surpassed national targets for 2023 (19). The country's digital transformation roadmap, supported by EU funds, focuses on enhancing healthcare and cross-border e-health services, including electronic medical records. In the same report, it is mentioned that the national targets set for e-health Greece's align with the EU's 2030 goals, surpassing its 2023 forecast with a score of 73.8 and 21.6% annual growth. The health sector's digital transformation is a priority in Greece's national strategy, supported by EU funds through the Recovery and Resilience Facility (RRF) (20). Of the €5.23 billion allocated to support the domain of health services, €394.8 million have been allocated to support e-health infrastructures.

Along these lines, the interconnection between research and academic institutions and industry/public sector is highlighted as a crucial factor in terms of providing know-how gained via international collaborations, research projects etc. to the industry in order to capitalize in real-world services and/or products. In this context, smartHEALTH brings together expertise in the areas of AI, cybersecurity, and HPC, to facilitate digital transformation and foster innovation in digital health in Greece. This article focuses on the smartHEALTH test-before-invest services (TBI) and outlines the relevant private/public organizations participating in the project as "service recipients," i.e., organizations who receive consulting services highlighting the areas of activity and the preliminary results from its initial 20 months of operation. It also discusses the challenges it confronted, lessons learned so far in terms of applying novel technical paradigms in real-world conditions, and outlines next steps.

2 Materials and methods

The initiative of EDIHs aims to bridge the gap between research and market deployment by fostering ecosystems where innovation can thrive. The smartHEALTH setup and operation framework selected for community engagement, as well as the methodology selected for the brief presentation of research outcomes are detailed in the following subsections.

2.1 The smartHEALTH approach

As already mentioned, the Network of the EDIHs operates across Europe with the support of the European Commission, bringing together relevant national initiatives, SMEs, and public sector organizations (PSOs) to make the EU's Digital Decade 2030 targets a reality. The EDIH Network is a community of tech experts dedicated to guiding Europe's businesses and public sector organizations on their path to digital transformation. EDIHs serve as one-stop shops throughout all EU regions, equipping companies with the essential digital tools to improve their competitiveness, upgrade their infrastructure, and boost their overall success (21). The mission of EDIHs is three-fold:

- Advance digital transformation across the EU by bringing cutting-edge tech (AI, Cloud, Big Data) to 75% of European companies.
- Ensure that 90% of companies have a basic level of digital know-how.
- Create new value chains within Europe.

SmartHEALTH is designed as a "one-stop-shop" where SMEs, start-ups, mid-caps, and the public sector can get help to improve their processes, products and services by means of digital technology. The hub is co-funded by the EC and the Greek State and brings together some of the main Research and Innovation leaders of the Greek ecosystem in the field of digital and smart health to facilitate the digital transformation of the private and public sector (22). Prominent actors in the fields of research and innovation (Foundation for Research and Technology - Hellas (FORTH), Centre for Research and Technology Hellas (CERTH), National Centre for Scientific Research Demokritos (NCSRD), ATHENA Research Center), in tertiary education (National and Kapodistrian University of Athens (NKUA), University of Crete (UOC), Technical University of Crete (TUC), University of West Macedonia (UWM)), an experienced ICT -integration company (UNISYSTEMS) and a business support organization (SEVPDE) have joined forces to offer a large variety of specialized services in 54 main areas of expertise and 3 main technological fields, namely AI, Cybersecurity and HPC. The list of the main areas of expertise which can support smartHEALTH TBI services is shown in Figure 1.

The list of TBI expertise areas for services depicted in Figure 1 is not exhaustive and portrays the main expertise available in the knowledge intensive organizations that form the core of the hub. The scheme develops state of the art methodologies and strategies based on years-long research on the needs of EU and worldwide representative ecosystem stakeholders. The expertise utilized for each recipient is based on their real needs and may differ.

In line with the overall implementation strategy of the EDIH Network, smartHEALTH provides a portfolio of four distinct types of services. More specifically:

- *TBI services* to SMEs and the public sector to assist in their digital transformation and the support of innovation, through added-value technical consultation and use of state-of-the-art infrastructure. TBI services include (i) Awareness raising on available digital technologies, and implementation of a "Digital Maturity Assessment" (DMA) using a structured tool provided by the EC for measuring the digital maturity of the client, (ii) the elaboration of a specific plan of action for further services based on a "Visioning for digital transformation" exercise, the DMA results and a Strengths-Weaknesses-Opportunities-Threats (SWOT) and market trends analyses, (iii) "Demonstration and proof-of-concept" in which SMEs and public sector entities demonstrate in a lab the idea behind a new product, service or process and smartHEALTH experts assess the validity and feasibility of the new concept providing additional support, (iv) "Fostering integration" in which smartHEALTH experts support clients to integrate digital technologies and skills in their

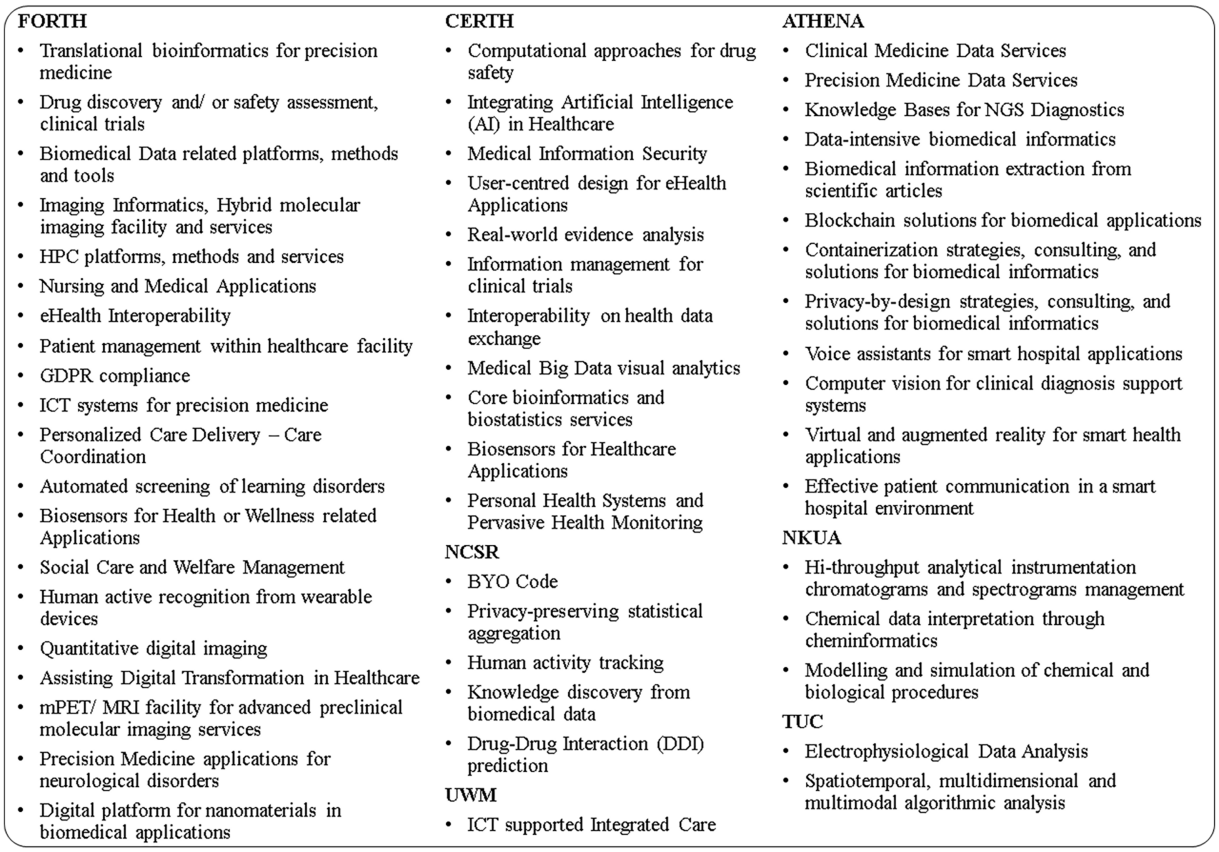

FIGURE 1
TBI expertise areas for services offered by smartHEALTH grouped by each of the service provider organizations.

processes and products, (v) "Testing, experimentation and prototyping" through which clients have the opportunity to pilot test innovative technologies and products using available infrastructure with the guidance of skilled smartHEALTH personnel, and (vi) "Flagship" services of increased importance and added-value in the specific areas of precision medicine, cancer, and the digital transformation of the public sector.

- *Skills and training services* to SMEs and the public sector to assist in their personnel's digital skills development. These services include the organization of seminars and workshops, tailor-made specialized training courses, hackathons, bootcamps and other competitions.
- *Access to public and private financing services* to SMEs and the public sector, to assist them in securing financial resources for the implementation of digital transformation activities. These services include 1–1 coaching and mentoring on available public and private funding opportunities, as well as advanced consultation on preparing funding proposals, pitch-decks, business plans, etc. At the same time, smartHEALTH has set up an extensive support network of financial institutions, such as banks, private funding bodies, venture capitals, angel seeds, etc., which is being used for connection with recipients seeking funding.
- *Ecosystem development and networking* services to support, facilitate, and animate the digital health ecosystem in Greece and empower all relevant actors. smartHEALTH organizes partnering events and participates in common activities with the EEN, clusters, and other key stakeholders with the aim to foster synergies and promote collaborative projects with partners from the quadruple helix.

In this paper, results for the TBI type of services will be presented and analysed since they lie at the core of the smartHEALTH service portfolio and provide its unique selling proposition.

2.2 Framework for community engagement and its application

The engagement of interested organizations from the Greek ecosystem is being performed through different channels such as: (i) contact to or from smartHEALTH experts, (ii) the submission of an online application, (iii) online inquiry through the contact form on the smartHEALTH website.

After the initial contact is made, a clear workflow for the provision of services ensues with a structured process of operation. Service provision is divided into 4 distinct but interrelated stages:

- *Preparatory stage*: This entails introductory meeting(s), online submission of application, evaluation of application by the smartHEALTH Management Board, preparation and signing of first Cooperation Agreement

- *Stage 1*: This entails the successful provision of Phase 1 TBI services (awareness raising, digital maturity assessment, and visioning), the delivery of a technical report to the client, and a signed certificate of delivery and acceptance by them.
- *Stage 2*: This entails preparation and signing of additional Cooperation Agreements and the provision of Phase 2 TBI services (demonstration/proof of concept, fostering integration, testing/prototyping/experimentation, flagship). In addition, delivery of a detailed technical report to the client.
- *Stage 3*: This entails the impact analysis of provided services, as well as customer satisfaction, including quality control and assessment, through a signed certificate of delivery and acceptance by the client, as well as an optional automated rating scheme.

The overall client journey is depicted in Figure 2.

In parallel to the provided TBI service, the entire set of other EDIH services activities are run based on recipients' needs, offering the opportunity for collective training services on areas of common interest as well as networking/matchmaking between the community stakeholders. This way smartHEALTH provides to service recipients both collectively as well as individualized access to specialized knowledge and expertise, together with support to find investments.

2.3 Data collection process

The authors gathered data from the Client Relationship Manager (CRM) system developed by smartHEALTH, which is used by the private companies and public organizations acting as TBI service recipients. The CRM system is used by these organizations to submit their application, and smartHEALTH consortium to manage and report on the provided services. The organizations which can receive services from the smartHEALTH (inclusion criteria) are public and private organizations that have (i) initiated the application process at the online dedicated platform; (ii) submitted a formal application, accompanied by all the required formal documents; (iii) been positively evaluated (for financial viability and satisfying the pre-conditions for inclusion in the program); (iv) selected at least one TBI service; and (v) signed a cooperation agreement with smartHEALTH. There was no limit placed on the type of service or technology involved.

The data screening procedure involved two rounds. The following data elements were extracted from the EDIH database for all open applications: entity applied to EDIH, category of service requested, type of legal entity, staff size, region based on the nomenclature of territorial units for statistics 2 (NUTS2) classification (23), phase (for contracted entities only), type of services requested (for contracted entities only), digital technologies involved (for contracted entities only), and short description of the requested services. Authors screened the data, in order to eliminate possible errors or bias in the selection process. The names of all clients were removed and all relevant data retrieved were assessed for their eligibility according to the inclusion and exclusion criteria. Data was processed, codified, and analysed in order to provide an outline of the EDIH recipients' profiles, as well as the existing demand.

In the sections below, current progress and lessons learnt from the provision of TBI will be presented, while significant barriers toward the EDIH adoption and integration into the wider innovation ecosystem will be identified.

3 Results

In its first 20 months of operation, smartHEALTH achieved significant milestones. The hub provided added-value TBI services to a diverse range of organizations, including SMEs, civil society organizations, and public sector organizations, such as hospitals. Additionally, through the organization of seminars and workshops, smartHEALTH created valuable opportunities for participants to deepen their knowledge in the field of digital health and engage with the broader research ecosystem. In parallel, smartHEALTH organized and participated in numerous networking events in order to foster cooperation and create synergies between different actors of the ecosystem.

As of 23 August, 2024, 83 public and private organizations had initiated the process of submitting a formal application for support services by smartHEALTH experts. Data from 51 applicants had been collected from the smartHEALTH CRM platform, following their formal application submission. Eight of them were in the process of evaluation by the smartHEALTH Management Board (MB). Forty-three had submitted an application which had been positively evaluated. Forty-two included a request for the delivery of a TBI and were incorporated into the study. Those that did not include a TBI service request, as well as those that for any reason did not get approval by the Management Board of smartHEALTH were excluded. This process is depicted in Figure 3. The data set for the performed analysis and outcomes are detailed in the Supplementary Table S1.

A preliminary analysis of the filtered data has produced the following results:

- With regards to differentiation between private and public organizations which have applied for smartHEALTH services, there is a significantly larger proportion of private organizations that have applied (86–14%), and consequently that have received services (38 private and four public organizations, out of 42 total). This gap could be attributed to public sector bureaucratic constraints, as well as non-prioritization of the adoption of digital technologies and lack of awareness of their benefits.
- Concerning geographical coverage, there is a much stronger interest from organizations based in Attiki, Central Macedonia, and Crete (45 out of the 51 applicants and 38 out of 42 contracted entities, were from these three regions). Interest in other parts of Greece is much lower. This can be attributed to the concentration of the majority of project partners/service providers in these three regions, but more importantly to a relevant gap in digital maturity level as well as financing and business opportunities that exists between metropolitan centres (Athens, Thessaloniki, Heraklion) and the periphery.
- The size of applicant organizations also provides interesting results. Micro and small size organizations are responsible for 82% of the submitted applications, while only 18% are medium and large size entities. When looking at contracted organizations, the difference is even larger with 86% being micro or small size, while 14% being medium or large size. The reasons vary, from a stronger innovative capacity and interest of small companies

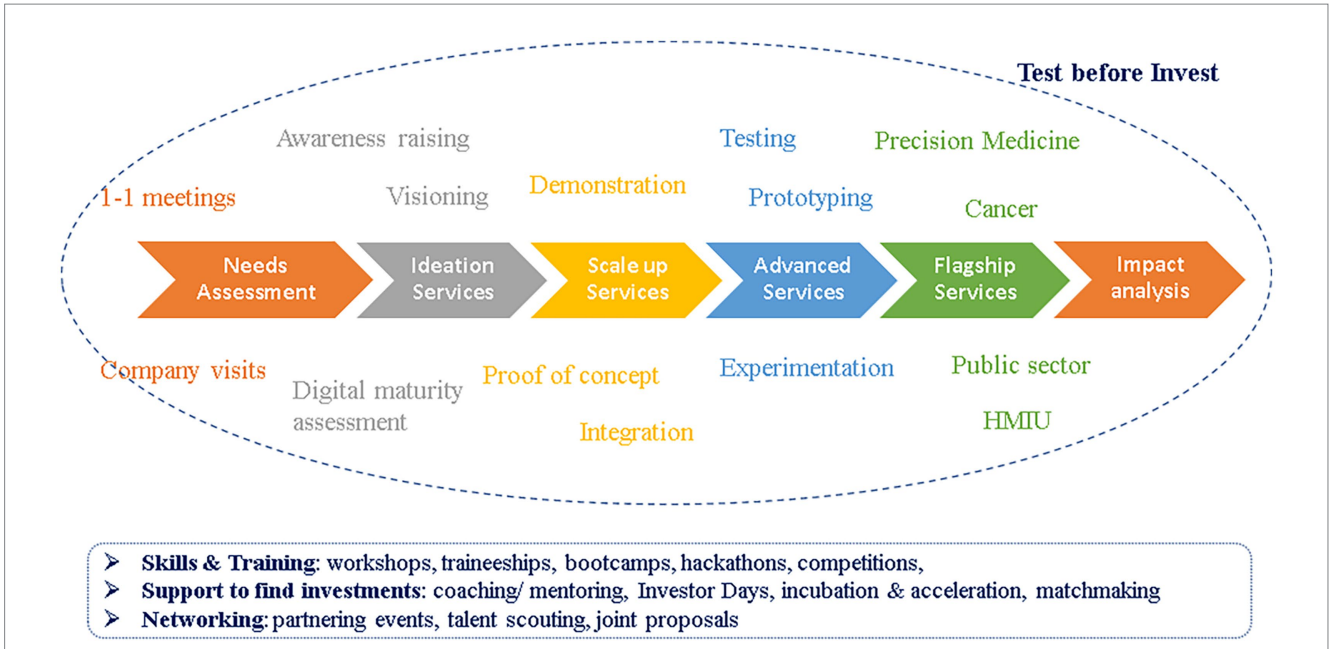

FIGURE 2
Client journey. The steps from the first meeting with the potential client to the analysis of the impact of the provided service. Scale up, advanced and flagship services are provided only as needed.

