HARVARD UNDERGRADUATE CBE

Emerging Directions for Digital Biomarkers

CBE | Fall 2025

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CBE Team Introduction

The Harvard CBE team represents a diverse range of backgrounds and interests within its members. We are excited to present the key findings of our Life Science Think Tank's research into digital biomarkers over the past semester!

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Executive Summary

Our goal is to provide an overview and structured assessment of the current digital biomarker landscape by examining the underlying biological mechanisms, market adoption, and regulatory and ethical considerations shaping the field.

Case Objectives

Defining the Landscape

- Establish the biological basis, measurement mechanisms, key differentiators, and clinical relevance of digital biomarkers.
- Evaluate use cases across disease diagnosis and monitoring, research settings, and commercial deployment.
- Assess the maturity of the field by analyzing evidence from clinical trials, disease-specific use cases, and market trends.

Evaluating Systems and Constraints

- Examine factors impacting digital biomarker adoption, including validation, regulatory oversight, and reimbursement pathways.
- Identify sources of bias, representation gaps, and data privacy risks that affect digital biomarker performance and patient trust.
- Analyze how governance structures influences scalability, accountability, and long-term adoption of digital biomarkers.

Presentation Overview

Establishing Scientific Foundations

- Define core digital biomarker concepts, mechanisms and signal types.
- Map how digital signals translate to clinical contexts using established biomarker frameworks and current research evidence.

Landscape and Use Case Analysis

- Assess when, where, and how digital biomarkers are used in practice.
- Synthesize findings from disease case studies and company profiles to illustrate real-world deployment patterns.

Pathways to Clinical Adoption

- Trace how digital biomarkers move from validation to clinical application.
- Outline the key regulatory approval and reimbursement touchpoints that influence implementation timelines and feasibility.

Risk Mitigation and Governance Frameworks

- Apply an ethical and governance lens to digital biomarker deployment.
- Identify recurring challenges in consent models, data privacy and usage, and user trust across real-world cases.

Section 1: Foundations of Digital Biomarkers

Section 2: State of the Field

Section 3: From Innovation to Implementation

Section 4: Ethics and Governance

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Foundations of Digital Biomarkers

This section establishes the scientific and clinical foundations of digital biomarkers. It defines key concepts, signal types, and monitoring approaches while linking digital measures to underlying biological mechanisms and clinical relevance.

Biomarkers as Signals of Biology

Biomarkers are objective, measurable indicators of biological processes. They are considered useful when validated, clearly linked to meaningful clinical outcomes, and distinct from symptoms and clinical endpoints.

What are Biomarkers

A biomarker is a characteristic **measured and evaluated** as an **indicator** of normal biology, disease processes, or responses to an intervention. It provides a quantifiable link to clinical outcomes.

Biomarkers are **biological signs, not symptoms**, that can be consistently measured, ranging from molecules (like cholesterol or HbA1c) to imaging features and wearable-derived signal.

Differences Between Digital Health Data & Digital 'Biomarkers'

Digital health spans mobile health (mHealth), health IT, wearable devices, telemedicine, and personalized medicine. These include tools that can **improve diagnosis, treatment, and healthcare delivery**. Digital biomarkers, by contrast, are **specific health indicators** derived from those digital data streams and processed into **defined, validated measures**. Examples of data-generating digital health tools include smartphones, wearables, and home sensors.

NIH (I), NIH (II), NIH (III), U.S FDA

Types of Biomarkers

Biomarkers vs Clinical Endpoints

Biomarkers are objective biological proxies that **may not reflect patient well-being** while clinical endpoints measure how patients feel, function, or survive and are the **better standard** for treatments, **directly capture outcomes** that matter to patients

Classes of Biomarkers

Traditional Biomarkers

- These include measurable indicators of **biological or pathogenic processes**, organized by the BEST framework into **seven clinical-goal types**
- Examples include **cholesterol, blood pressure, body temperature**, and body-mass index as a susceptibility/risk biomarker.

Digital Biomarkers

- These are **physiological/behavioral** measures captured via portable, wearable, implantable, or digestible devices. They are typically **less invasive** and enable **continuous monitoring.**
- Examples include smartphone **finger-tapping/memory tests** for Parkinson's and wearable real-time seizure detectors.

Active and Passive Monitoring of Digital Biomarkers

Healthcare monitoring devices can be categorized as having either active or passive models. While passive models may have more effective health applications, active models pose a less invasive threat to data privacy.

Active Monitoring

- Active monitoring describes the process of tracking health metrics **directly and intentionally**.
- Active monitoring accounts for **most historical health monitoring**, but it may lack the rigorous, consistent tracking required for effective health management.

Purpose	• Active monitoring is not uniformly defined within healthcare. • In the context of digital biomarkers, we will define active biomarkers as tools with which patients interact for the express purpose of **collecting relevant medical data**. • Active monitoring means directly searching for **evidence of a specific disease** or attempting to explain existing symptoms.
Traditional Applications	• Active monitoring is frequently used to **track disease progression** and onset. • Chronic diseases including **cancer, Alzheimer's**, **heart disease and diabetes** can be managed with the aid of active monitoring; periodic memory tests are one example. • The CDC and other public health agencies describe **testing and tracking disease** transmission as a form of active monitoring.

Passive Monitoring

- Passive monitoring describes the process of tracking health metrics continuously with an emphasis on **subtle, minute changes**.
- Passive tracking poses **potential data privacy concerns** because users may be uncomfortable with continuously monitored data.

Purpose	• Passive monitoring is a newer concept in healthcare than active monitoring. • Devices and platforms that passively monitor healthcare **continuously track subtle changes** in health metrics, such as heartrate, over prolonged periods time. • Passive monitoring generally **lacks the user input** characteristic of active monitoring and may be intended to more broadly track health without a specific disease focus.
Traditional Applications	• Passive monitoring has been more applied to chronic diseases that **develop over time**. • For example, wearable diabetes devices allow diabetics to passively **track blood sugar**. • Passive monitoring devices can also be used to make **informed health recommendations** by tracking heart rate, steps, cognition, blood pressure and other health metrics. • Passive monitoring **may be more effective** when used for continuous monitoring.

Emerging Application Areas

1. **Wearable Sweat Monitors**: These devices may soon be used to track health using electrolyte, glucose and hormone data.
2. **Smartphone Data**: Smartphone applications may be soon used to track physical and mental health data.

ACS, AHCJ, Karger, Medium, NHS, NIH

The BEST Glossary of Biomarkers

The Biomarkers, Endpoints, and other Tools (BEST) framework classifies biomarkers by clinical role (risk, diagnosis, monitoring, prognosis, prediction, response, safety), which determines the level of evidence and validation required for use.

Framework

NIH, UConn

Criteria

1 – SUSCEPTIBILITY AND RISK
Indicates the **likelihood** of developing a disease in individuals without clinically apparent diseases and is used for **risk classification** and prevention studies.

2 – DIAGNOSTIC AND PROGNOSTIC
Detects or **confirms** disease presence or subtype to guide treatment decisions. Estimates the likelihood of clinical events like progression in affected patients.

3 – MONITORING AND RESPONSE
Measured over time to assess disease **status, progression, or treatment** response to indicate whether an intervention has produced a biological effect.

4 – SAFETY
Indicates the likelihood, presence, or extent of **toxicity**. Also supports dose adjustment, treatment interruption, or **population-level risk** mitigation.

5 – PREDICTIVE
Indicates whether a patient is likely to benefit from or experience adverse effects from a specific therapy, informing **treatment selection** and **clinical trial design**.

General Mechanisms and Types of Digital Biomarkers

Digital biomarkers convert continuous sensor data into early, real-world indicators of physiological, biological, and neurological health, offering a dynamic view of how the body functions and changes over time.

Physiological & Autonomic Signals

- **Physiological Focus:** Digital biomarkers can track subtle changes in the body such as heart rate, breathing, and temperature
- **Measurement Approach:** Wearable devices measure **heart rate variability (HRV)**, which reflects how well the nervous system balances stress and recovery
  - Low HRV indicates fatigue, poor sleep, disease, or nervous-system imbalances.
  - Sensors also monitor skin temperature and electrodermal activity (sweat response), which can provide insight into **circadian rhythm and emotional stress**.
- **Clinical Significance:** These continuous, real-world signals offer **early warnings** of physiological strain, long before traditional tests detect problems.

Biological Motor & Mobility Signals

- **Biological Focus:** Motor-related digital biomarkers capture how neurological changes affect **movement & coordination**.
  - In **Parkinson's disease**, loss of dopamine-producing neurons leads to tremors, stiffness, and slowed motion.
- **Measurement Approach:** Wearable sensors on the wrist or ankle can measure **gait** speed, stride length, and variability, revealing **early signs** of instability & fall risk.
  - They also detect tremors and bradykinesia (slowness of movement).
- **Clinical Significance:** These patters enable doctors to track disease progression and medication effects continuously rather than only during clinic visits.

