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Digital dimensions in medicine: exploring the interplay of biomarkers, phenotypes, and twins

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DIGITAL DIMENSIONS IN MEDICINE: EXPLORING THE INTERPLAY OF BIOMARKERS, PHENOTYPES, AND TWINS

Research Paper

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Abstract. Personalized medicine tailors treatment to individual characteristics, leveraging advances in digitized healthcare and Artificial Intelligence (AI). This study highlights the role of digital biomarkers, phenotypes, and twins in enhancing healthcare personalization. Despite their potential, vague definitions of the constructs present a challenge to their application. Through a systematic literature review, this research explores the distinctions and applications of the constructs, aiming to clearly define and classify them. It emphasizes the need for a common language, interdisciplinary collaboration, and effective treatment strategies. The study also underscores the importance of data quality and ethical data use, contributing to the coherent integration of digital health constructs into personalized medicine.

Keywords: personalization, digitalization, biomarker, phenotypes, twins

1 Introduction

The advancement of digitized healthcare and powerful systems such as AI can increasingly capture and analyze data on environmental exposures, behavioral patterns, and real-time sensor data, thus greatly expanding potential data sources (Ho et al., 2020). The goal of such data-driven approuches digital healthcare is to generate data for treatment planning to reduce side effects, offer necessary treatments based on individual needs, and involve patients more transparently in their treatment (Goetz and Schork, 2018). Factors such as genetics, environment, and lifestyle uniquely define each individual, shaping their specific health needs and challenges and allows to reinforce the capabilities to utilize personalized medicine. The essence of the achievable personalized medicine lies in providing customized therapeutic strategies tailored to the specific patient (Goetz and Schork, 2018). The integration of these patient-specific factors forms the core of personalized medicine (Goetz and Schork, 2018). In this context,

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digital biomarkers (Puntmann, 2009; FDA, 2021), digital phenotypes (Birk and Samuel, 2020), and digital twins (Kamel Boulos and Zhang, 2021) are promising and broadly discussed constructs for the development and implementation of personalized medicine. There are already many definitions that primarily describe the nature of these individual constructs in clinical application. Against this background, it is important to note that their implementation as digital innovations and the ensuing digital transformation are strongly influenced by institutional frameworks. Burton-Jones et al. (2020) define professional, administrative, and scientific logics as the main drivers. Professional logics include clinical practices and ethical content that influence the acceptance of new technologies. Administrative logics include management and regulatory processes that determine organizational implementation, while scientific logics relate to research and innovation processes for the development and dissemination of new technologies. Additionally, according to Jones et al. (2019), data should not be seen as a static, objective resource but rather as the result of a complex social and technical process. The boundaries between the constructs are fluid in the scientific discussion. The purposes for which they are used vary, which inevitably impacts their implementation. Precise distinctions are necessary for successful application, taking into account the specific requirements and contexts (such as technical systems, processes, structures, etc.) for the respective data sources, and also defining clear use cases for proper application. Thus, distinctions support the better integration of digital constructs like digital phenotypes, biomarkers, and twins into existing clinical, administrative, and scientific practices. A unified understanding and clear definitions create a common language for collaboration among different disciplines, peoples and are considered crucial for the successful implementation and use of digital technologies in healthcare. These addressed views of institutional logic and processual perspective emphasize important factors of implementation and acceptance to harness the innovative potential for monitoring, analyzing, and treating health conditions that go beyond the possibilities of traditional medical approaches.

Therefore, the systematic literature review aims to illuminate the scientific landscape and identify the differences and similarities between the constructs digital biomarkers, phenotypes, and twins. The following research question is answered: How can the distinctions and specific applications of digital biomarkers, digital phenotypes, and digital twins within – as a prime aspect of personalized medicine be precisely defined and classified? We conducted a systematic literature review, which is detailed in section 2. A background to exisiting definitions and their transformation into the digital realm is provided in section 3. The following results section presents the categories for distinguishing these constructs. The paper concludes with a summary in section 5 and 6.

