PRECISION FOR MEDICINE℠

THE FUTURE OF MEDICINE IS PRECISION

Understanding and Applying Digital Biomarkers

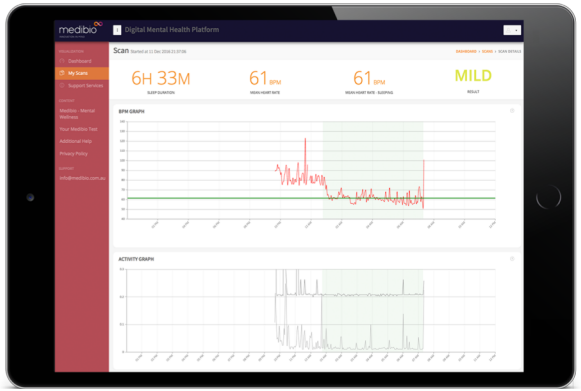
A “Beyond-the-Lab” Approach to Diagnostics Development

October 27, 2017

Digital Health enters a new era of “Digital Medicine”

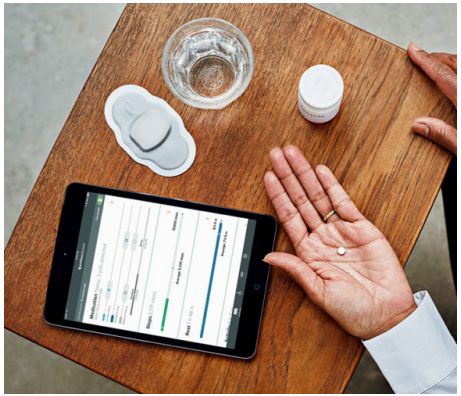
SONDE

AKILI™



medibio
INNOVATION IN MIND

empatica



proteus
DIGITAL HEALTH

WATCH

Digital Therapeutics Alliance launched this week

DIGITAL THERAPEUTICS ALLIANCE

DTx Solutions | Industry Insights & News | About DTA

What are Digital Therapeutics?

Digital therapeutics represent a new generation of healthcare that uses innovative, clinically-validated disease management and direct treatment applications to enhance, and in some cases replace, current medical practices and treatments.

DTx products demonstrate safety and efficacy in randomized clinical trials, receive regulatory clearance when used as a medical device, integrate into clinical practice, may be prescribed by healthcare providers, and tailor to patients' clinical needs, goals, and lifestyles.

LEARN MORE

Presentation Agenda

What's a Digital Biomarker anyway?

Key Concepts and Terminology

Validation Framework for Digital Biomarkers

Digital Biomarkers as Drug Development Tools

Applying Validation Strategies

Example Case Studies

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What's a Digital Biomarker anyway?

Definition of a "Digital Biomarker"

Biomarker
As Defined in FDA/NIH's BEST Glossary

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives.

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Digital Biomarker
From various sources - not yet formally defined!

An objective, quantifiable physiological, cognitive or behavioral characteristic that is collected and measured by means of digital devices such as portables, wearables, interactives, implantables or ingestibles. The data collected are typically used to explain, influence and/or predict health-related outcomes. A digital biomarker is not a qualitative or patient-reported assessment.

What's a Digital Biomarker anyway?

Definition of a "Digital Biomarker"

Biomarker
As Defined in FDA/NIH's BEST Glossary

- ☑ Tumor Volume Measured by Computed Tomography
- ☑ Plasma Fibrinogen in COPD
- ☑ Total Hip Bone Mineral Density (BMD)
- ☑ Cerebral Spinal Fluid (CSF) Markers in Alzheimer's Disease
- ☒ Exacerbations of Chronic Pulmonary Disease Tool (EXACT)
- ☒ Asthma Daily Symptom Diary (ADSD)

Digital Biomarker
From various sources - not yet formally defined!