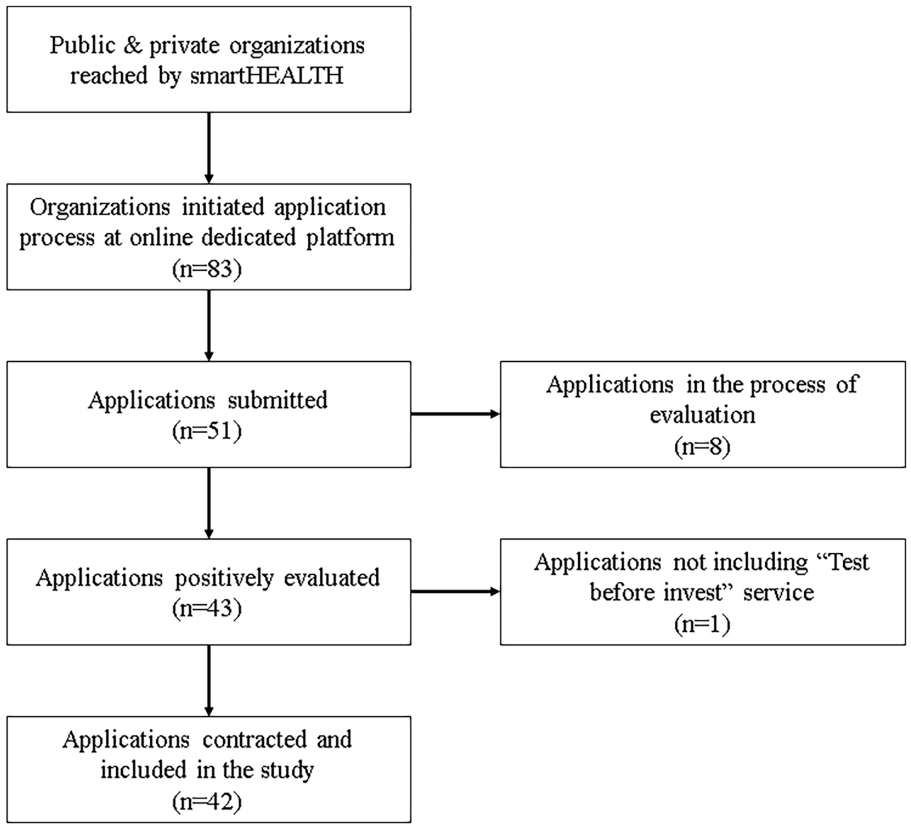

FIGURE 3
Flow diagram for study inclusion. Number of applications and TBI contracts in each phase.

(such as start-ups) that want to take the next step in their development, to a relative lack of interest in smartHEALTH services from larger organizations that have other means to promote their digital transformation.

- The types of advanced TBI services that were requested do not provide any significant realizations. Almost half of the requested services had to do with demonstration and proof of concept (20 out of 45), while 12 requests involved testing/prototyping/experimentation, and 11 involved fostering integration. Only two cases qualified as flagship services.
- Concerning technologies used, there is a strong preference for Software Architectures, AI and Decision support, and Internet services and applications. This is again not surprising given the fact that software development for internet services and apps is the core business in the ICT sector, while AI has been the focal technological sector of the last few years. Although not surprising, this preference for established technologies shows the relative conservativism that permeates business culture in Greece.

A schematic depiction of EDIH services offered by type/size/region of recipient, as well as type of service requested, and technology used, can be found in Figure 4. This is central to the article objectives since it illustrates preliminary smartHEALTH analysis outcomes, discussed in the previous paragraph.

An indicative example of the services provided by smartHEALTH is the published success story of HERADO SA (24). The Greek company offers a disruptive solution for radiation protection, a patented active dosimeter. The dosimeters connect to a dedicated monitoring and reporting platform, through Internet of Things (IoT). The platform is developed from a third-party, with no knowledge of the health requirements concerning privacy, interoperability and cybersecurity. The company addressed smartHEALTH to check if the platform was complying with the needed set of standards for Health IT software. Another concern for the company was how to expand the platform for responding to an expected scaling-up of users and an addition of future services. smartHEALTH experts reviewed the platform in a series of interviews with the company. Then, it provided a detailed report in which they listed what the platform should have and specific proposals for future developments. This case is similar to many other in which Greek SMEs address smartHEALTH for receiving a proof of concept and advice for their software. There is no other body in Greece providing such services.

4 Discussion

Transitioning into its second year of operation, significant insights were gained for the Greek eHealth ecosystem, highlighting a strong desire for digital integration and enhancement of services and products through innovative digital approaches. The free provision of consulting services by smartHEALTH, facilitated by support from the EU and the Greek state, emerged as a vital facilitator for the EDIH's operations. However, challenges regarding the workload of service provision were identified as significant barriers to overcome during this period, as well as administrative issues relevant to guaranteeing national funding. Large capital companies were hard to reach and collaborate with, since all large size organizations depicted in Figure 4 are PSOs. In contrast small companies, start-ups etc. are open to collaboration. Despite the fact that there is a huge investment in eHealth in Greece through RRF, smartHEALTH did not manage to have contractors incorporated as recipients of TBI services. This lack of involvement for this type of companies could imply lack of capacity as this is a very busy period for them or lack of interest for the adoption of innovative technologies, lack of collaboration mentality, or fear for exposing potential commercial secrets.

Some important findings/lessons learnt from the 20-month period have to do with the fact that since the focus of TBI services rely on the fulfillment of the needs for digitalization of recipients with different and in many cases not fully crystalized agendas, the ability to adapt to changing customer needs is crucial. This requires a business mentality which is not evident to all researchers or academia professionals. Nevertheless, it is exactly those who are closely situated to knowledge production (such as RTOs and academia) that can provide the confidence and build long term relationships and partnership with the clients that seek continuous improvement. In addition, researchers need to have clear incentives and understanding that through the EDIH they do not conduct research, but rather assist the ecosystem innovate and set the ground for stronger partnerships. Preliminary findings indicate also that red tape remains still an issue as well as the identified difficulty in attracting PSOs.

The first-year achievements of smartHEALTH, in the direction of supporting businesses and the public sector on their path to digital transformation, are quite encouraging for the coming years' operation. To this end, multiple ways to achieve sustainability are currently being investigated. The operation of smartHEALTH has unveiled several key advantages, demonstrating the value of uniting efforts for shared goals. First, by working together, researchers and the service recipients reached into innovation areas that had a wider impact in the digital transformation of each organization. The well-structured application process that defined the purpose of each collaboration, identifying the appropriate multidisciplinary team to address it and aligning it with the performance indicators of the hub became seamless. Within the national context, smartHEALTH simplified activity planning, given the shared work culture and emphasized research and public-private partnerships. Any emerging issues were addressed using the combined operational and communication cultures the organizations involved, fostering innovation and problem-solving. The allocation of resources was based on principles of efficiency and effectiveness, achieved through meaningful dialog between the EDIH service recipients and the hub organizations. The collaboration has helped into creating a deep understanding of each organization's characteristics, as well as prior experiences. Particularly crucial was the involvement of researchers who had targeted expertise facilitating smoother interactions. An initial agreement, including a tentative timeline for implementation and a clear definition of roles, was essential to the collaboration's success. Furthermore, the strategic promotion of the partnership helped reinforce its value.

This collaboration is now recognized as a best practice model for other hubs with complementary goals across the country. However, one of the main challenges encountered was the diversity of perspectives among the various EDIHs, each serving different sectors and regions with unique priorities. While smartHEALTH focuses on digital health, other hubs have focused on agriculture, energy, the environment, and the public sector, leading to differing views on the ecosystem's most pressing challenges and how to address them. Despite these differences, these divergences were ultimately seen as

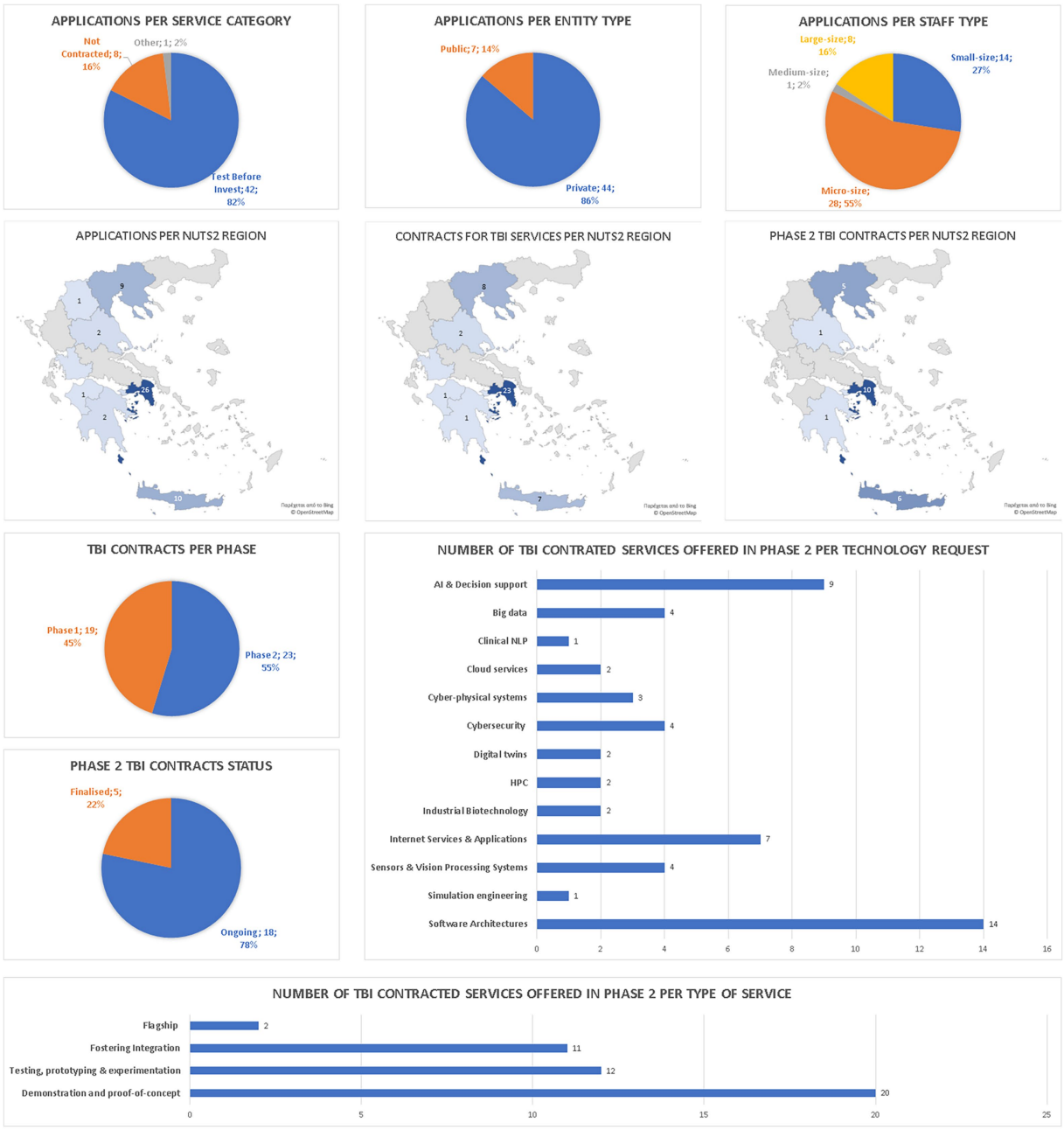

FIGURE 4
The EDIH services offered be type/size/region of recipient, as well as type of service requested, and technology used. Top row: Breakdown of TBI services per entity type and per client company size. Middle row: Geographical spread of (left) the successful TBI service applications on CRM, containing the contracted and the ones that are about to be contracted, (centre) the contracted (phase 1 and 2) TBI services and (right) the TBI services that have proceeded to phase 2. The bottom left pie charts provide a more detailed visualization of the stage of TBI contracts under phase 1 and 2. The bottom right and bottom down bar charts show a breakdown of TBI services per technology request and per type of phase 2 service.

opportunities for growth. Through collaborative actions, the hubs were able to align on shared goals, leverage their complementary strengths, and contribute to a more holistic national digital transformation strategy. Though sectors differ, cross-cutting challenges such as cybersecurity, data management, and workforce digital upskilling emerged as shared areas of concern. AI, data analytics, and IoT, are at the core of all EDIHS and are relevant across sectors. Cross-pollination of ideas contribute to the expansion of the innovation ecosystem. The collaboration fostered a more unified approach to digital transformation in Greece by recognizing that each EDIH's unique focus could contribute to an overall national innovation strategy.

5 Limitations

The conclusions are subject to several limitations. First, all findings are based on a small dataset, restricted to the Greek healthcare ecosystem. Additionally, the approach followed by the authors might have influenced the results, as the concept of EDIHs is relatively new

and smartHEALTH is still in its early stages. Furthermore, the majority of services offered so far have not been fully completed. Information about the overall service impact monitoring for all beneficiaries will require more time, along with plans to engage/support the beneficiaries on the long term. The EDIH received very few spontaneous applications; most were generated through discussions and engagements at scientific events and forums. This approach may distort the understanding of the practical needs of the Greek ecosystem.

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

DK: Writing – review & editing, Writing – original draft. DF: Writing – review & editing, Writing – original draft. KK: Writing – review & editing, Writing – original draft. AKo: Writing – review & editing, Writing – original draft. AF: Writing – review & editing, Writing – original draft. PN: Writing – review & editing, Writing – original draft. AKr: Writing – review & editing, Writing – original draft. EC: Writing – review & editing, Writing – original draft. MA: Writing – review & editing, Writing – original draft. DP: Writing – review & editing, Writing – original draft.

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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.

Generative AI statement

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1503235/full#supplementary-material

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Innovation ecosystems in health and care: the Andalusian Reference Site as an example

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Innovation ecosystems foster collaboration between academia, industry, public bodies, and civil society to drive technological and social advancements. The European Innovation Partnership on Active and Healthy Aging (EIP on AHA), launched in 2012, aimed to extend healthy life years, improve healthcare efficiency, and stimulate economic growth. Reference sites (RSs) and action groups (AGs) were key components, with RSs adopting collaborative approaches to improve health outcomes. Andalusia, Spain, achieved top recognition across multiple EIP on AHA calls for its digital health strategies and strong Quadruple Helix collaboration. In 2022, Andalusia's self-assessment using the SCIROCCO tool highlighted strengths in digital transformation and citizen empowerment. Andalusia's innovative practices in health have contributed to regional improvements in healthcare efficiency, life expectancy, and research initiatives.

KEYWORDS

innovation ecosystem, active and healthy living, European networks, health and care systems, Reference Site Collaborative Network

1 Introduction

Innovation is a central tool for the advancement of the economy and society (1). Innovation ecosystems refer to a context or environment in which technological and other innovations are favored by a set of dynamic agents following a Quadruple Helix implementation based on the design thinking innovation model (2): research/academia, industry, public bodies and healthcare providers, and civil society. Different actors merge in innovation ecosystems where each one contributes something to its construction, either with investment, ideas, or work (3). Although innovation clusters and ecosystems may vary, a common operational and organizational scheme can be found in all of them (5).

In social and health issues, innovation addresses regional needs with a coordinated, participatory, integrated, and intersectional approach. Health and care systems across Europe are challenged by demographic changes, with increased longevity as an achievement of modern societies but with more people requiring more care. European Union health and care systems, despite diversity, are crucial for Europe's social protection and contribute to social cohesion and sustainable development.

Recognizing innovation's role in these challenges, the European Innovation Partnership on Active and Healthy Aging (EIP on AHA) was launched in 2012 (5) within the Innovation Union policy of the European Commission (EC) and was operational till December 2020 (6), when the financial framework 2014–2020 ended. Its main aim was to increase 2 years of healthy life for European Union citizens by 2020 by improving the sustainability and efficiency of healthcare systems and generating growth and market opportunities (the triple win). The EIP on AHA had three pillars: prevention, screening, and early diagnosis; care and cure and active aging and

independent living; and horizontal issues, vision, and foundations. Its components included reference sites (RSs) and action groups (AGs).

Reference sites were initially described as "regions, cities, integrated hospitals/care organizations that implement a comprehensive, innovation-based approach to active and healthy aging and can give evidence and concrete illustrations of their impact on the ground" (5, 6). This definition later evolved as a collaborative alliance of all stakeholders in a region, rather than a single entity organization. Therefore, RSs are ecosystems aimed at adopting and transferring creative and practicable solutions to improve the quality of life and health of older people and the whole community, increasing equity and social sustainability, and bringing together leading regional organizations committed to investing in and implementing innovation.

Action groups gathered of professionals, entrepreneurs, researchers, and experts committed to working on active and healthy aging in several areas included in its main pillars.

Since 2012, four calls for RSs have been launched. The first one (2013) emphasized key overall strategies addressing the demographic challenge in Europe. Calls opened in 2016, 2019, and 2022 adopted the following key characteristics:

- The "Quadruple Helix" model (public authorities and health and care providers/researchers/SMEs/civic society) to ensure all stakeholders have a common understanding of the organizational, technical, and financial challenges facing the region or area within health and active and healthy aging and are working collaboratively to define and implement innovative solutions and possibilities for economic growth.
- Comprehensive strategies being in place, or under development, which directed and guided policies and practices in the region, including supporting an active and healthy aging population, e.g., innovation strategies, R&D strategies, smart specialization strategies, older people strategies, education and training strategies, economic strategies, and regional development strategies.
- A strategic "whole system approach" in responding to health, societal, and economic challenges that delivered against the EIP on AHA triple win objectives.
- The degree of their alignment with the EIP on AHA through both contributions to the three EIP on AHA pillars and commitments of the EIP on AHA action plans.
- Partnerships with other regions for the transfer and exchange of good practice and/or joint working on projects to support health and care, including active and healthy aging.
- Commitment to contributing to the European evidence base demonstrating impact on outcomes for patients and service users; effectiveness of developed solutions in meeting need; and how provider organizations have adapted to deliver new services and service models.
- Evidenced impact of good practices and the degree to which smart health and care solutions for active and healthy aging have been scaled up or are being scaled up.

The fourth call for RSs (2022) included the following key criteria, together with the essential one on the "Quadruple Helix" approach:

1 Political, organizational, technological, and financial readiness.
2 Sharing learning, knowledge, and resources for innovation.
3 Contributing to European co-operation and transferability.
4 Delivering evidence of impact against the triple win approach.
5 Contributing to the European Digital Transformation of Health and Care.
6 Scale of demonstration and deployment of innovation.

This 2022 call for RSs was supported by the EC (General Directorate of Communication Networks, Content and Technology) and organized by the Reference Site Collaborative Network (RSCN). RS application assessment included the above-mentioned criteria as Phase 1 and Phase 2 of self-assessment of the maturity of the health system for active and healthy aging with a life course approach, using the tested and validated SCIROCCO tool (7–9). The SCIROCCO tool was adapted to measure the maturity of systems to address an active and healthy life in a certain territory. The tool facilitates comparison and learning, focusing on a collaborative assessment. The model consists of 12 dimensions: readiness to change, structure and governance, digital transformation, stakeholder coordination, funding, removal of inhibitors, population approach, citizen empowerment, evaluation methods, breadth of ambition, innovation management, and stakeholder's capacity building and development. Using a restricted-access online survey tool, each dimension is evaluated using a six-position maturity scale by a group of Quadruple Helix experts.

After the first call for RSs of the EIP on AHA and following a self-assessment and a peer review process in 2013, 32 RSs from 12 member states were recognized, ranking from 1 to 3 stars. These 32 RSs collectively formed the RSCN (10, 11). The RSCN was enlarged after the 2016 call (12), with 74 RSs, and became a formal non-for-profit association under the Belgium law in 2017. The 2019 call recognized 104 RSs, a number that was reduced to 65 RSs after the last call in 2022. Currently and after this last call of 2022, the network has evolved toward addressing active and healthy living (AHL). The RSCN helps to facilitate twinning and advisory activities that help regions and organizations to better understand the local conditions that enable the successful deployment of the AHA and AHL in the European community.

