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Industry Perspectives of Digital Health in Clinical Trials

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Disclaimer:

Employee of Sanofi

Presentation and views are my own and not necessarily of Sanofi

28 . FEB. 2024

Overview

Digital Health

Digital Diagnostics

Remote Data Capture

Digital Outcome Measures

E-health monitoring

Registries

Digital Technology in Clinical Trials

"It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to change."

-Charles Darwin

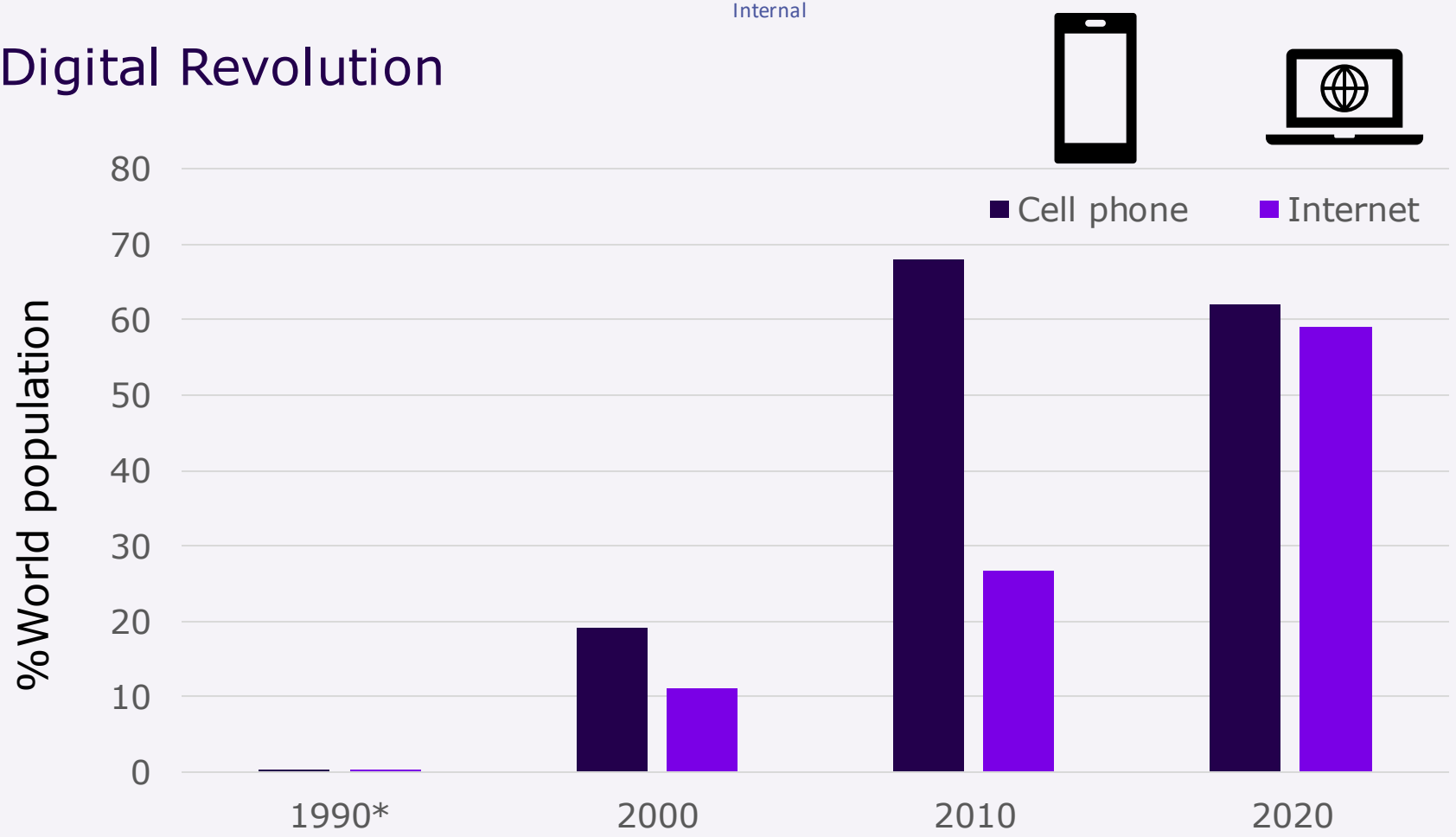
Digital Health

Digital Revolution

- **Third Industrial Revolution**
- Shift from mechanical and analogue electronics towards digital in the latter half of the 20th century
- Changes brought by digital computing and communication technology
- Digital Revolution marked the beginning of the “Information Age”

1 E. Schoenherr, Steven (5 May 2004). "The Digital Revolution". Archived from the original on 7 October 2008.
^ "Information Age".

Digital Revolution



*Cell: 0.25%
Internet: 0.05%

Digital Health

- In 2005 the World Health Assembly urged Member States "to consider drawing up a long-term strategic plan for developing and implementing eHealth services…to develop the infrastructure for information and communication technologies for health…to promote equitable, affordable and universal access to their benefits."

- "Countries and stakeholders were urged to direct their efforts towards creating a consistent eHealth vision in line with a country's health priorities and resources, developing an action plan to deliver the proposed vision, and creating a framework for monitoring and evaluating eHealth implementation and progress"

