How is medicine changing?

More Than Half of Kaiser Permanente's Patient Visits Are Done Virtually

Last year, patients and doctors interacted more than 110 million times in total.

By Kia Kokalitcheva Oct 6, 2017

How is biopharmaceutical R&D changing?

FDA issues new guidance to facilitate expanded use of real-world evidence in medical device Development  Deborah Kotz

Digital Health Innovation Action Plan
Digital Health Software Precertification (PreCert) Program
Bold Digital: **What are we solving for?**

**How are patients changing?**

They are active, connected, informed and savvy.

Ill Literates or Illiterates? Investigating the eHealth Literacy of Users of Online Health Communities.  
Petrič G¹, Atanasova S¹, Kamin T²

The reliability of patient reported outcomes is still highly variable.

The Impact of Participation in Online Cancer Communities on Patient Reported Outcomes: Systematic Review.  
van Eenbergen MC¹, van de Poll-Franse LV¹,², Heine P³, Mols F⁴.

They desire price transparency but do not yet understand how to shop.

Patients’ views on price shopping and price transparency.  
Semigran HL, Gourevitch R, Sinaiko AD, Cowling D, Mehrotra A¹.

The younger & next generation is very different.

Exploring the digital technology preferences of teenagers and young adults (TYA) with cancer and survivors: a cross-sectional service evaluation questionnaire.  
Abrol E¹, Groszmann M², Pitman A³,⁴, Hough R⁵, Taylor RM⁶, Aref-Adib G⁴,⁷.

**Direct-to-consumer R&D is becoming mainstream.**

The RUDY study: using digital technologies to enable a research partnership  
Harriet J A Teare,¹* et al

The #1 reason patients use pharmacies is information.  
**Bold Digital: What are we solving for?**

How is product selection and delivery changing?

80 Million Prime Subscribers Ready for Amazon's Pharmacy?
Moyet Moken, Jun. 9, 2017

**What will that look like?**

Bayer Aspirin Regimen, Low Dose (81 mg), Enteric Coated, 300 Count

**Bayer** 4.7 out of 5 stars 1,170 customer reviews, | 67 answered questions
#1 Best Seller in Aspirin

Top customer reviews

4.0 out of 5 stars It's aspirin! By Serge Mikhaylov on December 9, 2016

1.0 out of 5 stars The Bayer product is great, but I received the bottle with the security...
... By SILVIA DE BARRAZA on August 29, 2016

1.0 out of 5 stars Short expiration date By Joyce Koppel on January 25, 2014
“There is currently a lot of hype and hope about progress at the intersections of technology, health care and biomedical R&D, but transformational change and increased value still seem distant.”

Strategies for delivering value from digital technology transformation
Does the fact that something can be measured make that something relevant?

or

Maybe both?
WHY DIGITAL PHENOTYPING?

Early safety signal
- DOSE AND SCHEDULE ADJUSTMENT
- BETTER UNDERSTANDING OF DRUG PROFILE
- EARLIER GO / NO-GO DECISIONS

Novel endpoints
- QUALITY OF LIFE
- SLEEP DATA
- MORE SENSITIVE MEASURES COMPARED TO TRADITIONAL DISEASE SCALES

Medication adherence
- IMPROVED ADHERENCE
- DOSE ADJUSTMENTS
- INCREASED EFFICIENCY IN DATA COLLECTION

Clinical trial engagement and retention
- FEWER OBSTACLES FOR ENROLLMENT
- REDUCED BURDENS FOR PATIENTS
- INCREASED PATIENT OUTREACH
KEY HISTORICAL EVENTS FOR WEARABLE DEVELOPMENT IN HEALTHCARE

1903: ECG
1958: Commercial Holter ECG
1962: Pacemaker
1973: Cell Phone
1981: Commercial Pulse Oximeter
1993: Electric BP Cuff
2007: IPhone model
2011: MedWatcher Mobile App
2014: FitBit model
2016: Fitbit recorded activity to assist arrhythmia management case report
For wearables to become a “mainstream” of drug development, we need to develop and establish acceptance for these commonly shared methodologies:

- Medical need – not device seeking applications
- Device choice
- Context of use
- For-for-purpose validation
- Operational requirements defined upfront
- Data collection, processing and interpretation
CONSUMER & MEDICAL GRADE DEVICES

CONSUMER GRADE

Intended use:
recreational/individual use only

Regulations for medical devices do not apply

Performance not verified

Manufacturing doesn’t comply with GMP

No lock down design

Users have access to their data, can interpret their data and make decisions based on the results

Easy access and convenience of use

MEDICAL GRADE

Intended use: diagnosis, disease prognosis or treatment decisions

Approved/ cleared by regulators

PMA or 510K in the US

Lock down design

Manufactured under GMP

Established standardized performance

Administered by HCP

Results are usually interpreted by HCP

IQ/OQ/PQ established if applicable
SOME ANTICIPATED CHALLENGES

EXPECTATIONS

DATA VOLUME

DATA INTERPRETATION

PRACTICALITIES

CYBERSECURITY

Cybersecurity in health care. *Perakslis ED*. 
Phase 1 Pilot: TAK-935 Bioavailability Study

Goals

- Confirm device acceptability (subjects / staff)
- Confirm data is interpretable
- Comparison to “conventional” measures
- Gain institutional experience

PHILLIPS ActiWatch
Data provided:
Movement, sleep, ambient light
Extended, continuous monitoring

VITALCONNECT HealthPatchMD
Data provided:
Single lead ECG, heart rate, heart rate variability, respiratory rate, skin temperature, steps
Extended, continuous monitoring
Example of Pilot Study Design: TAK-935 BA study

- **Device deployment**
- **Dosing**
- **ECG**
- **Vital signs**

**Period 1**
- D1
- D3

**Period 2**
- D1
- D3

**Period 3**
- D1
- D3

End of device collection data

Discharge/Study exit

9 subjects enrolled in the study
6 consented to wearable device component of the study
## Data loss: compliance vs device performance

### Completeness of Data

<table>
<thead>
<tr>
<th>SUBJECT</th>
<th>VITAL SIGNS</th>
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<tbody>
<tr>
<td>58001_0003</td>
<td>99.2%</td>
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<tr>
<td>58001_0007</td>
<td>98.6%</td>
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<tr>
<td>58001_0011</td>
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<tr>
<td>58001_0012</td>
<td>83.6%</td>
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<tr>
<td>58001_0015</td>
<td>95.2%</td>
</tr>
<tr>
<td>58001_0018</td>
<td>83.8%</td>
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</table>

### Device not worn?

<table>
<thead>
<tr>
<th>SUBJECT ID</th>
<th>ACTIGRAPHY</th>
</tr>
</thead>
<tbody>
<tr>
<td>58001_0003</td>
<td>98.6%</td>
</tr>
<tr>
<td>58001_0007</td>
<td>78.6%</td>
</tr>
<tr>
<td>58001_0011</td>
<td>98.2%</td>
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<tr>
<td>58001_0012</td>
<td>97.2%</td>
</tr>
<tr>
<td>58001_0015</td>
<td>98.3%</td>
</tr>
<tr>
<td>58001_0018</td>
<td>62.6%</td>
</tr>
</tbody>
</table>

### Poor contact?
Validation: data follow expected diurnal patterns

Actigraphy

Heart Rate

Respiratory Rate

Skin Temperature
Validation: actigraphy monitoring during exercise
Limitations: single-lead ECG interpretation

- No PR, QRS, QTc, ST analysis
- ‘Atypical’ waveforms
- No rhythm diagnosis (alerts for low / high HR)
- Variable access to raw data, depending on supplier
- Algorithms proprietary; incomplete audit trail
Validation: heart rate

Validation of Measure

\[ r = 0.71 \]

Gold Standard HR (beats/min)

Mobile HR (beats/min)
Validation: pharmacologic intervention

TAK 041 1002 Imaging (amphetamine challenge)

TAK-041

Amphetamine

Increased activity

Rested, supine HR

TAK17 Study (Rat)
Validation: respiratory rate

**Validation of Measure**

- Mobile Resp Rate (breaths/min)
- Clinic Resp Rate (breaths/min)