- ☑ Physical mobility over time in Parkinson's
- ☑ Attention task performance in Alzheimer's
- ☑ Sleep quality tracker in COPD
- ☑ Analysis of vocal features in CHF
- ☑ Measures of social engagement in MDD
- ☒ Compliance/adherence data
- ☒ ePROs or other outcome assessments
- ☒ Broad cognitive assessments
- ☒ Telemedicine interviews, text messaging

Integrating Digital Health into Biomarker Programs

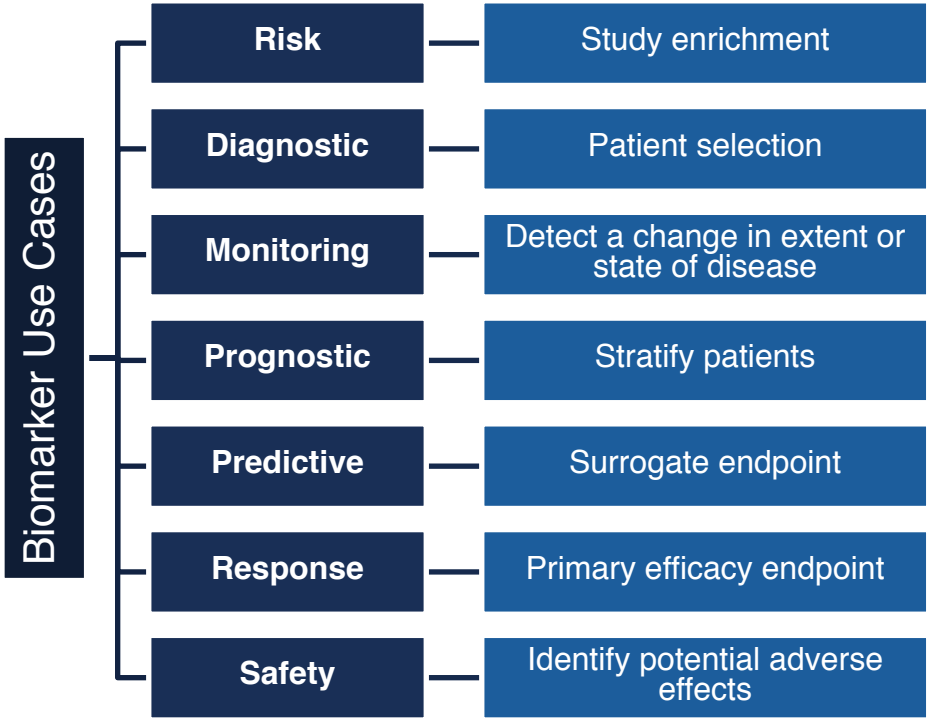
Goal: Enrich the ability of diagnostics to provide a more complete picture of the patient to pharma developers and to clinicians

- Initial, easy pre-screen for more complex, burdensome Dx
- Ongoing, at-home analyses to identify need for additional Dx workup
- Generate contextual patient metadata to inform Dx results
- Hybrid biological-digital signal for improved detection

Result: total picture of health, allowing for better interpretation of study results, improved detection of outcomes and trends

How can we use Digital Biomarkers?

