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POTENTIAL APPLICATIONS OF DIGITAL HEALTH TECHNOLOGIES IN ADULTS WITH INHERITED METABOLIC DISORDERS

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ABSTRACT **–** Inherited metabolic disorders are rare genetic disorders that often require lifelong, ideally continuous, monitoring to prevent acute complications and disease progression. Current care of inherited metabolic disorders relies on periodic clinical evaluations and static assessments, which fall short of capturing the rapid variability of metabolic parameters. Advancements in digital health technologies are making noninvasive wearable sensors available to a growing number of users. These wearables may help monitor patients affected by inherited metabolic disorders to continuously monitor key biomarkers (such as glucose, lactate, ketones, and ammonia) along with vital signs, nutrition, heart rhythm and physical activity. Such a novel monitoring approach may proactively identify trigger factors and metabolic instability, enabling personalized preventive medicine. A large amount of dynamic clinical data, enhanced by artificial intelligence and machine learning systems, could also support diagnosis, prognostic stratification and therapeutic strategies. This narrative review aims to describe potential future applications of digital health technologies in inherited metabolic disorders. In particular, we focused on the potential use of wearable sensors and digital tools, and on the capabilities of artificial intelligence for diagnostic, prognostic, therapeutic and research purposes.

Keywords: Digital health technologies, Wearables, Artificial intelligence, Inherited metabolic disorders.

List of Abbreviations: AF: Atrial fibrillation; AI: Artificial intelligence; CGM: Continuous glucose monitoring; DHT: Digital health technologies; ECG: Electrocardiogram; FD: Fabry disease; GSD: Glycogen storage diseases; IMD: Inherited metabolic disorder; ML: Machine learning; PKU: Phenylketonuria.

INTRODUCTION

Inherited metabolic disorders (IMDs) are rare monogenic disorders occurring in children and adults, caused by the impaired function of a specific metabolic pathway. The clinical picture, which varies depending on the type of metabolic defect, is often systemic and clinical manifestations can occur at all ages, from the fetal period to adulthood. For some metabolic defects, specific dietary and/or pharmacological treatment is available, e.g., enzyme replacement therapies, which makes the diagnosis of these disorders even more important. IMDs are variably classified in the literature[1]; according to the International Classification of Inherited Metabolic Disorders (ICIMD)[1], they are primarily grouped based on the metabolic pathway involved, which often reflects shared pathophysiological mechanisms and clinical features, as well as common diagnostic approaches. Some IMDs may present

with acute, chronic, or slowly progressive clinical courses, with potential overlaps depending on the specific disorder. Although heterogeneous in clinical presentation, IMDs represent a specific group of disorders sharing features, such as rarity, underdiagnosis, systemic impairment, chronic progressive course with possible acute crisis, and high economic burden linked to disease complications, frequent hospitalization and high cost of specific treatments, such as enzyme replacement therapies, when available[2].

The development of digital health technologies (DHT), such as wearables, mobile apps, electronic healthcare records, registries, and telemedicine, may have an interesting application in such rare disorders. For example, acute metabolic decompensation could be prevented by wearables, which could detect dynamic changes in biomarkers like glucose, lactate, ketones, and ammonia, along with vital signs, nutrition parameters, heart rhythm and physical activity[3-6]. Moreover, metabolic control in IMD patients is often influenced by nutritional status and physical activity. Stressful events, such as prolonged fasting and intense physical activity, increase the risk of metabolic instability and must be managed proactively[7]. IMD care is currently managed with periodic and static clinical and laboratory assessments. Given the dynamic nature of the metabolic processes and their rapid variability, an optimal management approach would include close, ideally continuous, monitoring across multiple biomarkers, physical and nutritional parameters. Wearable electronic devices offer a promising shift from conventional diagnostic tools, enabling noninvasive and real-time monitoring of physiological parameters and providing valuable insights into the body's internal status[8]. In the context of IMDs, wearable sensors present a transformative opportunity, potentially enhancing disease management, early detection of metabolic crises, and timely interventions.