2 Background

Personalized medicine is already a highly cited field of research. Personalized medicine is viewed by the NIH (2022) and the NHGRI (2024) as an approach for decision support in the individual prevention, diagnosis, and treatment of diseases through ge-

netic profiling. Goetz and Schork (2018) take it a step further by describing personalized medicine as the integration of not only genetic but also environmental and lifestyle information to optimize therapeutic outcomes. These approaches go far beyond traditional methods, highlighting the interplay of data and structured knowledge in personalized medicine. This requires extensive datasets and a deeper understanding of these data and their application contexts. Recent studies emphasize the importance of digital constructs such as digital biomarkers, digital phenotypes, and digital twins for enhancing personalized medicine by providing precise real-time data that can be integrated into treatment decisions. The constructs are not always clearly delineated in the literature, complicating their comparability and practical application (Jones et al., 2019; Burton-Jones et al., 2020; Lebovitz, Lifshitz-Assaf and Levina, 2022).

To distinguish digital biomarkers, digital phenotypes, and digital twins, it is necessary to consider their development and origins. Therefore, it is important to compare the original form with its digital counterpart. This development is often seamless, as digital approaches expand and redefine traditional characteristics. The following section attempts to describe the constructs in terms of their shared goal of achieving a deeper understanding of health.

To ensure a precise delineation of traditional and digital biomarkers, Suddaby (2010) recommends precise definitions and clear boundaries for constructs.

2.1 Definition of traditional and digital biomarkers

The U.S. Food and Drug Administration (FDA) defines traditional or analog biomarkers as a "characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions" (Puntmann, 2009; FDA, 2021). These traditional biomarkers are objective evaluation criteria subject to strict regulatory control and encompass several categories, including risk assessment, prediction, diagnosis, and monitoring (FDA, 2021). The extent of objective validation through these evaluation criteria depends on the context of use (Islam et al., 2022). In the clinical context, biomarkers are defined based on criteria such as ease of measurement, sufficient sensitivity, appropriate specificity, and applicability to medical interventions (Kohn et al., 2007; Lippi and Mattiuzzi, 2015). Traditional biomarkers include molecular, histological, radiological, or physiological measurements and changes in biological effects (Lenzenweger, 2013; Califf, 2018). These markers are generally confined to the clinical setting and largely exclude subjective data (Guthrie et al., 2019). The focus is thus on capturing and measuring objective, quantifiable physiological and behavioral data (Montag, Elhai and Dagum, 2021; Au, Kolachalama and Paschalidis, 2022; Vasudevan et al., 2022). In contrast, the FDA defines digital biomarkers similarly to traditional biomarkers as indicators of biological or pathological processes or responses to exposure or intervention. Digital biomarkers extend traditional biomarkers by integrating digital technologies for continuous and comprehensive data collection, gathering real-time data on physiological and behavioral parameters (Califf, 2018). Digital biomarkers thus enable the capture of more comprehensive health indicators (Puntmann, 2009; FDA, 2021).

The advancement of traditional biomarkers through digital technologies requires the combination of multiple markers and the use of intelligent systems. This is a crucial factor in increasing precision in personalized medicine (Califf, 2018). The collection of more comprehensive data allows for a more thorough assessment of health status (Montag, Elhai, and Dagum, 2021). Thus, biomarkers provide a mean or proxy data of vital signs that could be used to measure stress or movement, which can give indications of specific complaints regarding chronic but also non-chronic diseases. The required high quality of measurements necessitates that digital devices are capable of ensuring this quality (Fröhlich et al., 2018).

2.2 Definition of traditional and digital phenotypes

A phenotype represents biological processes and describes the actually observable characteristics and traits of an organism (Johannsen, 2014; Jain et al., 2015). It is understood as the physical expression of genes, encompassing both the observable traits of an organism and the interactions between genotype and environment (Engelmann, 2022). The phenotype can vary even among organisms with the same genotype depending on external living conditions, making it a dynamic construct that reflects the manifestation of genetic potentials in a specific environment (Johannsen, 2014).