Digital Biomarkers leverage existing Biomarker Use Cases…

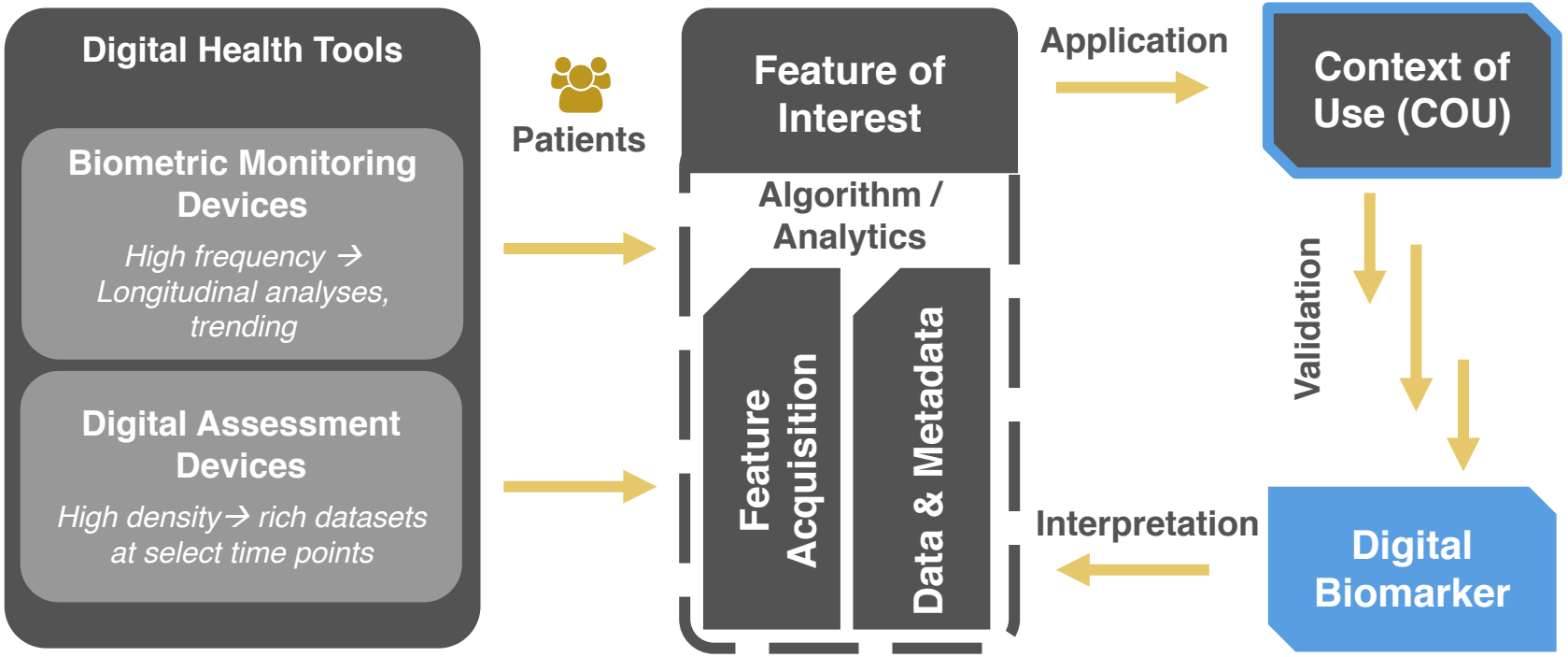


…and offer unique advantages

- Can objectively capture broader context of disease, including measurement of activities of daily living and QoL indicators
- Can be measured directly in actual patient use settings
- High frequency of measurements enables longitudinal analyses
- Complex datasets good candidates for Big Data and AI analytics
- Highly compatible with virtual studies, real world evidence collection

How do we get from Digital Health to Digital Biomarker?

Generating a "Digital Biomarker"



Understanding Digital Biomarkers: 3 Case Studies

Activity Biomarker: Response Prediction

Biometric Monitoring Device
- Wearable
- Medical-grade Activity tracker

Patients
- Parkinson's Disease patients

Feature of Interest
- Longitudinal measure of activity (weighted analysis of multiple features of activity, mobility) as indicator of disease severity

Cognitive Biomarker: Study Enrichment

Digital Assessment Device
- Interactive
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Vocal Biomarker: Screening Tool

Digital Assessment Device
- BYOD
- At-home voice recording
- Machine-learning analytics

Patients
- Patients at risk for lung malignancies

Feature of Interest
- Monitor lung function and pulmonary health as indicator of need for further work-up