Neurological Sleep & Circadian Signals

- **Neurological Focus:** Sleep-based digital biomarkers reveal how brain and body rhythms become disrupted in neurological and metabolic disorders.
- **Measurement Approach:** Actigraphy from wearable devices tracks rest–activity patterns, detecting nighttime movements and sleep disruptions like REM Sleep Behavior Disorder (RBD), which can signal early neurodegeneration
  - At the same time, HRV and heart rate patterns during sleep reflect how well the body's autonomic system powers down at night, providing insights into stress, sleep quality, and nervous system health
- **Clinical Significance:** These digital signs reflect early brain and body dysregulation that clinical tests may miss.

Frontiers , *JCSM* , *NIH (I)*, *NIH (II)*, *NIH (III)* , *NIH (IV)*, *NIH (V)*

Illustrative Examples of Digital Signals and Disease Biology

These examples show how specific digital biomarkers reflect distinct biological mechanisms, linking everyday physiological and behavioral signals to measurable changes in disease and health.

	Biological Mechanism	Clinical Insight
Gait Speed, Stride & Variability	• Loss of **dopaminergic neurons** in the substantia nigra impairs motor control and coordination, leading to **slower and less stable movement patterns.**	• **In Parkinson's disease**, reduced gait speed and increased stride variability indicate motor decline, disease progression, and higher fall risk.
Sleep Fragmentation & Actigraphy	• Neurodegeneration in circadian and **REM-control centers** disrupts melatonin and orexin signaling, altering normal **sleep-wake regulation**.	• In **Alzheimer's disease**, irregular sleep cycles and night-time restlessness reflect neurological dysregulation and disease-related changes in brain rhythms.
Heart Rate Variability (HRV)	• **Reduced parasympathetic activity** and increased sympathetic drive create autonomic imbalance, affecting **cardiovascular and stress regulation.**	• In **chronic stress, depression, and cardiovascular disease**, lower HRV serves as an indicator of impaired nervous system control and poor physiological recovery.
Speech and Voice Features	• Changes in motor planning, vocal cord control, and cognitive processing can alter **speech timing, pitch, and sentence articulation.**	• In **ALS, Parkinson's disease, and depression**, slower speech, reduced pitch variation, or slurred words track disease severity and neurological decline.

AASM, Frontiers, NIH (I), NIH (II), NIH (III)

Evidence from Current Research & Trials

Current digital biomarkers research utilizes cardiac signals and movement data which effectively predict disease like cardiac illness and Parkinson's. However, it needs improvement upon multi-model fusion and non-discriminations.

Important Aspects	How do current research and trials handle these aspects?
Key Research	• **mPower** studies 8,320 Parkinson's patients and has proven that tapping test on a smartphone can **reliably capture Parkinson's signals**. This result was improved by the **Parkinson's DREAM Challenge**, which used crowdsourcing to enhance **predictive performance on the severity** of Parkinson's (best AUROC ≈0.87). • The **Apple Heart Study** utilized data from ~419K Apple Watch users, which showed that **irregular-pulse alerts have a 0.84 positive predictive value** when combined with ECG recordings for atrial fibrillation.
Signals Utilized	• **Cardiac PPG/ECG**, exemplified in Apple Heart, could be very useful for accompanying clinical records. • **Movement** data from **accelerometers** and gyroscopes are key to detect severity of diseases like Parkinson's. • **Speech** data in voice features can report neurologic and psychiatric states but **needs cross-site validation**. • **Key-stroke and typing dynamics** can reflect fine-motor decline and mild cognitive impairment. • **Sleep data** in consumer wearables can estimate total sleep time and identify **sleep disorders**.
Current Deficiencies	• Despite the existence of extensive longitudinal studies, many published digital-biomarker studies remain **small, single-site, short-term observational pilots** rather than long-term, multicenter effectiveness trials. • The problem of selective bias is very common, as flagship cohorts like Apple Heart recruit their own device owners. This ends up **skewing** samples toward **younger, wealthier** participants who have high proficiencies with technologies, hence **lowering the overall representativeness** of the studies among minorities.
Future Directions	• **Multi-modal fusion** (e.g. gait + voice + typing + PPG) consistently outperforms single-signal models in key accuracy benchmarks and validation studies. Meta-reviews find observable trends on the use of multiple biomarkers for **higher accuracy**, enhanced by **machine learning** techniques to incorporate. • Improving on the issues of non-discrimination and data privacy, primarily through **explicit informed consent** in collections of user data when training models, is key to creating **ethical digital biomarkers**.

Karger Publishers, Nature, NPJ (I), NPJ (II), NEJM, PLOS, PMC, PubMed

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State of the Field

This section examines how digital biomarkers are currently used across research, clinical, and commercial contexts. It highlights market trends, disease-specific use cases, and representative company examples to illustrate real-world deployment.

Section 1: Market Landscape

Section 2: Disease Applications

Section 3: Company Case Studies

Market Overview of Digital Biomarkers

The digital biomarkers market is led by large companies including Biofourmis, FitBit and Evidation Health. The market is large and involves academic groups, government agencies, startups, and established pharmaceutical companies.

$3.4B

In 2023, the estimated global digital biomarkers market size was approximately **3.417 billion**, representing recent innovations and interest in technology.

+2.7%

The year-over-year growth rate for the digital biomarkers market reflects **improvements in healthcare technology** and rising overall healthcare expenditures.

$14.0B

The digital biomarkers market is expected to grow significantly over the next 5 years, with **51% growth** from its size in 2023.

Biofourmis	This company has developed a product that integrates wearables, analytics, and digital endpoints for trials and remote monitoring. Biofourmis has announced many major pharmaceutical agreements and is active in the oncology space. Biofourmis' work demonstrates demand for platforms that facilitate the use of digital endpoints.
FitBit/Google Health	Google and FitBit have integrated their products to allow consumers to repurpose wearable devices into digital biotrackers. The continuous collection of data facilitates more accurate health data for users. FitBit's commercialization demonstrates the potential for broad reach of applications of digital biotracking on the mass market.
Evidation Health	Evidation Health analyzes real-world health data from wearables, apps and connected devices to connect everyday behaviors to health outcomes. Evidation Health partners with pharmaceutical companies, public-health organizations and governments to deploy digital biomarkers and bridge the gap between collected data and researchers.
Key Stakeholder Interactions	Academic groups generate candidate digital biomarkers, the NIH funds larger projects, then the data allows the academic groups to apply for FDA approval. Startups and device sellers generate products with money from pharmaceutical companies and provide technology or innovation.

Key Takeaway

Digital biomarkers represent a large and growing segment of the wellness and healthcare markets with established stakeholders and large-scale industry leaders.

Evidation, GrandViewResearch, Google, PR Newswire

Market Evolution of Digital Biomarkers

Biomarkers, particularly those derived from wearables, are driving the digital biomarker market, which is projected to grow nearly ninefold from 2021 to 2028, signaling increasing integration into healthcare and research.

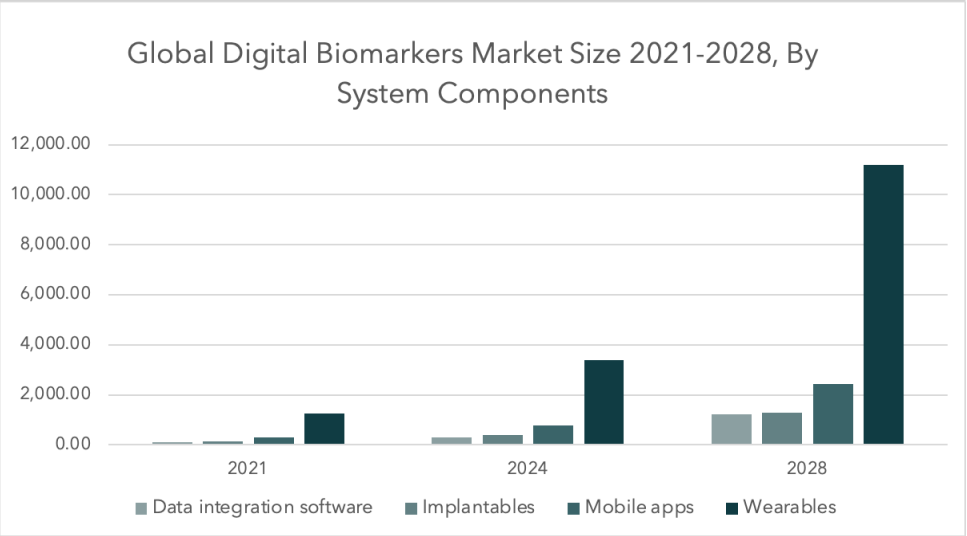
Timeline of Digital Biomarkers

Emerging Field (Pre-2021)

- Digital biomarkers were primarily **research-focused**, limited to pilot studies and academic validation.
- Adoption was slowed by **data integration challenges** and lack of standardized frameworks.
- Most tools remained disease-specific.
- **Investment and scalability were limited** to early-stage biotech and academic projects.