Integrated software could capture, analyze, and predict metabolic changes in patients with IMDs. Employing artificial intelligence (AI) and machine learning (ML) systems, this approach could offer a comprehensive view of the patient's metabolic status and provide proactive, tailored preventive interventions to improve quality of life and reduce life-threatening decompensations and disease burden[9]. Telemedicine can increase the possibility for these patients of regular evaluations, as well as for those physically or logistically disadvantaged. Furthermore, the collection of a large amount of selected clinical data, both from wearables, registries or electronic healthcare records, analyzed through AI and ML systems, could also support diagnosis, prognostic stratification and therapeutic research in IMDs, in which patients' enrollment is limited by needs due to the rarity of the single disorders[10-12]. In this narrative review, we analyze the potential future applications of some DHT in IMDs, providing suggestions for future research.

METHODS

For this narrative review, we conducted a literature search on the PubMed database using combinations of keywords such as "inherited metabolic disorders," "digital health technologies," "wearables," or "digital tools." The search was performed up to February 2025. Only articles written in English and with full-text availability were screened for inclusion. Given the paucity of studies regarding applications of DHT in IMDs, we also considered literature on related conditions (e.g., digital tools in Pompe disease) and broader entities (e.g., DHT in rare disorders) or similar conditions (e.g., smartwatches in hypertrophic cardiomyopathy, which resemble Fabry cardiomyopathy). Final selection was based on relevance to the topic and clinical applicability. Additionally, the authors' experience and knowledge of ongoing DHT applications were integrated to suggest potential future directions for IMDs.

RESULTS

In the following section, we present an overview of current digital health and AI-based technologies applied in the management of IMDs. For each domain, both existing evidence and possible future directions are described in an integrated manner. Figure 1 shows the potential applications of wearables in patients with inherited metabolic disorders, including dynamic monitoring of body temperature, energy expenditure, nutrition, heart rate and rhythm, and blood metabolite levels. Figure 2 illustrates the integration of digital health technologies, such as wearables, registries, and electronic health records, analyzed through AI and machine learning systems to support clinicians in patient management.