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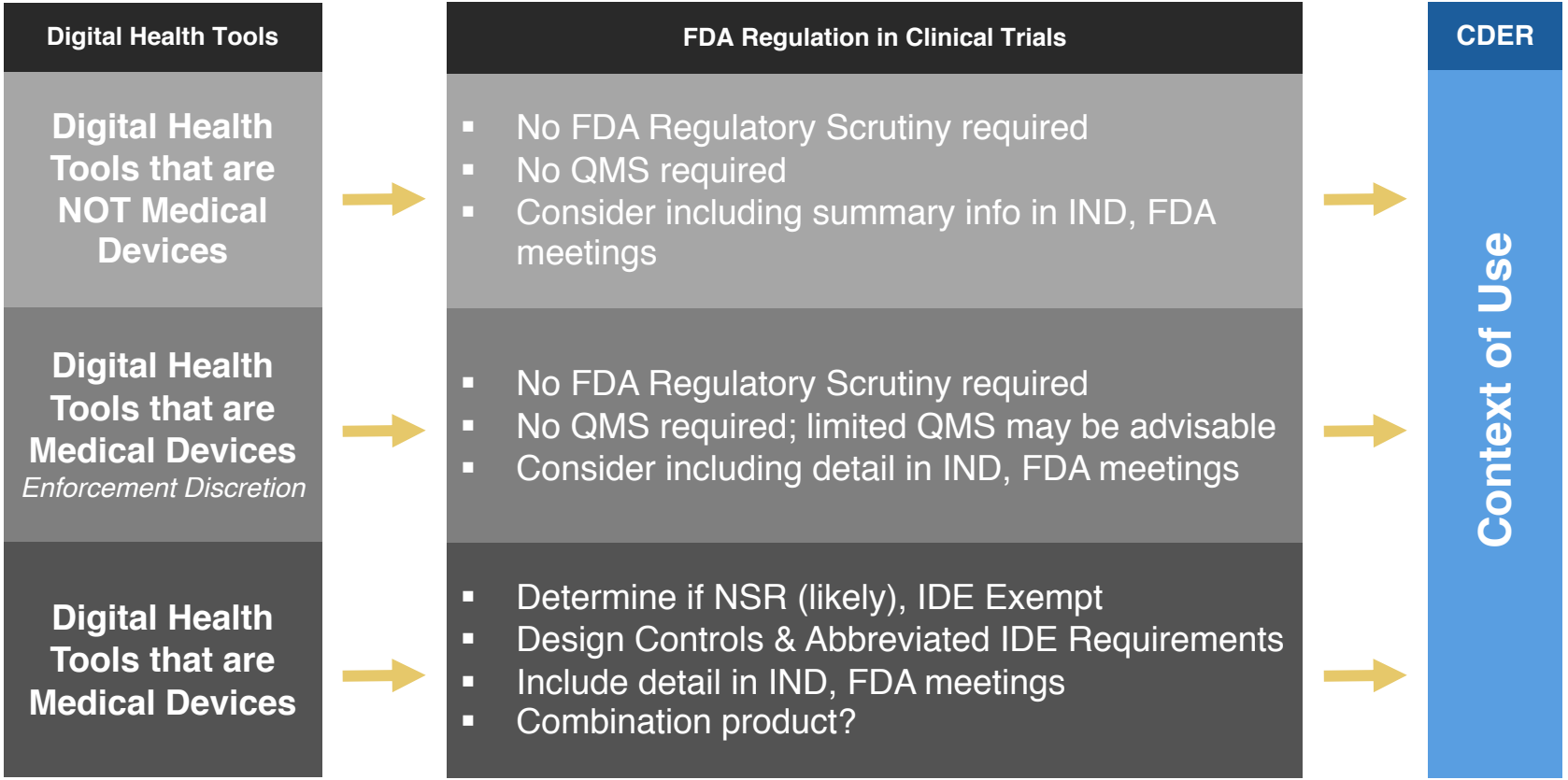
How do we validate Digital Biomarkers?



