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Commentary

Advancing Personal Health Data Spaces: Governance, Interoperability, and Real-World Evidence for Learning Healthcare Systems

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Background: Healthcare systems increasingly generate large volumes of clinical, imaging, genomic, wearable and real-world healthcare data. However, fragmentation across healthcare infrastructures continues to limit interoperability, integrated evidence generation and coordinated patient management.
Objective: This commentary examines how Personal Health Data Spaces (PHDS) may support interoperable, patient-centred, and evidence-informed healthcare through the integration of governance, real-world evidence (RWE), artificial intelligence (AI) and health data infrastructures.
Approach: Drawing on regulatory science, digital health policy, interoperability frameworks and RWE practice, this commentary proposes a conceptual framework for PHDS that distinguishes them from existing health data initiatives and presents an implementation-oriented roadmap for their adoption within learning healthcare systems.
Discussion: Personal Health Data Spaces may support continuity of care, multimodal evidence generation, regulatory science, AI-enabled analytics and personalised medicine across increasingly interconnected healthcare environments. However, their successful implementation depends on interoperable infrastructures, harmonised governance, methodological transparency, cybersecurity, workforce capability and meaningful multi-stakeholder collaboration to avoid reinforcing existing healthcare inequities and operational fragmentation.
Conclusion: Personal Health Data Spaces represent a patient-centred operational framework for integrating healthcare data across clinical care, research, and regulatory decision-making, supporting the transition towards interoperable and continuously learning healthcare systems. Their long-term success will depend not only on technological capability, but also on trustworthy governance, scalable implementation strategies, and sustained public trust.

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Introduction

Healthcare systems are undergoing rapid digital transformation driven by the convergence of electronic health records (EHRs), real-world evidence (RWE), artificial intelligence (AI), genomics, imaging systems, wearable technologies, and increasingly interconnected healthcare infrastructures. This digital transformation is also reshaping how healthcare evidence is generated and applied. Healthcare evidence generation has evolved substantially over recent decades, progressing from predominantly clinical trial-based models towards broader integration of RWE, AI-enabled analytics, and multimodal healthcare data ecosystems supporting personalised and continuously learning healthcare systems [1][2][3][4]. This framing is consistent with the Learning Health System model, in which data generated

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through healthcare delivery are continuously translated into evidence and subsequently reintegrated into practice to support iterative improvement in care [2].

Simultaneously, regulatory and policy initiatives across Europe, North America, Asia, the Middle East, and Latin America increasingly recognise that sustainable healthcare systems require interoperable, patient-centred, and longitudinal evidence ecosystems capable of supporting continuity of care, lifecycle evidence generation, and precision medicine [5][6][7][8]. Regulatory agencies including the European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA), Medicines and Healthcare products Regulatory Agency (MHRA), Health Canada, and other global stakeholders increasingly support the use of RWE, AI-enabled analytics, and interoperable health data infrastructures to strengthen regulatory science and healthcare decision-making [9][6][7][8].

The digital transformation of healthcare is generating unprecedented volumes of structured and unstructured information across clinical care, imaging, genomics, wearable technologies and other digital health environments. Advances in AI and machine learning (ML) increasingly enable integration and analysis of heterogeneous healthcare data to support personalised medicine, regulatory science, and continuously learning healthcare systems [10][11][12][13][14]. Social media and online patient communities may additionally provide complementary insights regarding patient experiences, treatment patterns, quality of life (QoL), and digital epidemiology [14].

Despite substantial technological progress, healthcare information frequently remains fragmented across hospitals, primary care systems, imaging repositories, laboratories, registries, payer databases, pharmaceutical research infrastructures, and digital health applications [2]. Importantly, fragmentation is not solely a technological problem. It directly affects continuity of care, longitudinal understanding of patient journeys, and the ability of healthcare professionals to access clinically meaningful information across healthcare settings and over time [6]. Patients with chronic or complex diseases frequently transition across multiple healthcare providers and institutions without seamless transfer of clinically relevant information, potentially contributing to duplicated investigations, delays in care coordination, fragmented treatment decisions, and incomplete understanding of long-term outcomes [7].

The evolving needs of patients, healthcare professionals, regulators, payers and policymakers are increasingly driving the development of longitudinal patient-centred architectures capable of integrating healthcare information across the patient lifespan. Such architectures may improve continuity of care, emergency decision-making, patient safety and longitudinal understanding of chronic disease trajectories across healthcare settings [2][15][16].

The emergence of Personal Health Data Spaces (PHDS) represents an evolution beyond conventional health data spaces. While health data spaces primarily provide the legal, governance and technical infrastructure required for secure health data exchange and secondary use, PHDS place the individual at the centre of the ecosystem. In this commentary, PHDS are defined as interoperable, patient-centred ecosystems that enable secure integration, access and responsible reuse of health information across clinical care, research, regulatory science and public health. Here, “patient-centred” refers to the organisation and governance of the data ecosystem around the longitudinal healthcare needs, rights, participation and continuity of care of the individual, rather than around a particular institution, provider or data holder. This should be distinguished from “patient-centric data”, which describe data generated by, collected from, or directly concerning an individual patient. A PHDS may therefore integrate both patient-centric and other clinically relevant healthcare data while remaining patient-centred in its architecture and governance. Beyond interoperability alone, they seek to support continuity of care, patient agency, transparency, dynamic consent and lifelong stewardship of health information [2][15][16][17].

Within Europe, the European Health Data Space (EHDS) initiative represents one of the most ambitious policy efforts to establish harmonised frameworks for cross-border health data exchange and secondary use of healthcare information [17]. Importantly, the EHDS should not be interpreted as a PHDS itself. Rather, it provides the regulatory, governance and

interoperability framework that may enable the development and implementation of PHDS across European healthcare systems. Parallel initiatives such as the European Medicines Agency's Data Analysis and Real-World Interrogation Network (DARWIN EU®) and the European Health Data & Evidence Network (EHDEN) seek to operationalise federated RWD infrastructures capable of supporting regulatory evaluation, pharmacovigilance, observational research, and public health decision-making [18][19]. Comparable developments are increasingly observed internationally through the FDA Sentinel Initiative, MHRA real-world data guidance, Canadian interoperability initiatives, Saudi Arabia's digital health transformation programmes, and national digital health strategies emerging across Brazil and other rapidly digitising healthcare systems [20][21][22][23][24].

However, expansion of digital infrastructure alone does not guarantee patient trust, evidence quality, equitable healthcare transformation, or meaningful integration of healthcare information across systems. Large-scale health data ecosystems introduce substantial methodological, ethical, regulatory, organisational, and societal challenges related to interoperability, governance, cybersecurity, algorithmic bias, transparency, data privacy, informed consent, secondary use of health data, and equitable access across healthcare systems [15][16][17]. Concerns regarding ownership, stewardship, commercialisation, and monetisation of healthcare information have further intensified public debate regarding trust, accountability, and the social legitimacy of increasingly data-driven healthcare ecosystems [16][25].

Unlike existing health data initiatives that primarily focus on regulatory frameworks, technical interoperability, or federated data infrastructures, this commentary proposes PHDS as an operational, patient-centred framework that integrates governance, interoperability, AI and RWE across the healthcare journey. Rather than introducing another health data platform, PHDS provide a conceptual model for connecting existing digital health capabilities into continuously learning healthcare systems.

This commentary is based on a narrative synthesis of peer-reviewed literature, international policy documents, regulatory guidance and major interoperability initiatives relevant to PHDS. Sources were selected to provide representative examples of contemporary international developments rather than through a formal systematic review methodology.