Clinical Integration (2024-2028)

- Digital biomarkers are now moving toward **regulatory validation** and **clinical deployment** with a rapid growth in data analytics and integration platforms supports large-scale adoption.
- **Wearables, mobile apps, and implantables** are being integrated into real-world clinical trials.
- The global market is projected to reach over **$16 billion by 2028**, driven by wearable-based monitoring and AI-powered analysis.



Key Takeaway

Digital biomarkers are transitioning from experimental research tools to validated, data-driven components of modern healthcare. Their rapid market growth, especially in wearables, reflects a shift toward continuous, personalized, biologically grounded patient monitoring.

Statista, Yahoo Finance

Section 1: Market Landscape

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Digital Biomarkers in Huntington's Disease

Huntington's Disease is a fatal neurodegenerative disease that causes the brain to decay over time. Symptoms including motor function, cognitive abilities and psychiatric changes can be tracked using digital biomarkers.

Rationale for Use of Biomarkers

- Huntington's Disease (HD) causes patients to experience **multi-domain changes** in motor, cognitive and psychiatric function. Since these changes occur at a continuous, objectively-measurable rate, constant monitoring using digital biomarkers helps to **detect changes** that occur **between clinical tests**.
- Some examples of tracked signals include gait, **upper limb movement**, speech, finger tapping, balance and **sleep**. Early studies suggest that tracking phone typing speed could also be an effective biomarker.

Comparison to Existing Tools

- The current standard for tracking Huntington's Disease system is the **Unified Huntington's Disease Rating Scale** and tracks motor symptoms, cognitive function, behavioral symptoms and functional capacity, requiring frequent monitoring in clinics.
- Digital biomarkers allow more frequent, consistent monitoring with a **moderate variation** from the gold standard system.
- Digital biomarkers could potentially be more accurate than clinical tests because they **evaluate real-world functioning** and fluctuations that are not present in clinics.

Limitations and Barriers

- Limitations to the use of digital biomarkers to track HD include **patient adherence** to the wearing of devices, hardware/software homogeneity, **data privacy concerns**, and environmental influences on data collection.
- Data collected by digital biomarkers may also be **confounded by external factors** related to contextual events unrelated to HD. For example, stress at work may cause changes to psychiatric data that could be confused with changes in the progression of the disease.

Key Takeaway

Digital biomarkers serve as an appropriate tool to **supplement the existing framework** for tracking the progression of Huntington's Disease over time. While digital biomarkers more continuously track disease evolution, they may provide a less accurate measure of the evolution of the disease due to confounding variables, such as environmental factors.

> "Digital measures offer a promising solution by providing objective and sensitive assessments of a spectrum of impairments in early HD."
> -Dr. Quinn, PubMed

Scheid (2022), Waddell (2021), Quinn (2025), Lipsmeier (2022), Nunes (2024), Andrzejewski (2016)

Digital Biomarkers in Schizophrenia

Schizophrenia is a chronic brain disorder than progressively causes disordered thinking and hallucinations. Symptoms including changes to sleep, cognitive decline, and social withdrawal can be tracked using digital biomarkers.

Rationale for Use of Biomarkers

- Schizophrenia causes patients to experience **multi-domain changes** in sleep, cognitive ability and social withdrawal. Since these changes occur at a continuous, objectively-measurable rate, constant monitoring using digital biomarkers helps to **detect changes** that occur **between clinical tests**.
- Some examples of tracked signals include **sleep quality**, facial expressions, **iPhone usage**, and speech quality. For example, a decrease in outgoing calls and texts can indicate an increase in symptoms.

Comparison to Existing Tools

- The current standard for tracking schizophrenia involves **clinical tests and subjective monitoring systems** that require evaluation by a professional psychiatrist.
- Wearables and smartphone tracking provides a potentially more **objective measure** of the progression of schizophrenic tendencies. For example, tracking facial expressions using objective, consistent standards may be more accurate.
- Digital biomarkers allow more frequent, consistent monitoring with a **moderate variation** from the gold standard system.

Limitations and Barriers

- Limitations to the use of digital biomarkers to track schizophrenia include **patient adherence** to the wearing of devices, hardware/software homogeneity, **data privacy concerns**, and environmental influences on data collection.
- Data collected by digital biomarkers may also be **confounded by external factors** related to contextual events unrelated to schizophrenia. For example, stress at work may cause changes to psychiatric data that could be confused with changes in the progression of the disease.

Key Takeaway

Digital biomarkers serve as an appropriate tool to **supplement the existing framework** for tracking the progression of schizophrenia over time. Schizophrenia tends to be a highly subjective and biased diagnosis, so the use of objective standards to track the development of the disease provides a potential solution to a lack of transparent medical standards.

> There are currently no objective biomarkers that allow the quantification of negative symptoms of schizophrenia.
> -Qing Zhao, PubMed

Yang 2025, *Abbas 2022*, *Zhao 2022*, *Wigman 2025*

Digital Biomarkers in Parkinson's Disease

Continuous, objective monitoring of motor fluctuations is the key focus on current biomarkers. Along with other data sources like sleep and acoustic measurements, diverse, continuous biomarkers is a new trend in Parkinson's detection.

Motor Detection and Quantification

- Parkinson's disease (PD) is **uniquely amenable to digital biomarkers**, as its symptoms (e.g. tremor, bradykinesia, rigidity) can be **quantified in kinematic** changes. Such data are **easily detectable by inertial sensors** and motors on wearable devices.
- The critical focus is on mitigating **over-reliance on episodic, subjective assessments** like the MDS-UPDRS. Such metrics may fail to capture fluctuation in a patient's daily life when PD is manifested, which happens on a **continuous, longitudinal level**.
- In particular, metrics for resting tremor demonstrate **high technical maturity**, with a high **r=0.97** ($p < 0.001$) between **accelerometer data** and the UPDRS tremor score. However, difficulty arises for **quantifying slowed movement with r=0.67**.
- This may be solved by **deep learning models (DeepFoG)** using Inertial Measurement Unit (IMU) data, which achieved high specificity (90%) in Freezing of Gait (FoG) detection, demonstrating **potential for fall-risk mitigation** for PD patients.

Early Detection through Other Data

- The detection of PD extends beyond motors, focusing on the **prodromal phase** through utilizing non-motor digital biomarkers. Specifically, **multimodal assessment** can capture the full spectrum of the disease, enabling early detection.
- **Hypokinetic dysarthria** (affects 90% of Parkinson's patients) can be monitored through combining **acoustic measurements**. Using data like Harmonic-to-Noise Ratio (HNR), jitter, and shimmer, a **70~90% accuracy** can be achieved for early detection.
- **Eye movement** can also identify PD, making distinctions that sets PD apart from other healthy conditions. A **high sensitivity** of **0.93** and specificity of **0.86** is achieved with **eye movement analysis**, based on data like anti-saccade error rate.
- Combining detection based on **sleep disturbances**, which often manifested in PD patients before clinical diagnosis, can achieve sensitivities up to 0.86 and specificities up to 0.83 based on nocturnal respiratory signal analysis.

Notable Progress and Hurdles

- Notable current projects include the **Movement Monitor for Parkinson's Disease (MM4PD)**. It utilizes **Apple Watch** inertial sensors as indicators of motor fluctuation, which successfully identifies on/off patterns in 94% of the case identified.
- Similarly, the **FDA-cleared Parkinson's KinetiGraph (PKG)** tracks unperceived bradykinesia/dyskinesia, which identifies kinetic patterns based on the ignored movement disorder symptoms through a **6–10 days monitoring process**.
- The primary barrier to adopt these successes into clinical treatment is a **relative lack of key standardized algorithms**, with very limited consensus on data-processing methods across a range of highly fragmented hardware that are not open-source.
- Furthermore, **patient adherence** remains a significant obstacle in long-term remote implementations. Data suggests that PD cohorts' adherence rates **over six months** can drop by significant amounts from **34% to 53%**, significantly lowering efficacy.

Advanced Clinical Chemistry, *BMC Medical Information Decision Deck*, *Frontiers*, *Nature*, *New England Journal of Medicine*

Digital Biomarkers in Respiratory Diseases

Audio-based digital biomarkers, primarily cough and breathing sounds analyzed by AI, demonstrate high diagnostic accuracy for respiratory diseases, but methodological and application gaps remain to be bridged.