Global Strategy on Digital Health 2020-2025

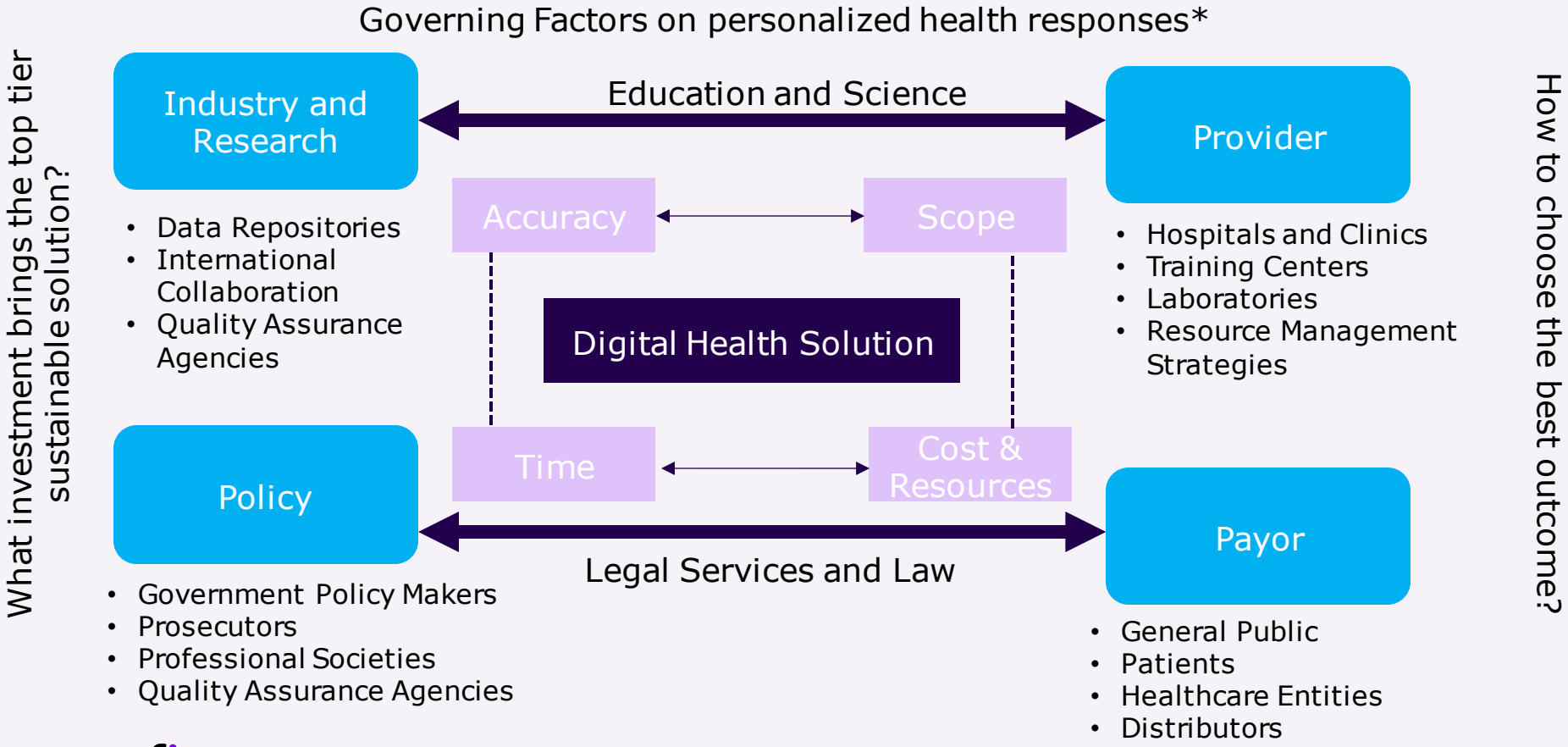
Digital Health

- Mobile health (mHealth)
  - The use of weekly virtual health care visits for Medicare beneficiaries increased from 13,000 before the COVID-19 pandemic to 1.7 million in April 2020[a]
- Health information technology (IT)
- Wearable devices
- Telehealth and telemedicine
- Personalized medicine

- From mobile medical apps and software that support the clinical decisions doctors make every day to artificial intelligence and machine learning, digital technology has been driving a revolution in health care[b]

a. Verma, et al, 2020 Health Affairs Blog. 10.1377/hblog20200715.454789/full/; b. What is Digital Health? | FDA

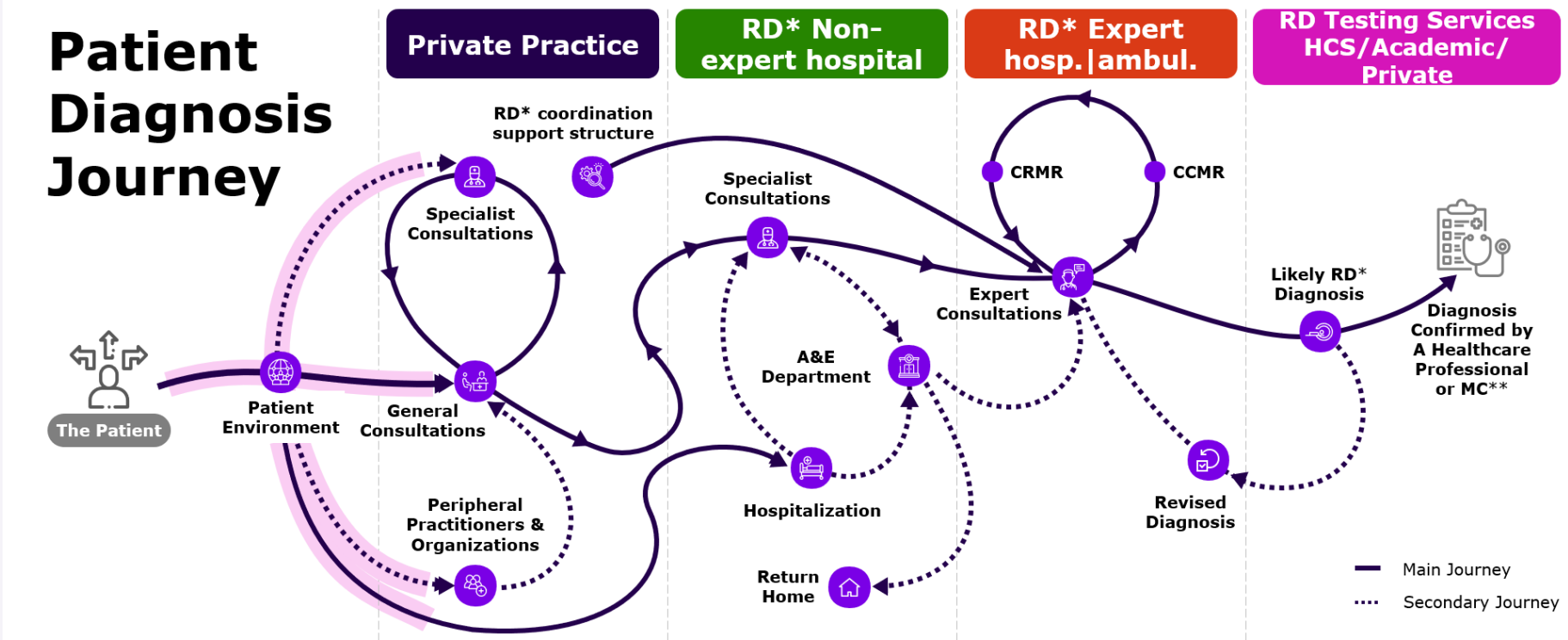
Digital Health Solutions



Naik N, et al. 2022. *Front Digit Health* 4:919985

Digital Diagnostics

Rare Disease Patient Diagnostic Journey



https://www.sanofi.fr/dam/jcr:88db8aaa-4c75-4a3b-b836-864523b45e59/UniR-LIVRE_BLANC_A-BD.pdf

Digital Diagnostics

- Highly configurable software application platform to capture diagnosis results, trigger and manage referrals, communicate with patients and health workers[a]
- Digital diagnostic algorithms
  - Uses signs/symptoms of a disease to raise alerts of a potential diagnosis
  - Symptom checker
- Deep Machine learning approaches use associative inference—they identify diseases based on how correlated they are with a patients' symptoms and medical history (in contrast to physician approach of selecting the diseases which offer the best causal explanations for the patients' symptoms)[b]
- Challenges
  - Accuracy

a. http://greenmash.com/; b. Richens, et al, 2020. *Nat Commun* 11, 3923

Project Searchlight - Development and Testing

Rare Disease Algorithm (RDA) for Gaucher vs. Clinical Diagnostic Algorithm (Mistry 2011)

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Development of a rare disease algorithm to identify persons at risk of Gaucher disease using electronic health records in the United States

Wilson et al. Orphanet Journal of Rare Diseases (2023) 18:280
https://doi.org/10.1186/s13023-023-02868-2

Models show reduction in testing versus a clinically applied diagnostic algorithm

Model/Filter	Screen	Gaucher Patients	RDA vs. Clinical Diagnostic Algorithm
Clinical Diagnostic Algorithm (Mistry 2011[1])	20,743	28	
Age Model	1,204	28	**17x**
Prevalence Model	2,862	28	**7x**

