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A Holistic Approach to the Measurement of Physical Function in Clinical Research

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Abstract
Background: This commentary highlights the evolution of our understanding of physical function (PF) and key models/frameworks that have contributed to the current holistic understanding of PF, which encompasses not only a person's performance but also the environment and any adaptations an individual utilizes. This commentary also addresses how digital health tools can facilitate and complement the assessment of holistic PF and enable both objective and subjective input from the participant in their real-world environment. Lastly, we discuss how successful implementation of digital tools within clinical research requires patient input. ***Summary:*** This commentary highlights how our understanding of PF has evolved to be more holistic. ***Key Messages:*** Inclusion of digital tools within clinical research can provide a path forward to holistically assess PF in a patient-focused manner.

Introduction

Physical function (PF) has traditionally been defined as the sum of an individual's ability to perform tasks requiring physical effort [1]. These tasks include, but are not limited to, activities of daily living such as eating, bathing, dressing, using the toilet, and getting in and out of bed [1] and other tasks that are more performance-oriented (e.g., grip strength, one legged standing time, 6-min walk test, etc.).

Currently, PF is considered a core health-related quality of life (HRQoL) domain, alongside psychological (including emotional and cognitive), and social functioning [2]. Accordingly, in many clinical populations, reductions in PF are associated with a loss of patient HRQoL and an increase in disease severity and/or decreased survival. For example, in non-small cell lung cancer, PF was shown to be the HRQoL (measured using the EORTC-QLQ-C30 instrument) domain that was most predictive of survival [3]. Similar results have been reported in sarcoma [4] and chronic kidney disease [5] where PF was strongly predictive of HRQoL.

Beyond its influence on HRQoL, PF has also been demonstrated to be indicative of disease progression and poor prognosis. For example, PF status has been informative of declining cognitive function in aging and dementia and a recent meta-analysis determined that poor PF and prognosis were strongly linked among heart failure patients [6]. Increasing impairments in PF are also a central part of the experience of rare disease patients, accumulating over time alongside worsening anxiety, depression, fatigue, and pain symptoms [7]. Consequently, PF is frequently included as an outcome in clinical trials across a wide range of indications.

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Given the important role of PF and its influence on quality of life and disease prognosis, our ability to accurately measure all the components that comprise PF is of great relevance. In this commentary, we critically examine the evolution of our understanding of PF to a present-day holistic concept model. Furthermore, we will identify how novel digital measures can augment existing evidence tools to facilitate a more holistic assessment of an individual's PF.

Holistic Concept Models for PF

How Has Our Conceptual Understanding of PF Developed over Time?

Our conceptual understanding of PF has evolved over the last century. The Person-Environment Fit model [8] is one of the earliest models and has been highly influential for subsequent models. Rather than defining PF based on performance within a series of tasks, this model examines the interaction of an individual with their surroundings and their personal requirements for functioning in that environment. More specifically, the Person-Environment Fit Model posits that an optimal fit between individuals' characteristics (e.g., abilities, skills, values, etc.) and their environment can facilitate behaviors (Lewin 1951). By extension, this model also helps us understand that functional limitations can be seen as a "lack of fit" between a person and their environment. However, in some instances, the lack of fit between a person and their environment may not negatively impact an individual if the resultant behavior is not important to them. The Competence-Press Model [9] builts on this theme to develop the idea that adaptations (i.e., use of a walking aid) are a mediating factor between a person's ability (i.e., competence) and the requirements of their environment (i.e., environmental press). For instance, older adults often make adaptations to their physical environment. Examples of such modifications may include relocating to a single level home or a ground floor apartment to avoid stairs, moving closer to family so that they may assist with care-taking [10]. These types of adaptation within the home environment may occur or expand following a change in health status, which can lead to an improvement in the person-environment fit and overall well-being. Subsequent models [11–14] refined competence to differentiate an individual's capacity (i.e., their absolute PF or ability to perform required tasks) and behaviors (i.e., their routinely performed/expressed level of capacity or self-determined level of PF).