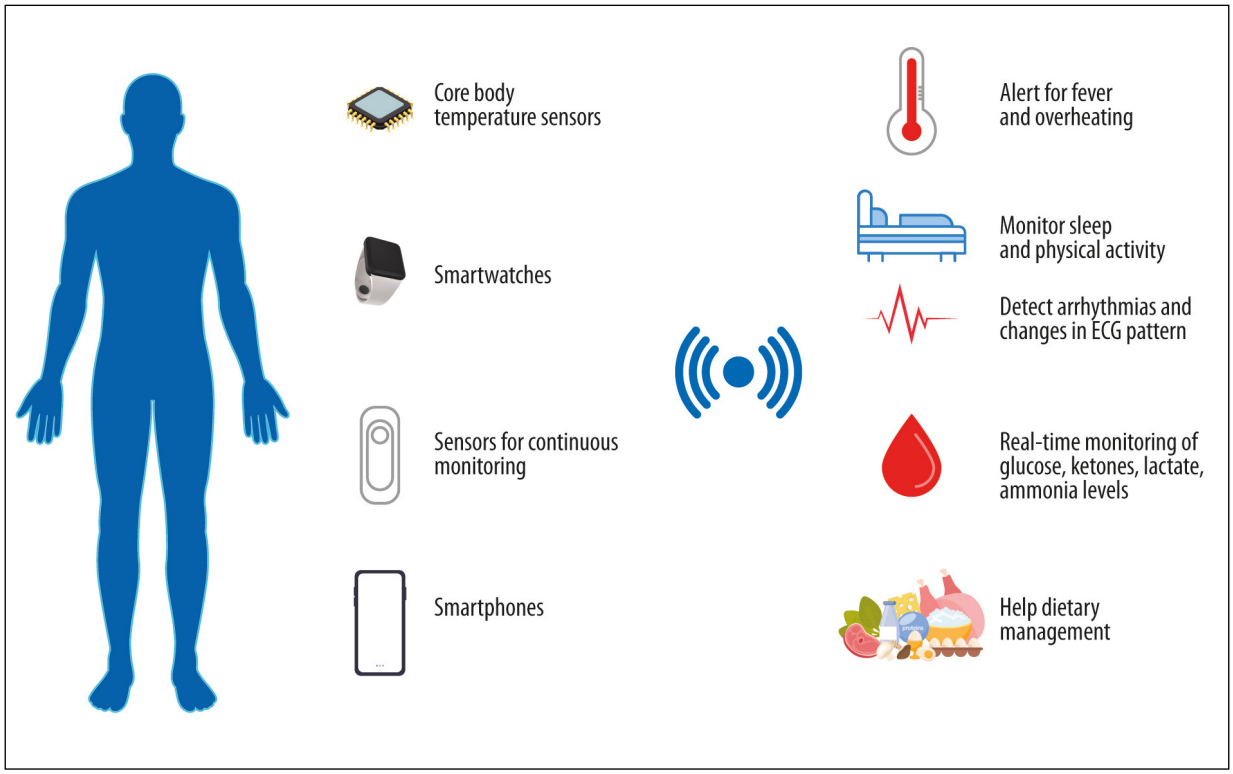

Figure 1. Potential applications of wearables in patients with inherited metabolic disorders. Wearable-assisted dynamic assessment of body temperature, energy expenditure, nutrition, heart rate and rhythm and blood levels of crucial metabolites could prevent acute decompensation and complications.

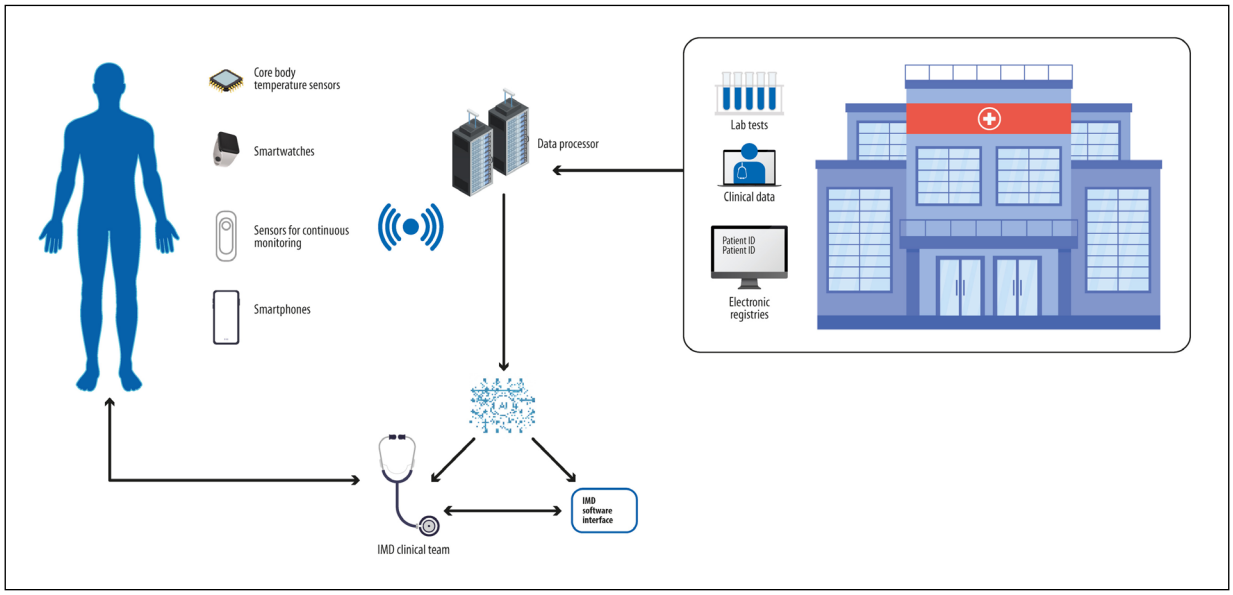

Figure 2. Integration of digital health technologies to manage patients with inherited metabolic disorders. Data collected by wearables, registries and electronic healthcare records, analyzed through artificial intelligence and machine learning systems and managed by an inherited metabolic disorder software interface, could serve the clinician to support patient management.