[1] Mistry PK, et al. A reappraisal of Gaucher disease-diagnosis and disease management algorithms. *Am J Hematol*. 2011 Jan;86(1):110-5. doi: 10.1002/ajh.21888

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The ART of Diagnosing Gaucher

Implementation and Evaluation of a Rare Disease Algorithm to Identify Persons at Risk of Gaucher Disease Using Data From Electronic Health Records (EHRs) in the United States (Project Searchlight)

Apply

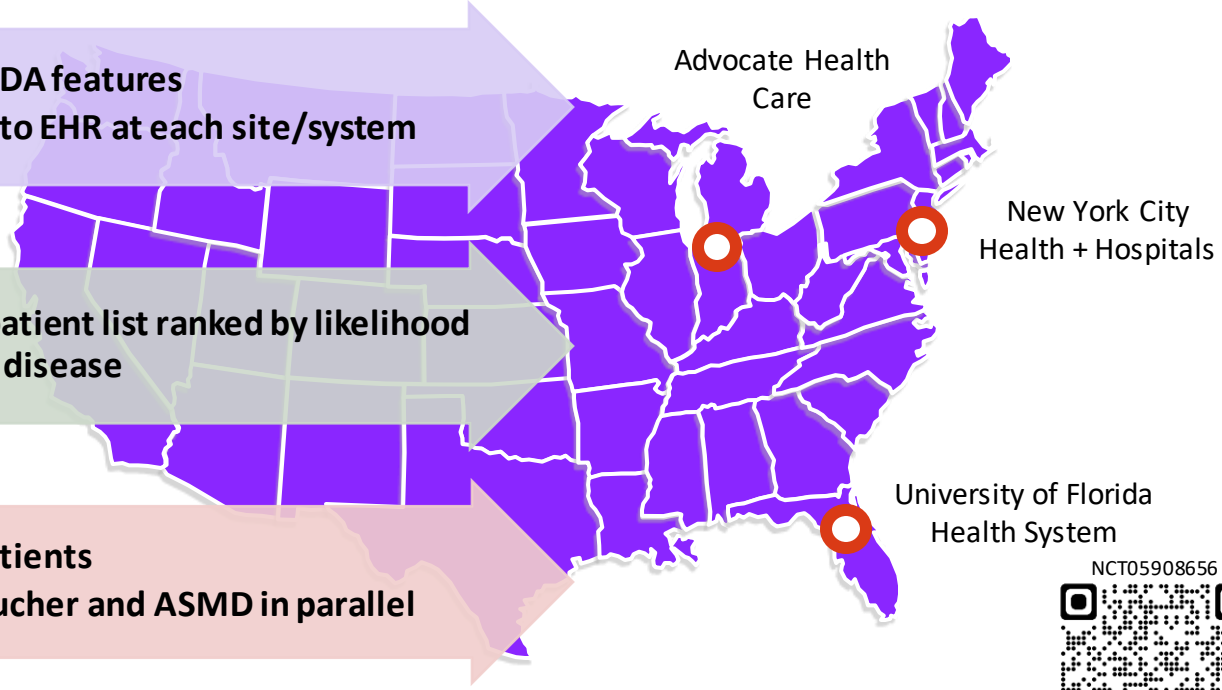
- Optimize RDA features
- Apply RDA to EHR at each site/system

Rank

- Generate patient list ranked by likelihood of Gaucher disease

Test

- Consent patients
- Test for Gaucher and ASMD in parallel



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accelRare®, Artificial Intelligence to accelerate the diagnosis of patients suffering from a rare disease

accelRare® is a pre-diagnostic digital solution for physicians of the primary care network to help them:

- Identify a rare disease as soon as possible based on their patients' symptoms,
- Speed up the referral of their patient to the closest expert center

Key features:

- Includes 270 rare diseases for which an adapted care exists in EU – 100% reviewed by French experts
- 84% of reliability – 159 diseases tested – 390 tests
- Pilot Performance study: Diagnosis among the top 3 suspicions improved from 53,2% to 93,6% thanks to accelRare
- HCP experience: >90% of HCP satisfaction about accelRare outcomes to help them for decision making

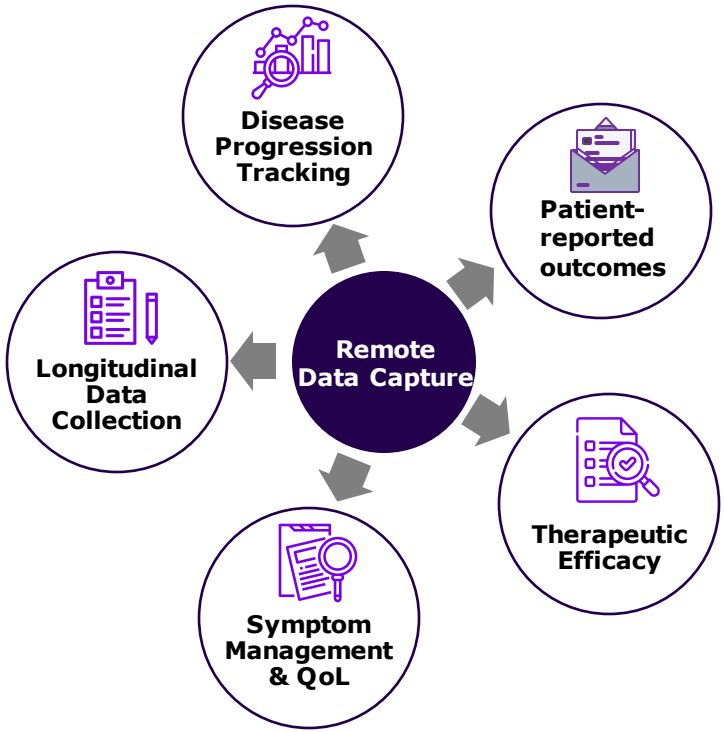
accelRare®

https://www.accelrare.com/en/

Remote Data Capture

Applications of Remote Data Capture in Rare Diseases

"After the diagnosis, I felt abandoned. I took charge myself with the low energy that I had, I found the best center and I went for it. The biggest frustration is the feeling of being abandoned, you are on your own while everything is unraveling."
Rare Disease Patient



FDA Guidance on use of digital health technologies for remote data acquisition in clinical trials

- Selecting suitable DHTs for reliable data collection in clinical investigations.
- Describing DHTs in regulatory submissions for clinical trials.
- Verifying and validating DHTs for use in clinical investigations.
- Utilizing DHTs for collecting data related to trial endpoints.
- Identifying and managing risks associated with DHT implementation in clinical contexts.
- Ensuring retention and protection of data collected by DHTs.
- Defining roles and responsibilities for sponsors and investigators in DHT implementation for clinical trials.