In 2001, the World Health Organization (WHO) formalized a consensus International Classification of Functioning, Disability and Health (ICF) model [15]. The ICF model describes functioning and disability in relation to a health condition and is a complementary framework to the International Classification of Disease (ICD), which is the global system for classifying, monitoring, and reporting diseases. By itself, the ICD provides information on diagnosis and health condition, whereas the ICF provides information related to the functional status. When used together, the ICF and ICD provide a more holistic understanding of the overall health status of an individual and provide insight related to interventions and treatments. While not specifically a PF model, this broad description of health and functioning represented a significant paradigm shift in our thinking as it relates to PF. The ICF framework defines performance capacity as an individual's structural ability to function, which is determined by both their musculoskeletal and nervous system capability. The ICF framework defines behavior as the routine PF performed in an individual's real-world environment and adaptations refer to the compensation and coping strategies an individual utilizes in their real-world environment. Importantly, this framework views disability as a consequence, not purely as a reduction in performance capacity but as a lack of fit with the environment, which can be altered through adaptations.

The Physical Functioning and the Environment Model (PF-E; [16]) places an even heavier emphasis on adaptation and attempts to more completely characterize both habitual indoor (individual level) and outdoor (community level) environments. In this model, adaptation is achieved when the environmental "press" or degree of challenge provided by the environment is matched with an individual's level of competence. Accordingly, this model highlights the importance of the home and neighborhood environment to ensure comfort for individuals with less physical and cognitive capacity [10].

As demonstrated in Table 1, our conceptual understanding of PF has reached, over several decades, a high level of maturity. Additionally, Figure 1 highlights the evolution of our understanding of PF and the key adaptation select models have made to move toward our current understanding of holistic PF. There is good consensus that while the limits of our PF are defined by our bodies, the specific requirements of good PF for each individual can be defined by their environment and their adaptations to that environment. The formal adoption and consideration of adaptation to the environment by the ICF model has shaped all subsequent models and enabled a deeper and more well-rounded understanding of PF.

Accordingly, much work has been done to examine how the specific symptomology and dysfunction

Table 1. Examples of general conceptual models developed for PF and how they compare to the watershed International Classification of Functioning, Disability and Health (ICF) proposed by the WHO in 2001

Model	Therapeutic area	Citation	Performance capacity	Real-world behavior	Environment	Adaptations
Person-Environment Fit Theory	All	[7]	Not explicitly, but the "person" clearly contains this component	Yes, Lewin was the first to articulate behavior as a function of fit between the person and the environment	Yes, the interaction between the person and the environment is central to understanding behavior	To a degree, adaptations due to a lack of fit between the person and the environment could be understood as behavior
Competence-Press Model	Aging	[8]	Yes, as the "competence" component	Not directly, behaviors are considered in terms of adaptation	Yes, the environment provides the "press"	Yes, CPM seeks to explain adaptations in terms of imbalance between press and competence
Exercise and Health Consensus		[10, 16]	Yes, as "health-related fitness"	Yes, as "physical activity"	Yes, as "other attributes" specifically the social and physical environment. Does not differentiate local and community environments, but does include "heredity" specifically	Indirectly, as "other attributes" such as lifestyle behaviors and personal attributes
Functional Capacity Model	All	[11]	Yes, as "functional capacity"	Yes, as "functional performance"	Indirectly, as "functional reserve" and "capacity utilization," i.e., the environment influences how much capacity is required for an individual to perform a given activity	Indirectly, as "functional reserve" and "capacity utilization"
Continuous-Scale Physical Functional Performance Model	Aging	[12]	Yes, as "physiological capacity"	Yes, as "physical performance"	Indirectly, as "psychosocial factors"	Indirectly, as "psychosocial factors"
Functional Performance Framework	All	[13]	Yes, as "physical parameters"	Yes, as "functions"	Indirectly, as "activity goals" in that requirements are to a large degree determined by the environment and that person's interaction with the environment	Not explicitly, though an alteration in "activity goals" could be seen as an adaptation. A change in what is required to achieve a certain goal is not included
The ICF	All	[14]	Yes, as functioning and disability/body functions and structures	Yes, as functioning and disability/ activities and participation	Yes, as contextual factors/ environmental factors	Yes, as contextual factors/personal factors

Table 1 (continued)

Model	Therapeutic area	Citation	Performance capacity	Real-world behavior	Environment	Adaptations
LaMonte and Ainsworth	All	[17]	Indirectly, as "energy expenditure," i.e., the individual cost of a given behavior	Yes, as "physical activity"	Indirectly, as "energy expenditure," i.e., the individual cost of a given behavior	Indirectly, as "energy expenditure," i.e., the individual cost of a given behavior
PF-E	Aging	[15]	Yes, as "individual performance capacity"	Yes, the model seeks to explain behavior (or "physical function performance relevant to the individual")	Yes, PF-E specifically includes a broad definition of "environment" both local/individual and outdoor/community as well as resulting press	Yes, compensation strategies represented in this model are considered "performance qualifiers" within the ICF
Webber, Porter, and Menec	Aging	[18]			Yes, heavy emphasis on environment and determinants "5 fundamental categories of determinants (cognitive, psychosocial, physical, environmental, and financial), with gender, culture, and biography (personal life history) conceptualized as critical cross-cutting influences"	
Brady et al	Aging	[19]	Yes, as "muscle capacity" and "body composition"	No	To a degree, as "contributing factors" like "sleep"	To a degree, as "contributing factors" like "self-efficacy"