In parallel, EIT Health was established in 2015 as a "knowledge and innovation community" (KIC) of the European Institute of Innovation and Technology (EIT), focusing on health and aging. The so-called "knowledge triangle" (research, business, and education) is the principle that when experts from business, research, and education work together as one, an optimal environment for innovation is created.

2 Policy options and implications

Andalusia, a region in the south of Spain with 8.5 million inhabitants, has been an active participant in both innovative

Abbreviations: AHL, Active and healthy living; AHA, Active and healthy aging; CSCJA, Regional Ministry of Health and Consumer Affairs of Andalusia; EIP on AHA, European Innovation Partnerships on Active and Healthy Aging; FPS, Andalusian Public Foundation Progress and Health; RSCN, Reference site collaborative network; SAS, Andalusian Health Service; UJaén, University of Jaén; US, University of Seville.

initiatives in EIP on AHA since its beginning and later joining EIT Health. The region has been recognized as the reference site with the highest category among all the different calls for RSs. Led by the Regional Government of Andalusia, particularly by the Regional Ministry of Health, the region has been actively involved and has fulfilled the different assessment criteria. In 2013, it was recognized as a three-star RS due to its active and healthy aging and e-health strategies. In 2016, Andalusia was awarded as a four-star RS due to its excellence in adopting the Quadruple Helix approach, seeking synergies that design knowledge ecosystems with a commitment to exchange and collaboration (13, 14). In 2019, Andalusia also achieved the highest recognition as a four-star RS with special recognition of excellence, continuing the Quadruple Helix approach and contributing to the European Digital Transformation of Health and Care. The region has a formal policy commitment that sets active and healthy living as a strategic priority, several plans and strategies addressing main health and care challenges, and a priority in its smart specialization strategy (S4Andalucía).

In the 2022 call, various entities involved in the Andalusia RS covered the Quadruple Helix spectrum in which the academic world, private initiatives, the public sector, social organizations, and citizens actively participate. Among these actors, it is worth highlighting organizations dependent on the Departments of Health and Consumer Affairs and Social Inclusion, Youth, Families, and Equality, such as the Andalusian Health Service, the Andalusian Social Services, and Dependency Agency or the Andalusian School of Public Health; the Public Universities of Andalusia (Almeria, Cádiz, Córdoba, Granada, Huelva, Jaén, and Sevilla); the industry (Indra-Minsait, Fujitsu, Phillips, NTT Data, and Tunstall); and civil society such as the Andalusian Council of Official Colleges of Pharmacists, scientific societies, local social services, pharmacies, scientific societies, technology companies, active participation centers, senior associations, and patient associations. Even without a formal statement for this involvement, multilateral collaborations have been crucial in the development and implementation of innovative initiatives in the region.

Overarching regional strategies have contributed to the recognition of Andalusia as RS, such as the Andalusian Health Plan or the Andalusian Plan for the Promotion of Personal Autonomy and Prevention of Dependency, as well as several comprehensive plans (care plan, integrated care for patients with multiple chronic diseases, diabetes, oncology, palliative care, and others). In addition, Andalusia RS has a well implemented Digital Health Strategy, which includes a corporate electronic health system -Diraya-, e-prescription system, and ClicSalud+ platform for patients' online access to their health data, as well as links with other innovation systems, Reference Sites and initiatives, such as EIT Health.

All entities from the Quadruple Helix approach in Andalusia contributed to Phase 2 of the 2022 call in the self-assessment of the maturity of the health system for active and healthy aging with a life cycle approach, using the adaptation of the SCIROCCO tool specially designed for this purpose. The results of the voting and consensus were achieved through a virtual meeting on 13 September 2022. The tool offers a visualization of the results for Andalusia in a spider net diagram (Figure 1), which allows analyzing the level of consensus of the respondents, including individual scores and consensus. The number of responses was sufficient to obtain significant results. The final scores for the 12 dimensions were readiness to change: 3, structure and governance: 3, digital transformation: 4, stakeholder coordination: 2, funding: 4, removal of inhibitors: 1, population approach: 3, citizen empowerment: 4, evaluation methods: 3, breadth of ambition: 4, innovation management: 4, and stakeholder's capacity building and development: 2.

Several innovative Andalusian practices have been shared within the RS community and are listed in the EC repository of good practices—Futurium platform—on active and healthy living in the digital world. These practices are as follows:

- Diraya-ClicSalud+, a corporate health information system including a shared electronic health record for each individual and secure online access to their health data.
- The population health database, curated data repository incorporating health information of all individuals with a healthcare record in the public healthcare system.
- The Andalusia Health App, to access different services and the repository of corporate apps.
- EnBuenaEdad, an online platform fostering active and healthy aging.
- Andalusian Telecare Service (ASSDA), a proactive telecare service for the prevention of loneliness in elderly and vulnerable populations.

Andalusia was once again recognized as an RS with the highest rating of four stars in the fourth call of 2022, reflected in the Certificate of Award in Figure 2.

Collaboration and exchange of good practices among RSs and participation in EU-funded projects have been an added value since the beginning of the EIP on AHA. Andalusia RS has been involved in several twinnings and study visits, strengthening synergies and facilitating the development and scaling up of innovative solutions: with the City of Zagreb RS on the Andalusian Digital Health Strategy—Diraya—and with Scotland to learn more about the Scottish "Living it Up" platform, in 2017. In 2018, a study visit to Basque Country to learn about the Basque Social-Health Strategy. During 2022, the Andalusian ClicSalud+ best practice was shared with Scotland, and the population health database was shared with Algarve (Portugal). In addition, a specific workshop "Digital Health for all" organized by Andalusia RS was held at the Committee of the Regions in Brussels on 25 October 2018 to share the priorities established in the "Communication of the European Commission for the transformation of health services in the digital single market, contributing to the empowerment of citizens and the construction of a healthier society" [COM (2018) 233 final].

It is not easy to assess the impact of the different regional policies and strategies addressing innovation in active and healthy living. Several indicators have been selected to show some results on the different dimensions of the EIP on AHA, such as the use of healthcare services, the overall health status of the population, and knowledge generation.

The first selected indicator is the average length of stay, reflecting an overall proxy of healthcare service utilization and its impact on efficiency and sustainability. Figure 3 depicts its evolution from 2016 to 2023, including the average length of stay for the total inpatient population and those over the age of 65. The average length of stay remains more or less constant for the total inpatient population but decreases for those over the age of 65 except the years affected by the COVID-19 pandemic. Multiple factors can influence this trend, but shorter inpatient stays contribute to the overall sustainability of the healthcare system.

FIGURE 1
Andalusian average dimensions diagram representation of regional maturity self-assessment using the SCIROCCO tool.

FIGURE 2
Andalusian RS Certificate of Award 4 stars.

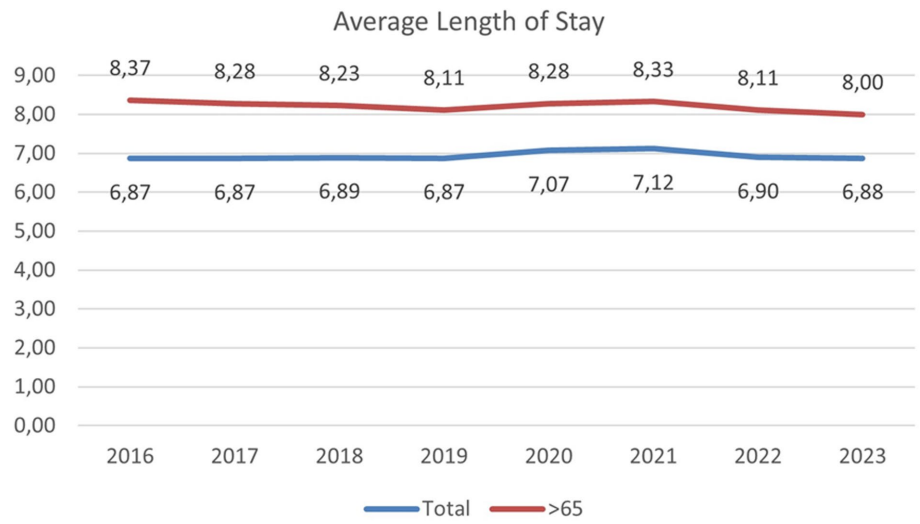

FIGURE 3
Andalusian average length of stay. Source: data from the Cartography and Statistics Institute of Andalusia.

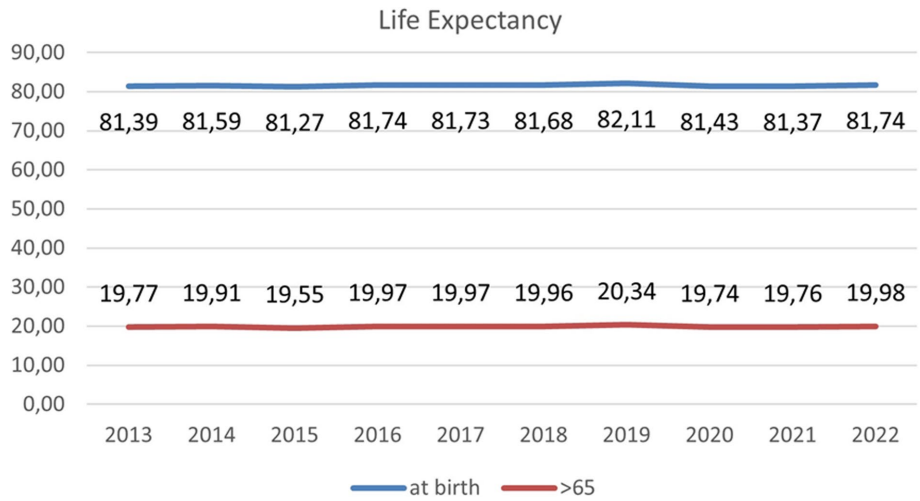

FIGURE 4
Andalusian life expectancy at birth and > 65. Source: data from the Cartography and Statistics Institute of Andalusia.

A more comprehensive indicator for assessing the overall health status of the population is life expectancy at birth and at 65 years, as depicted in Figure 4, covering from 2013 to 2022. Both indicators follow an upward trend, also affected by the years of the pandemic, showing a positive direction. Like the previous indicator, a wide variety of factors affects its evolution.

Exploring the implications of the options for generating research, development, and innovation (RDI) projects active in the region between 2019 and 2023, an upward trend is clearly reflected, as depicted in Figure 5. The total number of active RDI projects has moved from 1,094 in 2019 to 1,523 in 2024, roughly a 50% increase during these 5 years. Participation in EIT Health has also fostered collaboration with businesses and higher education institutions, and several projects have been developed, which have contributed to the positive trend in this indicator.

3 Actionable recommendations

The commitment to improving the health of the overall population including the elderly one in the region of Andalusia has been maintained and supported by the successive governing teams, with different political parties. This continuous political engagement has remained since the beginning of the EIP on AHA and remains today and has been reflected in the overarching regional plans and strategies.

Overall positive results regarding the impact on healthcare utilization, population health status, and fostering research and innovative projects have encouraged the participation in this European initiative and the continuity of the political support to date, inspiring policymakers' involvement, even with major changes in political leaders that have challenged this support.

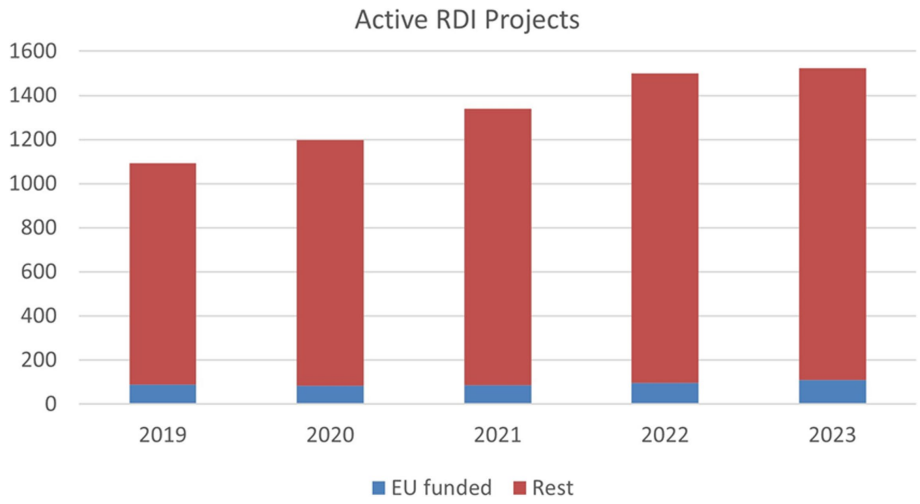

FIGURE 5
Andalusian Active Research and Innovation Projects. Source: data from the cartography and Statistics of Institute Andalusia.

Reference Sites have been most successful when they have brought together all the key stakeholders—regional government, health and care providers, industry, academia, and civil society—into a coherent partnership or ecosystem. This "Quadruple Helix" arrangement has enabled all stakeholders to be more aware of the health and care priorities, challenges, and needs. This has enabled researchers and industry to focus on more rapidly developing solutions to be tested, and where a positive evidence base is demonstrated, offering mechanisms to scale up within the region and allowing mutual learning with other initiatives and innovative ecosystems in other territories. Lacking a formal statement for the formation of the regional partnership has not limited the development of research and innovation in the region, as has been reflected in their contribution to the SCIROCCO maturity model self-assessment. Minor difficulties in understanding the model and its dimensions were overcome with the support of the technical team at the Regional Ministry of Health.

The adoption of a strategic approach within an innovative ecosystem has allowed us to focus on the benefits of innovative practices and solutions. Participation in the RSCN has contributed to the exchange of knowledge and identification and sharing of practices between RSs, enhancing the network and all RSs involved (15). Assessing the impact of these initiatives is challenging, but some positive results in several aspects have been shown. Having this focus on outcomes therefore provides a "Triple Win," which all stakeholders have contributed to.

4 Conclusion

The participation of Andalusia as RS first on active and healthy aging and now on active and healthy living has strengthened the collaboration of all stakeholders involved in the formation of innovative ecosystems under the Quadruple Helix approach. Showcasing the initiatives implemented in the region and mutual learning and connections with other RSs have been facilitated by the RSCN, in which Andalusia has been involved since its creation and formal constitution as vicechair of the network.

Different actors from academia, industry, and policy, together with civil society, influence the structure and design of a knowledge ecosystem in Andalusia. Complementary effects from innovations interact and propagate the effect of overarching policies and strategies to achieve better health for the population in the region (16).

Specific tools, such as the SCIROCCO one, help regions to understand the strengths and weaknesses of their regional context and inform policymakers about possible areas for improvement and foster innovation. It can also be used to compare the level of progress in a region before and after introducing reforms or innovations. Comparisons with other territories are also possible, and opportunities for exchange and shared learning can arise, strengthening collaborations in the field of health and care innovations. Minor difficulties in the understanding of its different dimensions do not limit its usage.

Author contributions

AC: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. FA-T: Investigation, Methodology, Writing – original draft, Writing – review & editing. FV-G: Validation, Writing – review & editing. IT: Validation, Writing – review & editing. MM-L: Supervision, Validation, Writing – review & editing.

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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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Interoperability of health data using FHIR Mapping Language: transforming HL7 CDA to FHIR with reusable visual components

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Introduction: Ecosystem-centered healthcare innovations, such as digital health platforms, patient-centric records, and mobile health applications, depend on the semantic interoperability of health data. This ensures efficient, patient-focused healthcare delivery in a mobile world where citizens frequently travel for work and leisure. Beyond healthcare delivery, semantic interoperability is crucial for secondary health data use. This paper introduces a tool and techniques for achieving health data semantic interoperability, using reusable visual transformation components to create and validate transformation rules and maps, making them usable for domain experts with minimal technical skills.
Methods: The tool and techniques for health data semantic interoperability have been developed and validated using Design Science, a common methodology for developing software artifacts, including tools and techniques.
Results: Our tool and techniques are designed to facilitate the interoperability of Electronic Health Records (EHRs) by enabling the seamless unification of various health data formats in real time, without the need for extensive physical data migrations. These tools simplify complex health data transformations, allowing domain experts to specify and validate intricate data transformation rules and maps. The need for such a solution arises from the ongoing transition of the Estonian National Health Information System (ENHIS) from Clinical Document Architecture (CDA) to Fast Healthcare Interoperability Resources (FHIR), but it is general enough to be used for other data transformation needs, including the European Health Data Space (EHDS) ecosystem.
Conclusion: The proposed tool and techniques simplify health data transformation by allowing domain experts to specify and validate the necessary data transformation rules and maps. Evaluation by ENHIS domain experts demonstrated the usability, effectiveness, and business value of the tool and techniques.

KEYWORDS

FHIR Mapping Language (FML), TermX, semantic interoperability, data transformation, HL7 Clinical Document Architecture (CDA), HL7 Fast Healthcare Interoperability Resources (FHIR)

1 Introduction

Electronic Health Records (EHRs) are shared patient records that contain historical data about a patient compiled from all local Electronic Medical Records (EMR). EHRs serve a dual purpose in the healthcare ecosystem. Primarily, healthcare professionals use EHRs in healthcare delivery to access patient medical histories, diagnoses, treatments,

and treatment outcomes (1). Additionally, routine clinical data is valuable for secondary use in clinical research, public health assurance, healthcare financing, and health policy-making (2) by enabling the aggregation and analysis of health data to improve healthcare (3, 4).

The European Health Data Space (EHDS) initiative (5) aims to build a health data sharing ecosystem (6) within the European Union (EU), establishing standards, practices, infrastructures and governance to support the primary and secondary use of EHRs (7). It facilitates healthcare access across borders in a mobile world where people travel for work and leisure (8). While the EHDS has ambitious targets to improve data sharing and patient access across the EU, there are concerns that it might be too large an undertaking to succeed (9). Additionally, it could undermine patients' control over their data (10), complicate the work of healthcare professionals (9), and reduce public confidence (11). Furthermore, the challenges include inadequate compliance with existing regulations, such as the GDPR (12), potential excessive dominance and control by large tech companies (13), and deepening digital divides (14).

One possibility for adjusting the EHDS to more manageable goals with incremental steps is to utilize federated EHRs at different levels. These levels include the national level, such as the Estonian National Health Information System (ENHIS) (15), the healthcare institution level, such as in Austria where data is stored by the healthcare provider who first collected or generated it (16), and the citizen level, stored on citizens' devices (17). A more radical federation approach involves decentralized content-addressable storage networks fully owned and controlled by citizens (18). Federated EHRs, particularly at the citizen level, offer several benefits compared to those stored in unified data silos (17, 18):

- *Privacy and security*: Reduces the risk of large-scale data breaches by allowing patient data to remain within national borders.
- *Single points of failure*: Reduces the risk of single points of failure, enhancing system resilience.
- *Patient trust*: Ensures transparency and control over data sharing, encouraging greater patient engagement in healthcare initiatives.
- *Compliance with regulations*: Supports compliance with national and EU regulations, particularly the GDPR, by keeping data within jurisdictions and providing patients with control over their health information.