The literature was identified through targeted searches of PubMed, Google Scholar and official websites of regulatory agencies and international organisations (including the European Commission, EMA, FDA, MHRA, Health Canada and WHO). Searches focused on publications and policy documents available up to July 2026 using combinations of terms including "Personal Health Data Space", "European Health Data Space", "interoperability", "real-world evidence", "artificial intelligence", "learning healthcare systems" and "digital health governance". Sources were prioritised when they directly addressed health-data interoperability, governance, secondary data use, RWE, AI-enabled healthcare or learning healthcare systems, with preference given to peer-reviewed literature, primary regulatory and policy documents, and established international initiatives. Sources without direct relevance to these domains were not included. The international initiatives discussed were selected as illustrative examples of differing regulatory, governance, interoperability and digital-maturity contexts rather than as a comprehensive or geographically representative sample. Accordingly, country examples are used to illustrate alternative implementation pathways and should not be interpreted as a systematic comparison of global PHDS development.

The following sections first examine why conventional healthcare information systems have become insufficient before discussing how PHDS may address these challenges through interoperable, patient-centred data ecosystems.

From Fragmented Data to Longitudinal Patient Journeys

Historically, healthcare information systems evolved primarily to support local operational and administrative needs rather than integrated patient-centred continuity of care. Hospitals implemented EHRs to facilitate documentation and billing processes, laboratories developed independent information systems for diagnostics, payers established reimbursement

databases, while disease registries and clinical research infrastructures emerged separately to address epidemiological or regulatory requirements [1][2][3]. As a result, many healthcare systems evolved without mechanisms capable of supporting integrated longitudinal patient journeys across providers and care settings.

This fragmentation has significant implications for patient care and healthcare decision-making. Patients with chronic or complex diseases have long received care across multiple healthcare providers, institutions and, in some cases, national healthcare systems. What has changed substantially in recent years is the volume, diversity and digital availability of health information generated throughout these care pathways. Electronic health records, imaging, genomics, wearable technologies, PROs and other digital health sources now create opportunities to integrate longitudinal patient journeys in ways that were previously not technically feasible. Consequently, the growing demand for interoperable PHDS reflects not only increasingly complex care pathways, but also the need to transform expanding volumes of heterogeneous health data into clinically meaningful, patient-centred information capable of supporting continuity of care, research and regulatory decision-making [4][5][6].

The challenge is particularly pronounced in chronic and highly specialised therapeutic areas such as oncology, ophthalmology, cardiovascular disease, and rare diseases, where patient journeys frequently span multiple years and involve numerous healthcare interactions. In oncology, for example, patients may transition across screening programmes, molecular diagnostics, surgery, systemic therapies, imaging centres, survivorship monitoring, and palliative care services, often within different institutions and healthcare systems [7][8]. Similarly, in ophthalmology, long-term management of neovascular age-related macular degeneration (nAMD) or diabetic macular oedema (DME) requires repeated imaging assessments, longitudinal treatment interval optimisation, and monitoring of functional outcomes over extended periods of time [10][11][12]. Importantly, longitudinal health data should not assume that the first recorded diagnosis or symptomatic presentation represents the biological onset of disease, as underlying pathological processes may precede clinical recognition by months or years. PHDS may therefore support a more complete reconstruction of disease trajectories by integrating information generated before, during and after formal diagnosis.

A typical example is a patient whose care transitions across multiple healthcare providers following hospital discharge. Subsequent specialist treatment, imaging follow-up, primary care monitoring, rehabilitation, and management of treatment-related adverse events frequently occur across different organisations. Where interoperability remains incomplete across technical, semantic or organisational dimensions, clinically relevant information may be incomplete or delayed, increasing the risk of duplicated investigations, fragmented decision-making, and suboptimal continuity of care. PHDS aim to address these gaps by enabling secure longitudinal access to relevant health information throughout the patient journey.

The increasing adoption of digital technologies has substantially expanded the availability of healthcare data across clinical care, imaging, genomics, pharmacy systems, wearable technologies and patient-generated environments [13][14]. However, greater data availability alone does not automatically translate into meaningful interoperability or integrated longitudinal patient journeys, because digitally available information may remain structurally, semantically and organisationally incompatible across systems owing to differences in data models, terminologies, coding practices and governance arrangements [15].

Interoperability itself remains multidimensional. Technical interoperability refers to the ability of systems to exchange information electronically. Semantic interoperability concerns the consistent interpretation of exchanged information through harmonised coding systems and terminologies. Organisational interoperability involves governance alignment, operational workflows, and legal frameworks that enable practical integration across institutions and jurisdictions [15][16]. Failures across any of these dimensions may compromise continuity of care even when digital infrastructure is technically available.

The EHDS initiative represents one of the most comprehensive efforts to address these challenges through a harmonised framework for primary and secondary use of health data across European Union member states [17]. The initiative aims to build upon existing electronic health information and patient-access capabilities by strengthening individuals' access to and control over health information across healthcare systems, while simultaneously enabling secure secondary use of data for research, regulatory science, healthcare planning, and innovation. Similarly, DARWIN EU® and the EHDEN seek to operationalise federated RWD infrastructures capable of supporting distributed analytics while respecting national governance requirements and privacy protections [18][19].

Comparable initiatives are also emerging globally through programmes such as the FDA Sentinel Initiative, MHRA real-world data frameworks, Canadian regulatory collaborations, Saudi Arabia's digital health transformation strategy and Brazil's national digital health agenda, demonstrating that interoperable healthcare infrastructures are increasingly recognised as strategic priorities worldwide [20][21][22][23][24].

Despite this progress, operational fragmentation remains substantial. Cross-border interoperability challenges persist even within highly digitised regions such as Europe. Variability in coding standards, data quality, governance procedures, consent models, and data access requirements frequently delays or limits multi-country evidence generation and integrated patient follow-up [15][18]. Furthermore, many healthcare systems continue to operate under institution-centred rather than patient-centred information architectures, where data ownership and operational incentives remain fragmented across providers, payers, industry, and regulatory stakeholders [25]. These challenges illustrate that interoperability is not solely a technical objective but also an organisational and governance challenge requiring alignment across healthcare stakeholders.

The transition from fragmented healthcare data environments towards integrated PHDS is summarised in **Figure 1**, illustrating how integrated governance, interoperability frameworks, and federated analytical infrastructures may support continuity of care, regulatory science, and RWE generation across increasingly connected healthcare systems.

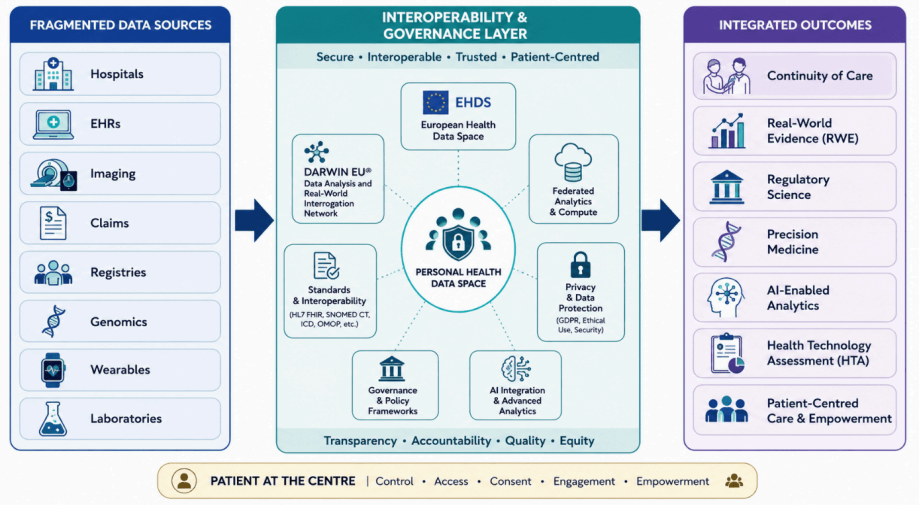

Figure 1. Evolution from Fragmented Healthcare Systems to Integrated Personal Health Data Spaces. Within this framework, patient-centredness refers to organising interoperable information, governance and data use around the individual's longitudinal healthcare needs, rights, agency and continuity of care, rather than merely positioning patient data within a central repository.