associated with specific indications influence PF. This work has resulted in several disease-specific examples of PF models which incorporate symptoms and dysfunction into the overall framework (Table 1). For example, within cancer, patient feedback related to the PF limitations they experienced throughout cancer (treatment and remission) led to the development of the Patient-Reported Outcomes Measurement Information System-Physical Function (PROMIS-PF) metric, which contains unique PF questions specific to cancer [17]. The PROMIS-PF metric aligns with the holistic model by including a series of questions that were previously captured within separate questionnaires (fatigue vs. PF vs. self-care vs. community and social life). Accordingly, PROMIS-PF is considered to be a better assessment of PF and is associated with a greater ability to capture a wide range of PF levels with less error, greater precision, and lower burden [18]. These disease-specific models have helped us identify and articulate how a given patient's journey may involve alterations in PF through changes in capacity or through changing interactions with the patient's environment. For example, an older person living with a physical limitation in the upper extremities may experience alterations in the ability to perform self-care PF like washing their hair. However, this individual may be able to compensate through adaptations like visiting a

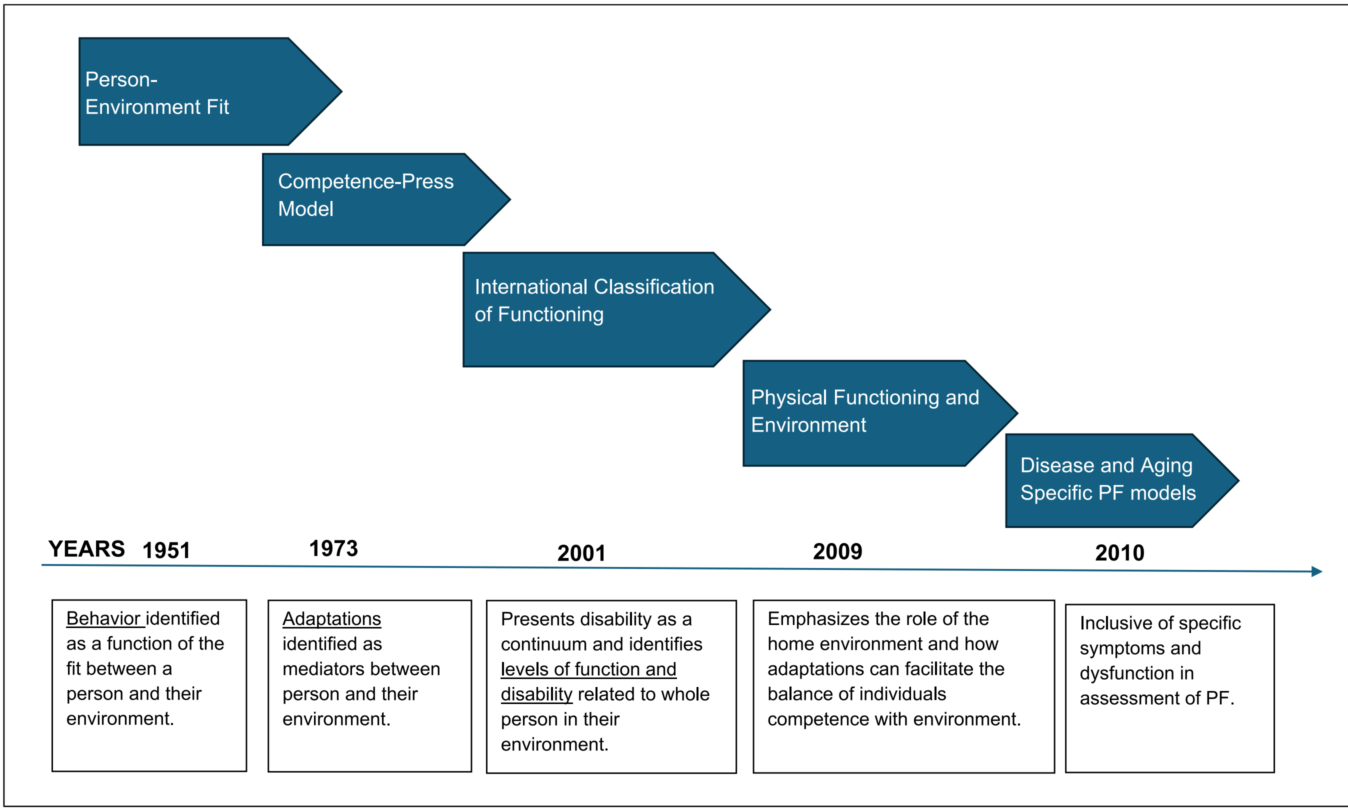

Fig. 1. Evolution of PF. This figure highlights the key contributions and advances some of the different theories and models have made toward our current understanding of holistic PF.

hairdresser or having a carer visit, such that despite their physical limitations, they do not report the degree of PF limitation that one might expect.

The idea of assessing all conceptual aspects of PF is what we would refer to as "holistic" measurement of PF. This holistic approach of conceptualizing PF has relevance for evidence selection in clinical trials. For example, traditionally PF may have been singularly assessed with a 6-min walk test; however, a holistic approach would entail assessing any changes in the environment, patient adaptations in the context of capacity, and behavior. An example of this approach can be seen in Heart Failure, whereby clinicians utilized wrist actigraphy to objectively capture changes in daily activity and sleep quality as markers of quality of life in patients taking part in a clinical trial (NCT02970669).

Failure to adopt a holistic approach to assess PF can result in situations where changes in physical performance are not mirrored by improvements in self-reported PF by patients [19–21]. For example, despite exhibiting an improvement in distance walked in a 6-min walk test, if these improvements were facilitated by the use of a walker or cane that the patient found to be cumbersome and/or felt embarrassed by, the self-report of PF would likely be worsened or unchanged relative to the distance achieved in the 6-min walk test. Similarly, a patient's disease status may progress, but should their environment change to be more accommodating to their functional decline, their self-report of PF may improve [22].