WEARABLE SENSORS AND REMOTE MONITORING

Continuous Glucose Monitoring

The integration of continuous glucose monitoring (CGM) into the clinical management of IMDs has shown significant potential, particularly in the context of disorders characterized by dysregulated glucose metabolism, such as glycogen storage diseases (GSD) and congenital hyperinsulinism[13,14]. CGM devices offer real-time insights into glucose fluctuations, enabling clinicians to better understand and manage metabolic disturbances[15]. CGM technology has proven useful in detecting hypoglycemic events and providing personalized treatment strategies for conditions such as GSD, in which glucose homeostasis is disrupted[3,16,17]. However, the application of CGM in these rare metabolic disorders is not without challenges. Discrepancies in sensor accuracy have been reported, with some studies[13,14] suggesting that CGM may underperform in non-diabetic hypoglycemia, where sensor readings may not always accurately predict hypoglycemic episodes in these populations. Despite these limitations, CGM has been demonstrated to improve glucose control and growth outcomes in children with GSD, contributing to more stable metabolic management and potentially reducing the frequency of acute metabolic crises[14]. Moreover, recent advancements in digital health and AI have opened new avenues for enhancing CGM's clinical utility. AI algorithms, when integrated with CGM data, have the potential to refine glucose prediction models, enabling more precise and individualized treatment plans for patients with complex IMD. These AI-enhanced systems could assist clinicians in identifying subtle metabolic shifts that may go unnoticed with traditional monitoring methods, thereby improving long-term metabolic stability and patient outcomes. Nevertheless, the real-world efficacy and long-term impact of these digital health tools remain subjects of ongoing research. For instance, prospective studies[14,16] examining the effectiveness of AI-driven CGM systems in predicting hypoglycemia and improving clinical outcomes are still in the early stages. Furthermore, while CGM has been instrumental in managing glucose fluctuations in conditions such as GSD[17,18], its role in broader IMD management, particularly in non-diabetic hypoglycemia, requires further investigation. The few studies[13,14] that have addressed this gap emphasize the need for more comprehensive research to validate CGM's applicability and reliability across a wider spectrum of metabolic disorders. As the field of digital health continues to evolve, the integration of CGM with other technologies, such as mobile health applications and AI, promises to revolutionize the clinical management of IMDs, enhancing both treatment precision and patient quality of life.

Ketone, Lactate and Ammonia Levels Monitoring

Several key biomarkers and physiological parameters could be continuously monitored to provide real-time insights into metabolic status, enabling early detection of instability and timely intervention. Ketone levels can be tracked using continuous ketone monitors that assess interstitial fluid composition, providing critical data on metabolic shifts during fasting or catabolic stress[19,20]. Ketone monitoring may offer clinical utility in several IMDs, particularly those managed with ketogenic dietary therapies. In glucose transporter type 1 deficiency syndrome, the ketogenic diet is the mainstay of treatment, and regular assessment of ketone levels is essential to ensure therapeutic efficacy and metabolic stability[4]. Furthermore, in organic acidemias such as propionic aciduria, real-time monitoring of ketones may help detect early signs of metabolic decompensation and guide timely interventions[21]. Ketone tracking could also be relevant in hepatic and muscular glycogen storage diseases, particularly when combined with glucose monitoring, to optimize metabolic control[22]. This is particularly important in disorders, such as GSD type III or IV, in which ketogenic dietary strategies have been explored as potential therapeutic options to improve energy balance and prevent hypoglycemia[23,24]. In these contexts, ketone monitoring could support individualized dietary adjustments and improve long-term disease management.

Similarly, lactate levels, which indicate metabolic stress and anaerobic metabolism, could be measured through continuous lactate monitors *via* subcutaneous or sweat-based sensors, helping to prevent lactic acidosis episodes[5]. Lactate monitoring may represent a valuable tool in the clinical management of several IMDs characterized by impaired energy metabolism. In hepatic glycogen storage diseases (e.g., GSD type I), elevated lactate is a hallmark of poor metabolic control and may guide nutritional interventions[25]. In organic acidemias such as methylmalonic and propionic aciduria, lactic acidosis can occur secondary to mitochondrial dysfunction during catabolic stress, making lactate a useful marker for early decompensation[21]. Similarly, in long-chain fatty acid β-oxidation disorders (e.g., very long-chain

acyl-CoA dehydrogenase deficiency), lactate accumulation may reflect impaired energy production and a shift toward anaerobic metabolism[26]. Moreover, in primary mitochondrial disorders, where defects in oxidative phosphorylation directly lead to elevated lactate levels, lactate monitoring is often essential for diagnosis, disease monitoring, and response to therapy[27]. In these contexts, point-of-care or continuous lactate measurement could provide timely insights into metabolic status and support individualized clinical management. Although wearable devices for continuous monitoring of lactate and ketones have been developed, they are not yet approved for clinical use.

Also, serum ammonia levels are used as a biomarker/diagnostic marker for urea cycle disorders[28]; the assessment of blood ammonia with portable ammonia analyzers could facilitate early detection of hyperammonemia before clinical symptoms emerge, although these wearables are still in an ideation phase. Recent advances in chemiresistive sensor technology and material design have significantly improved sensitivity, enabling the detection of trace amounts of ammonia and opening new possibilities for early noninvasive monitoring applications[6]. Integrating these sensors into wearable or mask-based devices could offer real-time tracking of exhaled ammonia, improving disease management in patients with urea cycle disorders. However, further work is needed to validate these devices in clinical settings and ensure long-term safety, accuracy and usability.