Acoustic Signals and Detection Efficacy

- The monitoring of respiratory diseases (**Asthma** and Chronic Obstructive Pulmonary Disease, **COPD**) is transitioning from episodic, **clinic-based Pulmonary Function Tests (PFTs)** toward continuous, acoustic monitoring.
- The key focus for COPD detection is through **analysis of acoustic signals**, primarily through identifying pathological respiratory sounds (wheezes, persistent coughs) or variations in breathing patterns preceding **acute exacerbations (AEs)**.
- Automated detection is **reliant on Machine Learning (ML)**, particularly **Artificial Neural Networks (ANN)**. Such technologies are used to enhance efficiencies through the isolation of abnormal respiratory signals from noise in home settings.
- The detection efficacy can also be improved through the close integration of a **digital Peak Expiratory Flow (PEF)** meter in the wearables, which improves monitoring adherence in patients through correlating digital measures with PFT metrics.

Highly-accurate Early Predictions

- Acoustic biomarkers consistently achieve high performance metrics, shifting focus from reactive management of respiratory symptoms toward proactive **early-interventions and prevention** well before clinical diagnosis based on symptoms.
- In Asthma diagnosis, **80% of researchers** reported **high sensitivities** (80–96%) and specificities (83–100%). When scholars **predict asthma exacerbations** through combining cough sounds with clinical features, they achieved a notable **AUC of 0.93**.
- The predictive power is even stronger in COPD. Through the use of **AI-driven predictions** based on **Acute Exacerbations of COPD, very high sensitivities** (83~100%) and specificities from 74% to 91% were discovered for patients in early stages.
- Such high predictions both in asthma and COPD studies can enable **high economic savings** projected in the billions. This effectively mitigates the burden of acute developments, which is critical for situations of limited availability of resources.

Key Barriers and Further Directions

- Despite promising accuracy, widespread clinical adoption is constrained by key barriers like problems in patient selections. Furthermore, the **applicability of current data and analysis** to real scenarios remains a critical question in practice.
- A quality assessment (QUADAS-2) indicated that **80%** of foundational studies has potential problems with **patient selections**, in particular bias and limited variations in age groups. **43%** of surveyed studies also have **questionable reference standards**.
- Critically, a key question exists in the applicability of **clinical findings to real-world cases**, as only a very small fraction (8 out of 81 studies) are based on **audio data in real-world settings**. This indicates the need for a transition towards in-site studies.
- Notable ongoing activities addressing these problems include the DIGIPREDICT prospective study (using smart devices and cough monitoring to develop an AI asthma risk prediction model) and the AeviceMD pilot (remote wheeze detection).

BMJ Innovations, *BMJ Open Respiratory Research*, *European Respiratory Journal*, *European Respiratory Review*

Digital Biomarkers in Amyotrophic Lateral Sclerosis (ALS)

Digital biomarkers provide objective, continuous measures of ALS progression that complement traditional clinical assessments, enabling earlier detection and more precise monitoring of functional decline.

Overview

- ALS is a neurodegenerative disorder characterized by progressive **loss of motor, respiratory, and bulbar** (speech) functions.
- While these factors are constantly changing, they can be measurable through digital tools.
- Traditional clinical scales like the ALS Functional Rating Scale–Revised (ALSFRS-R) are limited due to **subjectivity and infrequent assessments**, while remote digital monitoring enables more in-depth and **more frequent tracking** of disease progression in natural environments.

ALS patients in **46 states** are unable to access Medigap plans, leaving many reliant on private Medicare Advantage programs that often restrict provider networks and **limit essential services.**

Core Digital Biomarkers for ALS	Upper-limb activity data collected through **wearables or smartphones** can detect motor decline **over 20 weeks**. Combining movement data with **gait, speech, respiration, and cognitive** measures offers a more comprehensive progression assessment. Additionally, mobility patterns via sensors can assist with early detection.
Correlation with "Gold Standards"	Digital measures like **movement tracking and speech** features show a clear relationship with the ALSFRS-R, the clinical gold standard for measuring ALS severity. When a patient's ALSFRS-R score declines, these digital markers also show corresponding declines, indicating that they accurately reflect functional loss
Barriers and Limitations	Variability in devices and data quality can affect **standardization and comparability** across studies. Patient adherence declines in later stages due to **fatigue, dysarthria**, or ventilator use. Ethically, **privacy concerns** emerge with video and voice data collection.. Healthcare access and insurance plans also constrains digital integration.
Current Studies and Future Outlook	**Target ALS × Modality.AI** is conducting a large, home-based study measuring speech, motor, and respiratory function. **EverythingALS** is conducting patient-led digital studies, while Johns Hopkins' **CortiCom** trial explores brain–computer interfaces (BCIs) to restore communication for patients with advanced paralysis.

Key Takeaway

Digital biomarkers in ALS, such as movement, speech, and respiratory measures, closely mirror ALSFRS-R scores and detect changes earlier than clinic visits. While device variability and access barriers remain challenges, large ongoing studies are advancing these tools toward clinical use.

Hopkins Medicine, *Lancet*, *NIH (I)*, *NIH (II)*, *NIH (III)*, *NIH (IV)*

Digital Biomarkers in Major Depressive Disorder (MDD)

Digital biomarkers capture subtle, real-time behavioral and physiological changes in major depressive disorder (MDD), enhancing the sensitivity, objectivity, and continuity of traditional symptom-based assessments and tests.

Overview

- MDD is characterized by **fluctuations in mood, energy, sleep, and cognition**, making it highly suitable for continuous digital monitoring.
- Traditional assessments such as the **Patient Health Questionnaire** (PHQ-9) provide only a few details, while wearable and smartphone-based technologies enable the capture of subtle, real-time behavioral and physiological changes that reflect underlying **symptom variation** in daily life.

An estimated **21 million adults** in the United States had at least one major depressive episode. This number represented **8.3%** of the total of U.S. adults.

Core Digital Biomarkers for MDD	**Step count, heart rate variability, and sleep** regularity from wearable devices indicates about **80%** accuracy in identifying high-risk depressive states. Voice features tone and pitch correlate with symptom severity, while smartphone data on mobility, social activity, and typing patterns offer additional noninvasive measures.
Correlation with "Gold Standards"	Digital biomarkers for depression have demonstrated **moderate-to-strong correlations** with established clinical scales. Voice- and wearable-derived features align closely with PHQ-9 and clinician-rated depression scores, validating their potential as adjunctive tools in clinical monitoring.
Barriers and Limitations	Variations in data processing and validation methods **limit reproducibility.** Small, homogeneous study populations **reduce generalizability**, while privacy and consent remain key ethical concerns for continuous monitoring. Future studies should focus on standardized methods and **diverse** cohorts to ensure reliability.
Current Studies and Future Outlook	The **Kintsugi Voice Device** is being clinically validated against structured diagnostic interviews (SCID-5), while **Ellipsis Health** has integrated vocal biomarkers into health systems for large-scale testing. These efforts reflect a shift from early research based on tools like the PHQ-9 toward clinically validated voice biomarkers.

Key Takeaway

Digital biomarkers for MDD such as wearable, voice, and smartphone-based measures show strong alignment with clinical scales and can detect changes earlier and more objectively than self-report tools. These technologies are paving the way toward clinical-grade, real-world applications for depression monitoring.

EllipsisHealth, *Frontiers*, *NIH (I)*, *NIH (II)*, *NIH (III)*

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Section 3: Company Case Studies

Case Study: Indivi

Indivi represents an example of commercial applications for digital biomarker applications as a professional-grade tool for pharmaceutical and academic research. These technologies could eventually be expanded to offer to consumers.

Indivi

- Indivi is developing smartphone-based digital biomarkers to remotely assess neurological function for patients with Multiple Sclerosis, Parkinson's Disease, Alzheimer's, and other dementias.
- The company is currently in a growth phase as it develops its technologies and looks to partner with major pharmaceutical companies.

Major Progress and Achievements

- ISO 13485 and ISO 27001 certified medical tech company, demonstrating compliance with international standards.
- Strategic partnerships with well-established companies like Biogen.
- Proof-of-concept Alzheimer's trial planned for 2026, making a key milestone for Indivi.

Goals and Origins	Founded in the early 2010s, Indivi is a Switzerland-based biotechnologies company focused on neurological disorders. An active growth company, Indivi is in the process of developing a dreaMS and Konectom application and has primary focused on research and development. The app has the potential for future commercial applications in partnership with pharmaceutical companies.
Core Product and Customers	Indivi's application uses inputs from smartphone and smartwatch sensors with artificial intelligence analysis and was originally designed for use in clinical trials (long-term monitoring and functional assessment). The primary customers for its commercial applications include pharmaceutical companies, contract research organizations, and academic research centers.
Stage and Business Model	Indivi holds ISO 13485 and ISO 27001 medical device and information security certifications. With these certifications, Indivi has used its digital biomarker platform in real clinical studies, including handling Konectom in a Phase 2b trial for Parkinson's research. Indivi has positioned themselves as a clinical-grade research tool, rather than a app designed for commercial customers.
Reception	Indivi has received peer-reviewed evidence in favor of the effectiveness of dreaMS (for multiple sclerosis). Partnership with major pharmaceutical companies also shows a degree of positive attention from the industry. As Indivi grows, it may draw broader attention from these companies and media sources, but the company has not yet faced any notable controversy.