Holistic Measurement of PF

Currently, when we assess PF, we collect evidence related to the different components of PF (performance, behavior, and adaptation) with subjective or objective information from controlled or uncontrolled (real-world) environments, either actively or passively by participants, caregivers, and/or clinicians. These assessment tools have been discussed and summarized in depth elsewhere [23], so we will only briefly recap here.

Subjective instruments like patient-reported outcomes (PROs) and clinician-reported outcomes (ClinROs) help us assess an individual's perception of performance, physical performance, and behavior. Anchored items such as "Are you able to shampoo your hair?" from PROMIS-

PF [24] enable us capture an individual's behavior and performance, while unanchored items such as "Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors, or carrying in groceries?" from the PROMIS-PF [25, 26] helps us gain insight into an individual's perception and behavior as it relates to what an individual thinks they do, what they are confident doing, or what they could do if needed. Patient input is critical to understanding what specific aspects of PF are meaningful to patients [27, 28]. Self-reported or perceived PF is one of the most used clinical outcome assessments and a lot of current research aims to extend and harmonize PROs for PF [25, 26, 29]. Subjective instruments are central to any evidence strategy, yet all existing PROs suffer from ceiling effects [25, 30], and so we also have a range of other tools available to us.

Performance assessments are intended to objectively understand the limits of what a person is capable of. Typically, these assessments are actively performed in a controlled environment (i.e., a laboratory or clinic setting where external context and influence is kept as uniform as possible), and the participant is asked to perform highly standardized actions. Common examples that aim to assess PF include the 6-min walk test (6MWT), Short Physical Performance Battery (SPPB), and Timed-Up-and-Go (TUG) [31–33]. More recently, digital health technologies such as wrist-worn actigraphy and cell phone-based apps are also leading to a new generation of performance tests that can be adapted to be independently undertaken in the real-world by the participant [34–36]. While the performance of these tests in an uncontrolled environment does add an additional degree of variation, the repeated measurements do appear to compensate [37].