Physical Activity and Sleep Trackers

Accelerometer-based wearables, like smartwatches and other wrist wearables, can provide insights into energy expenditure, step count, sleep and movement patterns[29]. These noninvasive tools are now widely available to the general population to record several parameters of personal health and training. These trackers may have wide use in IMDs with neuromuscular limitations and exercise intolerance, allowing, for example, more objective movement assessments and conscious prescription of training programs tailored to individual needs. They also may be helpful in IMD patients treated with diet approaches, helping to adjust nutritional interventions to physical activity demands to prevent excessive metabolic strain. An interesting application of this technology is that it may provide objective parameters to reinforce subjective symptoms reported by patients in clinical trials. This could be of particular relevance in rare disorders in which patients' enrollment is limited by needs. For example, mobility was assessed through a wearable tool in a study[30] on patients affected by late onset Pompe disease. In this study, patient-reported symptoms like fatigue and pain were significantly inversely correlated with step count and peak 1-min activity, highlighting the opportunity to use these digital devices, besides patient-reported outcome measures, for future outcomes data collection. Indeed, wearable-derived digital endpoints have been validated by regulatory agencies and included in the efficacy assessments in clinical trials regarding rare muscular disorders[31].

Additionally, wearable thermometers monitoring core body temperature[32] could serve as an early warning system for metabolic crises, as temperature fluctuations often correlate with metabolic instability. Also, sleep monitoring by actigraphy has been used in GSD to provide valuable information on sleep disturbances such as frequent nocturnal awakenings and reduced sleep efficiency, which may impact metabolic control[33]. Beyond sleep pattern assessment, actigraphy offers a noninvasive, continuous, and objective method to monitor rest-activity cycles in real-life settings, facilitating the identification of circadian rhythm disruptions. These insights could contribute to optimizing clinical management. Additionally, although heart rate abnormalities, such as nocturnal tachycardia, have been suggested as potential indirect markers of hypoglycemia, their role in this context remains to be thoroughly investigated.

Electrocardiogram-Supporting Smartwatches

Electrocardiogram (ECG)-supporting smartwatches can record and transmit to a connected application a single-derivation ECG, and some of them have been studied and validated by important scientific societies in the detection of atrial fibrillation (AF)[34]. The most recent guidelines of the European Society of Cardiology[35] about the management of AF state that AF diagnosis can also be performed by a single-derivation ECG of at least 30 seconds, allowing, therefore, AF diagnosis with ECG smartwatches. The sensitivity and specificity of AF diagnosis with smartwatches are 97-99% and 84-94%, respectively[35]. This ability to detect AF may be useful in many IMDs associated with cardiomyopathy and arrhythmia risk. Other potential applications, besides AF, are the detection of bradycardias, arrhythmic events in

patients with syncope, ischemic alterations in patients with chest pain, ECG patterns linked to sudden cardiac death (e.g., pre-excitations, long QT), QT interval monitoring in case of particular pharmacological treatments, and left ventricular dysfunction[36-38]. ECG smart watches available in Europe and bearing CE marking include the Apple Watch Series 4 and later (Apple Inc., Cupertino, CA, USA), Fitbit Sense (Fitbit Inc., San Francisco, CA, USA), Samsung Galaxy Watch Active 2 and Watch 3 (Samsung Electronics Co., Ltd, Suwon-si, Gyeonggi-do, South Korea), and Withings Move ECG and ScanWatch (Withings, Issy-les-Moulineaux, France). Their prices range from €150 to over €1,000, which is comparable to the cost of a multi-day ECG Holter and considerably lower than that of an implantable loop recorder[39].