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Digital Health Technologies (DHTs) for Remote Data Acquisition in Clinical Investigations. Guidance for Industry, Investigators, and Other Stakeholders. US FDA. December 2023

Selection of a Digital Health Technology and Rationale for use in a Clinical Investigation

Population

01

- Evaluate diverse characteristics of the population for DHT usability
- Ensure inclusivity by addressing specific needs
- Adapt DHT interfaces to accommodate varied participant requirements for successful participation

Specifications

02

- Identify minimum technical and performance specifications for suitable DHT
- Specify the chosen product to remain fit for purpose
- Stay flexible: Add new DHT models/versions if they meet criteria

Design and Operation of DHT

03

- DHT design and ease of use
- Operational specifications to minimize missing data
- Capacity of network systems to adequately handle the volume of data
- Ensure privacy and security of data

Use of participant's own DHT

04

- Consider using familiar and personal DHT
- Cautious use of personal DHT to ensure usability in customized or specialized uses
- Ensure availability of sponsor-provided DHTs are available to prevent exclusion of participants

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Digital Health Technologies (DHTs) for Remote Data Acquisition in Clinical Investigations. Guidance for Industry, Investigators, and Other Stakeholders. US FDA. December 2023

Digital Endpoints

Clinical Trials

- Traditionally, clinical trials collect data at a specific point in time when the participant visits the clinical site.
- Logistical and financial barriers for subjects
- Digital Health Technologies allow continuous remote monitoring of patients' health data while they continue their daily lives.

Mittermaier, et al. 2023. *npj Digital Medicine* 6:88

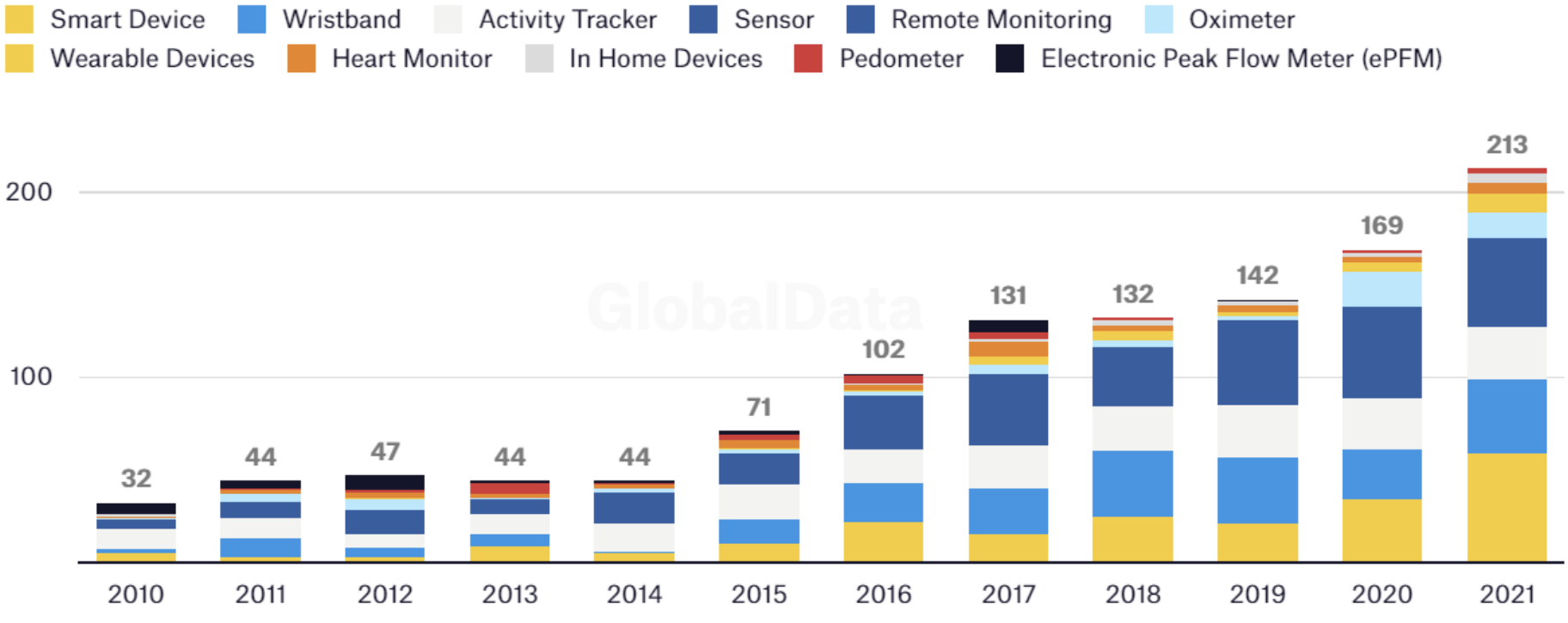
Digital Endpoints - Activity Monitors

- Types of activity monitoring
- Smart devices, wristbands, activity tracker, pedometer, wearable devices
- Purpose of monitoring
- feedback – goal oriented
- passive monitoring
- clinical trials

- Academic Research > pharma uses activity monitoring
- From 2014-2023 studies using activity monitors
- Phase I studies: 22% pharma vs 78% academic
- Phase II studies: 32% pharma vs 68% academic

Remote monitoring increasingly utilised in drug clinical trials

Wearable sensors and tracking devices in clinical trials by year



Source: GlobalData

Wearable study - Pompe

- Pilot study to evaluate the utility and practical applications of remote activity monitoring LOPD patients using a wearable device

- LOPD patients >18 yo were recruited for a 6-8 week study through a patient organization
- Eligible patients (n = 29) were provided a wearable device (Fitbit One) and completed a self assessment questionnaire
- Mobility outcome measures were median step count and peak 1-min activity

- Patient-reported "fatigue and pain" score was inversely correlated with step count (Pearson's $r = -0.42$, $p < 0.05$) and peak 1-min activity (Pearson's $r = -0.49$, $p < 0.01$)
- Patient engagement was high
  - 83% of the subjects who completed the baseline assessment uploaded wearable data during the study period
  - More than 80% of these participants uploaded data for ≥75% of the days during the study
  - 59% would recommend using an activity tracker to other patients with Pompe disease
-

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Hamed, et al 2019. *npj Digital Medicine* 2:70

Wearable study – Pompe conclusions

- Advances in technology and integrated data systems will improve wearable technology linked with patient self reports.
  - better characterization of Pompe patients
  - aid physicians in clinical decision making.
- Addition need of data standardization
  - Within disease to characterize heterogeneity
  - In relation to normative data from the general population and other disease controls.
- In a progressive neuromuscular condition like Pompe disease, there is a higher age-related rate of decline than healthy cohorts
  - To measure a significant improvement in any one patient, the trajectory of change must be referenced and calibrated to the disease population and healthy controls
- There are promising trends to indicate that wearable technology coupled with PROs offer a new approach to evaluate patient-relevant outcomes in both interventional and observational studies

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Hamed, et al 2019. *npj Digital Medicine* 2:70

Digital Endpoints

- Development of the digital endpoint Stride Velocity 95th centile (SV956) received EMA approval as a secondary endpoint for trials in Duchenne muscular dystrophy in 2019 and as a primary endpoint in 2023
  - Wearable device
  - Measures the speed of the fastest strides taken over 180 hours
  - Could replace the traditional 6MWT
  - Relieve uncontrollable factors such as fatigue from traveling to clinic
  - Better capture a patient's mobility in their daily lives, by measuring data over a longer time period in real life setting
- Development required collaboration and synergy among multiple stakeholders including industry, physicians, patients, care-givers, patient advocacy groups, regulators

https://www.ema.europa.eu/en/documents/scientific-guideline/qualification-opinion-stride-velocity-95th-centile-secondary-endpoint-duchenne-muscular-dystrophy_en.pdf; Final Qualification Opinion for Stride velocity 95th centile as primary endpoint in studies in ambulatory Duchenne Muscular Dystrophy studies (europa.eu)

Digital Endpoints

- Opportunities
  - Digital technology advances
  - Revolutionize how clinical trials measure efficacy
    - Mobility measures in Neuromuscular diseases
    - Smartphone=based cough detection for children with asthma
  - Reduce patient burden in studies by monitoring remotely
  - Capture real-world data
  - More data points which could reduce “noise” in a heterogeneous disorder

Digital Endpoints

- Challenges
  - Incorporation into clinical trials
  - Validation
  - Implementation (up to 5 years of development)
  - Access to adequate infrastructure, resources, and staff expertise
  - Complex Regulatory Barriers
  - Acceptance by Regulatory authorities
  - Inadequate funding
  - Overcoming the complexities surrounding big data (ensuring mobile technologies capture adequate data and selecting specific outcome data from the digital sources)
  - Data privacy and confidentiality
  - Is the endpoint clinically relevant?