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Personal Health Data Spaces: Conceptual Foundations

The concept of PHDS has emerged in response to growing recognition that fragmented healthcare information systems are incompatible with the evolving needs of modern healthcare delivery, regulatory science, and personalised medicine [1][2][5]. In this commentary, PHDS are defined as patient-centred, interoperable ecosystems enabling the secure access, exchange, integration, and appropriate reuse of longitudinal health information across clinical care, research, regulatory science, and public health. Rather than representing a single digital platform, they integrate governance, interoperability, AI-enabled analytics, and RWE within a socio-technical framework supporting continuity of care and continuously learning healthcare systems [2][5][15][16][17].

Although no universally accepted definition currently exists, this commentary distinguishes PHDS from health data spaces more broadly. Health data spaces primarily describe the governance, legal and technical infrastructures that enable secure exchange and secondary use of health information across healthcare systems [15][16][17]. Personal Health Data Spaces extend this concept by positioning the individual as the organising principle of the ecosystem. They integrate longitudinal health information across multiple providers while supporting patient participation, continuity of care, transparency, appropriate consent models, and responsible stewardship throughout the healthcare journey [2][5][16]. Where available and appropriate, this longitudinal perspective may also incorporate lifestyle, environmental, social and cultural determinants that influence health trajectories, healthcare access and treatment outcomes, recognising that meaningful personalisation extends beyond clinical and biological data alone.

Within this framework, a PHDS should be characterised by a minimum set of defining attributes: longitudinal linkage of health information around the individual; interoperable exchange through agreed technical and semantic standards; transparent mechanisms for access and consent or preference management where applicable; auditable governance for primary and secondary data use; documented data provenance and quality controls; privacy-preserving analytical capabilities, including federated approaches where appropriate; and mechanisms for patient and public accountability. These attributes distinguish a PHDS from infrastructures that provide data access, institutional record exchange or analytical capability in isolation. Where relevant, longitudinal integration should also capture physiological trajectories and clinically meaningful milestones that may precede, accompany or modify disease presentation, thereby allowing personalisation to reflect biological change over time rather than relying solely on diagnostic labels or discrete healthcare encounters.

The EHDS represents an enabling regulatory and interoperability framework rather than a PHDS itself. It establishes mechanisms for the primary use of electronic health data in healthcare delivery and their secondary use for research, innovation, public health, regulatory evaluation and policymaking, while strengthening individuals' access to and control over their health information. Within this broader architecture, PHDS describe the patient-centred operational ecosystems through which longitudinal health information may be integrated and used across the healthcare journey [17].

Implementation of the EHDS has been informed by the Towards the European Health Data Space (TEHDAS) Joint Action, which developed recommendations to support implementation of the secondary use of health data across Member States [17]. An important operational component of the EHDS is the establishment of Health Data Access Bodies (HDABs), which will oversee access to electronic health data for approved secondary uses in accordance with the Regulation's governance and data-protection requirements [17].

The distinction between primary and secondary use of health data is central to understanding the conceptual foundations of PHDS. Primary use refers to the direct utilisation of healthcare information for patient diagnosis, treatment, and continuity of care. Secondary use involves reuse of data for broader purposes including observational research, pharmacovigilance, healthcare planning, health technology assessment (HTA), AI development, and regulatory science [17]. While secondary use creates significant scientific

and public health opportunities, it also introduces substantial governance and ethical complexity regarding transparency, consent, ownership, and trust.

Operationally, these pathways require different but connected governance mechanisms. Direct clinical use should remain embedded within healthcare delivery and professional accountability; patient-mediated access should enable individuals to view and exercise applicable rights over their information; approved secondary uses should proceed through the relevant lawful basis, data-access governance and oversight mechanisms, including HDABs where applicable under the EHDS; and AI development or validation should additionally require purpose-specific governance, data-quality assessment, auditability and appropriate lifecycle oversight. Patient preferences and consent should operate within these applicable legal and governance frameworks rather than being treated as the sole basis for all forms of data use.

This stewardship model has become particularly important in the context of AI-enabled healthcare systems. Machine learning models increasingly require access to large-scale and heterogeneous datasets to support predictive analytics, diagnostic support, treatment optimisation, and personalised medicine applications [13][14]. Within the conceptual framework proposed here, PHDS may provide the patient-centred data environment through which AI-enabled applications securely access and analyse longitudinal health information [5][13][14].

Personal Health Data Spaces should not be considered synonymous with Health Data Spaces, federated analytical infrastructures, RWE platforms or Learning Healthcare Systems. These represent complementary components of the digital health ecosystem: Health Data Spaces provide governance and interoperability foundations; federated infrastructures enable distributed analysis; RWE platforms generate evidence from routine clinical practice; and Learning Healthcare Systems translate evidence into continuous improvements in care. Personal Health Data Spaces connect these components around the individual and their longitudinal healthcare journey. PHDS also differ from conventional patient portals and national electronic health record infrastructures. Patient portals primarily provide individuals with access to information held within a particular healthcare organisation or network, while national health record systems generally support information exchange and care delivery within defined healthcare-system boundaries. PHDS are conceptualised more broadly as an interoperability and governance layer connecting longitudinal information across multiple providers, data types and uses, including clinical care, research, regulatory science and public health. Their novelty therefore lies not in proposing a new standalone technology, but in integrating existing infrastructures around the individual through common principles of interoperability, governance, patient agency and responsible data reuse. **Table 1** summarises these distinctions.

Concept	Primary focus
Health Data Spaces	Governance, legal and technical infrastructure for health data exchange
European Health Data Space (EHDS)	European regulatory framework enabling primary and secondary use of health data
Federated analytical infrastructures	Privacy-preserving distributed analysis of health data
Real-World Evidence platforms	Generation of evidence from routine clinical practice
Learning Healthcare Systems	Continuous improvement cycle linking care and evidence generation
Patient portals / national health record systems	Patient access to and exchange of health information within organisational or national healthcare infrastructures
Personal Health Data Spaces (PHDS)	Patient-centred operational ecosystem integrating longitudinal health information across clinical care, research, regulatory science and public health

Table 1. Positioning Personal Health Data Spaces within the digital health ecosystem

At present, mature real-world implementations encompassing all components of the PHDS framework remain limited. Existing initiatives such as the EHDS, DARWIN EU®, EHDEN and the FDA Sentinel Initiative should therefore be understood as implementation examples of complementary components—including governance, interoperability, federated analytics and secondary data use—rather than as complete PHDS implementations. Their operational experience nevertheless provides important lessons for the progressive development of more integrated patient-centred health data ecosystems [17][18][19][20].

However, the integration of AI further amplifies governance challenges. Large-scale interoperable health data systems raise concerns regarding algorithmic bias, explainability, cybersecurity, discrimination, commercialisation of patient data, and unequal representation of vulnerable populations [13][14][16][25]. Without robust governance mechanisms, health data ecosystems risk reproducing or amplifying existing healthcare inequities.

Consent architecture represents another major conceptual challenge. Traditional static consent models may be difficult to apply in evolving digital ecosystems involving multiple secondary uses of healthcare data over extended periods. More adaptive consent and access-governance approaches may therefore be needed to balance innovation, patient autonomy and transparency [16][25].

Federated models have gained particular attention because they allow distributed analytics without requiring centralised pooling of sensitive patient-level data [18][19]. Under federated approaches, analytical queries may be performed locally within secure environments while aggregated outputs are shared across networks. Such models may strengthen privacy protection while simultaneously supporting large-scale multi-country evidence generation.

Sustainable PHDS require broader social legitimacy grounded in transparency, accountability, methodological integrity, cybersecurity, and meaningful patient engagement [16][17][25]. As healthcare systems become increasingly data-driven, maintaining this legitimacy may become as strategically important as the technological infrastructures themselves.

Having established the conceptual foundations of PHDS, the following section examines how these ecosystems enable trustworthy AI-enabled healthcare.

Artificial Intelligence and Advanced Analytics Within Personal Health Data Spaces

Building upon the conceptual framework described above, AI is increasingly becoming embedded within healthcare delivery, regulatory science, imaging analytics, pharmacovigilance, and RWE generation rather than functioning as a standalone technological innovation [13][14]. The expansion of PHDS creates the infrastructure upon which these advanced analytical capabilities can operate at scale.