Context of Use

1

Who: Who will use it?

- Patient demographics
- Patient conditions or disease state (inclusion / exclusion criteria)
- Patient setting: At home, in clinic, with or without coaching, care team interaction

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What: What is it designed to do?

- Measure and record longitudinal physical activity data
- Interactively engage patient to generate cognitive or other measures
- Periodically measure objective physiological features
- Recognize and record instances of a specific activity

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How: How does it generate its output?
- Quantitative
- Semi-Quantitative
- Trending/Longitudinal
- Advanced Analytics

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4

Why: How will its output be used?
- Enrichment – for reinforcing study entry criteria, enhancing subgroup enrollment;
- Diagnostic – for determining diagnosis, or screening for further diagnosis;
- Monitoring – for detecting changes in extent or state of disease;
- Prognostic – for determining course of illness or treatment; or
- Predictive – for treatment outcomes and safety assessment.

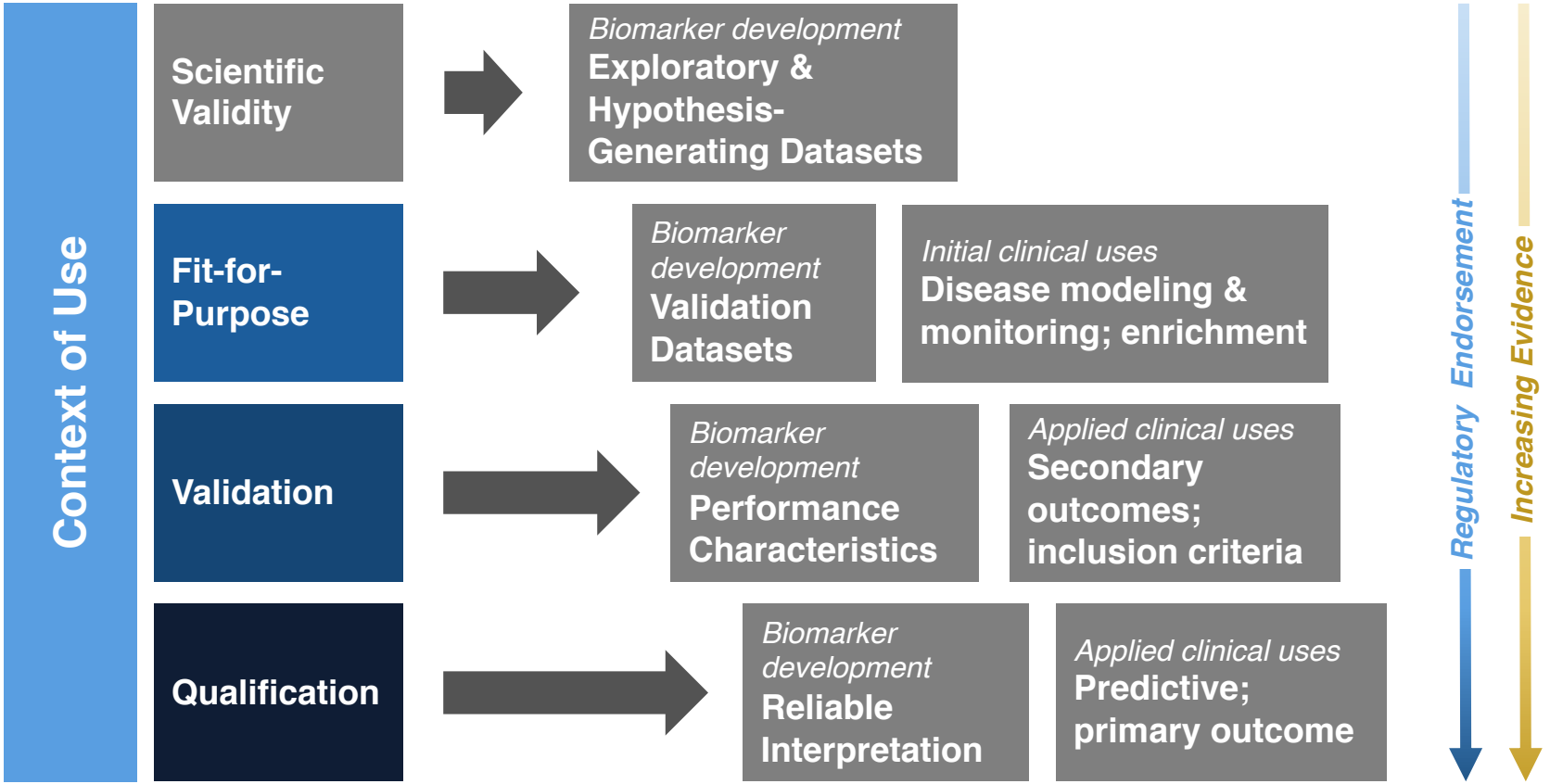