Validation

- Validation of the technology
  - Reliable
  - Accurate
- Validation as a digital endpoint
  - validated in the disease
- Robust clinical trial endpoint
  - Can measure change
  - Clinically relevant
- Regulatory recognition

E-Health Monitoring

E-Health Monitoring

- The use of ePROs (electronic patient reported outcomes), eCOAs (electronic clinical outcome assessments) and eConsent increased sharply from 2020 to 2021

- Challenges
- Data privacy concerns
- Ease of use
- Intrusiveness
- Attitude towards adoption

Naik N, et al. 2022. *Front Digit Health* 4:919985

FDA Guidance for development of a PRO instrument – An iterative process

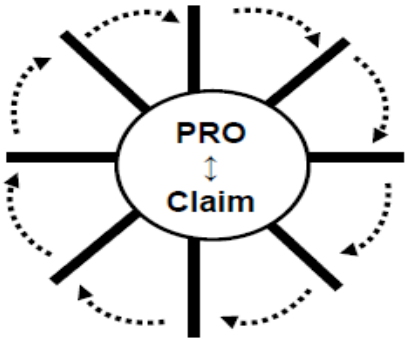
i. Hypothesize Conceptual Framework
- Outline hypothesized concepts and potential claims
- Determine intended population
- Determine intended application/characteristics (type of scores, mode and frequency of administration)
- Perform literature/expert review
- Develop hypothesized conceptual framework
- Place PROs within preliminary endpoint model
- Document preliminary instrument development

ii. Adjust Conceptual Framework and Draft Instrument
- Obtain patient input
- Generate new items
- Select recall period, response options and format
- Select mode/method of administration/data collection
- Conduct patient cognitive interviewing
- Pilot test draft instrument
- Document content validity

iii. Confirm Conceptual Framework and Assess Other Measurement Properties
- Confirm conceptual framework with scoring rule
- Assess score reliability, construct validity, and ability to detect change
- Finalize instrument content, formats, scoring, procedures and training materials
- Document measurement development

iv. Collect, Analyze, and Interpret Data
- Prepare protocol and statistical analysis plan (final endpoint model and responder definition)
- Collect and analyze data
- Evaluate treatment response using cumulative distribution and responder definition
- Document interpretation of treatment benefit in relation to claim

v. Modify Instrument
- Change wording of items, populations, response options, recall period, or mode/method of administration/data collection
- Translate and culturally adapt to other languages
- Evaluate modifications as appropriate
- Document all changes



Background

Pompe disease (PD) is a rare autosomal recessive disorder caused by **mutations in the *GAA* gene**, which encodes for acid alpha-1,4-glucosidase.[1,2]

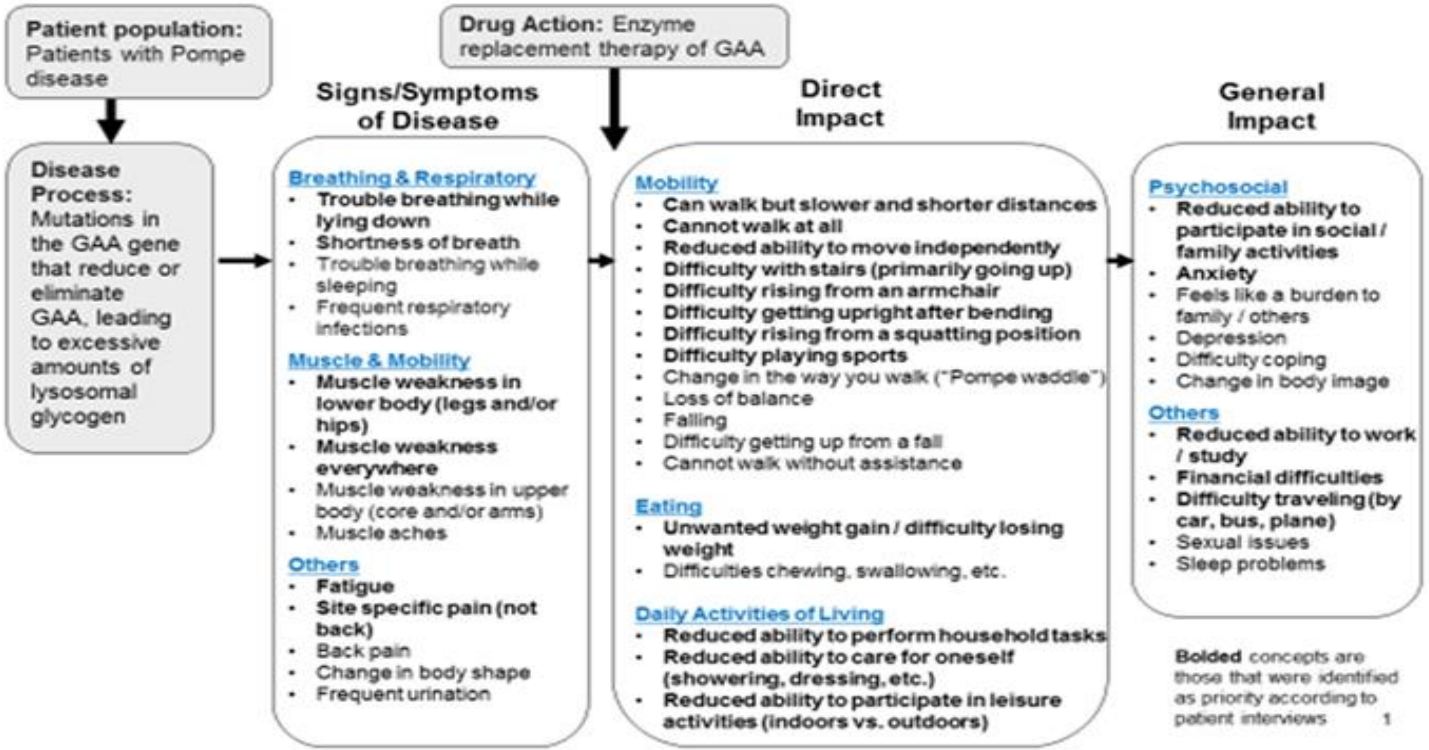
There are two types of PD namely, infantile-onset PD (IOPD) and late-onset PD (LOPD). IOPD often presents symptoms within the first few months of birth, while LOPD generally manifests in patients after the age of 12 months.[3]

Symptoms of LOPD range from progressive muscle weakness, respiratory symptoms, and progression to respiratory insufficiency. Progression of the disease often leads to significantly pronounced respiratory complications in patients with LOPD.[3]

Two disease-specific PROMs, the **Pompe Disease Symptom Scale (PDSS)** and **Pompe Disease Impact Scale (PDIS)** have recently been developed that measure the symptom frequency, severity, and impact of LOPD.