Key Takeaway

Indvidi is emerging as a pharmaceutical-focused digital biomarker application company that is using smartphone applications to generate medical-grade neurological assessments, positioning itself as a product for drug development.

Indivi, *BusinessWire*

Case Study: AliveCor

AliveCor offers FDA-cleared, smart-phone based ECG devices pioneered with native AI integration, bridging clinical cardiology and consumer well-being. It enables access to monitoring of heart rhythm and defections of arrhythmias.

ALIVECOR®

- AliveCor specializes in **ECG biomarkers**. Its flagship product, **KardiaMobile**, uses AI for remote heart rhythm monitoring.
- The series includes the six-lead KardiaMobile **6L** and the pocket-sized Kardia **12L**. They pair with the **Kardia app** for instant rhythm analysis and connect to the **KardiaPro portal for clinicians**.
- Kardia app's AI **flags ECGs** when they have possibilities of **Afib, bradycardia**, and other abnormalities. More advanced detection is available through a **KardiaCare subscription**.
- For Kardia, AliveCor has a **hybrid commercial model**, selling to **retailers like CVS and Amazon** while partnering with **health providers and clinics** for high-end subscription models.

Key Takeaway

AliveCor shows promising progress in having well-integrated digital biomarker systems. However, its future success depends on intense competition from Apple and further clinical validation.

Product Design and Evidence of Success

- AliveCor's product sequence is **progressive**, from KardiaMobile for basic checks with a single lead, the **6L for QTc** measurement with five electrodes, to the new **12L** to reconstruct a full **12-lead ECG**.
- AliveCor's results are validated by multiple studies. A UK trial showed Karida could **double AF detection rates** with hardly any false negatives, leading to a recommendation by the UK's NICE.

Business Model and Customer Base

- AliveCor takes a **multi-channel strategy**. Not only does it sell directly to customers, but it also offers subscription services for clinics. KardiaPro's platform integrates seamlessly with **clinics' EHR systems like Epic.**
- The revenues of AliveCor mainly come from **device sales** (e.g., $79 for a single-lead) and KardiaCare **subscriptions** (~$99/year/patient). Its newly-approved 12L ECG analysis indicates strong subscription growth.

Funding and Market-related Risks

- AliveCor has secured investments for over **$154M from Mayo Clinic, Omron, and GE**. For instance, a 2022 partnership with GE enables **integration of KardiaMobile 6L into GE's MUSE** cardiac management.
- In the market, despite some clinical studies showing high AF sensitivity, **others indicate risks of false positives**. The **competitive pressure from Apple** in ECG monitors is also high on the **B2C** side of the market.

Legal Risks

- AliveCor **sued Apple** for **monopolistic behaviors and IP infringement** after Apple Watch gained native ECG capabilities.
- The UC ITC ruled **in favor of AliveCor** in December 2022, resulting in a limited **import ban** for ECG-enabled Apple Watches, **displaying temporary success** in the law suit.
- However, the USPTO's Board then **invalidated AliveCor's patents**, while only keeping the import ban for limited products.
- In February 2024, a federal court **dismissed AliveCor's antitrust lawsuit** against Apple, further mitigating its import ban, which signals weaknesses in AliveCor's competition with Apple.

AAFP, Alivecor, Cleveland Clinic, FDA, NICE, Kardia (I), Kardia (II)

Case Study: Koneksa Health

By combining wearable sensors, mobile health tools, and AI-driven analytics, Koneksa Health enables continuous, real-world monitoring that transforms how clinical trials measure disease progression and treatment efficacy.

Company Overview

- Koneksa Health was founded in 2015 and is headquartered in New York, USA.
- It was founded by Chris Benko, a former Merck executive, with the mission to **accelerate clinical research** by using validated digital biomarkers derived from **real-world patient data.**
- Koneksa is a startup built around digital biomarker technology, then expanded into a healthcare company in later years and more clinical research.

50+ programs

These clinical programs are supported using digital biomarkers, spanning neurology, oncology, respiratory, cardiovascular, and other therapeutic areas.

20 publications

Koneksa Health has generated 20 peer-reviewed publications, demonstrating the scientific and clinical value of continuous, real-world data.

Core Products Overview	Koneksa Health integrates wearable **biomarker sensors** and **smartphone applications** to consistently gather physiological and behavioral data. Through AI-driven analytics and machine learning, they transforms data into validated digital endpoints to measure health results, spanning fields of **neurology, respiratory medicine, and oncology**.
Regulatory Status	Koneksa is commercially active and supports **Phase I–IV** clinical trials using its validated digital biomarkers across multiple therapeutic areas. Its technology aligns with **FDA-aligned validation standards,** ensuring that digital endpoints meet requirements for regulatory acceptance and **scientific reproducibility** needed to strengthen results.
Business Model	Koneska's operates a **business-to-business (B2B) model**, providing its digital biomarker analytics platform to pharmaceutical companies, biotechnology firms, and research institutions. Its revenue is primarily generated through **software-as-a-service (SaaS)** licensing and also **data-analytics consulting** for remote clinical trials.
Applications & Impact	Koneksa's technology is used in neurological and psychiatric research, including studies on **Parkinson's disease, sleep disorders, and depression**. Its validated digital biomarkers enable continuous at-home monitoring, capturing real-world data beyond traditional clinic visits, **reducing patient burden and improving retention**.

Key Takeaway

Koneksa Health is enabling a paradigm shift in clinical trials by using validated digital biomarkers and remote monitoring to deliver high-quality, real-world patient data outside of traditional clinic settings.

CrunchBase, Koneksa Health

Case Study: Koneksa Health (Cont.)

Supported by leading pharmaceutical investors and global research collaborations, Koneksa Health is scaling its digital biomarker platform to advance regulatory trust, scientific precision, and the future of AI-enabled drug development.

Funding & Partnerships	• Koneksa Health raised $45 million in Series C funding in 2022, bringing total investment to approximately $65–70 million. They had notable investors include **Takeda Ventures, McKesson Ventures, Merck GHI Fund, and Novartis dRx Capital**, underscoring strong support from leading life-science and digital-health backers. • In addition to financial support, Koneksa collaborates with **Roche, Takeda, and Regeneron** to integrate its validated biomarkers into ongoing Phase I–IV clinical trials, expanding the use of remote, data-driven endpoints across therapeutic areas and diverse patient and clinical populations.
Market Position & Reception	• Koneksa Health is widely recognized as a leader in decentralized and digital clinical trials, studies that use remote methods. They have been acknowledged and praised for their **scientific rigor, regulatory collaboration, and data quality**, while also facing challenges such as **data privacy, validation standardization, and market competition** with other digital biomarker companies and startups. • Several of Koneksa's biomarkers have demonstrated equal or superior accuracy compared to traditional clinical measures, reinforcing its **credibility** in the research community.
Key Takeaways & Outlook	• Koneksa Health exemplifies how digital biomarkers are redefining modern clinical research by enabling **continuous, patient-centric data collection** outside traditional medical settings. • With strong venture-capital support, an expanding validated biomarker pipeline, and strategic pharma partnerships, they are positioned to become a cornerstone in the **future of AI-driven, evidence-based drug development.**

Fierce Biotech, *Koneksa Health*, *Tracxn*

Case Study: Winterlight Labs

Winterlight Labs is transforming cognitive assessment by using speech-based digital biomarkers to enable remote, sensitive, and scalable monitoring for clinical trials, aging research, and neurological disease detection

550+

The platform analyzes more than **550 linguistic and acoustic speech features,** allowing it to capture subtle cognitive and linguistic changes that traditional assessments may overlook.

12+

Winterlight's technology has been deployed in over a **dozen** clinical studies across **Alzheimer's disease, dementia**, and psychiatric conditions.

5 of 10

Winterlight is trusted by **5 of the top 10 global life-science companies** for cognitive-endpoint measurement, reflecting its **credibility**.