Evidence to Support Context of Use

Context of Use

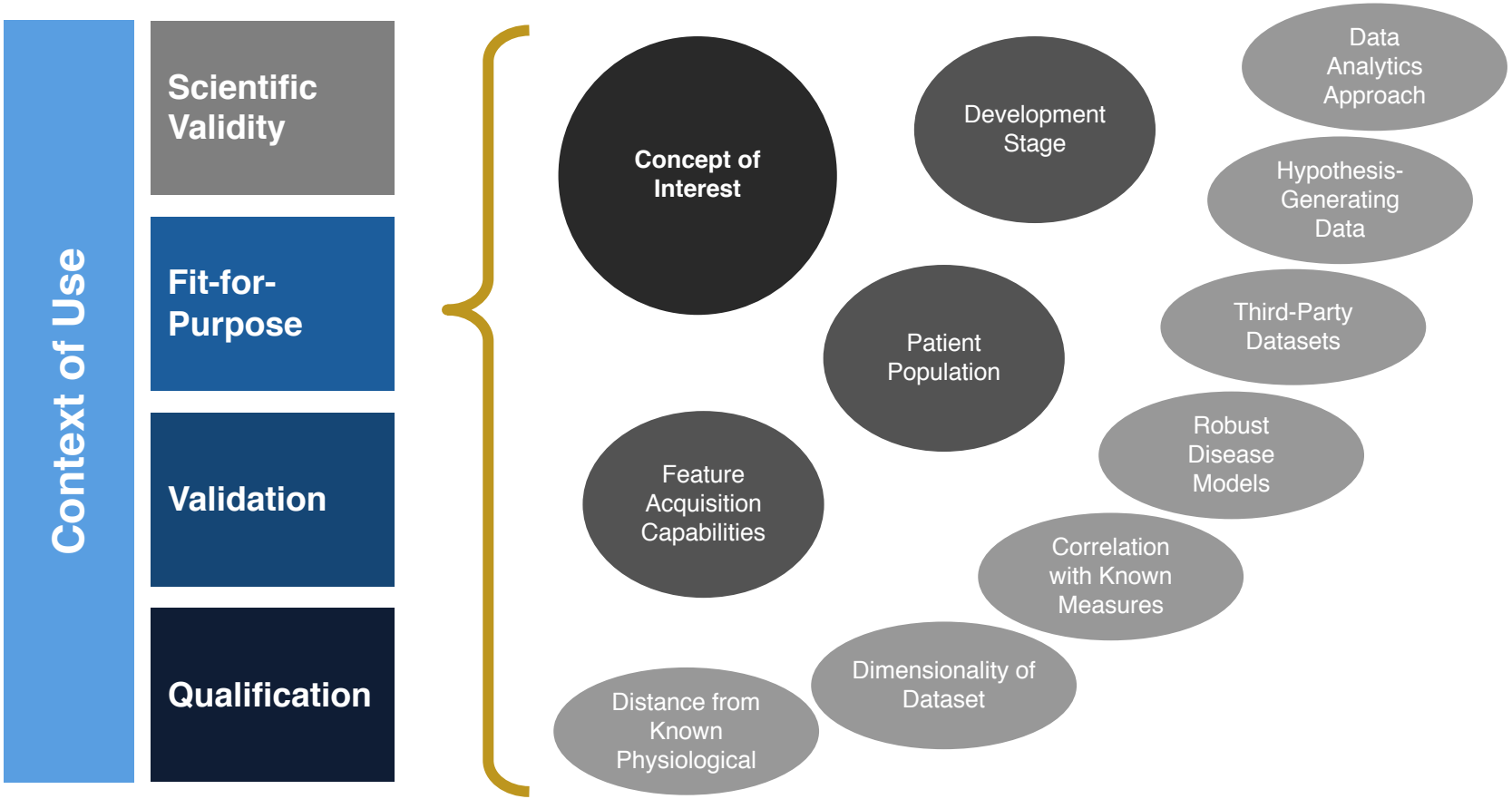
Scientific Validity	▪ Scientific validity: ***a clinical or scientific linkage*** between the Digital Biomarker and the condition being studied that supports use of the biomarker ▪ Typically substantiated by literature, mechanism of action, or a well-articulated scientific or clinical rationale
Fit-for-Purpose	▪ Targeted, evolving set of data that, as a whole, ***supports the use of the Digital Biomarker for its specific COU*** ▪ Recognizes dynamic nature of developing Digital Biomarkers and investigating drugs
Validation	▪ Validation of the performance (and/or other characteristics) of the Digital Biomarker that ***allows its output to be interpretable*** ▪ Based on COU: Clinical validity, Analytical validity, Construct validity, etc. (e.g., test-retest reliability; NPV/PPV; comparison to reference standard)
Qualification	▪ Qualification is a conclusion that within the stated COU, the Digital Biomarker ***can be relied on to have a specific interpretation*** in drug development ▪ Digital Biomarkers can be qualified case-by-case; formal FDA Biomarker Qualification Program can apply for traditional biomarkers