PD, Pompe disease; IOPD, infantile-onset pompe disease; LOPD, Late onset pompe disease; PROM, Patient-reported outcome measure; PDSS, Pompe disease symptom scale; PDIS, Pompe disease impact scale. 1. van der Ploeg AT, et al. Lancet. 2008;372(9646):1342–1353; 2. Peruzzo P, et al. Ann Transl Med. 2019;7(13):278; 3. Teener JW, et al. Semin Neurol. 2012;32(5):506-511; 4. Cuplet EJ, et al. Muscle Nerve. 2012; 45(3):319-333

Conceptual Model



PDSS and PDIS

PDSS

What is PDSS?[1]

- A 12-item self-administered questionnaire that measures symptoms
- Pompe Disease symptoms: general breathing difficulties, feeling of tiredness, fatigue or muscle weakness in different body parts, muscle aches, pain, and morning headache

Domains

- Shortness of Breath
- Overall Fatigue
- Fatigue/Pain
- Upper Extremity Weakness
- Pain

Response Scale

- Each of the five domains of PDSS will be scored as follows:
    - Ranges from 0 (none) to 10 (as bad as I can imagine)

PDIS

What is PDIS?[1]

- A 15-item self-administered questionnaire that captures the impacts
- There is a 7-day recall version of the PDIS as well as a 24-hour recall version of the PDIS.
- Pompe Disease Impacts: anxiety, feelings of worry and feeling of depression, and abilities and difficulties doing daily activities, including walking, climbing any stairs, rising from a sitting position, picking up an object from the floor, squatting down, and exercising.

Domains

- Mood (score ranges from 0–10)
- Difficulty performing activities (score ranges from 0–4)

Response scale as per item type

- 0 (none) to 10 (as bad as I can imagine)
- 3-point scale: no (not physically able) and yes
- 5-point scale: 0 (not at all difficult) to 4 (extremely difficult)
- The PDIS yields 9 scale scores.

PDSS, Pompe disease symptom scale; PDIS, Pompe disease impact scale

1. Dimachkie MM, et al. Neurol Clin Pract. 2023;13(5):e200181.

PDSS and PDIS were tested and validated

PDSS and PDIS were assessed in the COMET clinical trial[1] and an RWE study.

Reliability was assessed based on **internal consistency** where the Cronbach's α coefficient showed acceptable values.*

Test–retest reliability was assessed using appropriate intraclass correlation coefficients (ICCs)**.

Validity was assessed using Spearman's correlation coefficient (*r*). Moderately high-to-high correlations were reported between PDSS/PDIS and other PROMs.***

PDSS, Pompe disease symptom scale; PDIS, Pompe disease impact scale; SD, standard deviation; ICCs, intraclass correlation coefficients; RWE, real world evidence

1. Dimachkie MM, et al. Neurol Clin Pract. 2023;13(5):e200181.

*Acceptable score for the internal consistency Cronbach α>0.70

**poor (ICC <0.50), moderate (ICC = 0.50–0.75), good (ICC = 0.75–0.90), excellent (ICC ≥0.90)

***Spearman's correlation coefficient (*r*): moderate: 0.40–0.59; high: 0.60–0.79.

Registries

Registries

Type	Focus	Uses	Other
Patient (disease)	Collect data regarding the health status of the patient and care they receive	• Evaluate outcomes • Best practices • Treatment guidelines	Established by patient organization or industry
Specialty	Advancing care outcomes across a medical specialty/sub-specialty	• Develop guidelines and decision support tools • Advance research	May serve as QCDRs to allow clinicians to report to CMS under MIPS
Population	Focus on entire patient population spanning disease and specialty	• Seek to capture comprehensive population-level health status data	
Device	Tracking the safety and efficacy of a medical device	• Support post-marketing surveillance	Established by medical specialty organization and device company
Payor	Focus on improving outcomes and reducing cost	• Aim to measure and enhance value	Established by healthcare payor organization

CMS: Centers for Medicare and Medicaid Services; MIPS: Merit-based Incentive Payment System; QCDRs: Qualified Clinical Data Registries

Registry - Considerations

- Standardized data collection methods and data definitions
- Integrated tools for rapid feedback to participating institutions/regulatory bodies
- Proper ethical review processes
- Electronic data capture
- Representativeness of the patient population under investigation
- An audit process which assesses data accuracy
- Centralized data compilation and statistical analysis performed by professional statisticians
- Appropriate and transparent reporting

Hoque DME, et al (2017) *PLoS ONE* 12(9): e0183667

Rare lysosomal disease registries: lessons learned over three decades of real-world evidence

Total number of patients and person-years

Table 2 Total number of patients and person-years in the Rare Disease Registries

Registry	Year Registry was established	Current data			Person-years					
		Total countries*	Total Registry sites**	Total patients	Total person-years from birth to last follow-up†		Total person-years from diagnosis to last follow-up‡		Total person-years from treatment initiation to last follow-up§	
					Person-years	N	Person-years	N	Person-years	N
ICGG Gaucher Registry	1991	64	278	6872	266,543	6844	112,115	6481	67,470	5595
Fabry Registry	2001	47	243	7930	344,445	7897	78,220	7267	38,523	5017
MPS I Registry	2003	41	144	1325	18,598	1323	13,497	1297	10,086	1176
Pompe Registry	2004	47	240	2467	87,251	2463	21,761	2405	13,510	2210
Total			805	18,594	716,837	18,527	235,593	17,450	129,589	13,798

All Data as of February 2022

*Includes currently and historically active countries/regions

**Includes currently active sites where at least one patient is enrolled

† Data are shown for patients with non-missing dates of birth and last follow-up

‡ Data are shown for patients with non-missing dates of diagnosis and last follow-up

§ Data are shown for ever-treated patients with non-missing dates of treatment initiation and last follow-up

MPS I, Mucopolysaccharidosis type I

Mistry, et al. 2022, *Orphanet J Rare Dis*. https://doi.org/10.1186/s13023-022-02517-0