Importantly, AI systems are fundamentally dependent upon the quality, diversity, interoperability, and longitudinal depth of underlying healthcare data. Fragmented or poorly harmonised datasets limit model reliability, reduce generalisability, and increase the risk of algorithmic bias and inequitable healthcare delivery [13][26]. Consequently, the future effectiveness of AI in healthcare is closely linked to the successful development of interoperable PHDS capable of integrating heterogeneous clinical, imaging, genomic, operational, and patient-generated information.

Natural language processing (NLP) represents one particularly important area of development. Large volumes of clinically relevant healthcare information remain embedded within unstructured physician notes, pathology reports, discharge summaries, radiology interpretations, and patient narratives. AI-enabled NLP systems increasingly support extraction and structuring of these data into analysable formats capable of improving continuity of care and supporting regulatory-grade RWE generation [13][14].

Similarly, AI-enabled imaging analytics are transforming multiple therapeutic areas, including radiology, cardiology, neurology, oncology, and ophthalmology, through automated image interpretation, treatment response prediction, and biomarker identification. In ophthalmology, ML models applied to optical coherence tomography (OCT) and retinal imaging increasingly support identification of disease progression, treatment response prediction, and optimisation of anti-vascular endothelial growth factor (anti-VEGF) treatment pathways [10][11][12]. In oncology, AI-ready registries integrating imaging repositories, genomic data, and longitudinal outcomes increasingly support biomarker discovery, treatment optimisation, and personalised medicine strategies [7][8].

Beyond direct clinical applications, AI is also reshaping regulatory science and healthcare system governance. Regulatory agencies increasingly explore AI-supported pharmacovigilance, signal detection, and large-scale observational evidence generation using federated healthcare data environments [17][18]. These developments, together with federated initiatives such as EHDEN, illustrate how advanced analytics may support lifecycle evidence generation while simultaneously enabling more adaptive and evidence-informed healthcare systems [17][18][19][20].

However, the integration of AI within PHDS introduces substantial methodological, ethical, and organisational complexity. Artificial intelligence systems trained on incomplete or non-representative datasets may systematically underperform in vulnerable or underrepresented populations, potentially amplifying existing healthcare inequities [13]. Bias may emerge from unequal healthcare access, inconsistent coding practices, missing data, or structural inequalities already embedded within healthcare systems.

Explainability and transparency also remain central challenges. Many advanced ML models operate as highly complex systems with limited interpretability, making it difficult for healthcare professionals, regulators, and patients to understand how predictions or recommendations are generated [13][14]. Although high predictive performance may support clinical decision-making, a lack of explainability may undermine trust, regulatory acceptability, and implementation within routine care environments. Emerging governance frameworks such as the European Union Artificial Intelligence Act increasingly emphasise transparency, accountability, human oversight, and risk-based governance for AI-enabled healthcare systems and classify certain AI systems used in medical devices or other safety-critical healthcare contexts as high-risk, subjecting them to enhanced requirements

concerning risk management, data governance, documentation, human oversight, and post-market monitoring [27].

Cybersecurity and data governance further complicate AI integration. As healthcare systems become increasingly interconnected, PHDS may become vulnerable to cyberattacks, ransomware operations, unauthorised access, and misuse of sensitive patient information. Sustainable implementation therefore requires governance frameworks capable of balancing innovation with privacy protection, transparency, accountability, and patient trust [16]. Such governance should also support continuous validation, post-deployment performance monitoring across relevant population subgroups, detection of model and data drift, controlled recalibration and model updating, version control, audit trails, incident reporting, and clear accountability mechanisms to ensure that AI systems remain safe, reliable, and clinically relevant throughout their lifecycle.

Importantly, the future success of AI-enabled PHDS will depend on coordinated collaboration across regulators, healthcare professionals, industry, payers, policymakers, and patient communities. Well-designed governance frameworks may function as enabling infrastructures supporting trustworthy and scalable healthcare transformation. Industry contributes infrastructure investment and analytical innovation, while healthcare professionals contextualise AI-supported systems within real-world clinical practice. Payers and HTA bodies further shape expectations regarding comparative effectiveness, healthcare value, and evidence standards within evolving RWE ecosystems [16][28]. Patients and patient organisations should remain active participants in governance discussions regarding acceptable secondary use of health data, transparency, and integrated patient management [25]. Ultimately, sustainable AI adoption within PHDS requires governance models that align technological innovation with clinical practice, regulatory expectations, and societal values.

Figure 2 summarises how AI-enabled PHDS integrate heterogeneous healthcare data sources to support evidence generation, personalised medicine, and adaptive healthcare decision-making.

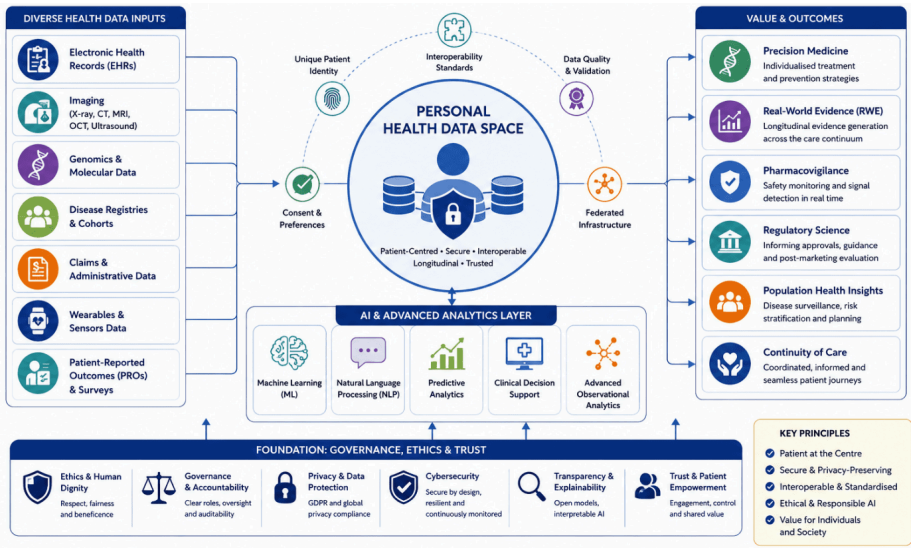

Figure 2. AI-Enabled Personal Health Data Spaces Supporting Continuous Learning Healthcare Systems

Real-World Evidence and Regulatory Transformation

Real-world evidence has evolved from a supplementary analytical approach into a central component of modern healthcare decision-making and regulatory science. Historically,

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randomised controlled trials (RCTs) represented the dominant evidentiary standard supporting regulatory approvals, reimbursement decisions, and clinical guideline development. While RCTs remain essential for establishing efficacy and internal validity, they are frequently limited by restrictive eligibility criteria, controlled treatment environments, short follow-up periods, and underrepresentation of heterogeneous patient populations encountered in routine clinical practice [1][2][3][4][5].

Increasingly, regulators, payers, healthcare professionals, and policymakers recognise that RWE can complement traditional clinical trial evidence by providing real-world insights into effectiveness, safety, treatment patterns, healthcare utilisation, and patient outcomes within real-world healthcare settings [1][4][9]. The growing integration of RWE into regulatory and HTA frameworks therefore reflects a broader transformation towards lifecycle evidence generation rather than isolated pre-authorisation evaluation alone.

This transition aligns closely with the development of PHDS and interoperable healthcare ecosystems. Rather than serving solely as repositories of health information, PHDS provide the longitudinal, patient-centred environment within which regulatory-grade RWE can be generated, validated, and reused across the healthcare lifecycle. Large-scale RWE generation depends fundamentally on the availability of harmonised and interoperable health data capable of capturing patient journeys across providers, settings, and therapeutic interventions. Personal health data spaces may therefore function not only as continuity-of-care infrastructures, but also as foundational infrastructures supporting adaptive evidence generation and regulatory-grade analytics.