Despite strong security and data protection properties, federated EHRs face a major challenge: semantic interoperability (19), which involves creating a common understanding of data elements and their relationships, aligning data structures, and standardizing terminology. Different healthcare providers often use different standards and vocabularies, leading to inconsistencies and data integration and interpretation difficulties. Even with the same standards and vocabulary, differences in interpretation arise (20, 21), whether among software developers or domain experts, including physicians.

1.1 Research problem

The article addresses the need for the semantic interoperability of health data in various formats. The ENHIS, operational since 2008 and maintaining lifelong health records of all Estonian citizens (15), is transitioning from the HL7 Clinical Document Architecture (CDA) format to Fast Healthcare Interoperability Resources (FHIR) (22). To mitigate the risks associated with data migration, the system must operate with legacy CDA data while storing new data in FHIR format, necessitating on-the-fly semantic interoperability between both formats.

In addressing the specific real-world issue of converting CDA to FHIR, we framed it as a broader problem of transforming EHR data from one format to another in a semantically interoperable manner.

1.2 Research questions

This paper focuses on using reusable components to transform health data from CDA to FHIR, an approach which serves as a methodical basis for developing and modernizing health information systems toward seamless semantic interoperability. It contributes to achieving federated semantic interoperability rather than integrated (common data format) or unified (common standard) interoperability (23). Federated interoperability allows different systems to work together coherently and efficiently, enabling dynamic networking with minimal costs (24). Each system can use its preferred data transmission protocol internally, with adapters performing the necessary conversions based on specified transformation rules and maps. Our paper provides tools and techniques for creating these transformation rules and maps, enabling semantic data transformations on the fly.

A Dutch study (25) compared CDA and FHIR representations for the inter-convertibility and consistency of Detailed Clinical Models (DCMs). While most aspects were adequately represented, issues with restrictions, coded values, narrative structures, and attribute meanings could lead to semantic challenges, emphasizing the need for the right DCM implementation standards. Austrian (26), Italian (27), and Estonian (28) studies demonstrate the potential for transforming International Patient Summaries (IPSs) (29) from HL7 CDA documents to FHIR resources. However, these transformations were hard-coded (30), making them opaque to business analysts, difficult to reuse, rigid, and challenging to maintain long-term (31).

Our goal is to provide a robust and reliable health data transformation process that can be replicated and reused in various contexts, with two important objectives:

- *The problem of clarity*: Implementing a low-code/no-code pattern should facilitate the faster delivery of transformations by minimizing hand-coding and utilizing a graphical user interface. Visual representation should conceal the complexity of the data transformation language, enabling analysts to

adapt quickly. This strategy should increase efficiency and productivity and reduce dependency on developers.

- *The problem of reuse*: Reusing transformation rules and maps should save time and costs and improve efficiency, consistency, and readability. It should also lessen challenges such as initial investment, compatibility, and flexibility. Ensuring reusability requires careful planning and standardization. Visual representations can simplify understanding and apply complex transformations, while clear guidelines should facilitate reuse. This approach should enhance data processing quality and reduce the learning curve, fostering a more collaborative and efficient work environment.

Research rigor is centered on systematically developing visual mappings to facilitate data transformation. It emphasizes enhancing the clarity of transformations and promoting their reuse. This is demonstrated by customizing CDA and FHIR models, developing effective transformation rules and maps, and instantiating FML transformations.

1.3 Research results

Our work consolidates the experience of mapping and transforming data between HL7 CDA and HL7 FHIR R5 within the Estonian National Health Information System.

Using a Design Science (DS) methodology (32), we developed techniques for domain experts to create and reuse visual health data transformation components, along with preliminary techniques for ensuring their correctness.

After analyzing existing data transformation languages and tools, we support the use of the FHIR Mapping Language (FML). To address the lack of suitable tools for domain experts (33), we designed, developed, and validated the TermX tool (34, 35) with input from domain experts (36, 37). TermX allows domain experts to specify and test transformation rules and maps between data formats using a WYSIWYG[1] approach with minimal technical knowledge (38).

1.4 Outline of the paper

The paper is organized as follows: Section 2. explains the HL7 CDA to FHIR transformation challenges, the TermX tool we developed for data transformations, and the methods we use in creating the data transformation techniques. Section 3. documents the transformation techniques. Section 4. evaluates the proposed techniques and discusses the related social impacts in the context of the EHDS. It also discusses related work, including an analysis of the pertinent tools and languages. Finally, in Section 5, we conclude and outline directions for future research.

[1]What you see is what you get.

2 Methods

We aim to improve data transformations by designing techniques and reusable WYSIWYG transformation components that domain experts can use to specify and validate data transformation rules and maps for semantic interoperability in EHR infrastructure, with only minimal technical expertise and skill needed. We adhere to the Design Science (DS) methodology (32, 39). A *transformation rule* is a specific instruction or set of instructions that defines how a particular piece of data should be transformed (40). A *transformation* refers to the overall process of converting data from one format or structure to another (40). A *transformation map* is a set of transformation rules and metadata used by the transformation engine during the transformation process (41). A *transformation component* is a visual representation of a transformation rule or map in TermX Visual Editor that contains an FML code that makes the necessary transformations. The techniques and transformation components, along with the TermX tool we use, are our artifacts. The context of these artifacts in performing health data transformations is the IT infrastructure of health organizations and state agencies. DS problems are improvement problems. This work aims to improve the federated semantic interoperability between heterogeneous healthcare EHRs. The proposed techniques are illustrated with data transformations from CDA to FHIR.

DS is part of the engineering cycle (Figure 1) and includes the problem investigation, treatment design, and treatment validation phases. The treatment implementation phase is not part of DS but forms an engineering cycle along with the DS phases. This paper reports two DS cycles and therefore also two engineering cycles. In the first cycle, we designed and developed the TermX tool. In the second cycle, we evaluated the TermX tool by designing the techniques and reusable WYSIWYG components for data transformation rules and maps from CDA to FHIR.

While the implementation of the artifact (TermX tool) is not part of DS but part of the engineering cycle, Figure 1 includes its implementation to illustrate the place and role of the TermX tool's development in our study. We designed TermX according to the DS methodology, encompassing the following steps: (1) investigating a problem, problem relevance, and research rigor by reviewing published papers on existing data transformation languages, tools, and implemented projects (see Section 4.1); (2) designing the TermX tool (38); and (3) validating the TermX design with domain experts from various countries (see Section 2.2).

In the second cycle, the main focus of the current paper is to evaluate the TermX tool by designing visual reusable transformation components that domain experts can use for CDA to FHIR transformations. We also generalize the transformation components' development process as techniques for developing reusable transformation components using TermX (Section 3) and explain the relevance of our research in the EHDS ecosystem, including how the proposed approach supports federated semantic interoperability (Section 4).

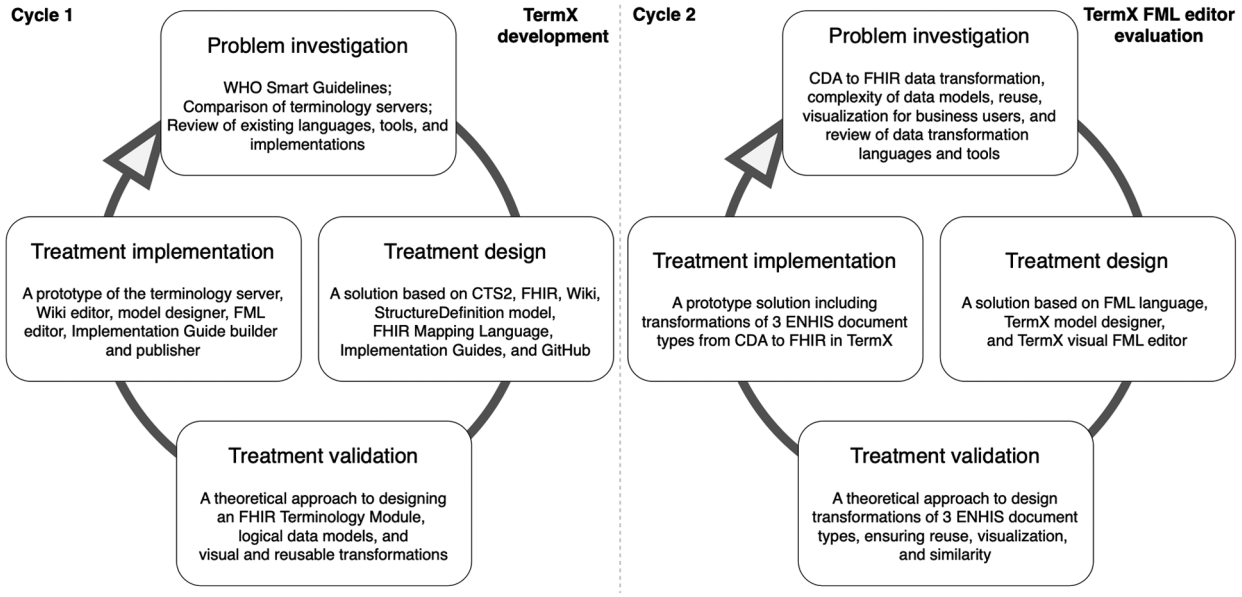

FIGURE 1
The Design Science methodology used for the development and evaluation of TermX.

2.1 HL7 CDA to FHIR transformation

HL7 CDA (42) and HL7 FHIR (43) are two widespread standards for the interoperability of health information systems. Although these two standards are designed to be interoperable, the semantic heterogeneity of various software vendors' implementations inhibits semantically correct model transformations between these standards (44). Additionally, model transformations between specific HL7 CDA and HL7 FHIR implementations are not straightforward and there is no single correct way to achieve them (27). Therefore, highlighting a new tool and the related techniques is pertinent, as transformation techniques between CDA and FHIR are relatively undocumented in academic literature.

HL7 CDA is a template-based and XML-centric standard for health data documents, first released in the early 2000s (42). It is a complex standard with many shortcomings in data redundancy and analysis. HL7 FHIR, by contrast, is a modern interoperability framework based on widespread web technologies, such as REST and JSON (44, 45). The shortcomings of HL7 CDA have been largely addressed in FHIR, which is why mapping and transforming existing HL7 CDA formatted health data to HL7 FHIR resources in a semantically interoperable way has tremendous potential and value in both health data usage and health data analysis-related innovation (46).

Although CDA and FHIR are designed to be interoperable, both standards are complex, and transformation between them is non-trivial (46). For example, the HL7 Reference Implementation Model (RIM) used within HL7 V3 and CDA aims to encompass the full spectrum of possible healthcare scenarios (47). In contrast, HL7 FHIR provides a model for the most common scenarios. Instead of defining a complete model for all aspects of healthcare, FHIR follows the 80/20 principle by defining only the most common health scenarios, adding the possibility of extension to cases where customization is necessary (48, 49).

The FHIR authors have identified various interoperability challenges when transforming data from CDA format to FHIR. Key points include clinical content mapping at the template level, managing differences in narrative granularity, and handling discrete-to-human-readable linkages, with some potential information loss when converting from CDA to FHIR (50). Additionally, both CDA and FHIR standards have evolved over time, and each new version brings changes that may not be compatible with previous versions (51–53). Efforts also exist to maintain forward and backward compatibility between versions, which is not guaranteed in all cases (53).

It is important to note that while CDA and FHIR are specifications for health data exchange, they differ in their approach and usage. FHIR's resource-based model allows for more granular control and flexibility, whereas CDA's document-centric approach provides a robust and standardized format for clinical documents. They also differ in their licensing requirements: CDA requires a license for use, whereas FHIR is dedicated to the public domain to encourage widespread adoption.

2.2 TermX: a game changer in interoperability

The necessity of robust, enduring, and relevant healthcare interoperability is universal across all clinical and health domains. However, we identified a gap in the availability of open-source, cost-free, high-quality tools that offer multilingual support and an advanced graphical interface (33). To address

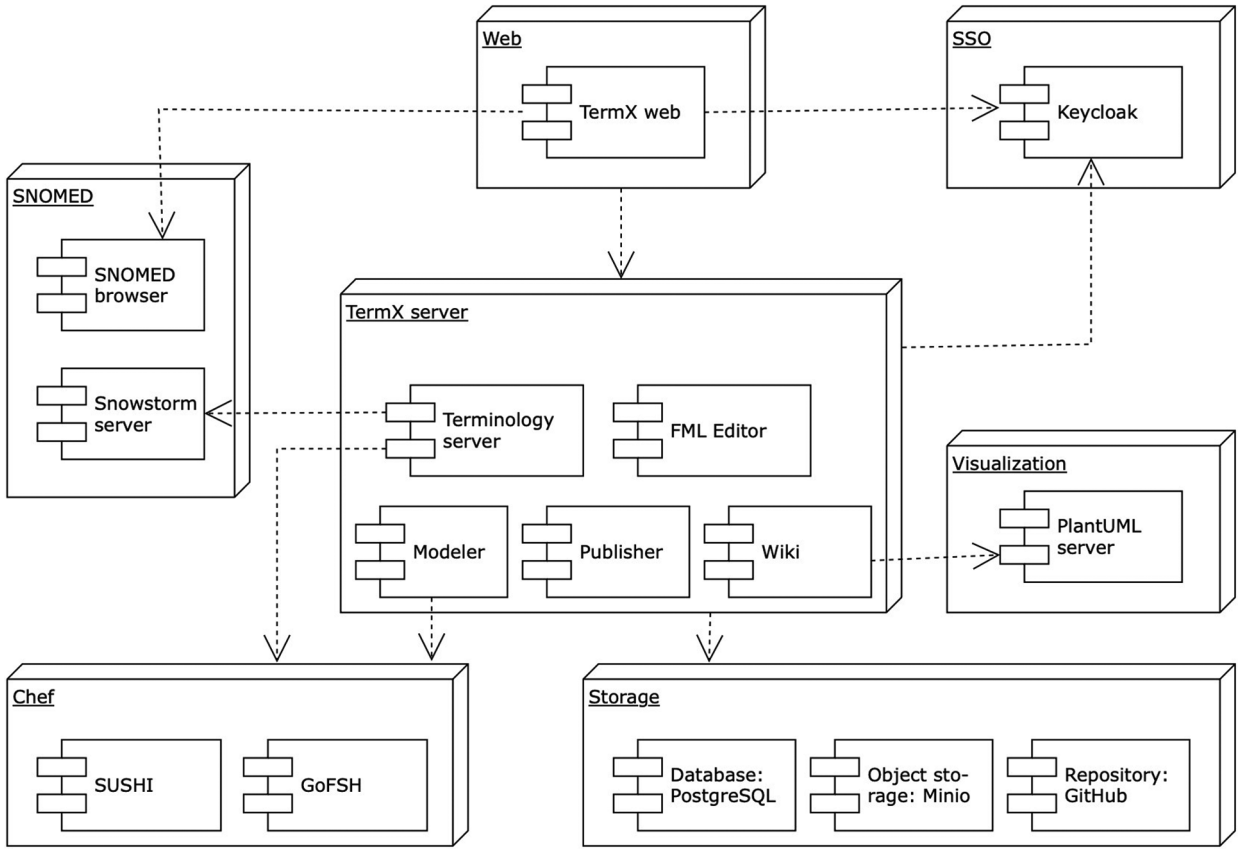

FIGURE 2
TermX component diagram.

this, we designed and implemented TermX – a novel, open-source platform for terminology management and data transformations to support interoperability between healthcare institutions and systems (34). TermX incorporates a terminology server, a Wiki, a model designer, an FML transformation editor, and tools for authoring and publishing (35). Figure 2 visualizes the TermX components (38). TermX is designed to manage data models and transformations and develop terminology and implementation guides for healthcare systems at international, national, regional, and hospital levels. It aims to ensure open, standardized access to published data and guarantee semantic interoperability based on the FHIR standard. We have validated TermX with TalTech (Tallinn University of Technology, Estonia), the private sector, and national standardization agencies in Estonia, Lithuania, Uzbekistan, and the Czech Republic.

TermX provides a visual model designer and FML Editor for creating and visualizing data models and FML transformation rules and maps through a user-friendly interface (Figure 3). They are designed specifically for business analysts rather than developers. The model designer implements the FHIR StructureDefinition specification (54) and provides the capability to manage data models through a user-friendly interface or formal specification in FML code. The FML editor's core purpose is to design transformation components, hide the complexity of the CDA, FHIR, and FML languages, and enable analysts to adapt quickly.

TermX uses the FHIREST (55) and HAPI FHIR (56) libraries to provide the FHIR API and uses HAPI FHIR (57) as the foundation for its transformation engine, transforming data from input sources into output sources (38). TermX was created as the result of an academic project at TalTech.

2.2.1 Reusable visual transformation components

CDA and FHIR are health data interoperability models developed by HL7 (44); both are designed with a hierarchical structure of data types and resources. For instance, CDA includes four code data types: CS (code simple), CV (coded value), CE (code with equivalents), and CD (concept descriptor) (see Figure 4). CS is the simplest, while CD is the most complex. Complex data types are composed of simple data types. In CDA, the simplest data type may be a subset of a more complex data type, for example, a CS is a subset of a CV data type. In FHIR, resources are categorized into metadata, special-purpose, general-purpose, and primitive data types (58). In both models, the depth of objects in the XML or JSON document tree can become very large. In the case of large CDA documents, the depth of the document trees results in very voluminous transformations.

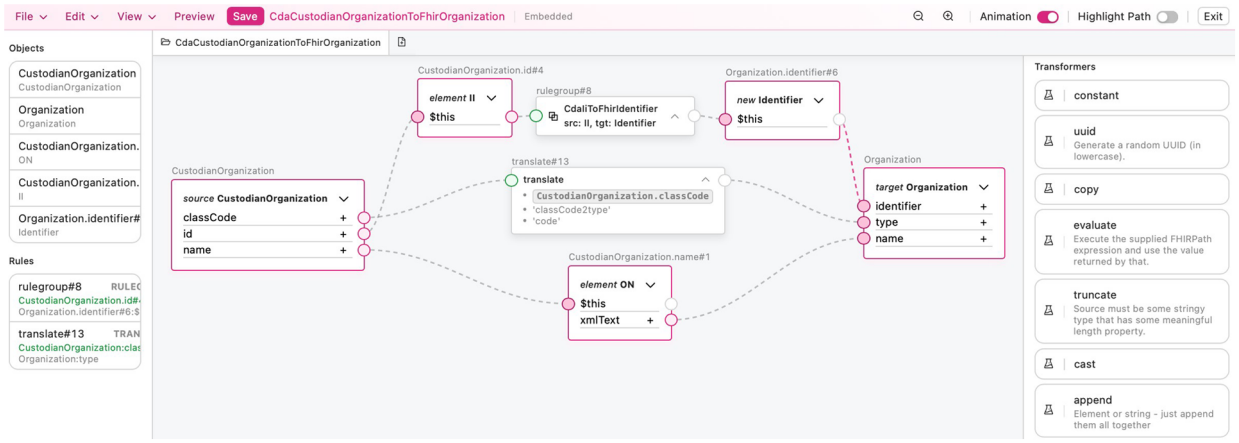

FIGURE 3
User interface of the TermX FML editor.