Timeline of Gaucher, Fabry, MPS I, and Pompe Registry Milestones

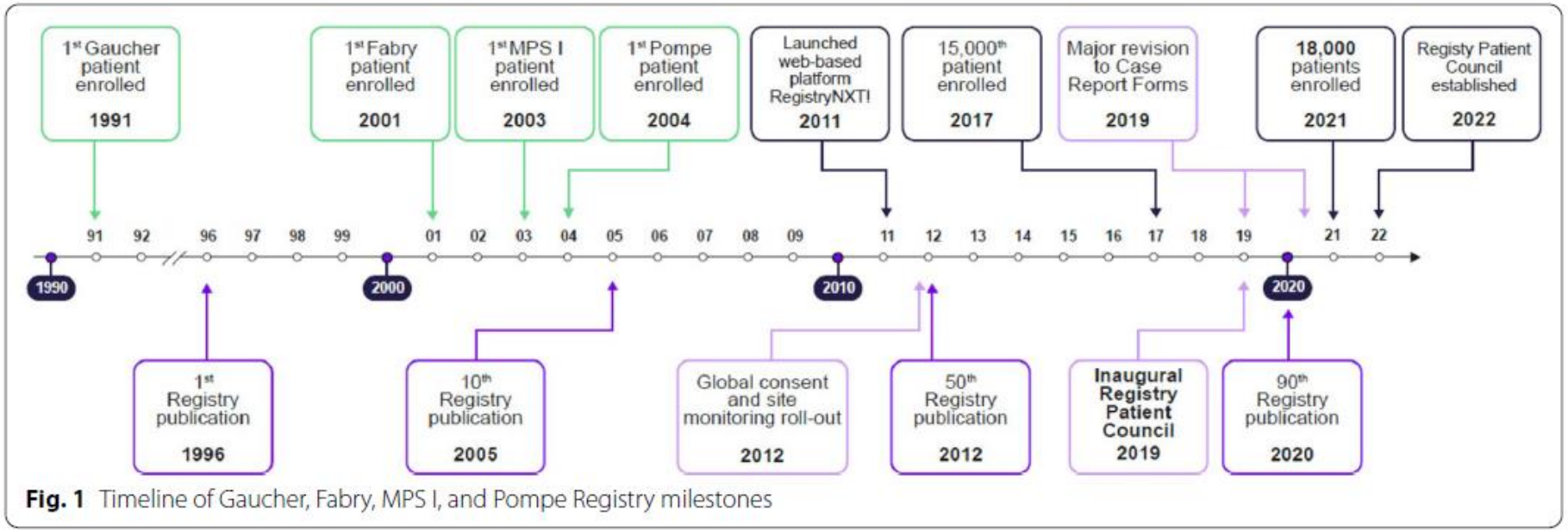


Fig. 1 Timeline of Gaucher, Fabry, MPS I, and Pompe Registry milestones

Mistry, et al. 2022, *Orphanet J Rare Dis*. https://doi.org/10.1186/s13023-022-02517-0

Impact of Rare Disease Registries Publications

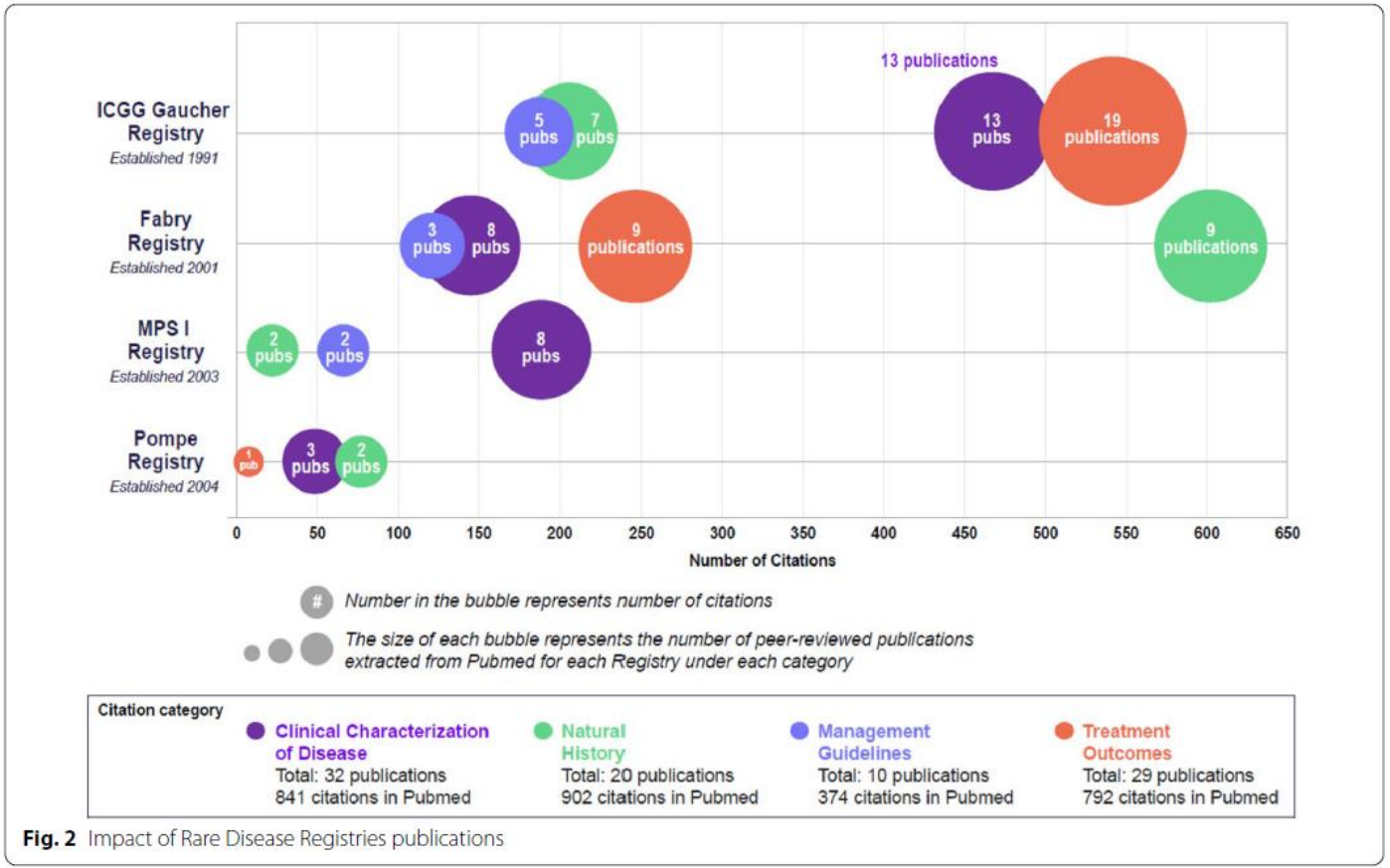


Fig. 2 Impact of Rare Disease Registries publications

Mistry, et al. 2022, *Orphanet J Rare Dis*. https://doi.org/10.1186/s13023-022-02517-0

Rare Disease Registries ePRO

ePRO is a digital innovation to directly collect electronic patient reported outcomes

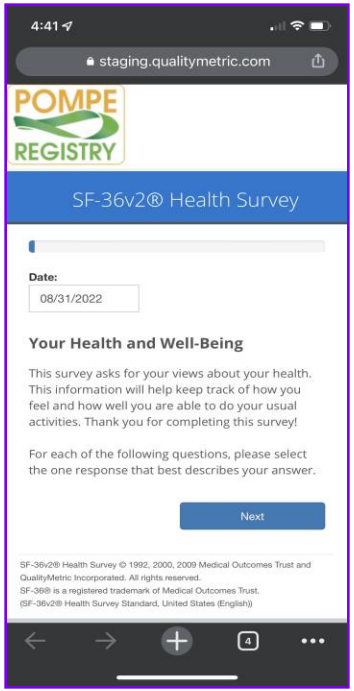
- Designed to improve patient engagement and participation in the Registries
- Patients become active participants in the Registries by entering their own PRO data
- Patients take ownership of their health outcomes and data entry