In contrast to biomarkers, which are rather quantifiable values, phenotypes include clinically assessed traits by experts as well as observations in physiological diagnostics or behavioral measurements, which can also include subjective data (Wenzel, Kubiak and Ebner-Priemer, 2016). These can be captured through questionnaires or self-assessments, commonly used in psychological treatments or to record emotional states. Phenotypes are individual, situational, repetitive, and characterized by systematic collection (Vasudevan et al., 2022). Phenotypic assessment is typically based on a defined normal state and aims to classify specific symptoms (Han et al., 2010; Robinson, 2012). As an advancement of the traditional phenotype, the digital phenotype describes the idea of measuring diseases using larger datasets and digital devices (MacRae and Vasan, 2016; H. Birk and Samuel, 2020). Digital phenotypes consist of digital behavioral phenotypes, mental health states, and digital biomarkers (Baumgartner, 2021). They utilize digital technologies such as sensors and digital questionnaires to collect real-time data or also reporting date-related data and quantify the individual phenotype in situ (Torous et al., 2016). Digital phenotypes extend traditional phenotypes through continuous and comprehensive data collection, enabling a more precise and dynamic assessment of health status.

2.3 Definition of the digital twin

The construct of the digital twin was first described in the 1960s in the field of space exploration and later developed in the manufacturing industry. It encompasses five dimensions: the physical entity to be replicated, the virtual model to be created, their common connections, the data used, and the specified purpose (Sun et al., 2022). The core tasks of digital twins involve simulating processes through virtual models (Lee et

al., 2013; Grieves, 2015). Lee, Bagheri and Kao (2015) already described the possibilities of continuous data transmission, for example, through sensors, to connect a physical object with an information system – the concept of Cyber-Physical Systems (CPS) (Lee, Bagheri, and Kao, 2015). IoT sensor technology (Internet of Things) also enables the easy integration of real-time monitoring of the physical source (Tao et al., 2014), making the original industrial application relevant for the medical field.

A digital twin in medicine is intended to be a digital replication or representation of a physical object, process, or service, fed by a vast amount of dynamic data in real time (Cluitmans, Plank and Heijman, 2024). The extension of this virtual model with external data such as environmental and social interactions can enable more precise personalized recommendations or simulations for the individual or patient (Kamel Boulos and Zhang, 2021). For example, interactions between drugs can be tested on a specific patient, or the effectiveness of the treatment or the safety of the procedure can be simulated (Kamel Boulos and Zhang, 2021). By using machine learning, complex data can be used to simulate events, which appears highly attractive in medicine (Niklas et al., 2023). Table 1 shows the most important defining characteristics, which will be analysed in more detail in the next step by analysing the literature.

Table 1. Overview of the most important definition contents of the constructs.

	Digital Biomarker	**Digital Phenotype**	**Digital Twin**
Definition	Indicators of biological processes	Behavioral, psychological data and biomarker	Virtual replication of a physical entity (diverse data sources)
Data Source	Physiological measurements	Behavioral and genetic data, mental states	Multi-source data (clinical, lifestyle, environmental)
Application	disease monitoring, diagnosis, intervention	Understanding well-being, mental health assessment,	simulation of treatment responses, disease prevention
Limitation	high-quality digital devices, limited to measurable data	Potential for data privacy issues, integration complexity	High data complexity, requires simulation technology

3 Method

The systematic literature review (SLR) was chosen for its rigorous approach to compile and summarize existing research, allowing for a comprehensive understanding of the constructs in question. It aims to consolidate the various influences of institutional logics, processual perspectives, and the transparency of digital innovative technologies to create a solid foundation for further research and implementation. Building on this, and following Burton-Jones et al., we aim to identify key relevant content, gaps, and contradictions in the literature to create a framework for classifying digital biomarkers, phenotypes, and twins. By incorporating subterms and related constructs, as suggested by Brocke et al., (2009), the thoroughness of the review process is further ensured. In aligment with Brocke et al. (2009) we conducted a SLR to describe the fundamental dimensions and characteristics of digital biomarkers, phenotypes, and twins. The sys-

tematic literature search was conducted between February 2023 and April 2023 in databases such as PubMed, Cochrane, and Scopus. The search string was developed based on previous research and included terms like "digital biomarkers," "digital phenotypes," and "digital twins." Works that included a comprehensive taxonomy and universally applicable use of the constructs in medicine were included. Exclusion criteria during the title/abstract search were applied to filter out works that did not include a comprehensive taxonomy, focused only on specific disease cases (e.g., a specific disease), pertained to another field of research (e.g., agriculture), or addressed purely ethical aspects, protocols, or works still in the development of innovative methods without current applicability. The individual exclusion criteria are visible in the footnote. In the full-text screening, the remaining works were also filtered based on the exclusion criteria.