The transformation is the entire process of converting the resource, while the transformation rules are the detailed steps that specify how each attribute within the resource should be handled. Transformation rules are applied to convert the extracted data from its previous form into the required form. These rules could involve various instructions, such as extraction, conversion, or formatting. The transformation map, conversely, is not just an abstract concept but manifests itself as a tangible artifact. Every transformation map may be reused as a transformation rule in another transformation. Correct transformation rules and maps are fundamental in defining transformations, such as transforming CDA documents to the FHIR Bundle resource (59), as needed in the ENHIS. We identified the required transformation rules and maps between the data types and models of these two standards and created corresponding transformation components. We found that transformation components of simple data types, such as CD to CodeableConcept and II (instance identifier) to Identifier (see Figure 4), can be reused in more complex data types and model transformations. Such reuse simplifies the development of transformation rules and maps, improves clarity, and reduces the needed FML source code.

2.3 Research towards reusable visual transformation techniques

2.3.1 Problem investigation

The data transformation from CDA to FHIR necessitates a profound comprehension of the data structures inherent in both standards. FHIR *StructureDefinition* (54) describes a resource structure and defines a set of data element definitions and associated usage rules. These structure definitions describe the content defined in the FHIR specification, such as resources, data types, and underlying infrastructural types, and how these structures are utilized in implementations.

In CDA, each element is comprehensively defined using standard schema definition (XSD) files. These XSD files act as architectural designs, delineating the structure and data types of CDA documents and simplifying the process of validating these documents against the prescribed schema. The CDA model is based on the HL7 Reference Information Model (RIM) and utilizes reusable data types, templates, sections, and components (50). For instance, patient demographics, medication information, and clinical observations are standardized and reused across different CDA documents. HL7 has implemented a representation of the CDA R2.0 specification using FHIR Logical Models expressed as FHIR StructureDefinition instances available under an open-source license (60).

Many models in CDA and FHIR have numerous attributes, are complex, and contain hierarchies. We need a way to reuse data type transformations and provide reusable transformation components for CDA and FHIR subtypes, such as CD to Coding and II to Identifier. This approach will enhance the efficiency and reliability of data-handling processes. For instance, the ENHIS "Outpatient Case Summary" comprises 24 sections, while the "Birth Summary" comprises 17 sections (61). Of the "Birth Summary" sections, only four are absent in the "Outpatient Case Summary". Our techniques involve creating transformation components for a single document type and then applying these components to different types of documents. If new sections are introduced in the new document type, transformation components are only developed for these new sections and included in the reusable transformation components library. With each new document type, the number of sections requiring transformation components development will decrease and eventually reach zero. We also need a solution to validate transformation components to identify problems during development rather than production and to avoid errors during the development of transformation components.

Transformations of simple data objects are straightforward, and the associated source code in FHIR Mapping Language is relatively uncomplicated. However, with the transformation of hierarchical complex objects, the source code becomes highly intricate and may pose comprehension challenges for domain experts. Complex transformations necessitate visualization (62).

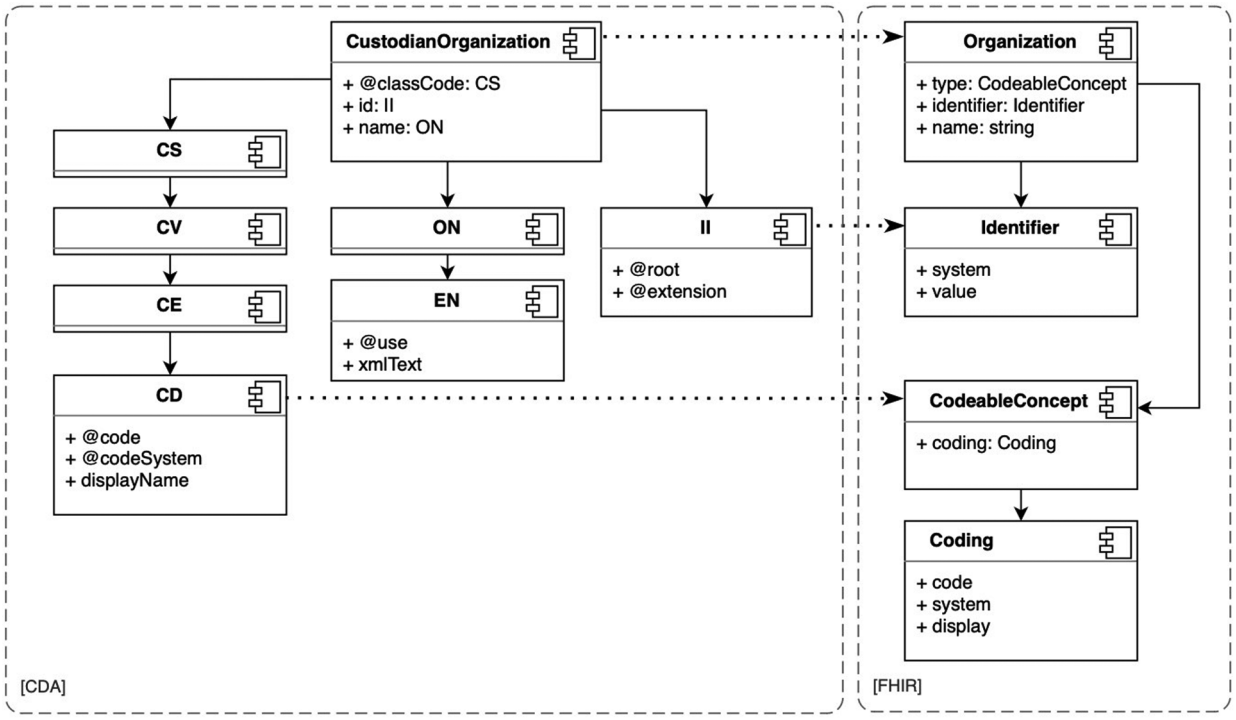

FIGURE 4
CDA CustodianOrganization and FHIR Organization resources, subtypes and related mappings.

We aim to establish a set of CDA and FHIR transformation components encompassing a broad spectrum, ranging from primitive data types to complex resources, and formulate appropriate techniques. We hypothesize the following:

(1) TermX as an artifact will apply to all CDA data types, sections, and documents.
(2) All transformation components can be developed using the TermX visual user interface.
(3) The developed transformation components can be reused.

This strategy would facilitate the reuse of prior transformation components, thereby augmenting the efficiency and uniformity of transformation procedures. Such an approach is designed to fortify the robustness and adaptability of the developed TermX tool, equipping it with the capacity to help domain experts develop and validate transformation components by hiding the details and complexities embedded within CDA and FHIR data models.

2.3.2 Treatment design

Based on the problem investigation above, we have established the following requirements for the visual reusable transformation components set:

(1) It must support strict data models
(2) It must support the reuse of transformation components
(3) It must have native support for CDA and FHIR
(4) It must support the WYSIWYG approach

This approach underscores our commitment to advancing the field of data transformation and management, ensuring that our data transformation techniques are accessible and understandable to a broad range of stakeholders.

The selected approach evaluates the usability of the TermX model designer and the TermX visual FML editor, the FML language, and the HAPI FHIR implementation of FML used by TermX (Figure 2 illustrates the TermX architecture and components). TermX enables the registration of HL7 V3 and CDA models in the TermX model designer, uses FHIR resource definitions, creates data transformation rules from CDA to FHIR in the TermX visual FML editor, and publishes the transformations on GitHub.

The transformation may be triggered by HTTP requests within scripts or through the web user interface. TermX is available as a set of Docker containers used for deployment. We use the logical models provided with the HL7 CDA R2.0 core standard (60) as a basis for ENHIS CDA input instances. These models were extended according to the ENHIS CDA standard implementation. We used FHIR Release 5 (R5) structure definitions (54) as the standard for output instances. The transformations handle one input CDA file and output one FHIR file.

2.3.3 Treatment validation

Treatment validation ensures that the chosen approach contributes to achieving stakeholders' goals when implemented. Our approach includes prototyping a set of transformation components using ENHIS version 8.2 CDA documents, the

FHIR R5 specification, and the TermX tool. The FML Editor achieved Technology Readiness Level (TRL) 5 according to the European Commission's classification (63) at the start of the validation process. The dataset, derived from three ENHIS HL7 CDA document types: the "Outpatient Case Summary", the "Notice of Growth", and the "Birth Summary", was established during the research to validate the proposed transformation techniques. For each selected document type, we used a sample CDA document from the ENHIS specification that includes all available sections.

The ENHIS "Outpatient Case Summary" includes 24 data sections, the "Notice of Growth" includes seven sections with two unique sections, and the "Birth Summary" includes 17 sections with four unique sections. Initially, we developed transformation components for all sections in the "Notice of Growth" and their associated classes and data types. Additionally, we created a transformation component to convert the "Notice of Growth" document into FHIR, incorporating all the transformations in the created section. For each subsequent document, we created a new transformation component that included the transformation components of the existing sections. Then, we added new section transformation components and linked them to the particular document transformation component. With the implemented prototype, we successfully verified that: (1) TermX was applicable for all necessary CDA data types, sections, and documents; (2) all transformation components were developed using the TermX visual user interface; and (3) the developed transformation components were reused in subsequent data types, sections, and documents.

The results obtained were first validated manually by comparing CDA and FHIR messages section by section to ensure the correctness of transformations. Next, we designed a technique (Section 2.3.4) to automate the validation process. Subsequently, the results were demonstrated to the IT department of the Health and Welfare Information Systems Centre (TEHIK), which operates the ENHIS. The feedback was overwhelmingly positive, with the team expressing their approval and satisfaction. Following the internal evaluation, TEHIK chose it as their transformation tool.

2.3.4 Advance techniques for validating transformation rules

Transformation validation should be deterministic, with each transformation having a dedicated test suite using predefined human-validated inputs and expected outputs. While developing these deterministic input-output pairs is time-consuming and can lengthen the development cycle, it is essential for robust production solutions and sometimes required by legislation (64, 65). We envision quicker heuristic feedback techniques for prototyping or experimentation, combining FHIR structure validation and an input-output content similarity assessment using a natural language processing (NLP) solution. However, supporting dedicated test suites in TermX and developing these heuristic validation techniques will largely be a part of future work.

Data similarity between the original HL7 CDA and the transformed HL7 FHIR documents was validated. No specialized out-of-the-box tool capable of statistically evaluating the correctness of the transformations was found. Therefore, CDA and FHIR documents were converted into collections of key-value pairs to which statistical tools were applied (66). The highest similarity percentage was achieved using the Term Frequency-Inverse Document Frequency (TF-IDF) methods (67). Further research in this direction is planned for the future.

3 Development techniques for reusable visual transformation components

Our study results in developing hierarchical, reusable transformation components for converting CDA documents into the collections of FHIR resources [Bundle (59)]. It highlights techniques that use the FHIR Mapping Language and the TermX visual editor to improve reuse and clarity in data transformations. First, we introduce the devised techniques. Then, we illustrate how the visual TermX editor supports our approach, making it accessible to analysts through a no-code visual interface. We provide practical examples using the ENHIS CDA documents, specifically the "Notice of Growth", "Outpatient Case Summary", and "Birth Summary", to demonstrate the application of these techniques in real-world scenarios. Furthermore, we outline preliminary techniques for validating transformation components, emphasizing the need for deterministic testing and proposing heuristic feedback techniques.

3.1 Techniques for hierarchical reusable transformation components

According to the authors of FHIR, transformations from CDA to FHIR should be performed at the template level (50). A CDA template follows a specific structure: the entire document is encapsulated within a <*ClinicalDocument*> element, which includes header information and a <*structuredBody*> element. The <*structuredBody*> element is composed of <*component*> elements, which in turn consist of <*section*> elements (Figure 5). These <*section*> elements comprise standard HL7 CDA classes, with optional extensions defined by the implementer. CDA classes are assembled using other CDA classes and complex and primitive data types. FHIR resource definitions also use other definitions and data types. A transformed CDA document is presented as an FHIR Bundle—a container holding a collection of FHIR resources.

We propose that the issues of reuse and clarity in CDA to FHIR transformations can be addressed through a hierarchy of reusable transformation components organized similarly to the structure of a CDA document. The FHIR Mapping Language allows the reuse of transformation maps that can be invoked from other transformation rules, thereby supporting our proposed approach.

We commence by delineating a hierarchical structure of data types and models. This hierarchy is instrumental in encapsulating the complexity and diversity of healthcare data. The fundamental

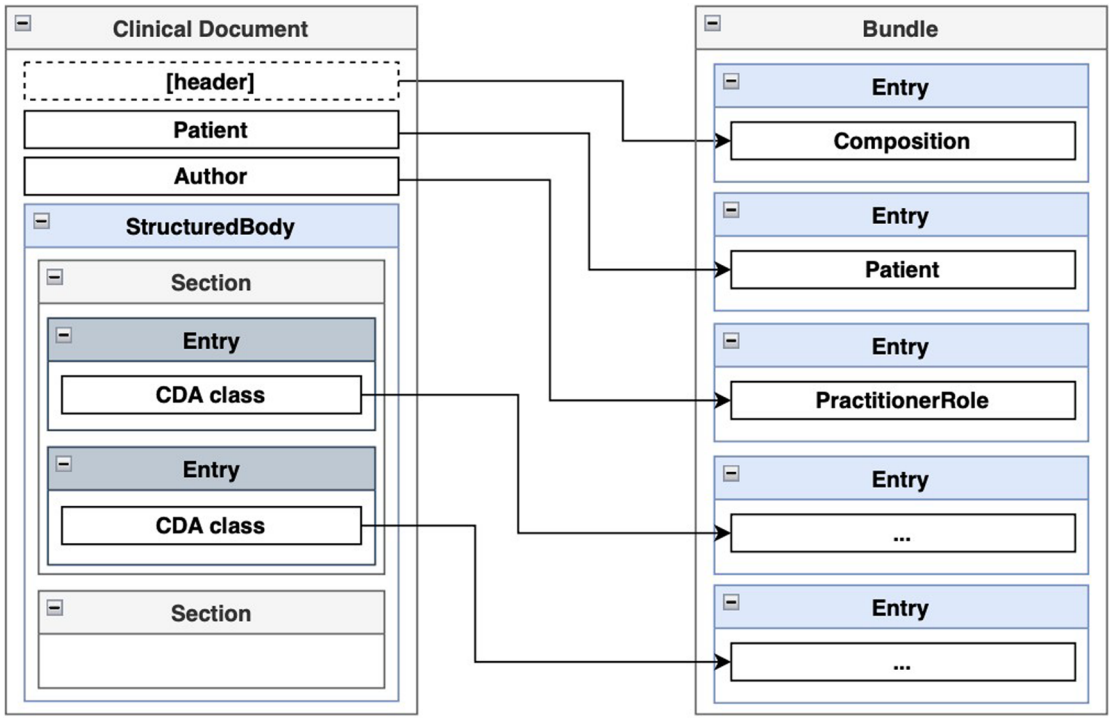

FIGURE 5
Mapping of ClinicalDocument to FHIR Bundle.

units can be categorized into primitive, basic, and complex data types. Each of these categories represents a different level of abstraction and complexity. Primitive data types are the simplest and most fundamental, representing basic data elements such as strings and numbers. Basic data types are slightly more complex, encapsulating the related data elements. Complex data types, on the other hand, represent a collection of basic and primitive data types, forming a more intricate structure. Subsequently, we establish transformation components between these data types. These transformation components elucidate the relationships and transformations between data types, thereby facilitating interoperability and data exchange. Lastly, we construct transformation components between different models.

Our findings demonstrate that it is feasible to define reusable transformation components at various levels of granularity of a CDA template: the complex data type level, the CDA class level, the section level, and the document level. The primitive data types between CDA and FHIR are already interoperable. Based on these levels of granularity, we establish sets of transformation rules to be maintained.

With the different granularity level transformation components, a set of *ConceptMap*, and the source and target *StructureDefinitions*, we define a set of software artifacts to be created and maintained for developing robust CDA to FHIR transformation components quickly. The list of artifacts is described in Table 1, and the dependencies among the artifacts are visualized in Figure 6. We designed the transformation components to transform basic and complex data types from CDA to FHIR. Mappings from CDA sections to FHIR resources are assembled using CDA class to FHIR resource transformation components and CDA complex data type to FHIR complex data type transformation components. Subsequently, the CDA document for FHIR bundle transformation components can be formed using the CDA section for FHIR resource transformation components. The CDA document header is considered a section in our approach. Lower levels of granularity transformation components are used in the transformation components with the higher granularity level, thus adhering to one-way dependencies—an important software architecture pattern.

In addition to these transformation components, two additional components are required. The *ConceptMap* (68) translates the set of concepts in one code system to one or more concepts in other code systems. The *StructureDefinitions* (54) are used to define source and target data models of the transformations.

The reuse problem is addressed using a single transformation component in multiple other transformation components where the same construct is mapped. For example, a component that maps a CDA *II* class to a FHIR *Identifier* data type can be used in components mapping both the CDA class *CustodianOrganization* to the FHIR *Organization* resource and the CDA class *AssignedAuthor* to the FHIR *Practitioner* resource. By solving the problem of reuse, we ensure that issues in transformations have a single point of failure, thereby enhancing the robustness of the transformations. Reuse also enables the faster development of transformation components from CDA templates to FHIR bundles, as it eliminates the need to repeatedly write the same transformation component for transforming the same section or class to FHIR when working with different CDA templates.

TABLE 1 CDA2FHIR artifacts.

Artifact	Source	Target	Explanation
I/O structures			The definitions of the structures for the inputs and outputs of the transformations in the form of FHIR StructureDefinition resources.
Classifier mappings			FHIR ConceptMap resources that map CDA coding systems to FHIR coding systems.
Data type Mappings	CDA data type	FHIR data type	Transformations between CDA data types and FHIR data types in the form of FML or FHIR StructureMap resources.
Class to Resources Mappings	CDA class	FHIR resources	Transformations between CDA classes and FHIR resources in the form of FML or FHIR StructureMap resources, constructed from the elements of data type transformations and classifier transformations.
Section to Resources Mappings	CDA *<section>*	FHIR resources	Transformations between CDA document sections and FHIR Bundle resources in the form of FML or FHIR StructureMap resources. A document section is a code-distinguished section within the structuredBody element of a CDA document or the CDA document header. These transformations are constructed from the elements of transformations between CDA classes and FHIR resources as well as data type transformations.
Document to Bundle Mappings	CDA document template	FHIR bundle	Transformations between CDA documents and FHIR Bundle resources in the form of FML or FHIR StructureMap resources. These transformations are constructed from the elements of transformations between CDA document sections and FHIR Bundle resources.