Increasing Evidence ↓

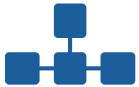
Evidence to Support Context of Use – Benefit/Risk



Evidence to Support Context of Use – Finding the Sweet Spot



Validation Strategies to Support Digital Biomarkers

Traditional Approach 	▪ Large, prospective validation studies ▪ Stand-alone or fully integrated into pharma study ▪ Dependent on clinical sites, CRO infrastructure
Virtual Studies 	▪ Decentralized, infrastructure-light ▪ Patient in home use setting ▪ Fast enrollment
Pooled Datasets 	▪ Validation study with multiple different studies as inputs ▪ Relies on poolability analysis across different studies ▪ Leverage multiple studies in parallel to validate quickly
Real World Evidence 	▪ Utilize on-market product to generate data and expand claims, COU ▪ Can leverage virtual study and phase 4 study infrastructure ▪ Allows for fit-for-purpose in pharma studies, to be validated later
Iterative / Bridging 	▪ Rely on multiple smaller studies, designed to allow for bridging ▪ Allows adaptation and refinement of product over time ▪ Can rely on all validation strategy features above

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1	Traditional	Exploratory Pilot in Healthy & Known PD	Validation
2	Traditional	Validation Study as a Phase 2 Substudy	Validation
3	Traditional	Qualification Study as a Phase 3 Substudy	Validation
4	Traditional	Predictive Primary Outcome → accelerated Phase 2/3 Study on novel therapeutic	Applied
5	RWE	Expanded label based on observed real world evidence	Applied