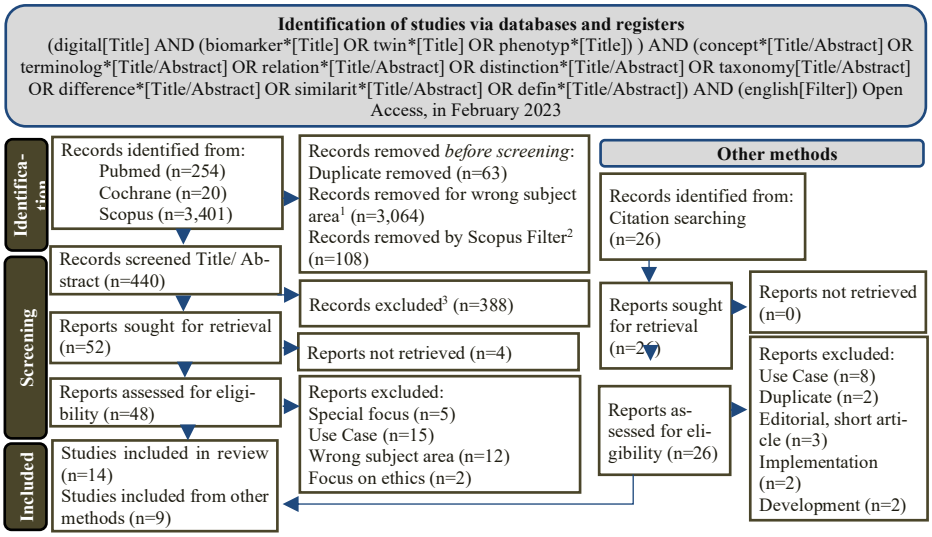

Figure 1.[1]PRISMA literature selection process.

The PRISMA flow diagram (Figure 1) illustrates the screening and selection process, showing the exclusion of 3235 works based on relevance and quality criteria.

The reviewers of the literature review, who are also the authors of this work, have expertise in health economics with a particular focus on research in information systems. Both authors reviewed all identified publications and discussed their content suitability. Only the literature deemed relevant by both was included in the review. The review process is depicted in Figure 1 and follows the PRISMA (2023) guidelines.

A total of 3,675 articles were found in the databases Pubmed, Cochrane and Scopus. The applied and described exclusion criteria (Figure 1) led to the elimination of 3,235

[11] Use of the filter criteria subject area in Scopus: all industry-associated fields, environmental sciences, economics, veterinary and dental medicine, chemical engineering.

[2] Use of the filter criteria keywords from Scopus such as industry-related keywords (e.g., industry 4.0, urban planning), as well as an editorial, note, book chapter, and short survey.

[3] Screening title/abstract and exclusion of papers: wrong subject area (108), special use case (247), ethics (7), special focus (5), protocol (8), development, utilisation (13).

studies. Thus, 440 studies remained, which were assessed for relevance based on title and abstract. After full-text screening, 14 studies were included. An additional 9 studies were included through backward searching, resulting in a total of 23 studies available for the final literature analysis. These studies were systematically reviewed, and an inductive categorization was performed to differentiate the constructs. Metacategories were formed to differentiate or cluster the described constructs. The categories include applicability, the type of data used, emerging subterms and classifications, and intended effects or goals. This approach aims to examine the potential of the constructs as well as possible challenges. In the following, the approach of Suddaby (2010) is taken up, who emphasises that a clear construct delimitation is achieved through precise definitions, operationalisation options, description of application areas and their usefulness.

4 Results

In the following, the results of the systematic literature review are displayed. Herby, distinguishments between i) data collection, ii) use cases, and iii) aims were made.