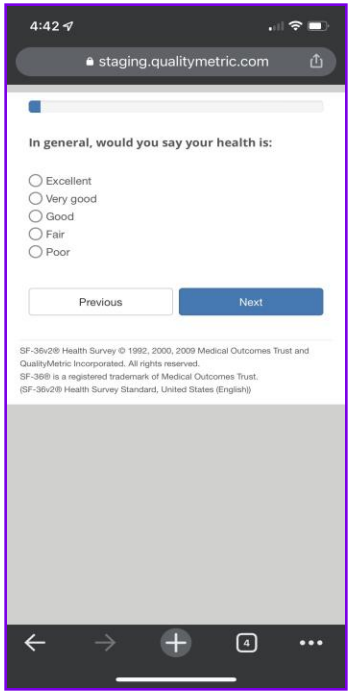
Benefits of ePRO:

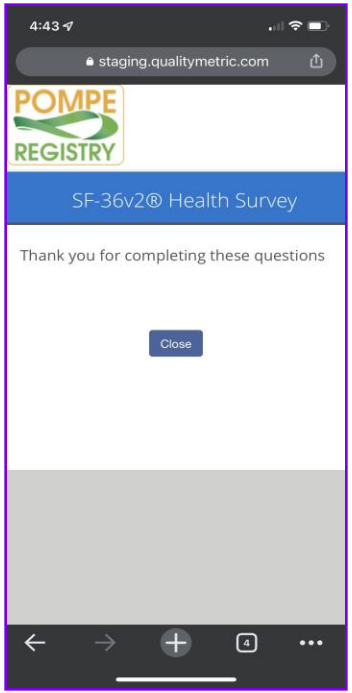
- Builds upon the existing technology of RegistryNXT! to enhance the patient experience
- Real-time patient-centric architecture
- Web-based mobile-friendly portal
- Integration of clinical and patient-reported data
- Streamlines data collection
- Provides patient insight to their own data through patient-facing reports

SF36v2 ePRO

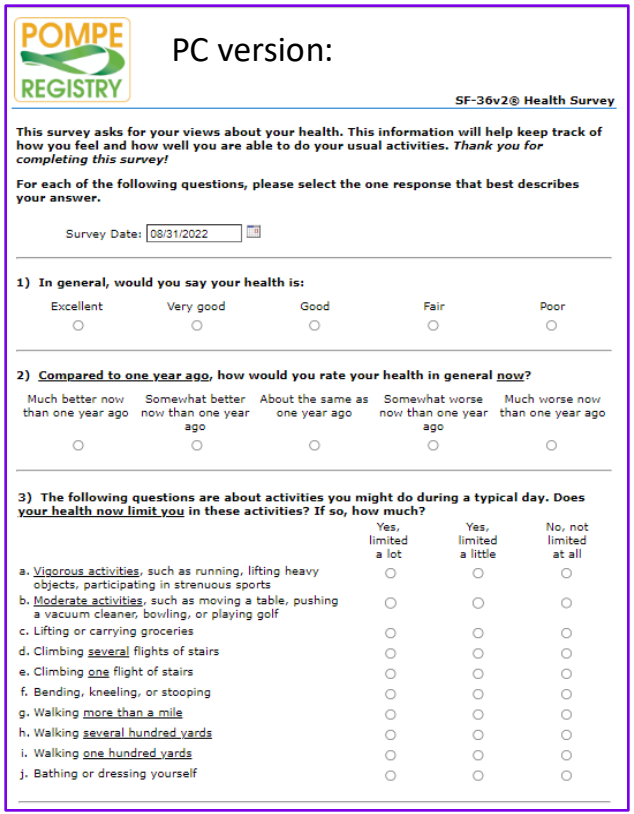
Mobile version:







PC version:



POMPE REGISTRY

SF-36v2® Health Survey

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please select the one response that best describes your answer.

Survey Date: 08/31/2022

1) In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

2) Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
○	○	○	○	○

3) The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	○	○	○
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
c. Lifting or carrying groceries	○	○	○
d. Climbing several flights of stairs	○	○	○
e. Climbing one flight of stairs	○	○	○
f. Bending, kneeling, or stooping	○	○	○
g. Walking more than a mile	○	○	○
h. Walking several hundred yards	○	○	○
i. Walking one hundred yards	○	○	○
j. Bathing or dressing yourself	○	○	○

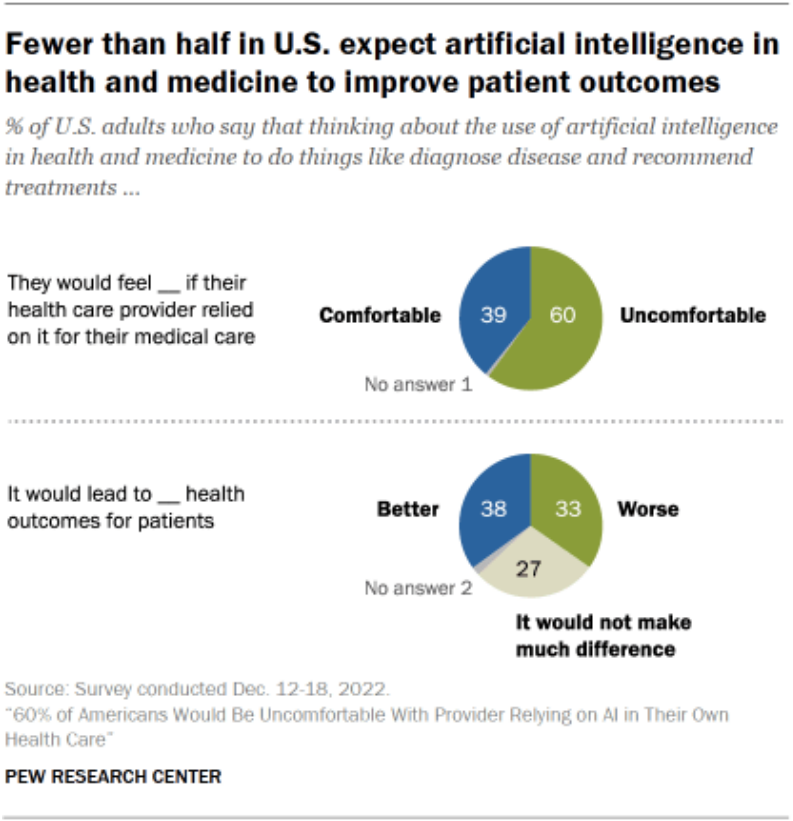
Digital Technologies in Clinical Trials

Uses of digital technologies in Clinical Trials

- The general population is increasingly comfortable with engaging in a variety of activities on smartphones, including downloading and using health and wellness mobile apps
- Mobile technology (smartphone applications, wearable devices, telehealth) offers an opportunity to enhance the efficiency and reach of clinical trials processes
  - Digital Diagnosis
  - Study Recruitment
  - Remote consenting
  - Evaluation of interventions (ie digital endpoints)
  - Collection of outcome data (ie Registries)

Carlo et al, 2019. *npj Digital Medicine.* 2, 54; Perry et al, 2018. *Digital Biomarkers.* 2(1), 11–30.; Marra et al 2020. *npj Digital Medicine.* 3, 50; Rosa et al 2021. *Contemp Clin Trials.* 100: 106219.

Digital tools and Patients



https://www.pewresearch.org/science/2023/02/22/60-of-americans-would-be-uncomfortable-with-provider-relying-on-ai-in-their-own-health-care/

Questions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