Regulatory implementation of RWE has accelerated through initiatives such as the FDA Sentinel Initiative, DARWIN EU®, and multiple national RWD programmes, illustrating an international shift towards integrating observational evidence within regulatory decision-making [18][20][21][22].

Within Europe, DARWIN EU® represents a particularly important development because it operationalises federated access to harmonised RWD sources capable of supporting regulatory studies across multiple European healthcare systems [18]. DARWIN EU® therefore illustrates how federated infrastructures can operationalise regulatory-grade evidence generation while maintaining data sovereignty and patient privacy across multiple jurisdictions.

Similarly, HTA bodies are progressively integrating RWE within reimbursement and value assessment frameworks. Organisations such as the National Institute for Health and Care Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH) increasingly rely on RWE to evaluate long-term outcomes, comparative benefit, treatment sequencing, and healthcare resource utilisation within routine clinical practice [4]. Through PHDS, the same longitudinal health data may simultaneously inform regulatory assessment, HTA evaluations, post-authorisation safety monitoring, and routine clinical care, reducing duplication of evidence generation while supporting more coordinated healthcare decision-making.

In therapeutic areas characterised by rapid innovation, rare diseases, or precision medicine approaches, RWE may become particularly important where traditional large-scale randomised evidence is difficult to generate or rapidly becomes outdated.

Oncology provides one of the clearest examples of this transformation. Modern oncology increasingly depends on biomarker-driven treatment pathways, adaptive therapeutic sequencing, and rapidly evolving standards of care. In this environment, traditional clinical trials alone may struggle to fully capture longitudinal treatment effectiveness, safety, and healthcare system impact across heterogeneous real-world populations [7][8]. Consequently, oncology registries, external control arms, integrated real-world datasets, and AI-supported analytical platforms increasingly contribute to regulatory and HTA decision-making.

Similarly, ophthalmology demonstrates how RWE infrastructures may support optimisation of chronic disease management. Long-term anti-VEGF treatment pathways in nAMD and DME frequently require ongoing treatment interval adjustments, adherence monitoring, imaging integration, and real-world treatment persistence evaluation over many years [10][11]

[12]. These dimensions are often difficult to fully capture within conventional RCT structures alone.

However, integration of RWE within regulatory science also introduces substantial methodological complexity. Observational data remain vulnerable to multiple forms of bias, including confounding, selection bias, information bias, missing data, and variability in coding quality [6][25]. Consequently, regulators increasingly emphasise methodological transparency, protocol registration, target trial emulation principles, predefined analytical plans, sensitivity analyses and reproducibility standards when evaluating regulatory-grade RWE studies [6][25][29].

Regulatory confidence depends not only on access to large-scale health data but also on governance transparency, interoperability, analytical reproducibility and clear fitness-for-purpose frameworks that ensure evidence is reliable, reproducible and appropriate for its intended regulatory context. Personal Health Data Spaces may also improve reproducibility by supporting standardised data capture, transparent data provenance, harmonised analytical workflows and consistent application of governance principles across healthcare settings, thereby strengthening confidence in regulatory-grade real-world evidence [6][17][18]. Compared with disease-specific registries or isolated common-data-model implementations, PHDS may add methodological value by enabling longitudinal linkage across care settings and integration of richer clinical context, imaging, genomic information and PROs, while preserving provenance metadata and auditable data transformations. When combined with standardised outcome definitions, pre-specified analytical environments and reproducible federated workflows, these capabilities may improve the traceability, completeness and reproducibility of RWE generated for regulatory and HTA purposes.

At the same time, sustainable implementation requires alignment across stakeholders with different evidentiary priorities. Regulators primarily focus on reliability, reproducibility, and patient safety. Health Technology Assessment bodies and payers emphasise comparative effectiveness, healthcare value, and budget impact. Clinicians require operationally meaningful evidence applicable to routine care. Industry stakeholders seek scalable evidence frameworks capable of supporting lifecycle innovation and global regulatory alignment. Patients increasingly expect transparency, representativeness, and meaningful participation regarding how their healthcare information contributes to broader evidence generation.

Sustainable implementation requires governance frameworks that maintain methodological integrity, transparency, accountability, and public trust while ensuring that evidence generated from routine healthcare continues to improve clinical practice, regulatory decision-making, and patient outcomes. These governance requirements also introduce important ethical questions regarding consent, privacy, equity, data ownership, and societal trust, which are discussed in the following section.

Ethical, Governance, and Trust Challenges

The expansion of PHDS and AI-enabled healthcare infrastructures has intensified ethical, governance, and societal debates regarding privacy, transparency, accountability, stewardship, and secondary use of healthcare information. While interoperable health data systems may support patient-centred care, regulatory science, personalised medicine, and healthcare innovation, they also introduce substantial concerns regarding privacy, transparency, accountability, fairness, and public trust [1][16]. Addressing these challenges requires governance frameworks that function not only as mechanisms for risk mitigation but also as enablers of trustworthy and sustainable healthcare transformation.

Importantly, health data differ fundamentally from many other forms of digital information. Healthcare information is deeply personal, longitudinal, and often sensitive, reflecting not only medical conditions but also broader aspects of identity, vulnerability, behaviour, and social context. Consequently, governance of PHDS cannot be approached solely as a technical or operational exercise. It also represents an ethical and societal responsibility requiring sustained legitimacy and public trust.

Trust increasingly represents a prerequisite for sustainable secondary use of health data. Patients may support reuse of healthcare information when governance frameworks

demonstrate clear societal benefit, robust safeguards, transparency, and meaningful accountability [16][28]. Conversely, opaque data-sharing arrangements, unclear commercial relationships, or insufficient oversight may erode confidence in healthcare institutions and undermine willingness to participate in data-driven healthcare infrastructures.

The concept of "social licence" has therefore become increasingly relevant within healthcare data governance discussions. Social licence refers to broader societal acceptance of how healthcare information is collected, managed, and reused beyond strict legal compliance alone. Even when data use is technically lawful, public trust may deteriorate if individuals perceive insufficient transparency, inequitable benefit sharing, or lack of meaningful patient participation within governance structures [16][28][30].

Concerns surrounding monetisation of healthcare information have become particularly prominent. Health data increasingly possess substantial scientific, operational, and commercial value. Pharmaceutical companies, technology organisations, insurers, digital health platforms, and AI developers all rely upon large-scale health data ecosystems to support innovation, analytical development, and strategic decision-making [14][28]. However, patients frequently remain uncertain regarding how their information is reused, who ultimately benefits from secondary use, and whether adequate safeguards exist to protect their interests.

This tension creates an important governance challenge. Commercial investment and public-private collaboration may accelerate innovation, improve infrastructure, and support development of advanced analytical systems. Yet healthcare systems must simultaneously ensure that patient trust is not compromised through perceived exploitation, opaque monetisation practices, or insufficient transparency regarding secondary data use and the distribution of economic and societal benefits generated from patient-derived health information [28].

Addressing these tensions requires governance frameworks that clearly define the roles and responsibilities of data custodians, healthcare organisations, technology providers, regulators and patients, ensuring accountability throughout the health data lifecycle.

Importantly, trust cannot be sustained through legal compliance alone. Sustainable governance requires alignment between institutional objectives, patient expectations, transparency mechanisms and accountable stewardship of healthcare information [16][17][28]. Public trust should therefore be viewed as a dynamic relationship requiring continuous transparency, stakeholder engagement and periodic review of governance arrangements. Accordingly, governance frameworks should incorporate ongoing monitoring, stakeholder feedback and adaptive mechanisms capable of responding to emerging technological, ethical and regulatory challenges.

Consent architecture remains another major challenge within evolving PHDS. Traditional static consent models may be poorly suited for continuously evolving digital infrastructures involving multiple secondary uses of health information across extended periods of time. Patients may initially consent to clinical care without fully understanding future applications involving AI development, observational research, cross-border analytics, or federated data networks.