4.1 Forms of Data Collection

In essence, data collection can be distinguished between passive data (gathered through specific automations like sensors or smartphone recordings) and active data (involving patients actively, as in the case of questionnaires) (Baumgartner, 2021). The collected data sets form the basis for the applied analysis methods such as machine learning (Maatoug et al., 2022). Both digital biomarkers and phenotypes and twins gather and analyze an extensive amount of passive and active data, but they target different types of data. Digital biomarkers rely on specific quantifiable measurements, such as heart rate measurement and computer-based tests (Babrak *et al.*, 2019) or physical activity with an individual cognitive status through speech patterns and memory disorders in the diagnosis of neurodegenerative diseases , and thus tend to roughly assume the existence of a disease (Au, Kolachalama and Paschalidis, 2022). This is intended to provide an objective foundation for health assessment.

In contrast, the digital phenotype, an extended form of the digital biomarker (Oellrich et al., 2016; Maatoug et al., 2022), also focuses on behavioural data and mental states (H. Birk and Samuel, 2020) . Data from epigenetics, microbiomics (Coghlan and D'Alfonso, 2021) as well as manifestations of diseases, stimulus reactions (Robinson, 2012) and psychological tests are utilized. Transfer capabilities, such as Bluetooth, enable the use of activity data or digital social interactions (H. Birk and Samuel, 2020) additionally, user-generated content is utilized (Huckvale, Venkatesh and Christensen, 2019). This variety of data offers the opportunity to gain insights into psychological states, intelligence, but also individual attitudes towards one's own health perception, illness, and health in order to understand the more precise interaction of influences on health or illness and their consequences (Coghlan and D'Alfonso, 2021). Digital phenotypes, based on changes in patient activities such as GPS data or phone usage, and through patient self-assessed and documented stress, enable the early detection of risks

such as special emotional states in neurodegenerative diseases, such as anxiety or depressive phases , in order to map the exact manifestation of the respective disease and individual characteristics (Huckvale, Venkatesh and Christensen, 2019).

Digital twins complement the desired holistic health assessment through multidimensional, dynamic, and historical data (Voigt et al., 2021) from various sources. This includes lifestyle data, environmental factors, and clinical data (Mulder et al., 2022). Thus, in addition to health or phenotypic data (Björnsson et al., 2019) non-health-related data such as weather data can also be incorporated (Armeni et al., 2022). In addition to the reaction to medication or behavioural changes, the prevention of diseases can also be simulated (Venkatesh, Raza and Kvedar, 2022). For example, the possible course of a neurodegenerative disease can be simulated, taking into account not only the prognosis but also individual phenotype characteristics. All three constructs share technologies such as sensors, smartphones, and wearables, which they leverage in real-time (Kamel Boulos and Zhang, 2021; Venkatesh, Raza and Kvedar, 2022). As summarised in Figure 2, the complexity of the data used between the constructs (see Figure 3) increases considerably with the scope and diversity of the data. The digital biomarker can be found here as the foundation for the digital phenotypes and twins. The twin uses biomarkers and phenotypes as a basis.

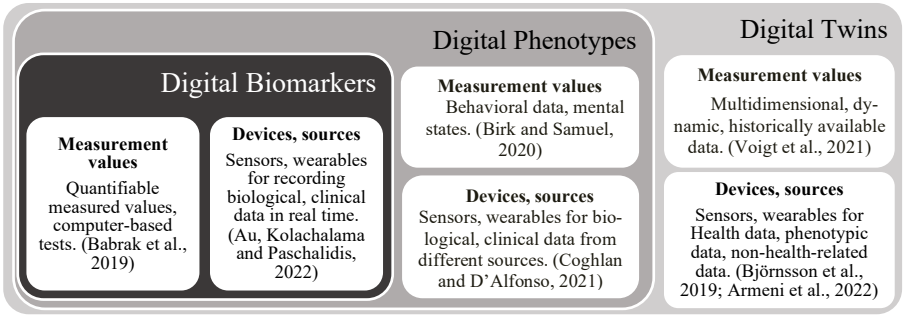

Figure 2. Illustration of the increasing data complexity between the constructs.

4.2 Types of Use

In the literature, different terms and definitions are used in the application of digital biomarkers, phenotypes, and twins. Additionally, these constructs in their definition do not always cover the entire range of their application fields.