Validation	Winterlight's speech-based assessments have been used in clinical studies to improve the consistency of cognitive testing, offering fast and low-burden evaluation for aging and dementia populations. Their collaboration with **Alector** showed that speech biomarkers can sensitively **track cognitive changes** in real-world research settings
Technology	The Winterlight platform analyzes hundreds of linguistic and acoustic features including **articulation, pausing, and pitch changes** to detect subtle cognitive shifts. Using **machine learning** and natural-language processing, it is able to link these speech patterns to clinical indicators of memory, cognition, and processing speed.
Products	Winterlight provides a **tablet-based cognitive assessment tool** that generates objective results from a brief speech sample. The platform is used in clinical trials, senior-care settings, and early-screening programs to monitor cognitive change quickly and **remotely, reducing patient burden** while offering more sensitive insights.
Partnerships	Winterlight works with major **pharmaceutical sponsors**, including five of the world's top ten life-science companies, to support sensitive and scalable cognitive-endpoint measurement. Its 2023 acquisition by **Cambridge Cognition** expanded its global reach and positioned the company as a **key provider** of speech and voice biomarkers.

Key Takeaway

Winterlight Labs strengthens cognitive research by providing reliable, speech-based biomarkers that help detect meaningful changes earlier and more objectively than traditional assessments.

Cambridge Cognition, NIH, PR NewsWire ,Winterlightlabs

Section 1: Foundations of Digital Biomarkers

Section 2: State of the Field

Section 3: From Innovation to Implementation

Section 4: Ethics and Governance

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From Innovation to Implementation

This section explores how digital biomarkers move from research into clinical practice. It examines validation standards, regulatory pathways, and reimbursement structures, as well as practical barriers that affect real-world integration and scale.

Section 1: Scientific Validation

Section 2: Regulatory and Payment Pathways

Impact and Application of Digital Health Frameworks

These frameworks collectively strengthen digital biomarker research by improving study quality, enhancing data interoperability, and promoting equitable, reproducible validation across healthcare and research settings.

	Key Impact	Application
CONSORT-AI & SPIRIT-AI	• These are reporting frameworks that set global standards for how **AI clinical trials** are **planned and published**. They have improved research **credibility** by requiring complete documentation of algorithms, datasets, and human oversight, reducing bias.	• Researchers apply these checklists when designing or publishing AI-driven clinical studies. They are now **mandatory** for submissions to major medical journals, ensuring that results can be **accurately reviewed and replicated.**
FAIR Data Principles	• The FAIR Principles (Findable, Accessible, Interoperable, Reusable) define how scientific data should be **managed and shared**, making biomedical research more **open** and **efficient** by allowing data from different institutions to be reused and compared.	• Research institutions like the NIH and NIAID follow **FAIR standards** in their datasets. This allows scientists to build on existing datasets, **validate** findings across populations, and **reduce redundancy** in digital biomarker studies.
FDA Health Guidance	• The FDA's Digital Health Guidance is a regulatory standard that defines how digital tools can be **safely** used to collect health data. It has made digital biomarkers **more reliable** by setting clear expectations for **validation, accuracy, and diversity** in clinical studies	• Technology companies and clinical researchers use this guidance when developing or testing digital health technologies. It helps ensure that their tools **meet FDA standards** for **quality**, participant **safety**, and **equitable data** collection.

FDA, JBiomed, NIH (I), NIH (II), NIH (III)

Frameworks for Reproducible Digital Biomarkers

Emerging frameworks such as CONSORT-AI, FAIR, and FDA guidance are shaping how digital health tools are validated, helping standardize evaluation practices and promote transparency, fairness, and reproducibility across research.

Validation Frameworks

- Global standards that ensure **transparency**, **fairness,** and **reproducibility** in digital biomarker validation.
- These frameworks combine principles from **clinical reporting**, data management, regulatory oversight, and **open data exchange** to promote biomarkers.
- This approach enables trustworthy, generalizable, and ethically grounded digital health innovations

"**94%** Wearable users are willing to share device data with their doctor to improve care."

-Powers Health

Core Structure & Purpose	**CONSORT-AI & SPIRIT-AI**: Set clear requirements for AI clinical trial reporting and protocols, promoting reproducibility and bias reduction. **FAIR Principles:** Establish data management rules (Findable, Accessible, Interoperable, Reusable) to promote openness and reusability.
Primary Stakeholders	Regulators like the U.S. Food and Drug Administration (**FDA**) and European Medicines Agency (**EMA**) apply these frameworks to **access evidence quality**. Researchers & clinicians tend to follow **CONSORT-AI and FAIR** for transparent design and reporting while tech & startups use **Open mHealth** schemas for data interoperability.
Global Influence & Addition	These frameworks are used by initiatives like **NIH Bridge2AI**, which develops diverse AI-ready datasets, and the Digital Medicine Society (DiMe), which promotes best practices for ethical digital health. Companies such as **Verily and Evidation Health** use them to validate wearable biomarkers, while the FDA applies similar principle.
Recent News and Trials	From 2023 to 2025, the **FDA formalized validation standards** for digital health technologies, the NIH Bridge2AI program applied FAIR data principles to expand diverse AI-ready datasets, and CONSORT-AI updated its guidelines to **enhance transparency in AI-driven clinical trials.**

Key Takeaway

Together, these frameworks set the foundation for trustworthy and inclusive digital health innovation, ensuring new technologies are tested, validated, and shared responsibly.

Bridge2AI, DiMe, Evidation Health, FDA, NIH (I), NIH (II), Powerhealth, Verily

Gaps and Challenges in Implementing Frameworks

Despite significant progress in reproducibility and transparency, these frameworks continue to face practical, structural, and ethical barriers that limit their consistent adoption and global impact across research and regulatory settings.

Uneven Implementation

- Although frameworks like CONSORT-AI and FAIR are well established, their **adoption varies widely.**
- Many smaller institutions and startups **lack the resources,** technical staff, or infrastructure needed to fully meet these standards, which results in inconsistent reporting and validation quality
- Even when adopted, frameworks are often applied **selectively or inconsistently**, reducing comparability across studies.

Limited Global Standardization

- Different countries and regulatory bodies apply their own digital health validation policies, creating a **fragmented ecosystem.**
- Without a unified international framework, it remains **difficult to share data**, compare study results, or scale digital biomarker validation globally.
- Misaligned regulatory requirements increase **costs and timelines** for multinational digital biomarker studies.

Data Bias & Representation

- Even with fairness-oriented initiatives like FAIR and the FDA's guidance, many datasets still **fail to represent diverse populations**.
- Biases related to race, gender, geography, and socioeconomic status **limit** how **generalizable and equitable** digital biomarker tools can be.
- Underrepresentation during data collection can lead to **systematic performance gaps** when tools are deployed in real-world settings.

Cambridge Journals, *NIH (I)*, *NIH (II)*

Section 1: Scientific Validation

Section 2: Regulatory and Payment Pathways

Regulations for Digital Biomarkers

Current digital biomarker regulations are relatively more conservative in the EU, while the U.S. and other countries are streamlining approval processes to enhance innovation, with oversight challenges in auditing and notified bodies.

Important Aspects	How do current research and trials handle these aspects?
FDA Regulations	• The FDA regulates digital biomarkers as **Software as a Medical Device** (SaMD). For market entries in SaMD, a typical procedure is the **510(k) pathway**. Its average decision-making time is around **112 to 124 days**. • FDA's requirements for SaMD includes three parts: **verification, analytical validation, and clinical validation**. Additionally, the newly released 2024 **Predetermined Change Control Plan** (PCCP) guidance enables **post-authorization updates** to developed products, i**ncreasing efficiency** in validation processes.
Non-U.S. Regulations	• Under the EU **Medical Device Regulation** (MDR), **Rule 11** upclasses most SaMD to a **higher risk class**. This is now complemented by the **EU AI Act**, which is **highly cautious** of medical AI, classifying it as high risk. • In other countries, the **UK's MHRA** is experimenting with new tests for AI-based medical devices using the **AI Airlock sandbox**. Most other major regulators, like **Health Canada and Singapore's HSA**, generally align with the **International Medical Device Regulators Forum** (IMDRF) principles for treating digital biomarkers.
Innovations with AI	• Mandatory measures such as **FDORA Section 524B** are essential for mitigating cybersecurity threats in AI development. Other boundaries like **Singapore's HSA** allows more room in **streamlined SaMD updates**. • Faster patient access is enabled by expedited pathways like the **Breakthrough Devices Program and TAP**. Instead of limiting companies to collect extensive pre-market data, these regulations **took post-market evidence as a substitute**, thereby **enabling faster processing under DHT trial guidance and regulations**.
Oversight Challenges	• A primary operational challenge facing digital biomarkers in the EU is the capacity of **Notified Bodies**, which delays market access. This indicates **concerns about hallucinations and data bias** for robust monitoring. • Most companies are also facing substantial audit burdens, primarily due to data integrity in **21 CFR Part 11**. Significant **gaps for the dataset's representativeness** still exists, despite close alignment between the **U.S. Quality Management System Regulation (QMSR) and ISO 13485** which mitigates this gaps.