$r = 0.08$

TAK 935 BA data
Validation: temperature

Validation of Measure

Clinic Temp (deg C) vs. Mobile Skin Temp (deg C)

Validation: temperature

TAK 935 BA data
Utility for Safety Monitoring: Specificity?
User Acceptability

Adhesive failures
Gel leakage
Hypersensitivity reactions
Hassle factor
  • Device (two devices)
  • Data transmission

11 / 47 (23%) declined to participate
1 subject withdrew consent after 1 day

Why?
  • Too complicated
  • Will interfere with activities (gym; work)
  • Got a bad skin rash before
  • Want more money

10. Do you have any suggestions for how the use of these devices could be improved in future studies? Data here, 101
WHAT WE HAVE LEARNED SO FAR

Scientific
- Many devices look promising but not ready for a wider deployment
- Algorithm transparency is an issue
- Data interpretation can be challenging
- Fit-for-purpose validation is essential

Regulatory
- Scientific Context of use is different from indications and intended use on the device label

Operational
- Site staff familiarity with devices
- Acceptability by subjects
- Data process flow, data transfer specs

Institutional learning
- Selection of partner: outsourced vs in-house (e.g., external stats inefficient)
- Believe the peer-reviewed literature, not the press releases

When, Who, Why

NEJM: Nov 8, 2017; DOI: 10.1056/NEJMp1713180
CONSIDERATIONS FOR DEVICE DEPLOYMENT IN CLINICAL TRIALS

Scientific considerations and validation

Health aspect/Condition/Need Statement
Hypothesis /Scope/Need Statement
Select technology
Clinical study design*
Analytical Validation
Clinical Validation

Operational

Consumer or medical device
Acceptability to study subjects and site personnel
Data process and collection logistics
Data type and collection frequency

Analysis plan
Analysis
Data interpretation
Conclusion about technology fit-for-purpose

* Appropriate for COU and intended study population
<table>
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<tr>
<th>Study</th>
<th>Devices</th>
<th>Questions asked</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>UAT studies</td>
<td>• Embrace by Empatica&lt;br&gt;• SEEQ by Medtronic&lt;br&gt;• BodyGuardian by Preventice</td>
<td>User acceptance</td>
<td>Completed</td>
</tr>
<tr>
<td>TAK-041-1001 SRD/MRD</td>
<td>• HealthPatch by Vital Connect&lt;br&gt;• ActiWatch by Philips</td>
<td>Device performance and compliance</td>
<td>Study re-start late 2017</td>
</tr>
<tr>
<td>TAK-935-1005 BA</td>
<td>• HealthPatch by Vital Connect&lt;br&gt;• ActiWatch by Philips</td>
<td>Device performance and compliance</td>
<td>External analysis completed, internal analysis in progress</td>
</tr>
<tr>
<td>TAK-041-1002 PET</td>
<td>• Body Guardian by Preventice&lt;br&gt;• ActiWatch by Philips</td>
<td>Device performance with positive control, amphetamine challenge</td>
<td>Device data collection is completed, external analysis completed, internal analysis pending</td>
</tr>
<tr>
<td>TAK-418-1001</td>
<td>• Body Guardian by Preventice&lt;br&gt;• ActiLink by Actigraph</td>
<td>Device performance and compliance in the unit and home</td>
<td>Study recruiting, 2017 (currently studying 5th SRD cohort)</td>
</tr>
<tr>
<td>TAK-831-1501 Ataxia</td>
<td>• Mobility Lab Test by APDM&lt;br&gt;• Speech characteristics</td>
<td>Digital measures of disease change</td>
<td>Study start in November, 2017</td>
</tr>
<tr>
<td>TAK-041-2001 Schizophrenia</td>
<td>• Actiwatch by Philips</td>
<td>User acceptance and sleep patterns in disease</td>
<td>Study start in January, 2017</td>
</tr>
</tbody>
</table>
Bold Digital: Agile Methodology and Hybrid Funding Model

Q1 2016
$1.5 MM
GPT Dashboard
Entyvio, Ninlaro, Trintellix, Early Dev.