Consequently, subtypes emerge to more precisely define these particularities. The literature describes various types of digital biomarkers, including biological biomarkers and diagnostic biomarkers (Au, Kolachalama and Paschalidis, 2022). Figure 3 provides an overview of these subcategories based on their data collection and objectives. Additionally, digital biomarkers can be classified as disease-associated and drug-related (Babrak et al., 2019). In contrast, the digital form of phenotyping distinguishes between various use cases. "Disease phenotyping" aims to represent an emerging disease, while the "endotype" describes an as-yet-unmanifested disease as a mechanism between genes and the clinical manifestation (Coghlan and D'Alfonso, 2021; Gould and

Gottesman, 2006). Depending on the target design, the reference phenotype can be depicted to understand phenotypic variations, and the generic phenotype can be represented to enable adjustments of specific characteristics (Oellrich et al., 2016).

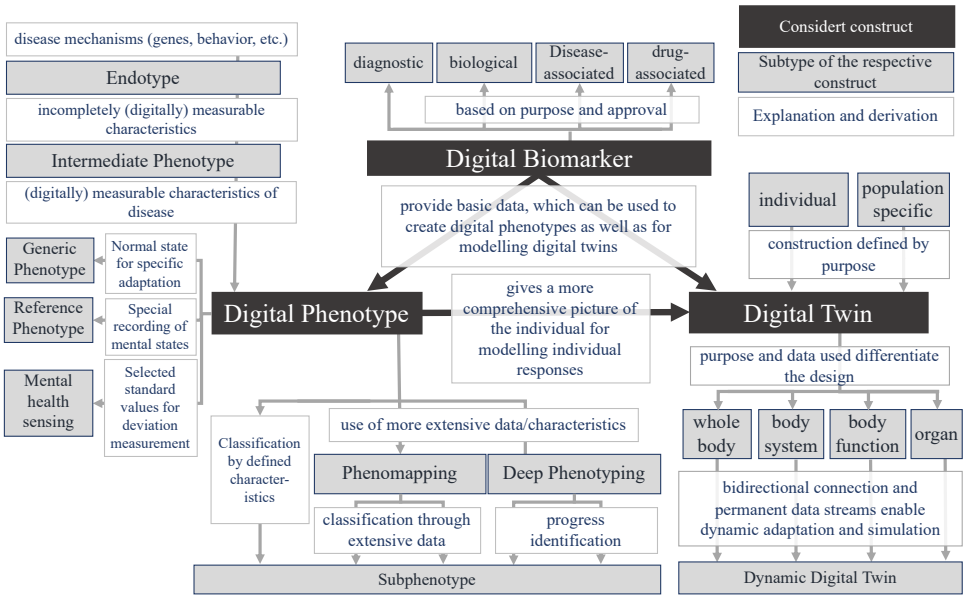

Figure 3. Relationships between the individual subtypes und types of use.

A finer classification of a predefined phenotype also distinguishes between subphenotype and phenomapping. A subphenotype can represent various manifestations based on defined features (Gould and Gottesman, 2006). The intermediate phenotype is described as an incompletely measurable precursor to a visible phenotype, emerging from an endophenotype (Meyer-Lindenberg and Weinberger, 2006; Rasetti and Weinberger, 2011). Mental Health Sensing, as a special form of digital phenotype, specializes in capturing mental health and thus significantly narrows its scope of application (H. Birk and Samuel, 2020). The use of much more diverse and extensive features for identifying subtypes of a specific disease with different courses and diverse treatment approaches can be depicted through Deep Phenotyping (Kamel Boulos and Zhang, 2021; Mulder et al., 2022).

In contrast, phenomapping does not restrict features but uses denser data by measuring more frequently (Deo, 2015; Shah et al., 2015). Deep Phenotyping aims to act as comprehensively as possible by describing the underlying phenotype in great detail to elucidate subphenotypes (Robinson, 2012).The higher data density and more frequent measurement points Wenzel, Kubiak and Ebner-Priemer (2016) already approach the construct of the digital twin. Digital twins can, depending on their purpose, represent the entire body, a body system, a bodily function, an organ, or a relevant organism. Additionally, they can be constructed individually or tailored to specific populations (Kamel Boulos and Zhang, 2021; Mulder et al., 2022). A special form is the dynamic

digital twin, characterized by the flexible adaptation of data based on life circumstances. The bidirectional connection between the physical and digital worlds enabled by this allows for dynamic simulations and models (Mulder et al., 2022).