A paradigmatic IMD that may benefit from such monitoring is Fabry disease (FD), a lysosomal storage disorder (LSD) characterized by progressive cardiac hypertrophy and fibrosis, causing arrhythmic burden, heart failure and risk of sudden death. Monitoring of signs and symptoms of FD cardiomyopathy is of paramount importance and strictly linked to appropriate therapeutic choices. Currently, international recommendations for disease monitoring in adult patients[40,41] suggest static and periodical evaluations of classic cardiologic exams, sometimes inferred from cardiology societies' recommendations in hypertrophic cardiomyopathy[42], therefore not specific for FD patients. Continuous ECG monitoring, through implantation of a loop recorder, revealed a high prevalence of clinically significant events that may go unnoticed with classic monitoring in FD patients[43]. However, being an invasive tool, it is feasible only in high-risk patients. ECG smartwatches may be the ideal noninvasive tool in this context. Along with prompt AF detection, the ECG traces from smartwatches in FD patients could detect early signs of Fabry cardiomyopathy progression[44,45], allowing timely therapeutic management.

DIGITAL TOOLS IN NUTRITIONAL THERAPY

Dietary management plays a crucial role in the treatment of IMDs, requiring precise control of macronutrient and micronutrient intake to maintain metabolic stability and prevent long-term complications. The complexity of dietary therapy, which involves tracking specific amino acids, proteins, carbohydrates, and micronutrients, has driven the development of digital health solutions to improve adherence and optimize patient outcomes. Among the digital tools for dietary management in IMDs, Odimet® (Mevalia GmbH, Munich, Germany) is an advanced online dietary calculation tool designed for IMD patients, first introduced in 2008 and updated in 2022[7]. It provides a comprehensive database of over 3,000 food products, including standard foods and specialized metabolic formulas, detailing their amino acid, protein, lipid, carbohydrate, vitamin, and mineral content. Longitudinal data analysis demonstrated that Odimet® was extensively used by IMD patients (mainly Spanish individuals), and its use was associated with stable biochemical markers during critical periods, including the COVID-19 pandemic[7]. For instance, median phenylalanine levels in pediatric phenylketonuria (PKU) individuals remained at 213.4 µmol/L, while maple syrup urine disease subjects maintained leucine concentrations at 144.2 µmol/L[7]. Furthermore, Odimet® facilitated 63 emergency dietary adjustments in intoxication-type IMDs in 2023, highlighting its role in real-time dietary adaptation[7]. Another tool, the Metabolic Diet App Suite[46] was developed to support dietary adherence across 15 IMDs that require specialized nutritional management[46]. This suite integrates a patient-friendly dashboard with features such as real-time nutrient tracking, personalized dietary targets, and a food diary. The app's database is based on MetabolicPro™ (Vitaflo International Ltd, Liverpool, UK), a North American database curated by the Genetic Metabolic Dietitians International Technology Committee, ensuring accuracy in nutrient calculations. Patient and caregiver feedback indicated high usability, with positive responses regarding its ability to support daily meal planning[46]. PKU Bite® (Vitaflo International Ltd, Liverpool, UK), described by Evans et al[47], was specifically designed for PKU subjects, addressing challenges related to food label interpretation, protein intake calculations, and dietary compliance. The app includes over 1,100 low-protein food items, color-coded for easy reference, and features a built-in protein calculator. A 12-week randomized controlled trial[47] evaluating the app's efficacy in 60 caregivers and 21 adolescents with PKU found a trend toward improved accuracy in dietary protein calculations, increasing from 35% to 48% in app users, compared to no improvement in the control group.

Emerging technologies are further enhancing digital dietary management in IMDs. The My Plate system is a novel smart monitoring prototype designed for pediatric maple syrup urine disease individuals[48]. It integrates a mobile application with a 3D-modeled hardware plate to assist caregivers in tracking dietary intake with greater accuracy; patients and families reported that such a system could facilitate self-management by reducing reliance on manual dietary logs and improving dietary com-

pliance[48]. Additionally, machine learning models are being explored to optimize individualized dietary recommendations. A recent study[49] developed a predictive model for dietary phenylalanine tolerance in hyperphenylalaninemia (HPA) patients. By incorporating genetic data (*PAH* gene variants), metabolic profiles, and long-term dietary records, the model achieved high sensitivity (0.77-0.91) and specificity (0.8-1) in predicting tolerable dietary phenylalanine intake[49]. This AI-driven approach represents a significant advancement in precision nutrition, allowing for more tailored dietary interventions. The integration of digital health tools into IMD dietary management is transforming patient care by providing real-time decision-making support, reducing the burden of dietary calculations, and enhancing adherence. The use of mobile applications, web-based dietary calculators, and AI-driven predictive models enables personalized nutrition plans and facilitates remote dietary monitoring. AI's primary role in nutrition has been dietary assessment, with virtual health assistants showing promising results in enhancing adherence to dietary guidelines[50]. However, limitations persist, including challenges in accurately identifying multiple food items on a plate, variations in image quality affecting recognition accuracy, and ethical concerns regarding data privacy and bias, all of which require further research and regulatory oversight[50]. Future research should focus on assessing the long-term impact of these technologies on metabolic control, patient adherence, and quality of life, as well as expanding their application to a broader range of IMDs.