Consequently, digitally enabled governance frameworks, patient portals, and more dynamic approaches to consent are increasingly explored as mechanisms capable of improving transparency and patient agency. Such approaches may strengthen patient agency by allowing individuals greater visibility regarding how their healthcare information is accessed and reused over time. They may also provide mechanisms for managing evolving consent preferences, including future secondary uses of health data, while recognising that the governance of previously authorised data use remains subject to applicable legal, ethical and regulatory frameworks, which differ across jurisdictions [16].

Cybersecurity further complicates governance of PHDS. Increasing interconnectivity between healthcare systems, cloud infrastructures, AI platforms, wearable technologies, and external analytical environments expands the potential attack surface for cyber threats [16]. Ransomware attacks against hospitals and healthcare organisations have demonstrated how

digital health infrastructures may become vulnerable to operational disruption, unauthorised access, and large-scale exposure of sensitive patient information. These risks reinforce the need for cybersecurity to be considered a core governance function rather than solely an information technology responsibility.

The governance implications of AI extend beyond technical performance to include accountability, oversight and responsible implementation within trustworthy health data ecosystems. These considerations reinforce that AI governance should be embedded within broader PHDS governance rather than managed as an independent process [13][14].

Global variability in governance maturity further complicates implementation of interoperable health data infrastructures. Different jurisdictions continue to apply heterogeneous approaches regarding consent, secondary use, interoperability, privacy protection and regulatory oversight [9][17][21][22][23][24]. Within Europe, the EHDS provides an important example of efforts to harmonise governance and secondary use of health data across Member States. Nevertheless, national differences in legal frameworks, digital maturity and organisational readiness continue to challenge implementation and limit the scalability of cross-border evidence generation.

Governance frameworks should be viewed not only as mechanisms for risk mitigation but also as enabling infrastructures that support trustworthy, scalable and socially legitimate innovation.

Achieving this balance requires coordinated engagement across stakeholders. Regulators must establish adaptive governance frameworks capable of supporting innovation while preserving patient rights and public trust. Industry stakeholders should contribute transparency regarding data use, analytical methodologies, and commercial partnerships. Healthcare professionals remain essential in contextualising governance discussions within real-world clinical practice and patient relationships. Payers and health technology assessment bodies increasingly influence evidentiary expectations regarding data quality, transparency, and representativeness. Patient organisations and broader patient communities should participate meaningfully within governance structures rather than functioning solely as passive data contributors, including through co-governance, priority-setting, access to their health information, and transparent involvement in decisions concerning acceptable secondary data use.

The long-term sustainability of PHDS will depend on governance models that successfully integrate ethical principles, interoperability, accountability, cybersecurity and meaningful stakeholder engagement. Maintaining public trust should remain the central principle underpinning the future implementation of interoperable PHDS.

Operational and Organisational Barriers to Implementation

Despite significant progress in digital health infrastructure, interoperability standards and RWE generation, implementation of PHDS remains operationally complex. European policy initiatives, including the European Strategy for Data, together with the EHDS, DARWIN EU® and national digital health strategies, provide an important strategic framework for developing interoperable health data ecosystems. However, successful implementation ultimately depends not only on technical infrastructure but also on coordinated organisational change, sustained investment and alignment across technological, methodological, governance and workforce domains [15][16][17][18][19][20][21][22][23][24][31].

One of the most persistent challenges involves variability in digital maturity across healthcare institutions and healthcare systems. Large academic centres and highly digitised healthcare environments may possess advanced EHR infrastructures, integrated imaging repositories, and dedicated analytical capabilities. However, many regional hospitals, primary care networks, and smaller healthcare providers continue to operate using partially digitised or fragmented systems with limited interoperability capacity [15][16]. Such heterogeneity complicates longitudinal integration of patient journeys across providers, healthcare settings, and jurisdictions.

Coding inconsistency and data standardisation remain additional operational barriers across interoperable healthcare infrastructures [15][32]. Even when healthcare data are digitally available, substantial variability frequently exists in terminology systems, outcome definitions, clinical protocols and standards of care, laboratory and imaging measurement methods, equipment, diagnostic thresholds, and documentation practices across institutions and countries [15]. These inconsistencies may compromise data harmonisation, reduce analytical reproducibility, and limit scalability of multi-country observational research and advanced analytical models.

Data quality itself also represents a critical implementation challenge within modern data-driven healthcare systems [3][6]. Real-world healthcare data are often generated primarily for operational or reimbursement purposes rather than research or regulatory evaluation [3][6]. Missing data, incomplete longitudinal follow-up, inconsistent coding practices, and variability in documentation standards may therefore reduce the reliability and interpretability of evidence generated within large-scale health data ecosystems [3][6]. As PHDS expand, improving data quality increasingly depends on consistent metadata, transparent data provenance and harmonised governance to ensure that health information remains fit for clinical care, regulatory science and AI-enabled analytics.

Workforce capability and organisational readiness also remain substantial barriers to sustainable digital health implementation [33]. Sustainable implementation of interoperable health data ecosystems requires healthcare professionals capable of working across clinical, analytical, regulatory, and digital domains simultaneously. However, many healthcare systems continue to face shortages of expertise in health informatics, data governance, AI oversight, interoperability standards, and advanced observational methodology [13][14]. In practice, technological implementation frequently progresses faster than workforce adaptation and institutional capability development. This highlights the need for multidisciplinary teams combining clinical expertise, health informatics, epidemiology, regulatory science, cybersecurity and data governance. Operational responsibility within PHDS should remain distributed rather than being assigned to a single actor. Healthcare organisations and designated data stewards should remain accountable for data curation, provenance and quality assurance; healthcare professionals should retain responsibility for clinical validation and patient-level decisions, including interpretation of AI-supported outputs; and consent preferences and secondary-use permissions should be managed through accountable governance structures in accordance with applicable legal and regulatory requirements. AI systems should therefore support, rather than replace, professional clinical judgement, with clear escalation and accountability mechanisms where automated outputs influence care.

Resistance to organisational change may further complicate implementation. Integration of interoperable PHDS often requires redesign of workflows, governance structures, and institutional responsibilities. Healthcare professionals may express concerns regarding administrative burden, algorithmic decision-making, data ownership, workflow disruption, or reduced autonomy within increasingly digitised environments. Addressing these concerns requires not only technological deployment but also leadership commitment, transparent communication, workforce engagement, education and continuous organisational change management.

Cross-border implementation introduces additional complexity, particularly when interoperability frameworks, governance standards, and operational maturity differ substantially across healthcare systems [17][18][19][20][21][22][23][24][32]. Even within regions pursuing harmonised digital health strategies, national regulatory and governance approaches frequently differ regarding consent models, secondary use permissions, cybersecurity requirements, and data access procedures [17][18][19][20][21][22][23][24]. Such variability may delay international collaboration and complicate federated evidence generation initiatives intended to support large-scale regulatory science and continuity of care.

Financial sustainability represents another major implementation consideration. Although interoperable PHDS may ultimately improve healthcare efficiency, research capability and

regulatory decision-making, substantial upfront investment is required for digital infrastructure, cybersecurity, workforce development, interoperability standards, governance mechanisms and long-term maintenance. Sustainable funding models will therefore be essential to support implementation beyond initial pilot programmes. The economic case for PHDS should therefore be evaluated alongside implementation, comparing infrastructure and operating costs with potential benefits such as reduced duplication of care and evidence generation, improved data access, more efficient research and regulatory processes, and longer-term healthcare-system efficiencies. Formal cost-benefit assessment will require empirical implementation data and should represent an important area for future research.

Incremental integration models, federated infrastructures, interoperability standards, and shared governance frameworks may support a gradual transition towards more connected healthcare infrastructures while avoiding unrealistic expectations of immediate system-wide transformation.