The problem of clarity is addressed through reusable transformation components that encapsulate complexity at various levels of granularity. When analyzing a component that transforms a CDA template to an FHIR bundle using our proposed techniques, we only need to understand the different sections defined in the template without being burdened by the details of the transformation component of CDA classes or complex data types. This principle applies to rules at each level of granularity, ensuring that each component remains focused and comprehensible by abstracting lower-level details.

3.2 Techniques for visualizing transformation components with TermX

To support the described techniques for developing CDA to FHIR transformation components using FML, a visual editor must support the following use cases: the management of *StructureDefinitions*, the management of *ConceptMaps*, the creation of FML transformation, and the ability to use existing transformation components in other FML transformations. According to our results, the TermX software supports all of these use cases through a visual user interface with low-code/no-code.

In TermX, the management of *StructureDefinitions* is part of the Modeler module. *StructureDefinitions* can be displayed as a tree-like visual structure and edited without modifying the underlying JSON or FHIR Shorthand (FSH) (69) source. Additionally, the HL7 CDA *StructureDefinitions* do not need to be implemented from scratch, as the FHIR authors have provided multiple core standard CDA specifications using FHIR Logical Models expressed as FHIR *StructureDefinition* instances (60). These logical models can serve as a basis for *StructureDefinitions* of a specific CDA implementation. The CDA *StructureDefinitions* can be created in TermX using the provided JSON or FSH syntax and then edited with the visual editor to fit specific implementation guidelines. A FHIR implementation generally includes an *Implementation Guide* containing the Resources' *StructureDefinitions*.

The Terminology module supports the management of *ConceptMaps* that represent the mapping between source and target terminology. The *ConceptMaps* can be used as a *transformation rule*.

TermX provides a visual FML editor as a designer of explicitly designed FML transformation components for business analysts (38). Every transformation has at least one source and target *StructureDefinition* and may reuse other FML transformation components and *ConceptMaps*. The imported elements can then be utilized on a visual canvas, dragging and dropping as boxes. Lines can be drawn between the boxes, visually modeling the control flow of the transformation rule from the source structure to the target structure, from which FML code is generated (Figure 3). The objective of the FML editor is to visually represent transformation rules, hide the complexity of the FML language, and facilitate rapid adaptation to the FML language.

In the work described in this paper, all the necessary transformation components were created with the visual editor of TermX; even the code generated behind certain transformation component visualization boxes and lines was not always intuitive to inexperienced users.

3.3 Techniques for developing CDA to FHIR transformation components

We evaluated the viability of the proposed techniques by developing a prototype development for transforming the ENHIS CDA documents "Notice of Growth", "Outpatient Case Summary", and "Birth Summary". We began by dividing the "Notice of Growth" into sections and then breaking those sections into classes and data types. We also documented the necessary *ConceptMaps* and *StructureDefinitions*. After this, we developed the transformation components, starting with lower granularity artifacts. This process was repeated for the other two CDA documents, reusing already specified transformation components wherever possible. Subsequently, we provide

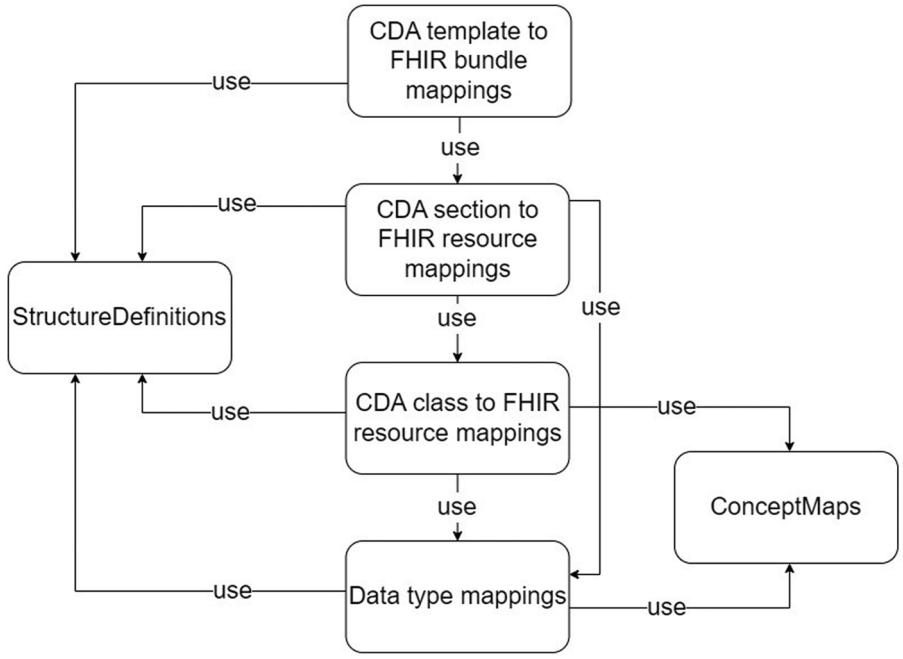

FIGURE 6
Usage dependencies between artifacts used in CDA to FHIR mappings.

FIGURE 7
Transformation of CDA administrative gender attribute to FHIR gender attribute using ConceptMap for concept translation.

examples from a real-world use case to illustrate the key points previously highlighted.

3.3.1 Specifying CDA data type level transformations

For the ENHIS CDA *StructureDefinitions*, we were able to use the logical models provided with the HL7 CDA R2.0 core standard (60) as a basis, which were then modified as needed according to the ENHIS CDA standard implementation. This implementation is available as Enterprise Architect models and PDF documents on the web and is accessible within the Estonian IP address space. The modifications required for the core standard *StructureDefinitions* were necessary to address the extensions of the base model defined in the Estonian implementation as well as instances of misuse of the standard. For example, in the CDA *Observation* class, the *Ratio* data type for the value attribute is denoted as *RTO-PQ-PQ* in the core standard, which employs hyphens. However, in the ENHIS implementation, it is referred to as *RTO_PQ_PQ*, where underscores are used instead. An example of an extension that needed to be accounted for is the *<asLicencedEntity>* element added to the *<assignedEntity>* element to provide information about the authority licensing the healthcare worker. As the transformation target structure, we used the base FHIR R5 release, for which we utilized URIs in a test server.

An example of using *ConceptMaps* and terminology translation between CDA and FHIR is illustrated when transforming the CDA Patient class into the FHIR Patient resource. The two standards use different sets of codes to represent the administrative gender of the patient. For instance, in the ENHIS CDA implementation, the code "N" represents the female gender, whereas in FHIR R5, the code "female" is expected. A *ConceptMap* was constructed and used with the transformation rule to perform translation between the two terminology code systems, as shown in Figure 7. In the figure, the *administrativeGenderCode* attribute of the Patient CDA class is piped into the transformation rule, the result of which is assigned to a new FHIR code data type and then to the gender attribute of the Patient FHIR resource.

One of the most common transformations we encountered was between the FHIR concept and different representations of the CDA

concepts. For example, FML transformation rules between the CDA CD class and the FHIR *CodeableConcept* resource as well as between the CDA CE class and the FHIR *CodeableConcept* resource provided significant value in terms of reuse. These transformation rules were very common in higher granularity level transformations. Due to the nested structure of the FHIR *CodeableConcept* and the three data attributes mapped between the structures, calling a reusable transformation rule with one line of code saved us from repeating the same six lines of code each time. An example of a reusable CDA CE to FHIR *CodeableConcept* transformation rule using the TermX visual editor can be seen in part A of Figure 8. The attributes of the CE CDA class are assigned to a new Coding FHIR resource. The Coding resource is then assigned to the target *CodeableConcept* coding attribute. Specifically, the CE CDA class's code attribute corresponds to the FHIR Coding's code attribute, the *codeSystem* attribute corresponds to the *system* attribute, and the *displayName* attribute corresponds to the *display* attribute.

Notably, FML also enabled us to handle semantically faulty XML at the data type level. In an *Observation* element in the "Outpatient Summary" test documents we used, we encountered a decimal value represented as text with a comma decimal separator inside an *EncapsulatedData* data type: *<value xsi: type="ED">12,2</value>*. To fix this issue, we were able to replace the decimal separator and cast the text into a decimal data type using FML's *evaluate* rule with a *FHIRPath* expression and a *cast* rule. We accomplished all of this using only the visual editor (see Figure 8 part B). The inner text of the XML tag represented by the *xmlText* attribute is piped into an *evaluate* block, where a *FHIRPath* expression is used to replace the comma with a period in the text string. The evaluated string is piped into a *cast* block, which casts it to a decimal data type and assigns it to an output value. In our opinion, this result illustrates that a visual editor can produce fault-tolerant and robust transformation rules.

3.3.2 Specifying CDA class level transformations

CDA class to FHIR resource transformation rules can be exemplified with Figure 9, which shows how a CDA *AssignedAuthor* class is mapped to a FHIR *Practitioner* resource using the TermX visual editor. The CDA *AssignedAuthor* class is split into the *II* data type from the id attribute, the CE data type from the code attribute, and the Person class from the

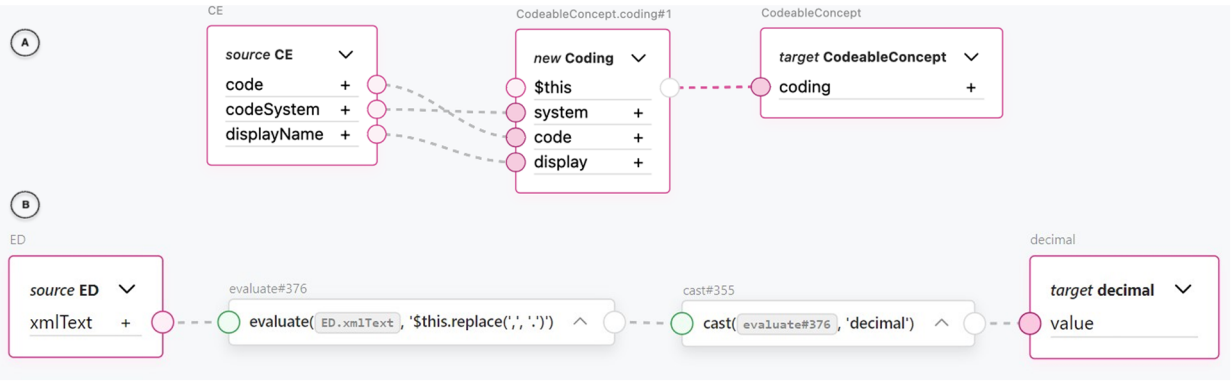

FIGURE 8
An example transformation from CDA CE class to FHIR CodeableConcept resource.

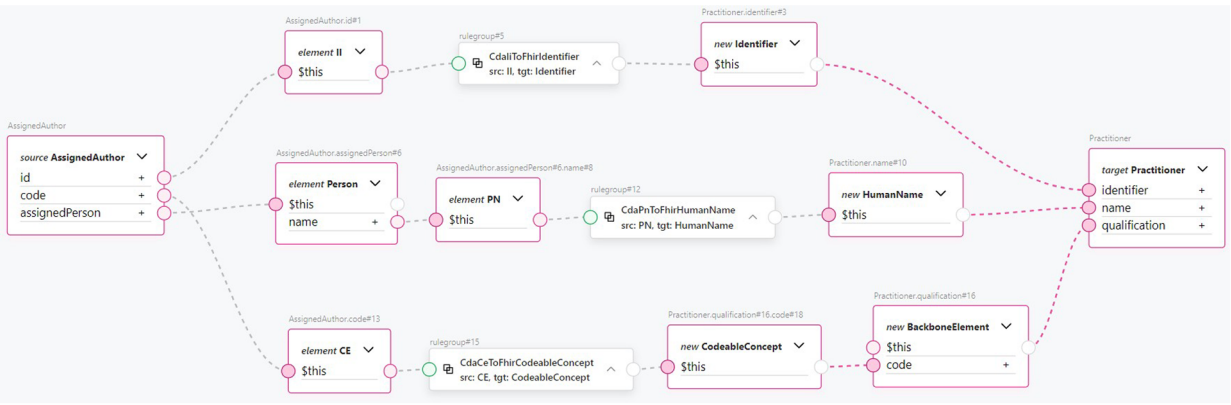

FIGURE 9
An example transformation from CDA AssignedAuthor class to FHIR Practitioner resource.

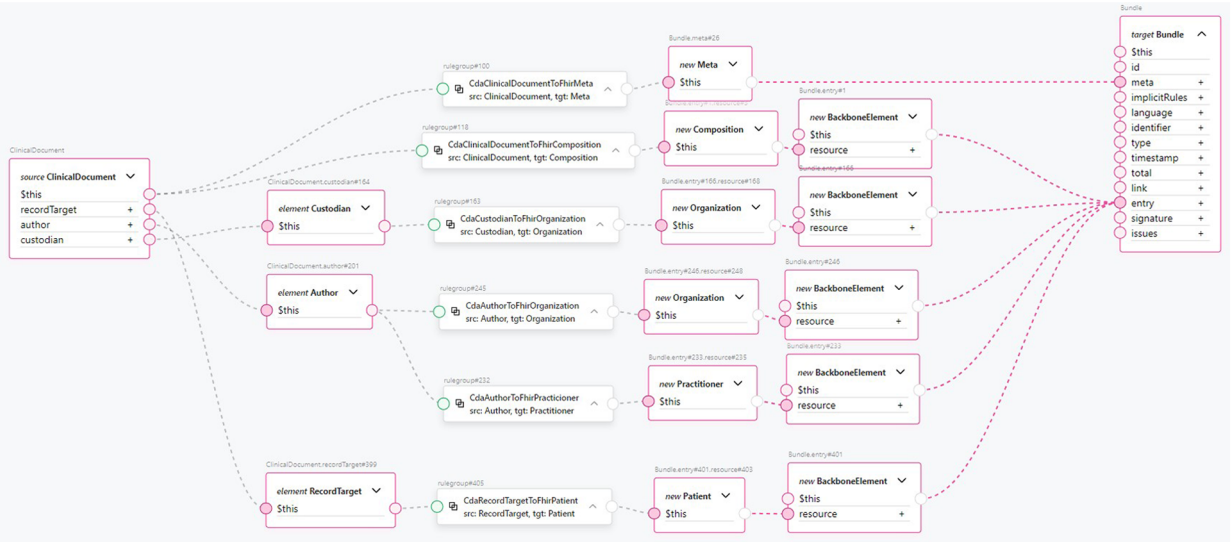

FIGURE 10
An example transformation from CDA ClinicalDocument header entries to FHIR Bundle entries.

assignedPerson attribute. Subsequently, the CDA *II* data type is transformed into the FHIR *Identifier* resource using the reusable transformation component *CdaIiToFhirIdentifier*. The CDA *CE* data type is transformed into the FHIR *CodeableConcept* resource using the reusable transformation component *CdaCeToFhirCodeableConcept*. The CDA *PN* data type is extracted from Person class and transformed into the FHIR *HumanName* data type using the reusable transformation component *CdaPnToFhirHumanName*. The transformed FHIR resources are then assigned to the target *Practitioner* resource's identifier, qualification, and name attributes, accordingly. Notice how data type transformation rules are imported and then used. Referring to Figure 8, which shows the implementation of the *CdaCeToFhirCodeableConcept* transformation, it is clear how our approach encapsulates complexity and promotes clarity at the CDA class to FHIR resource mapping level.

3.3.3 Specifying CDA section level transformations

Transforming the CDA document header to FHIR is an example of the transformation component from a CDA section to a FHIR resource. This is shown in Figure 10. The clinical document header contains a variety of information. The confidentiality codes, as top-level attributes of the header, are transformed into FHIR's Meta resource and assigned to the FHIR Bundle's meta attribute. The structural information about the sections in the document is compiled to form the FHIR *Composition* resource and added to the FHIR Bundle as an entry. The clinical document header's *custodian* attribute, a CDA *Custodian* class instance, is transformed into a FHIR *Organization* resource and added to the bundle as an entry. The *author* attribute of the clinical document, a CDA *Author* class instance, contains information about the author's person and organization. Therefore, two transformation components are used: one for transforming the data into a FHIR *Organization* resource and another for transforming the data into a FHIR *Practitioner* resource. Both resources are added to the FHIR Bundle as entries. Finally, the *recordTarget* attribute of the clinical document header, a *RecordTarget* CDA class instance, is transformed into a FHIR *Patient* resource and added to the FHIR Bundle as an entry. This concludes the scope of our *ClinicalDocument* header transformation component. The number of transformation components is approximately equal to the number of document types and CDA classes used in them, considering the CDA class hierarchy. By encapsulating transformation components such as *CdaCustodianToFhirOrganization*, *CdaAuthorToFhirOrganization*, *CdaAuthorToFhirPractitioner*, and others into reusable transformation components, the CDA header transformation rule remains comprehensible, even though the amount of information to be transformed is much larger.

3.3.4 Specifying CDA document level transformations

Finally, using CDA section transformation components, we compose a transformation component for the "Notice of Growth" CDA document (see Figure 11). We find a document section by section code, then apply a reusable component to transform this section into FHIR resources, and then combine them into a FHIR Bundle. The header section is extracted from the root level of the *ClinicalDocument*, while the other sections are extracted from within the <*StructuredBody*> element. From the <*structuredBody*> element, we extract two sections: the *AGE* section and the *GROWTH* section. The *AGE* section is transformed into an *Observation* FHIR resource containing the patient's age information using a single *CdaAgeSectionToObservation* reusable transformation component.