Aiin, European Commission, EFPIA, FDA (I), FDA (II), FDA (III), FDA (IV), FDA (V), Gov.uk (I), Gov.uk (II), HSA, IMDRF (I), IMDRF (II), TGA, WHO (I), WHO (II)

Payer Models for Digital Biomarkers

Existing payer models for healthcare can easily be generalized to digital biomarkers. Securing FDA approval and identifying appropriate pathways based on the type of data is essential.

Overview

Existing Frameworks

- Reimbursement for digital health and occurs primarily through Centers for Medicare and Medicaid Services (CMS) frameworks.
- These provide CPT codes for collecting or interpreting data from devices.

Adoption Strategies for Digital Biomarkers

- Digital biomarkers should seek FDA approval as medical devices.
- Integrating digital biomarker data into clinical workflows is essential to the incorporation of digital biomarkers into the existing payer framework.

Current Data Sets and Biomarker Application

CMS Remote Physiologic Monitoring

- RPM is a payer model for measurable and quantifiable data (e.g. heart rate, blood pressure, blood glucose, weight).
- RPM has a strong alignment with physiological digital biomarkers, such as heart rate variability and glucose trends.

CMS Remote Therapeutic Monitoring

- RTM covers non-physiologic, therapeutic adherence, and response data that can be self-reported or collected via software.
- RTM must collect data from a medical device, which includes software, so it closely aligns with digital biomarkers.

CMS Remote Patient Monitoring

- Remote patient monitoring refers to data collected generally outside of a clinical setting, which corresponds with all digital biomarker data.
- RPM requires physicians to monitor and provide recommendations for data, so this would not apply to devices like Fit-Bits or Apple Watches.

CMS vs Digital Biomarkers

- In order for digital biomarkers to use established payer models, devices must receive FDA approval.
- Different digital biomarkers more closely align with either RPM or RTM, but both provide valid potential payer models for clinical uses.

AMA, *OneHealthCare*

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Ethics and Governance

This section addresses ethical, social, and governance challenges associated with digital biomarker use. It considers issues related to bias, representation, data privacy, consent, and corporate accountability that influence trust and responsible deployment.

Section 1: Bias and Representation

Section 2: Privacy, Ownership, and Corporate Governance

Section 3: Forward-Looking Perspectives

Sources of Bias in Digital Biomarkers: Case Studies

In line with other medical studies, digital biomarker research expresses the biases contained within the identification and selection of data sets. Depression screening and atrial fibrillation research represent two case studies.

JMR Depression Screening

- Developing models using **small, unrepresentative data** sets contributes to algorithmic bias, particularly in the context of machine learning.
- Participants **wore a fit-bit for 14 days** consecutively, and the devices collected heart rate, sleep duration, step count, and activity level data.

Potential Sources of Sampling Bias	• This study attempted to develop of machine learning model for employing wearables to use digital biomarkers to screen for the development of depression. • The survey worked with **290 healthy adults**, but these adults were not representative of the broader public. Their average age was 33, 64% were female, **79% were Chinese**, and **89% had a college degree**.
Consequences	• A machine learning model developed from data collected from predominantly young, affluent, Chinese women may **not accurately identify depression** when applied to other populations. • The FDA generally avoids approving medical devices or findings that do not accurately represent the population for which they are marketed.

Atrial Fibrillation Wearables

- Digital biomarkers and wearables have been identified as an **emerging option for the detection of atrial fibrillation**.
- The use of light that fails to accurately detect the condition in individuals with darker skin tones **threatens the promising results**.

Potential Sources of Sampling Bias	• Wearable technologies that use photoplethysmographic sensors to detect atrial fibrillation underperform for users with darker skin tones, reflecting a **bias in the development and testing of the devices**. • Research conducted using this technology **misrepresents the heart rate** of patients who then receive inaccurate medical diagnoses.
Consequences	• In response to devices that fail to function for certain skin tones, the FDA can force companies to conduct **corrective studies**, update labeling, or restrict device use. • The under-detection of atrial fibrillation contributes to a **delay or lack of care** for Black and brown individuals with atrial fibrillation who have a pressing need for immediate medical care.

Key Takeaway

Digital biomarker research must be rigorously evaluated to prevent data set bias and resulting FDA approval, health, and patient risks. In particular, racial bias poses a potential risk.

Rykov et al. (2021), *Buda (2024)*, *Merid (2023)*

Dataset Diversity in Digital Biomarker Validation

Digital biomarker validation relies on fragile, homogenous datasets, threatening regulatory approval and global scalability. Strategic investment in diversifying new datasets is now underway but still in early stages for research programs.

Current Status of Datasets

- Digital biomarker validation needs further diversification it relies on datasets that are **highly homogeneous**, which makes it harder to receive regulatory approval and grow globally.
- Studies like **mPower (N about 9,500)** and the **Apple Heart Study (N over 250,000)** put **scale ahead of diversity**, which is why some cohorts had up to 91% Caucasian participants.
- The **Food and Drug Omnibus Reform Act** (FDORA) Section 3602 now **requires Diversity Action Plans for dataset.** This means that being representative is now required for regulation.

91%

Caucasian Representation in Parkinson's Research Cohorts (e.g. mPower)

25.9%

Low-Income Representation (<$25,000) in All of Us Research Program

Key Representation Risks

- Two primary risks arise in this context: **insufficient regulatory oversight** under the Food and Drug Omnibus Reform Act (FDORA) Diversity Action Plan mandate and **limited commercial viability** due to a restricted market size. These constraints **jeopardize the ROIs** for software as a medical device (**SaMD**) products in biomarkers.
- The mPower Parkinson's study and its associated cohorts comprised up to **91% Caucasian** participants. Despite the large sample size, **only 38.4% of participants were women**. Additionally, over 80% of individuals enrolled in major clinical (AI) model studies are from **North America or China**, showing major demographic bias.
- **Algorithmic performance is reduced** due to insufficient representation of varied demographic groups. For example, the disparity in clinical diagnosis rates of **atrial fibrillation between White and African-American** patients decreased from **4.7% to 0.7%** when equitable ambulatory monitoring was implemented.

Further Plans to Diversify

Emerging Research Programs

The **All of Us Research Program** and similar new initiatives are aimed at diversified datasets. For example, **43.8%** of participants are classified as underserved, and **25.9%** report annual incomes **below $25,000**. Precompetitive consortia, including the **Critical Path for Parkinson's**, aggregate data to develop diversified benchmarks.

Decentralized Clinical Trials

Decentralized clinical trials (DCTs) facilitate regulatory compliance and have demonstrated **increased enrollment diversity**. For instance, a fully decentralized U.S. trial achieved **25% Black participant** enrollment, compared to the industry average of 4%. DCTs also reduce average enrolment duration from **15.9 months to 4.0 months**.

AI Training and Data Bias

The use of generative AI tools, especially the ones trained with machine learning algorithms, could be **useful tools when it comes to extrapolations** and identifying underlying trends of datasets. However, the **data bias is deeply manifested** in the outcome of the model, which is a harm to be mitigated through **data cleansing**.

ACRP, All of Us Research Program, Brigham and Women's Hospital, FDA (I), FDA (II), NIH (I), NIH (II)

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Corporate Governance and Accountability in Digital Health

With users having no ownership of their data and typically only being offered one-time consent for its use, their privacy could be at risk in commercial digital biomarker, and Chief Privacy Officers may be a partial solution to this problem.

Ownership & Control

- **HIPAA** grants patients the right to **access their data and make edits**, but does not grant them ownership of their data, which is retained by providers. **GDPR** offers EU individuals the right to **access and delete data**.
- Digital biomarkers **providers own the medical records**, with tech companies like **Fitbit securing data licenses in their Terms of Service**, similar to researchers' informed consent forms at the start of the study.
- Specific examples include **Apple's policy that data is "not readable by anyone—even Apple",** while other biomarker providers like **Fitbit and Whoop explicitly vow not to sell** users' personal health data. Very few vendors like **Tidepool state that "You own your data. Period."** which suggests the users own the data.

Consent in Data

- Biomarker providers have a **one-time, generic consent** in the terms of service during set-up. Some have **toggles to opt out of data sharing**. **Few services**, like Apple Health, **offer granular permission controls**.
- **Fitbit and Google renewed their consent form** during their account migration from 2023 to 2025. Whoop and Abbot rely on initial consent. None of these biomarker providers has **periodic reconsent procedures**.
- In research spaces, **dynamic consent is emerging**. **The NIH's "All of Us" program and the Australian Genomics CTRL platform** enable participants to manage and update data-use preferences through a web portal. Meanwhile, such practices are rare in industries due to the possibility of **lowering user retention**.