4.3 Aims

The three constructs can be differentiated based on their different intended aims. The primary aim of the digital biomarker can also be derived from the presented use case of the generic neurodegenerative disease. Its use is not limited to medical aspects such as diagnosis, monitoring, and prognosis (Montag, Elhai and Dagum, 2021), but can also encompass early risk detection and intervention (Babrak et al., 2019). Areas of cost-effectiveness and health quality are also possible (Au, Kolachalama and Paschalidis, 2022). For example, data collected continuously or intermittently in conversations can derive a dynamic, quantitative signal of the speech pattern, which can serve as a marker for a neurodegenerative disease (Au, Kolachalama and Paschalidis, 2022). In addition to the goals of digital biomarkers, digital phenotypes are capable of providing a comprehensive understanding of human well-being (Oellrich et al., 2016; Coghlan and D'Alfonso, 2021). Certain conditions can be analyzed in more detail than by clinicians (Maatoug et al., 2022). A suitable presentation of results also has the potential to build health competence and literacy (Hsin et al., 2018) or health prevention (Coghlan and D'Alfonso, 2021). The passive collection of (everyday) data can lead to a better understanding of health behaviour (Davidson, 2022). Digital phenotypes can, for example, act as a kind of filter that automatically classifies incoming data and issues a warning or notification if a patient is potentially eligible for a clinical trial, is likely to benefit from a particular therapy or is at increased risk of certain complications(Oellrich *et al.*, 2016). Additionally, digital phenotypic systems are capable of detecting early warning signs and the slightest changes in health, sensitizing and alerting patients when they have difficulties maintaining appropriate self-monitoring, which allows early intervention before the actual event occurs (such as depression, anxiety disorders, etc.) (Huckvale, Venkatesh and Christensen, 2019). Building upon the goals of digital biomarkers and phenotypes, digital twins contribute to personalized and optimized medical decision-making, the simulation of stimulus responses, as well as the management of diseases and preventive measures. This is intended to enable the choice of various treatment options (Kamel Boulos and Zhang, 2021; Voigt et al., 2021; Mulder et al., 2022). By coupling with methods such as machine learning, data utilized, such as biomarkers, can be prioritized in a way that predicts the optimal treatment despite dynamic changes in the disease state (Björnsson et al., 2019).

5 Discussion

The present study distinguishes and classifies digital biomarkers, digital phenotypes, and digital twins based on their data sources, purposes of use, and aims. This differentiation facilitates practical implementation and understanding of these constructs, supporting their development and integration into medical care. To answer the research

question on how digital biomarkers, digital phenotypes, and digital twins can be precisely delineated, categorization based on data sources, purposes of use, and objectives was employed. Digital biomarkers are based on specific quantifiable measurements such as heart rate and computer-based tests. In contrast, digital phenotypes include behavioral data and mental states captured through technologies like GPS data and self-assessments. Digital twins complement health assessments through multidimensional, dynamic, and historical data from various sources, including lifestyle data and environmental factors. The application of these constructs also differs: digital biomarkers are primarily used for disease monitoring, diagnosis, and early intervention, while digital phenotypes provide a comprehensive understanding of human well-being and are used for analyzing health behavior and early warning systems for a specific view or perspective, such as for disease or treatments. Digital twins interlink multiple digitale phenotypes to provide a holistic view for personalized medical decision-making and simulation. Figure 4 illustrates this delineation and interdependence between the constructs, showing the increase in complexity within the defined categories.