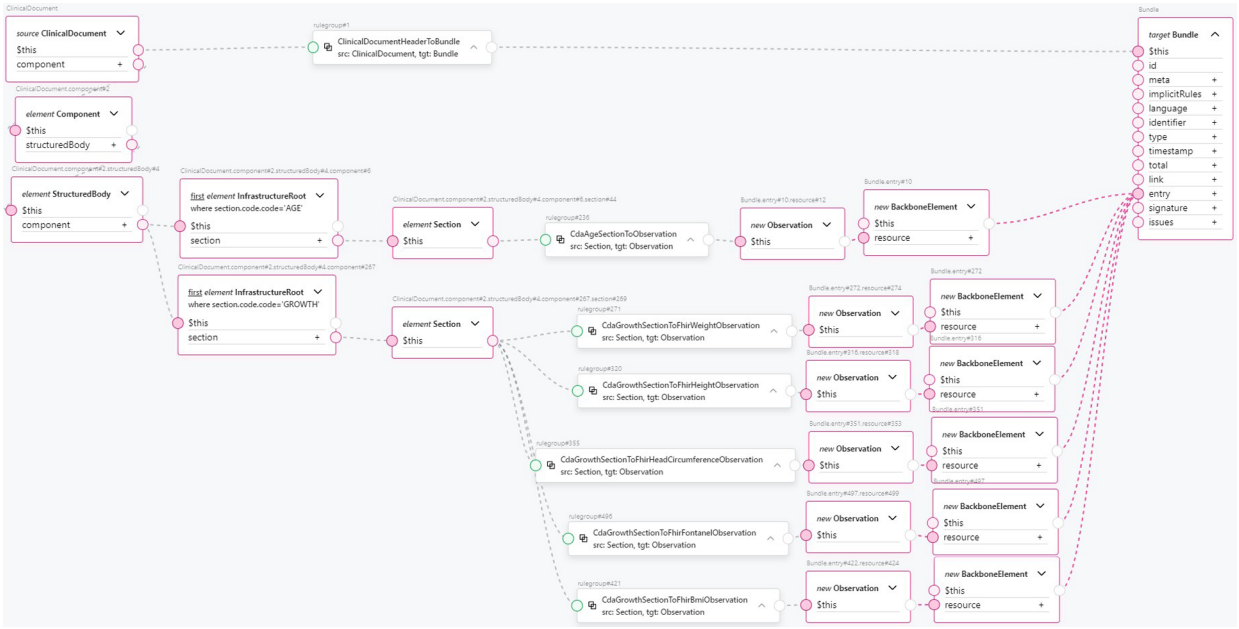

FIGURE 11
An example transformation from CDA Growth Report template to FHIR Bundle entries.

The transformed *Observation* resource is added to the FHIR Bundle as an entry. The *GROWTH* section is transformed into multiple observations, as this section contains CDA *Observation* classes in <*component*> elements for different measurements taken during the procedure: weight, height, head circumference, fontanel measurements, and body mass index. The following reusable transformation components are used:

- *CdaGrowthSectionToFhirWeightObservation*
- *CdaGrowthSectionToFhirHeightObservation*
- *CdaGrowthSectionToFhirHeadCircumferenceObservation*
- *CdaGrowthSectionToFhirFontanelObservation*
- *CdaGrowthSectionToFhirBmiObservation*

The resulting Observation FHIR resources are added to the FHIR Bundle as entries. Referring to Figure 10 for the complexity of just the CDA document header component, we see how this approach encapsulates the complexity of a single document section and enhances clarity and high-level understanding of the clinical document's mapping to FHIR. From the data type level up to the CDA template level, the amount of code duplication is significantly reduced, as is the number of points of failure. At the same time, the clarity and comprehension of the transformations are greatly improved.

With the development of the "Notice of Growth" CDA to FHIR transformation, the following transformation components were created:

- *CdaClinicalDocumentHeaderToFhirBundle*
- *CdaAgeSectionToFhirObservation*
- *CdaGrowthSectionToFhirWeightObservation*
- *CdaGrowthSectionToFhirHeightObservation*
- *CdaGrowthSectionToFhirHeadCircumferenceObservation*
- *CdaGrowthSectionToFhirFontanelObservation*
- *CdaGrowthSectionToFhirBmiObservation*

Numerous transformation components have been created to convert CDA classes to FHIR resources and support the composition of section-level transformations. The essential components include the following:

- *CdaAssignedAuthorToFhirPractitioner*
- *CdaCustodianOrganizationToFhirOrganization*
- *CdaObservationToFhirObservation*
- *CdaOrganizationToFhirOrganization*
- *CdaPatientRoleToFhirPatient*
- *CdaEntryRelationshipToFhirObservationComponent*

The necessary data type transformation components include the following:

- *CdaAdToFhirExtendedContactDetail*
- *CdaCdToFhirCodeableConcept*
- *CdaCeToFhirCodeableConcept*
- *CdaIiToFhirIdentifier*
- *CdaIvlTsToFhirDateTime*
- *CdaPnToFhirHumanName*
- *CdaPqToFhirQuantity*
- *CdaRtoPqPqToFhirRatio*
- *CdaTelToFhirExtendedContactDetail*
- *CdaTsToFhirDate*

The *ConceptMap* *CdaAdministrativeGenderCodeToFhirGender* was also created. All these transformation components were designed to be reusable for the future development of transformation components from other CDA templates to FHIR bundles.

4 Analysis and discussions

4.1 Related work

This section provides a comprehensive review of the related work in the domain of data transformation, with a particular emphasis on the transformation process from CDA to FHIR. The related work can be systematically classified into three distinct categories: mapping languages, tools, and implementation projects. This categorization facilitates a more structured and in-depth analysis of the field.

4.1.1 Mapping languages

The concept of "Mapping Language" (or Data Transformation Language) lies in establishing a platform-independent specification that can be implemented across various programming languages (70). Model-to-model transformations are typically articulated in specialized domain-specific languages, often known as model transformation languages (MTLs) (71). MTLs encapsulate algorithms that delineate the process of converting elements from one model (or multiple models) into elements of another model (or multiple models). Declarative MTLs (DTLs) only provide logic constructs to express relations between elements in these candidate models, and the execution engine is responsible for synthesizing an execution plan that uses these relations to perform the model transformation.

Query/view/transformation: "Query/View/Transformation" (QVT) is a specification developed by the Object Management Group (OMG) to describe transformation rules between different data models in the Model-Driven Architecture (MDA) domain (72). The language was intended to support the declarative specification of model transformations, avoid imperative constructs, and support change propagation from one model to another as well as the bi- (or multi-) directional interpretation of transformations. However, its semantics have many unclear or unsatisfactory aspects that are not precisely defined in the standard (73). The QVT Core language (QVTc) uses pattern matching as the primary logic construct. Pattern matching is done over a flat set of variables by evaluating conditions over those variables against the candidate models (74).

eXtensible stylesheet language transformations: XSLT is a language used to transform XML documents into other document formats or other versions of XML.[2] XSLT is a powerful tool and a widely adopted language for transforming XML documents, including healthcare-related XML standards such as CDA. However, it is unsuitable for directly programming transformations of semantically complex models due to its low-level syntax (75). XSLT is also not a specialized language for medical data (76). One of its disadvantages is the mandatory use of XML language, which imposes limitations on use. It is also poorly readable, making it difficult to learn and debug (77).

Whistle: The Whistle Data Transformation Language provides a means to express mappings between schemes, enabling users to convert complex, nested data models into other equally complex and nested data formats (78). Whistle does not require a description of logical models for the data to be converted. The conversion requires only source data in JSON format and a map that describes the conversion rules. The result of the transformation is output data in JSON format.

Liquid templates: Liquid (79) is a templating language developed by Shopify that uses a combination of objects, tags, and filters inside template files to convert any JSON or XML format into another JSON format. A transformation engine is required to convert input data into output data based on a *.liquid template*. Microsoft FHIR Converter (80) is one such engine, processing Liquid templates to convert input data into validated FHIR format. It includes extended methods for FHIR data and is part of Microsoft's FHIR server implementation, available in the Microsoft Azure Health Data Services product (81). Users can upload custom templates to the Azure registry, which Azure Health Data Services can then use via an API endpoint for data transformation.

FHIR Mapping Language: The FHIR Mapping Language (FML) (40) is a relatively new QVT-based transformation language specifically designed to transform HL7 FHIR resources to/from alternative representations, including different logical data models, FHIR resources, C-CDA documents (42), etc. (82). FML is a part of the FHIR specification. Conceptually, FML is similar to XSLT:

(1) It consists of declarative rules that are automatically matched to input data
(2) It includes a sub-language (*FHIRPath*) to reference parts of source parse trees
(3) It can reference external functions written in different languages

The source input of FML supports any object models and rendering syntaxes that conform with OMG's Meta Object Facility (MOF)[3] language. MOF is a general formalism for representing object models as directed acyclic graphs (DAGs). MOF-compliant models can use various syntactic constructs to represent the classes, attributes, and attribute values of such graphs. The applications of this language encompass several scenarios:

- Mapping FHIR resources across different versions of FHIR
- Converting sections of HL7 C-CDA documents into multiple FHIR resources
- Translating HL7 V2 messages into multiple FHIR resources
- Adapting any structured data format into another structured data format, including mapping to multiple FHIR resources

[2]https://www.w3.org/TR/xslt-30.

[3]http://www.omg.org/mof/.

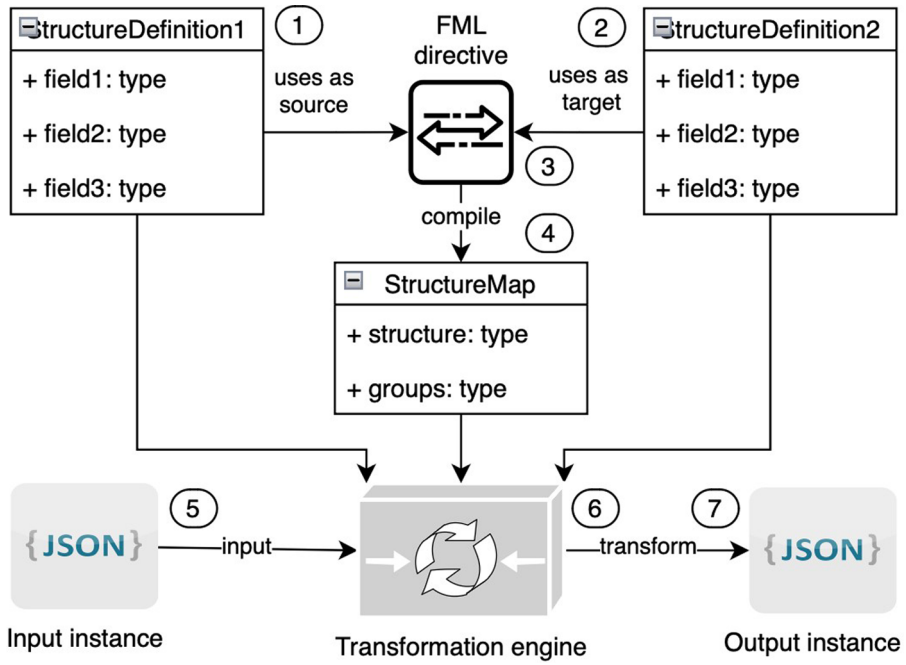

FIGURE 12
Components of FML transformation.

The technical specification of FML (40) has been published as an integral component of the FHIR specification (83). FML serves as a tool for transforming structured models from one form to another. Within the HL7 FHIR context, FML is utilized to map FHIR resources across different versions of FHIR. FML transformation requires the following (Figure 12):

- One input model (marked on the picture with the number "1")
- At least one output model (2)
- Human-readable transformation rules (also known as FML mapping directives) (3) that outline how to transform input into output
- A machine-processable transformation map (4) created as a result of the compilation transformation rules
- One input instance that corresponds to the input model in JSON or XML format (5)
- A transformation engine (6) that will transform the input instance to the output instance (7) based on models and transformation maps

4.1.2 Data transformation tools

NextGen connect: NextGen Connect (previously known as Mirth Connect) (84) is a robust, open-source healthcare integration engine widely used for its versatility and cost-effectiveness (85). One of its major strengths is its ability to support numerous data formats and protocols, such as HL7, XML, and JSON, making it highly adaptable to various healthcare systems (86). Its user-friendly interface and comprehensive documentation facilitate easier configuration and deployment, and the active community provides valuable support and resources. However, Mirth Connect has several drawbacks. Despite its user-friendly interface, it is primarily geared towards technical experts, making it challenging for domain experts without technical backgrounds to use it effectively (87). In our opinion, the learning curve is steep for new users unfamiliar with healthcare data standards and integration concepts. Performance can also be an issue with large-scale implementations, requiring careful optimization and resource management. Additionally, the clarity of implemented transformations can sometimes be lacking, making it difficult to understand and troubleshoot complex data flows (88). Furthermore, while the open-source version is feature-rich, some advanced features and enterprise-level support are only available in the paid version, which might limit its appeal to smaller organizations.

Other health data integration tools: Health data integration tools are essential for managing and transforming healthcare data, supporting interoperability within healthcare systems, and automating processes to realize cost savings. In addition to NextGen Connect, other well-known tools in this domain include Cloverleaf Integration Suite (89), Interfaceware Iguana (90), Corepoint Integration Engine (91), and Redox (92). Each tool offers numerous benefits, including connectivity and interface management, data transformation and workflow management, and support for various healthcare standards, protocols, and interfaces. They provide data mapping and support multiple data formats, leading to cost savings through reduced manual effort. However, there are challenges to consider when implementing these tools (93):

- *Complex implementation*: The process can be intricate, requiring IT professionals with expertise in healthcare data standards, protocols, and the specific tool's configuration.
- *Initial costs*: While cost savings can be realized in the long run, initial expenses associated with software licenses, hardware, and implementation can be challenging for smaller organizations.
- *Maintenance and support*: Regular updates, troubleshooting, and addressing issues are crucial for the tool's effectiveness, requiring dedicated resources.
- *Data mapping challenges*: Accurate and comprehensive data mapping can be challenging when dealing with disparate systems using different data standards and terminologies.
- *User training*: Staff may require training to use and navigate the tools effectively, and the learning curve can be costly.
- *Data security concerns*: Transmitting health data between systems raises data security concerns. Robust security measures are necessary to safeguard patient information and comply with data protection regulations.
- *Vendor lock-in*: Over-reliance on a specific tool or vendor can lead to potential issues if there are changes in the organization's strategy or the vendor's support changes.

FML implementations: The FHIR Mapping Language specification is implemented by code libraries such as the HAPI FHIR *StructureMap* implementation in Java (57) and its direct port to .Net (94), both of which offer transformation engines and open-source libraries. HAPI FHIR, a comprehensive Java library for FHIR, supports creating, parsing, and validating FHIR resources, providing robust tools for healthcare applications. The .Net FML implementation leverages these capabilities, bringing the same powerful functionality to the .Net ecosystem. Both libraries facilitate the transformation of healthcare data, ensuring interoperability and compliance with FHIR standards, which are crucial for modern healthcare systems.

Matchbox: Matchbox is an open-source initiative to support the testing and implementation of FHIR-based solutions (95). Matchbox utilizes the HAPI FHIR implementation, inheriting all its advantages while introducing additional flexibility for FML processing. Matchbox allows the preloading of FHIR implementation guides for conformance resources (*StructureMap*, *Questionnaire*, *CodeSystem*, *ValueSet*, *ConceptMap*, *NamingSystem*, *StructureDefinition*) and validates FHIR resources. Matchbox allows the defining of mapping in an FML text representation and its transformation into FHIR *StructureMap* resources. Matchbox applies the mapping to data to create FHIR-compatible data sets. Matchbox validates and executes FML transformations through the FHIR API, checking that the mapping conforms with the included validation stack.

4.1.3 Implementation projects

Austrian ELGA: The ELGA (Elektronische Gesundheitsakte) project launched in Austria is a nationwide EHR system designed to facilitate the exchange of medical documents across healthcare providers. ELGA uses CDA to manage medical data in a document-centric format. The project supports various document types, including Physician's Discharge Summaries, Nursing Discharge Summaries, Laboratory Reports, and Diagnostic Imaging Reports, with the addition of e-Medication reports covering prescription and medication summaries. To enhance interoperability and accessibility, recent efforts focus on mapping ELGA CDA documents to the FHIR standard using JSON mapping (96). Every element and section in JSON mapping has a "cda-path" that prescribes a rule for extracting data from a CDA document. This approach aims to generate International Patient Summaries (IPS) in FHIR format, enabling more granular access to health data and supporting cross-border healthcare data exchange within the European Union (26).

Italian patient summary: The Italian decree mandates that regional EHR systems support two types of documents: the Patient Summary and the Laboratory Report (27). The Patient Summary focuses on collecting the patient's most significant clinical information and uses the CDA format. During the *eHealthNet* project, a prototype was implemented for transforming the Patient Summary from CDA to FHIR. The proposed solution included the Mapping, Extractor, and Binding components. The Mapping component contains schemas defining correspondence between an element in FHIR and another in CDA. *XPath* was used for data extraction from CDA and binding to FHIR with a series of functions written in XSLT (27).

Swiss medications: The Swiss healthcare system has adopted the CDA standard, incorporating specific requirements unique to Switzerland (97). This has led to the creation of the CDA-CH standards (98). Switzerland transitioned to FHIR and developed equivalent FHIR-CH specifications for medication. To verify the equivalences, mappings have been defined with the FHIR mapping language, and Matchbox has been used for transformation from CDA to FHIR and back (99). To aid this transformation process, a consolidated library of CDA templates was employed (60). The use of FML in this context facilitates the automated transformation and validation of data, ensuring compliance with FHIR profiles and enhancing the utility of Swiss health data across various healthcare scenarios.

Estonian Andmevaatur: The *Andmevaatur* (Data Viewer) is a tool summarizing and visualizing patient data in the ENHIS (28). The ENHIS is built upon HL7 V3 and CDA standards (100). Due to the ever-increasing volume of documents, the task of gathering observations, procedures, vaccinations, and other clinical information from documents has become increasingly time-consuming for doctors (101). *Andmevaatur* uses *xQuery* to request CDA documents from the ENHIS database, transforms them into FHIR resources using a custom-developed mapping language, and forwards the resources to the user interface application for presentation. The custom-developed mapping language includes pairs of *XPath* and *FHIRPath* and a Java adapter for their execution. *XPath* is used for data extraction from CDA and *FHIRPath* is used for inserting data into the appropriate place in the FHIR resource. The development of an independent mapping language has been discontinued, and migration to FML is planned. Using *Andmevaatur*, doctors can save at least three minutes per visit, which is approximately 15 percent of the time typically spent interacting with a patient (101).

TABLE 2 Evaluation of artifacts

Artifact	Strict data models	Reuse	Native FHIR support	Execu- table software	Open-source	Visual editor
Query/View/Transformation (QVT) language (4.1.1)	+	+	−	−	+	−
Extensible Stylesheet Language Transformations (XSLT) (4.1.1)	+	+	−	−	+	−
Whistle (4.1.1)	−	+	−	+	+	−
Liquid (4.1.1)	−	+	−	+	+	−
FHIR Mapping Language (FML) (4.1.1)	+	+	+	−	+	−
FML implementations (4.1.2)	+	+	+	+	+	−
Integration tools (4.1.2)	+/−	+	−	+	−	+/−
Matchbox (4.1.2)	+	+	+	+	+	−
TermX (2.2)	+	+	+	+	+	+

Notes: "+" indicates that the criterion is met, while "−" indicates that it is not met.