Q2 2016
$1 MM
Portfolio
Investor Relations, MPR

Q3 2016
$1 MM
Procurement
Supplier Diversity

Q4 2016
$0.5 MM
DDU
Candidate Quality

Q1 2017
$2 MM
OTAU
Patient Profile Medical Review

Q2 2017
$1 MM
RWE
Cohort Builder

$0.5 MM
GDO
Metrics, Milestones

Infrastructure, Support & Maintenance, Licensing
$4 MM

Support & Maintenance
$1 MM

Foundational Capability  POC  Functions Investment
Harvard Medical School to play key coordination role in NIH Undiagnosed Diseases Network

By Raymond MacDougall  Associate Director of Communications, Division of Intramural Research

What’s Wrong With Summer Stiers?
http://www.nytimes.com/2009/02/22/magazine/22Diseases-t.html?_r=3&emc=eta1&

60 Minutes HEALTH & SCIENCE
Hard cases: Investigating rare & tough diseases

NIH Undiagnosed Diseases Program documents two-year pilot as clinic of last resort
Genomic tools prove integral to solving medical mysteries
'Most challenging patients' hope to get diagnoses from medical experts

Undiagnosed Diseases Network now based at Harvard Medical School

Seven clinical sites
1. Baylor College of Medicine and Texas Children’s Hospital
2. Duke Medicine with Columbia University Medical Center
3. Harvard Teaching Hospitals (BCH, BWH, MGH)
4. National Institutes of Health
5. Stanford Medicine
6. UCLA School of Medicine
7. Vanderbilt University Medical Center

UDN Gateway
Online “cloud” portal for patients to apply and clinicians/researchers to collaborate

Six additional research sites
Central Biorepository
8. Vanderbilt University Medical Center
Coordinating Center
9. Harvard Medical School

DNA Sequencing Core Facilities
10. Baylor College of Medicine
11. a. HudsonAlpha Institute for Biotechnology with illumina
b. Cleveland Clinic
Metabolomics Core Facility
12. a. Pacific Northwest National Laboratories with Oregon Health & Science University
b. Texas A&M University
Model Organisms Screening Center
13. a. Baylor College of Medicine with University of Oregon

https://undiagnosed.hms.harvard.edu/
UDN Coordinating Ctr. Clinical Cloud (UDN-C⁴)

- HIPAA/GCP
  - UDN Gateway
  - UDN CTMS/eCRF
  - UDN Archive
  - UDN User Identity Access Management (IAM) and Security Layer
  - UDN Clinical Sites

- FISMA
  - UDN Archive

- De-Identified
  - UDN Warehouse

Roles:
- UDN Patient/Provider Roles
- UDN CC/Admin/Clinical Network Roles
- UDN External Researcher Roles
- UDN Clinical Staff Roles
Compliance is not optional but can be a Strategic Advantage when done right.
How the Undiagnosed Diseases Network helped solve my daughter's medical mystery

“Science has not caught up with Avery yet!”

That is what we often heard from doctors about our 9-year old, Avery, the youngest of our four daughters.
Call for Papers: JMI R Theme Issue on Cybersecurity in Healthcare & Biomedical Research (Eds: @eperaks is + Stanley) jm ir.org/announcement/v...
Company with no privacy policy to collect brainwave data on 1.2 million students

BrainCo headbands to be used on students to collect biometric brainwave data on over one million students and ultimately create “the world’s biggest brainwave database.”
Exceptional Responders

- Exceptional responders are patients who respond to treatments in ways that are both dramatically and unexpectedly positive but also statistically insignificant within the usual context of biopharmaceutical drug trials.
Emily Whitehead, right, beat cancer through immunotherapy. She's pictured onstage with Lady Gaga at the launch of the Parker Institute for Cancer Immunotherapy. (Jonathan Leibson/Getty Images for Parker Media)
PIs, Governance, Advisory, Publication Strategy, Data Sharing Strategy are Common

**People-powered ARM**
- Prospective
- HMS IRB
- Inclusion criteria evolves
- Indication is all cancers
- Technology stack is HMS PPM
- Recruitment is crowd-sourced
- Data is medical-record based
- Compliance is HIPPA-driven