THE CONTRIBUTION OF AI AND ML SYSTEMS

AI and ML systems could process a large amount of data derived from DHT in IMD adult patients, enhancing early diagnosis, better prognostic stratification and proactive management. Regarding enhanced diagnosis, AI has been applied in the facial analysis of dysmorphic traits, demonstrating the ability to establish genotype-phenotype correlations, proving useful in the early phases of diagnosis[51]. Some platforms, like IEMbase[52], have been proposed to support clinicians in the diagnosis of IMD. IEMbase is an online tool that accepts an array of biochemical and clinical symptoms from a user and returns a ranked list of possible IMDs that match the input profile. Remarkably, these tools often show better performance in biochemical data analysis than in phenotypic pattern recognition, largely due to the quantity and accessibility of available biochemical data[52]. Another diagnostic advantage in IMD could regard the interpretation of variants of uncertain significance (VUS) in some patients and their relatives[53]. Given that diagnostic delay is associated with higher morbidity and costs, the use of AI systems could represent an advantage both for patients and the healthcare system.

AI is undoubtedly beneficial in data-intensive fields, such as radiological imaging. In IMD, the use of techniques like X-rays, computerized tomography, and magnetic resonance imaging provides valuable information for both diagnostic purposes and staging of organ damage. The volume of available data increases exponentially when integrating genomic, transcriptomic, and proteomic inputs. From this perspective, AI could not only represent a diagnostic tool by enabling the generation of novel algorithms but could also identify new pathophysiological mechanisms and support the classification of metabolic disorders[9]. The standardization and sharing of data could enable AI to identify biomolecular patterns predictive of disease progression and prognosis[54]. These insights could guide clinical decisions regarding treatment plans and follow-up protocols.

Treatment is another potential area of application for AI. Only a minority of rare diseases currently have available specific therapies. Challenges include difficulties in conducting clinical trials due to limited patient populations and the statistical constraints of working with small sample sizes. In this regard, AI could assist not only in evaluating the efficacy of existing treatments through drug repurposing strategies but also in identifying new therapeutic targets[55]. The identification of new molecular targets leads to personalized medicine aimed at maximizing therapeutic efficacy and optimizing the risk-benefit profile. Given the profound impact that treatments, such as enzyme replacement therapies, can have on patients' lives, discovering new therapeutic targets and biomarkers capable of predicting treatment response could significantly improve patients' quality of life[10].

However, several limitations remain in the application of AI to IMD. Despite the continuous growth of available data thanks to scientific progress, rare metabolic disorders affect a small population, which represents a major limitation for AI models. Additionally, clinical data collected by physicians are often difficult to standardize, leading to underrepresentation in clinical studies. Expanding disease registries, such as the first unified European registry for IMD[11], could provide a starting point for the sharing of clinical and radio-molecular data suitable for AI applications[12].

Ultimately, the future of clinical practice will inevitably be characterized by the integration of AI into diagnostic, therapeutic, and patient management workflows. Nevertheless, it is crucial to underscore that the utility of AI-generated data must be validated through clinical studies and real-world experience to ensure the efficacy and safety of diagnostic and therapeutic strategies.

CONCLUSIONS

IMD represents a fertile field for the application of DHT. A dynamic collection of data from wearables may enhance the proactive management of IMD at risk of acute decompensation. Large amounts of data collected by wearables, registries and electronic healthcare records, analyzed through AI and ML systems, could also support diagnosis, prognostic stratification and therapeutic research in this field.

Artificial Intelligence-Assisted Technologies:

No artificial intelligence-assisted technologies were used in the production of this article.

Authors' Contributions:

GG, CF, LL and MG wrote the manuscript. VN and GD critically revised the manuscript. All the authors approved the final version before submission.

Availability of Data and Material:

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Conflicts of Interest:

Giacomo Marchi and Nicola Vitturi have received fees for lectures from Sanofi and Amicus Therapeutics. Domenico Girelli has received fees for lectures from Sanofi. The other authors declare no conflicts of interest.

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