4.2 Comparison of languages, tools, and implementations

To find the most suitable tool for our needs, we embarked on a comprehensive comparison of various languages, implementations, and tools. Our evaluation was based on a set of carefully developed criteria; the results are summarized in Table 2 and the conclusion is as follows:

- *Strict data model support*: DTL-based languages, such as FML, and their implementations provided robust support for strict data models.
- *Reuse of transformation*: We found that all languages used in evolution, along with their implementations and software, commendably support the reuse of transformations.
- *FHIR native support*: FML implementations, Matchbox, and TermX may be classified as tools with native FHIR support.
- *Executable software*: All implementations and software are classified as executable software.
- *Open-source license*: All languages, implementations, and software, except for NextGen Connect, and tools in the section "Other health data integration tools" are available under open-source licenses, promoting transparency and collaboration.
- *Visual transformation editor*: TermX and the health data integration tools stood out with their visual editors, which greatly facilitate the management of transformation flow.

After a comprehensive evaluation, it became evident that none of the existing implementations or tools were suitable, as they did not meet all of our selection criteria. This aligns with the health data interoperability issues highlighted in various recent papers by other implementers (27, 96).

In response to this, we developed the TermX FML Editor using the DS methodology. The designers behind TermX leveraged the existing FML language and the HAPI FHIR implementation, validating and reusing them to mitigate the risk of failure. Upon evaluating TermX, it was unequivocally clear that it was the only solution that met all of our selection criteria, thereby establishing it as the optimal choice for our needs.

4.3 Evaluation of visual reusable transformation rules

4.3.1 Toward federated interoperability in the EHDS

Ensuring federated interoperability (23, 24) is essential in the EHDS as it reduces administrative, operational, and international coordination costs. Federated systems store data in appropriate locations and formats, avoiding the complexity of large central repositories (102). This respects data sovereignty and privacy rules while allowing interoperability and independent innovation (103).

Centralized systems require significant infrastructure investment and management, which can be inefficient. Federated systems distribute these responsibilities, leveraging existing infrastructure and expertise and reducing compliance burdens with diverse regulatory frameworks. Federated semantic interoperability facilitates real-time data sharing, which is crucial for informed healthcare decision-making. By enabling seamless health data exchange, federated systems support innovative healthcare solutions, such as integrated care platforms and personalized medicine networks, enhancing care quality and patient outcomes.

Federated interoperability also supports EHDS initiative evaluations by providing a robust data integration and analysis framework, essential for assessing health interventions and informing policy decisions. Leveraging diverse data sources without extensive migration accelerates innovation and evaluation in healthcare. However, an effective system for semantic data transformation is required, as subsystems use different standards and models. The EHDS will inevitably need semantic data transformation, necessitating the evolution of user-friendly tools such as TermX.

4.3.2 Empowering domain experts

Achieving semantic interoperability is challenging due to the complexity of data transformation processes, which traditionally require significant technical expertise. The proposed techniques and TermX tool enable domain experts with minimal technical skills to participate effectively. The visual editor allows them to create and manage data transformation rules through an intuitive interface, democratizing the process and reducing reliance on technical specialists. This expedites development and deployment, improving the efficiency and scalability of interoperability initiatives.

The TermX tool explained in this paper allows domain experts to develop and validate data transformation rules, accommodating the evolving landscape of health standards and technologies (104). Direct involvement of domain experts ensures accuracy and relevance, as they bring a deep understanding of specific data and context. This collaboration fosters a more comprehensive approach to data transformation, enhancing the quality and reliability of interoperable data. The tool's validation features enable domain experts to test and refine transformation components, ensuring that transformed data meets expected standards and requirements and contributes to effective and trustworthy interoperability solutions.

4.3.3 Continuous adaptation to emerging innovations

Achieving federated semantic health data interoperability is crucial for supporting innovation within the EHDS (17). The healthcare data landscape constantly evolves, driven by innovations and new requirements. Semantic interoperability requires continuous adaptation. The proposed techniques and TermX tool support a flexible, modular approach to data transformation, adapting to new standards and technologies as they emerge. This ensures long-term interoperability and prevents obsolescence.

For instance, the transition from CDA to FHIR represents a significant shift in data structuring and exchange. As new versions of these standards are released, the tool must incorporate these changes, facilitating seamless data transformation. This capability allows healthcare organizations to leverage the latest advancements without significant disruptions or reengineering.

The evolving standards highlight the need for a collaborative approach to interoperability. The tool leverages collective expertise to stay updated with the latest developments by fostering a community-driven repository of transformation components and best practices. This promotes continuous improvement and innovation in health data interoperability.

4.3.4 Open FAIR access to routine clinical data

The FAIR (Findable, Accessible, Interoperable, Reusable) data principles are key enablers of secondary data use for societal benefit (105). Opening FAIR access to routine clinical data can drive advancements in medical research, clinical trials, public health, and policy-making (2–4, 106). Achieving FAIR access while maintaining privacy and security is challenging and requires robust technical solutions (18). Federated semantic interoperability offers a solution by keeping data in its original location, ensuring privacy, and enabling the integration and analysis of anonymized or pseudonymized data.

The proposed techniques and TermX tool support FAIR principles by providing a framework for transforming and integrating clinical data in a standardized manner. This ensures that data is findable and accessible, consistently represented, and understood. By facilitating data reuse through interoperable transformation rules, the tool enhances the utility of clinical data for secondary purposes. Leveraging routine clinical data for secondary use has profound societal implications, providing researchers with data for studies, enabling public health officials to monitor and respond to health threats, and guiding policymakers with evidence-based insight (107).

4.3.5 Integrating health data with other sectors

Health data is interconnected with data from sectors such as education, social services, the environment, and the economy (108, 109). Integrating health data with these sectors is essential for a holistic understanding of health determinants and outcomes, as the World Health Organization (WHO) recommends (110).

Although TermX was designed with FHIR support for health data interoperability, it is versatile enough to integrate and facilitate interoperability with other data sets beyond healthcare. This adaptability allows TermX to connect health data with various sectors, such as education, social services, the environment, and the economy. TermX supports a more comprehensive analysis of factors influencing health outcomes by enabling seamless data exchange across these domains. This flexibility ensures that TermX can serve as a powerful tool for creating holistic data ecosystems where health data is enriched by insights from other sectors, ultimately contributing to more informed decision-making and improved public health strategies.

4.3.6 Toward resolving three health data dilemmas

Klementi et al. (18) identified three health data dilemmas: accessibility, comprehensiveness, and ownership. The *accessibility dilemma* involves balancing health data access for improved outcomes with protecting sensitive information. Ensuring FAIR (Findable, Accessible, Interoperable, and Reusable) access often conflicts with data protection requirements (111–113). The *comprehensiveness dilemma* concerns creating a complete health record from fragmented data stored across various systems. Issues such as semantic interoperability and legal barriers impede the consolidation of data into a comprehensive personal health record (PHR) (114). The *ownership dilemma* addresses the conflict between individuals' rights to control their health data and the practical difficulties of exercising these rights (115, 116).

An EHDS architecture where individuals own and control their health data could use decentralized content-addressable storage networks (18). The proposed techniques and TermX tool create conditions that enable individuals to share their health data with healthcare professionals and ensure FAIR access to routine clinical data for secondary use (117, 118). This empowers more stakeholders to participate in the data transformation process, keeping health data interoperability at the forefront of healthcare innovation.

4.4 Implementation scenarios

4.4.1 Execution of the transformations in the single installation

The technical implementation of the solution encompasses both the design and transformation phases. This paper focuses on the design phase, wherein data models and transformations are developed. The resulting artifacts can be stored either in GitHub or on a FHIR server. The TermX Editor is utilized for

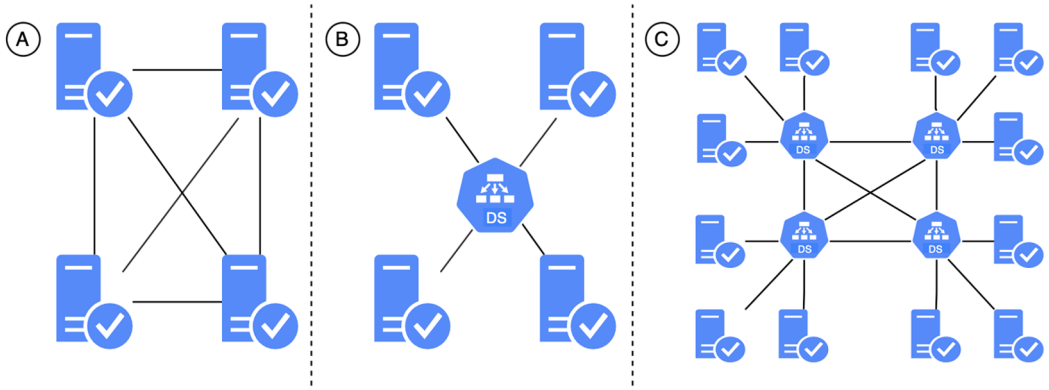

FIGURE 13
Possible topologies of EHDS: (A) every node is connected to every other node, (B) there is a central node to which all other nodes are connected, (C) a hybrid of topologies.

the design and testing of these transformations, but it is not required for their execution. For execution purposes, libraries such as HAPI FHIR, .Net, or their equivalents can be employed to compile and run the transformations. To enhance throughput, the application should support the caching of the utilized models (StructureDefinition instances) and compiled transformations (StructureMap instances). This application can function as a standalone service or as a module integrated into the FHIR server.

4.4.2 The transformations in the context of EHDS

When integrating two systems, two data models (source and target) and one set of transformations are required for one-way transformations or two sets for bidirectional transformations. If we consider that each medical system in the EHDS integrates with every other system and each has a unique data model, there will be N data models, resulting in an integration network with a complexity of $O(2^n)$ (Figure 13A). By creating a central model, we would have N+1 models and N (for one-way) or N*2 (for bidirectional) sets of transformations (Figure 13B). However, a single central model for all European countries is not realistic (9). It would be beneficial to reduce the number of models by creating smaller Data Spaces, where institutions within a country or region share a single model. Instead of a single central model, domain-specific Data Spaces could be established, connecting all EU laboratories (119), immunization records (120, 121), or radiology services into unified networks (Figure 13C). Such grouping would reduce the number of transformations and administrative burdens.

4.5 Limitations

4.5.1 Use-case-specific mapping of components

The current study was conducted and validated for a specific use case, namely the transformation of ENHIS documents. When comparing documents from Estonia with those from other countries, we find that documents of the same type, such as outpatient summaries, differ in the number of sections, section labeling, and terminology used. Additionally, country-specific extensions may be used. This implies that for each specific implementation, the representation at the business domain knowledge level may differ, and the set of transformations developed in this research study may require adaptation.

The foundational resources from the CDA and FHIR frameworks are highly compatible and could be suitable for use in any country. The ISO 23903 Interoperability and Integration Reference Architecture addresses the challenges associated with integrating such models and frameworks. Examples include mappings of HL7 V2 and HL7 V3 models and specifications, and the re-engineering and mapping of the higher-level specifications ISO 12967 Health Informatics Service Architecture and ISO 13940:2015 System of concepts to support continuity of care (122).

Although the detailing of base types in mapping may vary depending on the use case, for ENHIS, mapping of the CDA II to FHIR Identifier data types requires only the transformation of key attributes “root” to “system” and “extension” to “value” (Figure 4). However, in another information system, additional attributes such as “display” and “use” might be required, which we have not mapped, as this mapping is specific to the given use case. Nevertheless, it is easily generalizable if we extend the use case.

4.5.2 Mapping correctness

Actors from different scientific domains and disciplines, different communities, and different policy domains represent and understand related concepts differently (123). This decision on correct mapping is only possible at the business domain knowledge level, represented through domain ontologies and related terminologies.

- *Validation by analyst.* Business analysts, as domain experts, possess comprehensive knowledge of the domain’s ontology and terminology. They are responsible for planning and ensuring the accuracy of transformations. TermX is a robust tool specifically designed for analysts. Consequently, business

analysts are well-equipped to make transformation decisions and verify the accuracy of transformations by manually performing a reasonable number of tests.

- *Technical validation*. The technical validation of transformation correctness can be achieved through various methodologies. Section 2.3.4 elaborates on validation utilizing Natural Language Processing (NLP). Nevertheless, the ISO 23903 Interoperability and Integration Reference Architecture facilitates the accurate mapping of components across business, informational, computational, and engineering viewpoints. This framework supports the design and management of systems across diverse domains and contexts, thereby ensuring interoperability among ecosystem components (124).

Technical validation of transformations will make up future work.

5 Conclusion

Transforming health data from CDA to FHIR format is critical to achieving health data semantic interoperability. This paper presents generalized techniques for utilizing the TermX tool to develop reusable data transformation components and verify that the designed transformation components accurately transform data as expected. TermX leverages the FHIR Mapping Language to facilitate complex and technical data transformations. It is designed explicitly for domain experts, enabling them to develop and manage data transformation rules with minimal technical knowledge.

The pressing need for such a tool arises from the ongoing evolution of the ENHIS, which is transitioning EHRs from CDA to FHIR (22). This transition is not only a technical upgrade but also a strategic move to enhance health data's flexible and on-time semantic interoperability to improve the quality of clinical care and control healthcare costs, ensuring that patients' health information can be seamlessly shared and understood across systems and by healthcare practitioners in real time. Since vast amounts of historical EHR data in the ENHIS are stored in various HL7 CDA formats (15), transforming this data dynamically to FHIR as needed, rather than permanently, is essential. This approach utilizes federated semantic health data interoperability, ensuring that historical EHR data remains immutable but interoperable and accessible without requiring extensive and costly data migration efforts from one data repository and format to another.

The TermX tool was developed using the Design Science (DS) methodology, which emphasizes the creation and evaluation of artifacts designed to solve the problems identified. In the problem investigation phase, we conducted an analysis of languages, implementations, and tools to find a possible solution and tool to meet the ENHIS data transformation requirements. As we found no suitable solution or tool, and because the same health data interoperability issues were stressed in various recent papers, we developed TermX using the DS approach. TermX was designed (treatment design phase of DS) through the generalization, abstraction, and formalization of the needs of the ENHIS, ensuring that it is universal, usable, practical, and effective in most real-world health data transformation applications. The tool provides a visual editor for developing transformation components with FHIR Mapping Language support for transforming data from any data structure to any other. We evaluated (treatment validation phase of DS) that this tool might be usable and valuable for domain experts who may not have deep technical knowledge of information and communication technology. In the treatment implementation phase (not part of the DS but of the engineering cycle), we implemented the TermX solution with funding from the Estonian Business and Innovation Agency.

5.1 Research contribution

The primary business need addressed by the TermX tool is the efficient and validated transformation of health data from one data format to another. As healthcare organizations increasingly move toward adopting the FHIR standard, such tools are critical to bridge the semantic interoperability issues related to the concurrent utilization of legacy and new health data formats. Enabling domain experts to create and manage formal data transformation components in a simple WYSIWYG way using a visual editor, TermX reduces the need for technical specialists, which ultimately reduces costs and speeds up the deployment process needed to transform health data. Moreover, TermX ensures that data transformations can be carried out on the fly according to federated semantic interoperability, allowing data to be stored in different data formats while ensuring that healthcare providers have continuous and uniform access to both old and new data, in turn ensuring continuity of care and clinical decisions.

Socially, the implications of enhanced semantic interoperability are profound. Improved data interoperability means healthcare providers can share information more effectively, leading to better care coordination, reduced medical errors, and improved patient outcomes. This translates into more timely and accurate diagnoses, personalized treatment plans, and ultimately better patient health outcomes. Furthermore, integrating and analyzing data from diverse sources supports public health initiatives, research, and policy-making, contributing to the overall improvement of healthcare systems. The evaluation of the TermX tool demonstrated its effectiveness in developing reusable transformation components that domain experts can use for health data transformations. The tool was tested to ensure that the transformations were accurate and that they met the expected standards. The results showed that TermX could reliably perform the necessary transformations, supporting the hypothesis that a visual editor for the FHIR mapping language is both feasible and beneficial.

5.2 Future research and evaluation directions

While the TermX tool has shown promise, there are several areas for future research and development. One key area is the continuous improvement of the tool's user interface and experience, ensuring that it remains intuitive and accessible for domain experts. Additionally, expanding the tool's capabilities to handle more complex transformation scenarios and integrating machine learning techniques to suggest optimal transformation rules could further

enhance its utility. Another important direction is developing a comprehensive evaluation framework to continuously assess the quality and performance of the transformations. This framework could include metrics for measuring the accuracy, completeness, efficiency, user satisfaction, and adoption rates of transformations. Finally, fostering collaboration and knowledge-sharing among users of the TermX tool could lead to the development of a community-driven repository of transformation components and best practices. This repository could be a valuable resource for healthcare organizations worldwide, facilitating the broader adoption of FHIR and realizing truly interoperable health information systems.

5.3 Conclusion summary

In conclusion, the TermX tool represents a significant advancement in the quest for the unified federated semantic interoperability of health data. The tool addresses critical business and social needs by enabling domain experts to develop and manage transformation components with FHIR Mapping Language support. It supports the efficient and accurate transformation of health data, ensuring that historical data remains accessible and interoperable. As healthcare systems continue to evolve, tools such as TermX will play a crucial role in ensuring that data interoperability remains at the forefront of these advancements, ultimately leading to improved healthcare outcomes for patients and more efficient healthcare systems.

By addressing these critical areas, the TermX tool not only meets the immediate needs of the Estonian National Health Information System but also sets a precedent for other health systems seeking to enhance their data interoperability capabilities.

What was known on the topic:

(1) The EHDS aims to construct a health data-sharing ecosystem within the European Union, establishing rules and common standards to facilitate the use of EHRs.
(2) Each country that uses CDA tackles the transformation from CDA to FHIR in its own unique way, suggesting that there is no one-size-fits-all solution.
(3) Previously, no tools were available in the healthcare field for visualizing transformation with FHIR support.

What this study added to our knowledge:

(1) In the federated approach, systems that join the EHDS can store data in a location and format that suits them and transform the data to the EHDS standard in real time.
(2) TermX provides the ability to define and manage transformation components in a visual editor using the FML Mapping Language and strict data structures, such as FHIR resources and CDA classes.
(3) TermX enhances clarity, enables the reuse of transformation components, conceals the complexity of the FML mapping language, and allows analysts to quickly adapt to its usage.

Data availability statement

The TermX project[4] is available on GitHub, including the source code of TermX modules and applied projects. TermX modules include server, web application, and FML Editor (38). The source code of the developed CDA to FHIR transformations and the related presentations and screenshots are published in the TermX "cda2fhir" repository[5].

Author contributions

IB: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing; RR: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing; GP: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing; PR: Funding acquisition, Resources, Supervision, Validation, Writing – review & editing.

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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

[4]https://github.com/termx-health.

[5]https://github.com/termx-health/cda2fhir.

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