**BioPharma Consortium ARM**
- Retrospective
- IRB is TBD
- Inclusion criteria pre-determined
- Indications are cancers plus TBD
- Technology stack is TBD
- Recruitment depends upon original ICF content
- Data is RCT-based
- Compliance is GCP-driven

**Crossover - ARM**
- When re-contact is allowed by original informed consent
- When patients can be located
# Existing Programs

<table>
<thead>
<tr>
<th>Exceptional Responders Initiative</th>
<th>Undiagnosed Diseases Network</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Seeks to understand the molecular underpinnings of exceptional responses to treatment, primarily via chemotherapy, in cancer patients</td>
<td>• Bringing together clinical and research experts from across the United States to solve the most challenging medical mysteries</td>
</tr>
</tbody>
</table>

**Relevance:**

Patient criteria for NEER is much less restrictive; two arms to the network

**Relevance:**

NEER will mimic successes from UDN regarding network platform structure
Takeda Data Science Institute: Human Data Strategy

R&D Data Lake

<table>
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<td>TAK-851 15001 Ataxia</td>
<td>Mobility Lab Test by APDM &amp; Speech characteristics</td>
<td>Digital measures of disease change</td>
<td>Study start in November, 2017</td>
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</table>

Human Data Strategy

Deep Phenotyping: Wearable Digital Devices
Data Science Transformation @Takeda R&D

2015: Traditional Pharma Data/Capability Silos

- Drug Discovery & Pre-clinical
  - Bio-Informatics
  - Chemo-Informatics
  - Molecular Profiling
- First in Human
  - Non-Clinical Statistics
  - Clinical Statistics
- Clinical Development
  - Clinical Statistics
- Medical Safety & Medical Affairs
  - Clinical Statistics
  - PV Stats
  - RWE
  - PV Epi.

R&D Transformation

- Stats: 138
- Global Outcomes Research: 36
- DF Stats: 22
- Pharmaco-epidemiology: 10
- Competitive Intelligence: 7
- Pre-Transformation: 207
- + 5 new Data Sci. Positions: 212

Current: 165

2017: Takeda Data Sciences Institute

- 70 Clinical Statisticians
- 10 non-clinical Statisticians
- 5 Stats Programmers
- 8 Analytics/data architects
- 9 Informaticians
- 26 Outcomes/RWE experts
  - 7 epidemiologists
  - 1 molecular epidemiologist
  - 2 Molecular Profiling
  - 2 Devices/Diagnostics
- 6 Competitive Intelligence
- 19 Outcomes & Safety Statisticians
The Only 100% Integrated Data Science Strategy in Bio-Pharma: Takeda R&D Data Science Institute

<table>
<thead>
<tr>
<th>Human Data</th>
<th>Data Fluidity</th>
<th>Scientific Rigor</th>
<th>Technology</th>
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<tbody>
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<td>Biostatistics</td>
<td>Informatics</td>
<td>Medical Devices</td>
<td>Advanced Technologies</td>
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<tr>
<td>Epidemiology</td>
<td>Novel Analytics</td>
<td>Molecular Profiling</td>
<td>Forensics</td>
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<td>Safety Analytics &amp; Statistics</td>
<td>AI &amp; Deep Learning</td>
<td>Genomics</td>
<td>Cyber Security</td>
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<table>
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<tr>
<th>Our Capabilities</th>
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<th>Our Services</th>
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<tbody>
<tr>
<td>New &amp; Novel Data Types</td>
<td>Clinical Study Support</td>
<td>Data Delivery</td>
<td>Education</td>
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<td>Genomics</td>
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<tr>
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<td>Regulatory Response</td>
<td>Original Science</td>
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<td>Data Analysis</td>
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We Do & We Partner

<table>
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<tr>
<th>Execution</th>
<th>Support</th>
<th>Data</th>
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</table>
Acknowledgements

Clinical Teams
TAK-041
TAK-418
TAK-831
TAK-925
TAK-935

John Wagner
Eric Perakslis
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