Real-world measures utilize sensors to observe participants' actual behavior both objectively and passively in their everyday environment. These measures lend insight into routine behaviors as well as isolated instances and behavioral events, which are relevant to those individuals' daily lived experience [23]. For example, using sensors to longitudinally measure how fast an individual walks can provide insights not only into changes in typical walking speed and daily patterns of walking but also into rarer "best effort" bouts of walking [38, 39]. Such measures can be derived from body-worn sensors but also from other connected technologies including computers [40, 41], smartphones [42], and sensors installed in a participant's home environment [43–45]. Real-world behavior captured through digital measures (body-worn and in-home sensors) augment other forms of evidence by bridging performance assessments and subjective instruments [46, 47]. Recently, the European Medicines Agency fully qualified the use of a digital sensor that measures stride velocity in the patient's home environment for Duchenne muscular dystrophy patients enrolled in clinical trials (qualification opinion on stride velocity 95th centile as a secondary endpoint in Duchenne muscular dystrophy measured by a valid and suitable wearable device (europa.eu). This endpoint approval reflects a shift in the drug development industry, whereby drug developers now have access to tools that can objectively capture if a treatment can improve a patient's real-world PF.

An additional real-world measure is an *ecological momentary assessment (EMA) or ambulatory assessment* which is an emerging type of evidence tool that could be considered a type of subjective input that also provides contextual information. Typically captured via a smartphone, EMAs are usually composed of a small number (1–3) of items that an individual can complete very quickly in their real-world environment. These assessment items focus on "in the moment" information, for example, what level of pain an individual is experiencing right now. While technologically driven, EMAs have been shown to be feasible and valid to provide input on PF for older adults [48]. Bui et al. [49] used EMA in a longitudinal study of 200 stroke patients to not only report behaviors but also understand the context within the real-world environment. In this study, the authors reported that use of an adaptation (e.g., a mobility device) within a stroke patient correlated with a shift in PF from vocational activities to activities of daily living. EMAs can be scheduled or triggered by specific behaviors to gain context related to physical activities and function [50, 51]. It is also possible to trigger EMAs based on location and environment, something which is increasingly well developed as a method in psychology to understand mood [52], but not yet widely used in the assessment of PF.

Contextual information and metadata include demographic and socioeconomic data, medical records, billing information, self-reports, weather reports, and more. These data are critical to the interpretation of other forms of data. For example, most conceptual models of PF show that knowing that a participant lives in a rural environment, has been newly prescribed a walking aid, or lives in an area with heavy snowfall will impact their PF ability and requirements. Increasingly, these data are also being seen as an important form of clinical evidence, despite traditionally being utilized as real-world evidence [53].

Holistic Assessment of PF in Practice

In summary, with the array of tools described in the previous section, we are well placed to gather information relevant to all aspects of an appropriate PF conceptual model. In practice, clinical study protocol development is limited by many constraints, including logistical and budgetary challenges, and practical and ethical considerations around what it is reasonable to ask patients, sites, and other stakeholders to do. This frequently leads to situations where physical performance and subjective PF are measured, but real-world behaviors, environment, and adaptations are not.

Despite these challenging constraints, there are currently a number of endeavors underway to capture a more holistic picture of health and PF. Large scale projects like the UK biobank (www.ukbiobank.ac.uk) contain extensive amounts of data related to environmental, lifestyle, and genetic information from over 500,000 participants. Similarly, in the USA, the NIH supported "All of Us" (All of Us Research Hub (researchallofus.org) research program which aims to create a database from over 1 million participants to inform how factors like genetics, lifestyle, and environment impact different aspects of health. On a smaller scale, understanding how various diseases and their treatments impact PF and overall quality of life can be undertaken utilizing a number of the tools mentioned previously within the framework described in the ICF model of PF [46, 47].

Outlook and a Path Forward

Digital tools provide a specific opportunity to holistically measure PF, whereby they can complement existing tools and provide objective information on an individual's real-world behavior, their environment and adaptations. However, several steps remain before this approach can be more widely implemented. In particular, given the extensive work that has been done to understand patient perspectives on what PF is, we must redouble our efforts to take a patient-centric approach to understanding the "what" and "how" of measuring PF and including digital evidence into clinical trial protocols. There are a large number of different sensor technologies available, each with its own distinct differentiation that makes it either advantageous or disadvantageous for a given population (i.e., sampling frequency, outcome measures, wear location, battery life, etc.). Investigating patient preferences regarding acceptability and form factors will help us select technologies that integrate into the daily lives of patients participating in the trial. Taking a patient-centric approach to study design also means ensuring that the endpoints reflect something that is meaningful to patients [46, 47]. This will then provide a strong foundation to generate evidence that supports conversations with regulators to advance acceptance and qualification of novel, holistic, digital PF outcomes within the proposed context of use [27, 54]. This type of balanced and collaborative approach from all stakeholders will provide a much-needed foundation for patients and caregivers to garner meaning from data and insight into treatment benefits.

Conflict of Interest Statement

There is no conflict of interest for any author.

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