Existing initiatives such as DARWIN EU®, EHDEN, the FDA Sentinel Initiative and disease-specific registries demonstrate the feasibility of federated evidence generation while preserving local governance structures [7][8][10][11][12][18][19][20]. However, experience from these initiatives also shows that adoption remains heterogeneous because of differences in digital maturity, organisational readiness, institutional incentives and workforce capacity. These experiences support a phased implementation approach beginning with harmonised interoperability standards, governance principles and minimum data quality requirements before expanding towards federated analytics, AI-enabled applications and cross-border collaboration [15][16][17][18][19][20][21][22][23][24].

Table 2 translates the conceptual framework proposed in this commentary into a phased implementation roadmap. It identifies the principal implementation challenges, the sequence of recommended actions, the stakeholders responsible for delivery and the long-term objectives required for sustainable implementation of PHDS.

Challenge	Why it Matters	Immediate Actions (1-2 years)	Medium-Term Actions (3-5 years)	Long-Term Vision (>5 years)	Key Stakeholders
Interoperability fragmentation	Prevents longitudinal patient journeys and integrated evidence generation	Adopt common interoperability standards (HL7 FHIR), clinical terminologies (SNOMED CT), disease classifications (ICD) and common data models (OMOP CDM).	National interoperability platforms and federated networks	Cross-border interoperability supporting continuity of care and research	Governments, regulators, EHR vendors, healthcare providers
Governance variability	Creates inconsistent access, consent and secondary data use	Develop common governance principles and transparent data access processes	Harmonise regulatory interpretation and governance frameworks across jurisdictions	Trusted international governance framework supporting primary and secondary data use	Regulators, governments, policymakers
Data quality inconsistency	Reduces reliability of RWE and AI	Introduce minimum data quality standards and metadata documentation	Routine quality audits, validation frameworks and common quality metrics	Regulatory-grade, high-quality longitudinal health data	Healthcare providers, researchers, industry
Cybersecurity and privacy	Threatens patient trust and operational resilience	Security-by-design, privacy-by-design and continuous risk assessment	Shared cybersecurity standards and incident response capabilities	Secure, resilient and trusted digital health ecosystem	Healthcare organisations, regulators, technology providers
AI bias and limited explainability	Risks inequitable healthcare decisions	Use representative datasets, transparent documentation and human oversight	Continuous model validation, auditability and post-deployment monitoring	Trustworthy, explainable and equitable AI supporting healthcare	AI developers, clinicians, regulators
Workforce capability	Limits implementation despite available technology	Digital literacy programmes and interdisciplinary education	Establish specialised health informatics and AI capability across organisations	Workforce able to integrate digital innovation into routine care	Universities, healthcare organisations, policymakers
Patient engagement and consent	Trust is essential for sustainable implementation	Introduce patient portals, transparent communication and dynamic consent models	Increase patient participation in governance and policy development	Individuals become active partners in managing and sharing their health information	Patients, healthcare providers, regulators
Financial sustainability	Long-term investment is	Prioritise high-value pilot	Scale successful	Sustainable international	Governments, payers,

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Challenge	Why it Matters	Immediate Actions (1-2 years)	Medium-Term Actions (3-5 years)	Long-Term Vision (>5 years)	Key Stakeholders
	required	programmes and phased investment	national and regional infrastructures	ecosystem supporting learning healthcare systems	industry

Table 2. From Strategy to Implementation: A Roadmap for Sustainable Personal Health Data Spaces

Implementation should also be evaluated against measurable outcomes rather than infrastructure deployment alone. Relevant indicators may include completeness and timeliness of information exchange across care settings, reductions in avoidable duplicated investigations, improved treatment matching and continuity of care, inclusion of patient-reported outcomes, representativeness of populations contributing to evidence generation, patient access to and engagement with their health information, equitable access to data-enabled healthcare innovation, and improvements in relevant population health outcomes. At the system level, evaluation should additionally consider data quality, interoperability performance, evidence-generation efficiency, clinician workload and patient trust. These indicators should be adapted to the healthcare context and evaluated empirically as PHDS implementations mature.

The future success of PHDS will depend not on eliminating the inherent tensions associated with digital health ecosystems, but on governing them transparently and responsibly. Healthcare systems will increasingly need to balance the primary and secondary use of health data, patient-centred governance and legitimate commercial innovation, interoperability and professional workload, as well as technological innovation and public trust. These trade-offs should be recognised as enduring governance challenges rather than temporary implementation barriers, requiring adaptive governance frameworks, continuous stakeholder dialogue and proportionate regulatory oversight as technologies and societal expectations evolve.

Future Directions and Multi-Stakeholder Collaboration

Personal Health Data Spaces should not be conceptualised as isolated national infrastructures but as interconnected components of a global learning health ecosystem. Future progress will increasingly depend on internationally aligned interoperability standards, governance approaches and evidence frameworks capable of supporting cross-border healthcare collaboration, regulatory science and equitable innovation [9][15][16][17][18][19][20][21][22][23][24][32][34].

Regulators will continue to play a central role in shaping interoperable health data infrastructures through increasing convergence of real-world evidence frameworks, governance principles and lifecycle evidence generation [9][18][20][21][22]. Future regulatory frameworks will require adaptive oversight models capable of balancing innovation with transparency, methodological rigour, explainability and patient safety. Greater convergence of regulatory expectations may facilitate international evidence generation, reduce duplication of effort and accelerate patient access to innovation.

Importantly, future implementation efforts must also address the needs of low- and middle-income countries and rapidly developing healthcare systems across Africa, the Middle East, Asia, and Latin America. These regions represent the majority of the global population and increasingly contribute substantial healthcare data, patient diversity, and unmet medical needs. However, variability in digital maturity, infrastructure investment, interoperability capacity, workforce capability, and governance readiness may risk widening global inequities

in AI development, regulatory science, and evidence generation. Concrete implementation experience from countries such as India and Rwanda illustrates alternative pathways to digital health transformation, including nationally coordinated digital-health architectures, interoperable health-information infrastructures and digitally enabled service delivery that can progressively connect healthcare information even where comprehensive EHR infrastructure is not universally available [35][36]. At the same time, emerging healthcare systems may also create opportunities for more agile and scalable digital transformation models capable of bypassing certain legacy infrastructure limitations observed in highly fragmented healthcare environments. Sustainable global interoperability will therefore require not only technological innovation, but also equitable investment, international collaboration, and locally adaptable governance models capable of supporting diverse healthcare environments.

Sustainable PHDS will also depend on meaningful public participation and shared accountability across stakeholders. Each stakeholder contributes complementary responsibilities essential for trustworthy and socially legitimate healthcare transformation. While institutions must ensure transparency, privacy protection, interoperability, cybersecurity, and accountable governance, patients and broader communities may increasingly contribute to healthcare improvement through responsible participation in ethically governed data-sharing frameworks. When supported by clear safeguards, transparency, and societal benefit, responsible secondary use of healthcare information may contribute to more representative evidence generation, accelerated research, and improved healthcare outcomes across populations [16][28][34].

Payers and HTA organisations will similarly shape future evidence expectations. As healthcare systems face growing financial pressures associated with ageing populations, chronic diseases, and precision medicine, payers increasingly require real-world insights regarding comparative benefit, treatment sequencing, healthcare value, and long-term outcomes [4]. Consequently, future personal health data infrastructures may support more integrated regulatory and HTA evidence generation capable of reducing duplication and accelerating evidence-informed healthcare decision-making. This convergence may support more efficient evidence generation across the product lifecycle while reducing the burden on healthcare systems and research participants.

Artificial intelligence will likely remain a major driver of future healthcare transformation, particularly through predictive analytics, imaging interpretation, pharmacovigilance, workflow optimisation, and personalised medicine applications [13][14]. However, sustainable implementation will depend on governance frameworks capable of addressing explainability, fairness, cybersecurity, accountability, and equitable deployment across healthcare systems [13][14][27][28][33].

Importantly, future transformation should not be driven solely by technological ambition. Many healthcare systems continue to face workforce shortages, operational fragmentation, variable digital maturity, and healthcare inequities that may limit scalability of advanced digital infrastructures. Consequently, implementation strategies should remain pragmatic, phased, and adaptable to differing healthcare system capabilities and resource environments.