Legal Risks & Privacy

- WW International's **Kurbo collected weight data from children** without strictly verified parental consent, with a **2022 FTC order** required the deletion of the data, destruction of its algorithms, and a **$1.5M fine**.
- **FloHealth sent reproductive health data to Meta and Google** for targeted ads on Facebook from 2016 to 2019. A California jury later found Meta liable in 2025, while Flo and Google **settled the case for $59.5M**.
- Larger commercial providers of digital biomarkers, such as **Apple and Google, have Chief Privacy Officers** who publish a **biannual transparency report**. Google also has an independent **Integrity and Ethics Review Board** within its DeepMind Health Group, but these privacy procedures are **not specifically for biomarkers**.

AMA, Apple, Fierce Healthcare, FTC, Gibson Dunn, NIH

Ethical and Social Risks from Passive Health Monitoring

When developing digital biomarker tools for clinical and commercial purposes, it is important to consider and attempt to avoid potential ethical and social risks associated with the tools.

Ethical and Social Risks

- **Privacy and Data**: Once collected, data can be sold and repurposed for originally unintended uses. For example, location data could be sold and used for malicious intent.
- **Surveillance and Law Enforcement**: The development of surveillance tools can be used as evidence in criminal investigations, creating ethical concerns.
- **Discrimination and Harm**: Data collection may allow employers to discriminate against vulnerable groups. For example, digital health data could be used to screen for insurance rates in ways not currently possible.
- **Psychological Harms**: Constant monitoring can have negative psychological effects on patients and consumers.

Real-World Cases

- In 2018, the running tracking company Strava introduced a public "global heat map," which allowed users to view activity on an aggregated scale. This digital biomarker data **revealed covert activity** at sensitive military bases, causing Strava to remove the feature.
- Fitbit and Apple Watch data have been used as **permissible forensic evidence** in murder trials. These uses breached the intended purpose of the health/wellness data.
- Wearable logs have been used by insurers to **challenge benefit claims**, leading to a lawsuit from the law firm JDSpura. This use again breaches the intended purpose of collecting data for health and wellness improvement.

Representation and Bias

- **Sensor Bias**: Photoplethysmography-based measures for smartwatches and other trackers consistently underperform for uses with darker skin pigments, producing measuring error and inequality on the aggregate.
- **Participant Selection Bias**: As with many clinical trials, digital biomarker research's participants often skew towards younger, wealthier, and digitally-fluent users. This may have implications on the effectiveness of digital biomarkers for older and less affluent users.
- **Algorithmic Bias**: The biases of participant selection and sensor accuracy can coalesce into broader bias when artificial intelligence is used to develop recommendations. AI incorporated dataset bias into results.

JDSpura

Section 1: Bias and Representation

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Interview: Bioengineering Professor at Harvard Medical School

Based on his work in ultra-sensitive biomarker assays and promoting it in developing countries, this expert views AI as a powerful but data-dependent partner that augments biomarker discovery alongside researchers to discover pathways.

Background Information

- As a **Professor of Bioinspired Engineering**, the interviewee focuses on **biomarker assay technologies** for **early diagnosis** of infectious diseases, neurodegenerative diseases, etc..
- He is a **pioneer in microwell-array and single-molecule detection**. He cofounded multiple biotech startups and received **numerous national awards** for diagnostics innovations.

Emerging Role of AI in Biomarkers

- The interviewee **believes AI will not replace** biomarkers discovery but could be **helpful for detecting complex patterns** in difficult datasets.
- Within diagnostics in general, he expects AI to **suggest correlations** between biomarkers and underlying diseases, particularly **prioritizing promising candidates**/pathways for researchers.
- He highlights that AI systems can **integrate different biomarker profiles**, cytokine and gene-expression changes, and drug-response patterns to **propose disease pathways, narrowing mechanistic hypotheses** for human researchers.

Concerns in Population Bias and Equity

- In comparisons with genomic sequencing, the interviewee finds biomarker data as having **low re-identification risks** when data are anonymized, primarily **enhancing accuracy** on early detection.
- He suggests **recruiting geographically and ethnically diverse** participants in studies to reduce bias. Analyzing **participants as distinct groups prevents the majority population** from dominating models.

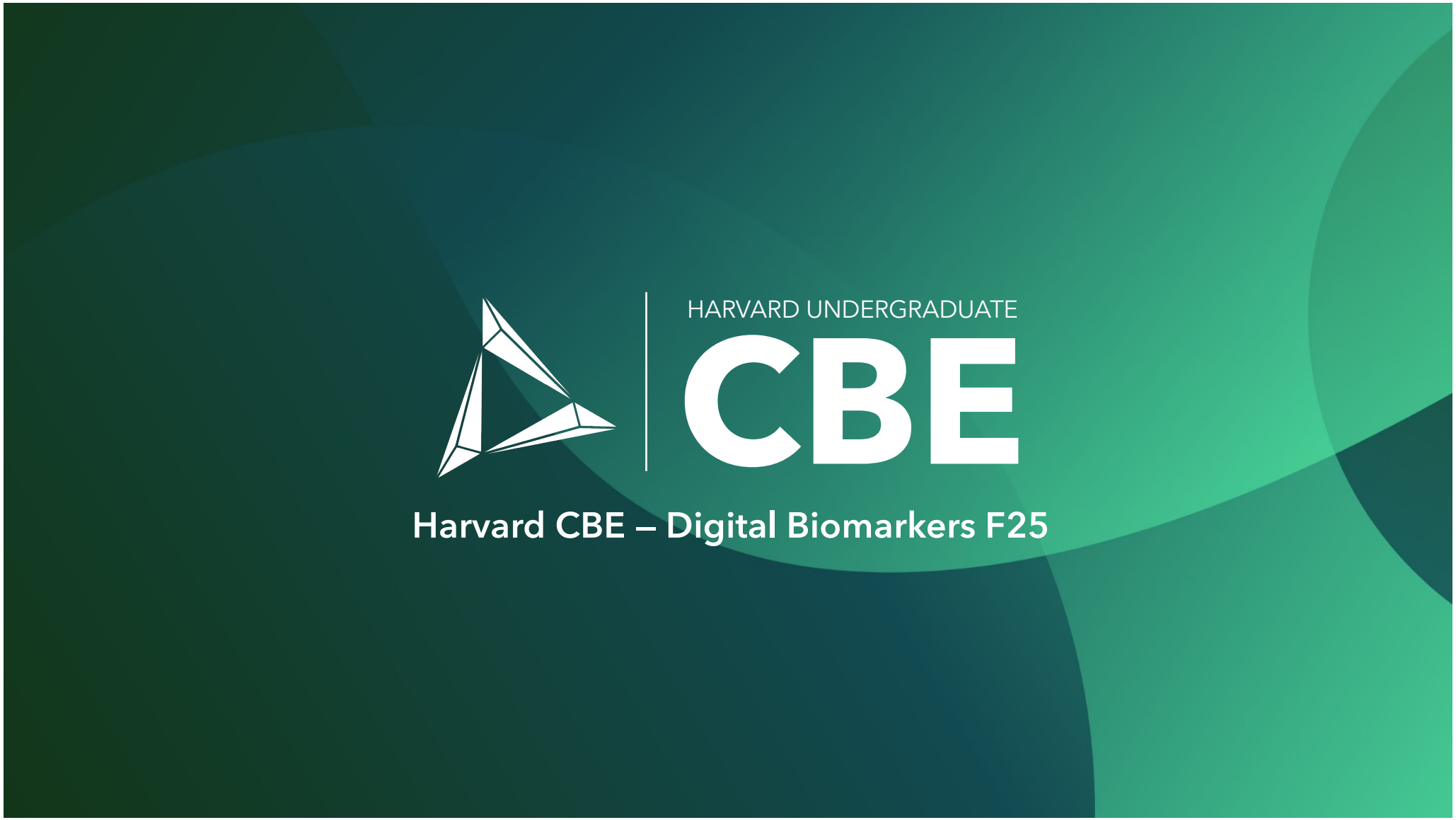
Links between Digital and Molecular Biomarkers

- He envisions studies that can **combine wearable signals** like those on Apple Watch and **correlate them with periodic blood tests** to uncover patterns of early cardiovascular diseases, which could be costly.
- Specifically, **utilizing algorithms to align digital patterns** with blood-based biomarkers can lead to the early detection of heart attacks, asthma exacerbations, or early cancers with sufficient **correlation evidence**.

Commercializing Biomarkers in Innovations

- The interviewee notes that **large integration studies** that link molecular biomarkers with digital data are **expensive and require longitudinal designs**, which **complicates the commercialization**.
- He warns that platforms owners and **large digital biomarker producers like Apple can capture the most economic benefits**, which will **weaken independent researchers**'/startups' incentives for these projects.

> Most of these digital platforms, whether it's Apple or Google, make it **tricky to incentivize startups** to do research, because in the end, **the ones who really benefit are the people who own the hardware**. If you discover a correlation on Apple Watch, who's going to make the money? Definitely Apple.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