The implementation of these constructs also implies several challenges, including data privacy issues, technical difficulties in data processing, and hardware reliability. The complexity of data processing and the need for advanced simulation technologies add to this picture. Despite these challenges, the constructs offer numerous opportunities: Personalised medicine can be improved primarily through comprehensive data analysis at digital phenotypes or digital Twins level in order to improve the medical decision-making. Early warning systems enable the early detection and intervention in health risks, leading to better healthcare. Moreover, the tracing of changes in individual digital phenotypes or twins by versioning different, but interlinked views health states can provide the foundation to compare patients health pathes in details, and thus provide a deeper and comprehensive understanding of individual behaviors, environmental influence factors, genetic prepositions and their implications onto invidual health. Incorporating the insights from the influence factors of institutional logics as described by Burton-Jones et al. (2020) can facilitate the clear delineation of these constructs. Professional stakeholders emphasize integration into practice through appropriate training to build sufficient technical competence. Administrative logics support the consideration of interoperability and adherence to data protection regulations, while scientific logics include system evaluation and collaboration between research and practice. Jones et al. (2019) highlight data as the result of complex processes. This perspective is crucial to ensure the correct interpretation of data by considering the context of data collection. The method of data collection can significantly influence the expected outcomes when applying digital biomarkers, digital phenotypes, and digital twins. Or in other word, digital biomarkers, phenotypes and twins can form the required meta model to embed the acquired data and make it accessible. Lebovitz et al. emphasize that only transparent decision support, ideally based on digital biomarkers, phenotypes, or twins, creates acceptance and trust among users. This research work and the SLR highlights several limitations that should be transparently outlined. The literature search was prefiltered in the Scopus database to narrow the selection of relevant literature, and only open-access literature was used. Additionally, the study is confined to a rapidly evolving research field, providing only a snapshot of the current state.

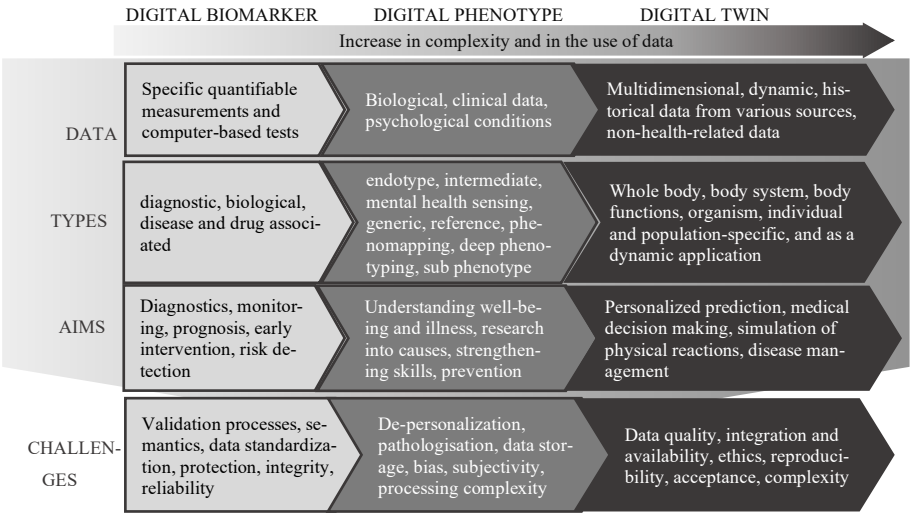

Figure 4. Overview of the classification for differentiation with derived challenges.

This can influence the selection of papers for the literature analysis as well as their results and conclusions. By applying the identified categories and insights, barriers to the acceptance and integration of digital constructs in healthcare can be overcome, optimizing their use in personalized medicine.

6 Conclusion

The present research provides intriguing insights into the application, construction, and differentiation of digital biomarkers, digital phenotypes, and digital twins. Their overarching goal is to develop a more comprehensive understanding of health and disease. These constructs rely on innovative data sources and modern technologies such as sensors, wearables, and smartphones to collect diverse health data from various sources. A central aspect lies in the individualization of healthcare and the complexity of the collected data and chosen procedures that all these constructs aim to achieve. While digital biomarkers can contribute to early identification of health risks, digital phenotypes and twins are designed to characterize individual health conditions and propose tailored treatment strategies. Nevertheless, numerous challenges need to be tackled. It is crucial to emphasize that these constructs support healthcare and do not compete with it. The deployment and selection of the appropriate construct in practice should be based on available data and individual goals. Additionally, it must be recognized that the implementation of these constructs requires strategies to overcome the outlined challenges. In the future, new opportunities for data generation and the secure and transparent use of these constructs should be given greater attention. User-centric presentation formats and maximum transparency can promote acceptance and further support research.

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