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1	Virtual		Virtual Study in Healthy Adults to generate a Normative Database	Development
2	Virtual		Virtual Study in Elderly Adults at Risk for MCI to identify measured Feature of Interest	Development
3	Pooled		Validation dataset from multiple Pharma Phase 2 Studies	Validation
4	Traditional		Enrich Phase 3 Study Population to accelerate enrollment, reduce non-responders	Applied
5	Virtual	Bridging	Bridging data to expand use into other patient populations / COUs	Validation

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1	Virtual		Voice analysis training and refinement in known healthy and diagnosed Stage 1	Development
2	Virtual		Robustness training across multiple environments and device types (BYOD)	Development
3	Virtual		Large population health study to validate algorithm / combined with early-stage Dx	Applied Validation
4	Traditional		Integrate into early-stage lung cancer treatment pharma study to identify and enroll patients	Applied
5	RWE	Iterative	Implement and iterate in real-world setting to inform monitoring of lung health during treatment & remission	Applied Validation

Medibio & Otsuka

Medibio Enters Into an Agreement with Otsuka Pharmaceutical Development & Commercialization, Inc.

- **Medibio will leverage its proprietary Digital Mental Health platform to process Otsuka clinical data with the goal of further clarifying the role of biomarker-based, objective measures in management of serious mental illness.**
- **Paid commercial arrangement for Medibio**

Sydney, Australia and Minneapolis, MN – 9 October 2017: Medibio Limited (**MEB** or the **Company**)(ASX: MEB)(OTCQB: MDBIF), is a mental health technology company that has pioneered the use of objective biometrics to assist in the screening, diagnosing, monitoring and management of depression and other mental health conditions, is pleased to announce it has entered into an agreement with Otsuka Pharmaceutical Development & Commercialization, Inc. (Otsuka).

Akili & Pfizer

Akili and Pfizer Present Positive Data from Digital Biomarker Study to Detect Subtle Cognitive Changes in Healthy Subjects at Risk of Developing Alzheimer's Disease

Digital platform may represent new, non-invasive method to screen for amyloid deposits in asymptomatic and early disease populations for Alzheimer's drug research and treatment

Data presented at the International Conference on Clinical Trials for Alzheimer's Disease

December 09, 2016 11:30 AM Eastern Standard Time

BOSTON--(BUSINESS WIRE)--Akili Interactive Labs, Inc. and Pfizer Inc. (NYSE: PFE) today presented positive topline data showing that Akili's proprietary technology platform detected a statistically significant difference between subjects with and without brain amyloidosis, the primary biomarker for Alzheimer's risk. The study was part of a collaborative trial designed by Pfizer and Akili, and topline results were presented at the International Conference on Clinical Trials for Alzheimer's Disease in San Diego, CA.

Science 37 & AOBiome

Science 37 and AOBiome Complete Industry-First Virtual Clinical Trial Through Metasite™ (Decentralized) Operating Model

Science 37 conducts entire interventional Phase 2b "site-less" clinical trial, enrolling 372 patients across 10 states using its proprietary mobile telemedicine-based platform, NORA®

October 24, 2017 08:01 AM Eastern Daylight Time

PLAYA VISTA, Calif.--(BUSINESS WIRE)--Science 37, a trailblazing company focused on "site-less" clinical trials, announced today the completion of a Phase 2b study for AOBiome, a clinical-stage life sciences company, in which it screened over 8,000 people with mild-to-moderate acne and enrolled 372 participants to take part in this research study all from the comfort of their own homes. This is the first time that a Phase 2b interventional randomized placebo controlled trial of this kind has been successfully run one hundred percent virtually. In a separate announcement, AOBiome reported positive efficacy and safety findings from the study, available at this link.

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For further questions:

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Digital Biomarkers: Additional Resources

- FDA Drug Development Tool (DDT) Program: Biomarkers
- FDA Guidance (CDER & CDRH)
- Critical Path Institute (C-PATH)
- CDISC (Data Standards)
- Clinical Trials Transformation Initiative (CTTI)
- Medical Device Innovation Consortium (MDIC)
- *Digital Biomarkers* Journal