Federated data architectures may become particularly important in this context. Rather than relying exclusively on centralised repositories, federated approaches may support distributed analytics, interoperability, and multi-country collaboration while preserving local governance structures and privacy protections [18][19][37]. Such models may improve scalability, interoperability and public acceptability while enabling regulatory-grade evidence generation, AI development and international collaboration without requiring centralised storage of sensitive patient-level data [18][19][37]. However, federated approaches do not eliminate privacy or methodological risks; model inversion and related inference attacks may permit unintended reconstruction of sensitive information, while heterogeneity in patient populations, clinical practice and data quality across participating sites may produce uneven model performance and limit generalisability [37].

Ultimately, PHDS represent more than a technological innovation. They offer a patient-centred vision for integrating interoperable health data, artificial intelligence, real-world

evidence and trustworthy governance into continuously learning healthcare systems. Realising this vision will require international collaboration and shared commitment across stakeholders to improve health outcomes through responsible use of health data.

Discussion

Healthcare transformation increasingly reflects the convergence of interoperable health data infrastructures, RWE, AI and multimodal information within connected healthcare environments. This commentary positions PHDS as an integrative framework for organising these capabilities around longitudinal patient journeys and continuously learning healthcare systems, addressing limitations of institution-centred infrastructures that were not designed for contemporary requirements in precision medicine, regulatory science and lifecycle evidence generation.

Rather than conceptualising PHDS as technical repositories or interoperability initiatives, this commentary proposes them as patient-centred operational ecosystems situated at the intersection of healthcare delivery, regulatory science, governance, AI-enabled analytics and evidence generation. Their strategic value lies not only in facilitating secure data exchange but also in enabling longitudinal understanding of patient journeys across providers, diseases and therapeutic interventions, thereby supporting continuously learning healthcare systems [1][7][13][14].

The convergence between interoperable health data infrastructures and regulatory transformation is particularly important. Regulatory agencies and HTA bodies increasingly recognise that traditional RCTs, while essential, may not fully address the evidentiary needs associated with rapidly evolving therapeutic landscapes, precision medicine, and long-term healthcare decision-making [1][4][9][18][20][21][22]. Consequently, lifecycle integration of RWE, AI-enabled analytics, and real-world observational data increasingly shapes regulatory science and healthcare policy discussions internationally.

A key contribution of this commentary is the conceptual distinction between PHDS and related digital health initiatives. While Health Data Spaces, the EHDS, federated analytical infrastructures, RWE platforms and Learning Healthcare Systems each address important aspects of digital healthcare transformation, PHDS provide an integrative patient-centred framework that connects these components into a coherent operational ecosystem. This distinction may help guide future policy development, implementation strategies and interdisciplinary collaboration.

At the same time, these developments introduce substantial methodological, ethical, organisational, and societal complexity. Expansion of interoperable health data ecosystems does not automatically guarantee evidence quality, equity, transparency, or patient trust. Fragmented governance structures, variable data quality, cybersecurity risks, algorithmic bias, and operational silos may undermine implementation if not addressed through coordinated governance and methodological oversight [5][15][16][17][28]. Indeed, poorly coordinated PHDS implementation could itself create an additional layer of fragmentation if interoperability standards, governance arrangements, institutional incentives and clinical ownership are not aligned across participating organisations.

Recent interoperability analyses continue to demonstrate that substantial operational variability persists across healthcare environments despite increasing policy momentum towards integrated health data ecosystems [38][39][40][41][42]. These findings suggest that future success will depend not only on technological capability, but also on semantic interoperability, governance harmonisation, clinician adoption, workforce capability, and organisational readiness.

Sustainable implementation depends equally upon organisational culture, institutional trust, workforce capability, governance maturity, and alignment of stakeholder incentives. Healthcare professionals, regulators, industry, payers, technology developers, and patients frequently operate under different operational priorities and evidentiary expectations. Implementation should therefore be viewed as an organisational transformation rather than solely a technological project, requiring leadership, stakeholder engagement and sustained investment alongside advances in digital infrastructure [16][17][28].

The oncology and ophthalmology examples presented throughout this commentary illustrate how PHDS may support implementation across diverse therapeutic areas. Although these examples differ clinically, both demonstrate the importance of longitudinal patient journeys, multimodal data integration, and continuous evidence generation beyond conventional clinical trials. Chronic disease management increasingly requires integration of imaging, treatment sequencing, adherence monitoring, PROs, and long-term effectiveness evaluation beyond the boundaries of conventional trial environments [7][8][10][11][12]. Personal Health Data Spaces may therefore provide the foundational patient-centred infrastructure required to support future precision healthcare models by integrating clinical care, evidence generation, and longitudinal patient management.

Several limitations should also be acknowledged. This work represents a commentary rather than a systematic review or empirical evaluation of specific health data infrastructures. Consequently, the perspectives presented reflect a synthesis of regulatory frameworks, published literature, digital health initiatives, and practical experience in RWE and healthcare data science. Accordingly, the framework does not provide quantitative estimates of implementation effectiveness, patient impact, healthcare-system efficiency or return on investment, as sufficiently mature and comparable empirical evaluations of PHDS remain limited. Future empirical research should evaluate the implementation of PHDS across different healthcare systems, assess their impact on patient outcomes, evidence generation, and healthcare efficiency, and determine which governance and interoperability models are most effective in practice.

Despite these limitations, the growing international momentum surrounding interoperability, AI governance, RWE integration, and longitudinal health data ecosystems suggests that PHDS provide a timely conceptual framework for future healthcare transformation [15][16][17][18][27][28][31]. Rather than replacing existing digital health initiatives, PHDS offer a patient-centred approach for integrating governance, interoperability, AI, and evidence generation across the healthcare lifecycle. Their long-term success will depend not only on technological capability but also on international collaboration, methodological rigour, public trust, and meaningful engagement of all stakeholders in the responsible stewardship of health data [17][27][28].

Conclusions

Personal Health Data Spaces offer a patient-centred operational framework for connecting longitudinal health information across clinical care, research, regulatory science and public health. Their conceptual contribution lies not in proposing another standalone data platform, but in integrating existing interoperability, governance, RWE and AI capabilities around the individual and their healthcare journey.

Realising this model will require interoperable standards, trustworthy governance, methodological rigour and clear accountability across healthcare stakeholders. Future research should move beyond conceptual development to empirically evaluate whether PHDS improve continuity of care, evidence generation, patient outcomes, healthcare efficiency and equitable access to innovation across different healthcare systems.

Abbreviations

- AI – Artificial Intelligence
- CADTH – Canadian Agency for Drugs and Technologies in Health
- DARWIN EU® – Data Analysis and Real-World Interrogation Network
- DME – Diabetic Macular Oedema
- EHDEN – European Health Data & Evidence Network
- EHDS – European Health Data Space
- EHR – Electronic Health Record
- EMA – European Medicines Agency
- FDA – Food and Drug Administration
- FHIR – Fast Healthcare Interoperability Resources
- GDPR – General Data Protection Regulation

- HDABs – Health Data Access Bodies
- HL7 – Health Level Seven
- HTA – Health Technology Assessment
- ICD – International Classification of Diseases
- MHRA – Medicines and Healthcare products Regulatory Agency
- ML – Machine Learning
- nAMD – Neovascular Age-Related Macular Degeneration
- NICE – National Institute for Health and Care Excellence
- NLP – Natural Language Processing
- OCT – Optical Coherence Tomography
- OMOP CDM – Observational Medical Outcomes Partnership Common Data Model
- PHDS – Personal Health Data Spaces
- PMDA – Pharmaceuticals and Medical Devices Agency
- PRO – Patient-Reported Outcome
- QoL – Quality of Life
- RCT – Randomised Controlled Trial
- RWD – Real-World Data
- RWE – Real-World Evidence
- SNOMED CT – Systematized Nomenclature of Medicine – Clinical Terms
- TEHDAS – Towards the European Health Data Space
- WHO – World Health Organization

Notes

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Data Availability

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