Transforming Clinical Research
The Return of the House Call
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Disclosures

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House calls were standard practice for physicians in the early 20th century

Brief history of house calls, 1930-1980
Proportion of patient-physician encounters that were in the home

Factors leading to the decline of the house call
- **Transportation** – Increasing availability of cars due to lower cost and improved roads
- **Technology** – Diagnostic and therapeutic technologies (e.g., x-rays, ECGs, labs) moved care from the home to more expensive institutions

Telecommunications and technology are bringing the house call back

Proportion of American adults with broadband access, 2000 – 2010

The result is the virtual house call ...

Virtual house calls for episodic conditions

Video Visits With Board-Certified Physicians

The fastest, easiest way to see world-class physicians from the comfort of home.

Source: Doctor on Demand. http://www.doctorondemand.com/medical
... that many organizations are now providing Virtual house calls for episodic conditions

<table>
<thead>
<tr>
<th>Organization</th>
<th>Example</th>
<th>Services Provided</th>
<th>Price, $</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic medical centers</td>
<td>Massachusetts General Hospital, University</td>
<td>1-time consultations for common conditions (e.g., sore</td>
<td>38 per visit</td>
<td>University of Pittsburgh Medical Center offers its AnywhereCare program to anyone in Pennsylvania; &gt;50 clinicians at Massachusetts General Hospital have conducted &gt;1000 virtual visits since 2013.</td>
</tr>
<tr>
<td></td>
<td>of Pittsburgh Medical Center</td>
<td>throat) Heart failure Neurology Psychiatry</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Long-term care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Federal entities</td>
<td>VA</td>
<td>Long-term care</td>
<td>Covered service</td>
<td>VA conducted &gt;200 000 video consultations in 2013 and has 4500 clinical video end points for telehealth.</td>
</tr>
<tr>
<td>Health insurers</td>
<td>Anthem, UnitedHealth Group</td>
<td>1-time consultations for common conditions (e.g., sore</td>
<td>45-49 per visit</td>
<td>Anthem plans to extend its service to 32.5 million members by 2016.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>throat) Mental health care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health care start-ups</td>
<td>American Well, Doctor on Demand, Teladoc</td>
<td>1-time consultations for “most common, most irritating,</td>
<td>40-49 per visit</td>
<td>Digital health companies raised &gt;$4 billion in 2014.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>most inconvenient” conditions</td>
<td></td>
<td></td>
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<tr>
<td>Prepaid health plans</td>
<td>Kaiser Permanente</td>
<td>Acne Substance abuse Urgent care</td>
<td>Covered service</td>
<td>The number of virtual visits at Kaiser Permanente Northern California is expected to surpass that of in-person visits by 2016.</td>
</tr>
</tbody>
</table>

VA = U.S. Department of Veterans Affairs.

We are using simple, inexpensive technology to reach patients around the world

Novel application of existing technology

Equipment

• Internet-enabled device
• Web cam, microphone
• Encrypted software

Personalized care

Global reach

• In-home care
• Remote patient monitoring
• Remote study participation
Virtual visits flip the care paradigm

Patient time spent on in-person versus telemedicine visits

**Door-to-door**

100% = 255 minutes

- Time spent with physician: 22%
- Time spent traveling and waiting: 78%

**On-to-off**

100% = 53 minutes

- Time spent connecting: 28%
- Time spent with physician: 72%

Virtual visits offer patients care, convenience, and comfort

Feedback from patients and families

- **Care**
  - “We had a good family crying moment after the appointment from just pure joy of finally having the opportunity for him to see a (Parkinson disease) specialist”
  - “The (Parkinson disease) literacy was amazing”

- **Convenience**
  - “It’s great not having to drive the 2 hours ... having the added expense of my wife missing an entire day of work, [and] saving on gas for the car, tolls, [and] parking”
  - “I could have access to a movement specialist, which I currently don’t where I live”

- **Comfort**
  - “I liked the interaction being personal despite the 3000 mile distance...it felt somehow protected by the veil of technology, which enabled the exchange to be more honest”
  - “I am more relaxed in my home setting”

We have completed a national randomized controlled trial of telemedicine for Parkinson disease in collaboration with Connect.Parkinson.org.
Physicians are generally satisfied but have concerns about the quality of the connection

Initial clinician feedback
N = 87 responses

Selected physician feedback

- “Visit interaction was great, but it was very difficult to determine actual ratings for rapidly alternating movements.”
- “Video quality, particularly for rating Unified Parkinson’s Disease Rating Scale is frustrating.”
- “I think it is fine for the interview part, and maybe for clinical follow-ups.”

Source: Connect.Parkinson Study
Patients are very satisfied with the telemedicine visits

Initial patient feedback
N= 85 responses

Selected patient feedback
• “I learned more in one visit than all the information provided by other physicians over a period of years!!!”
• “I felt it was a great doctor’s visit. Better than many I’ve had face to face.”
• “It was so good to not have to ride 45 minutes in a handicapped van each way to see a (movement disorder specialist).”
• “On a cold rainy day it was so nice not to have to worry about getting a ride and getting from the car to the office. I could concentrate on what I wanted to ask and the info the doctor provided.”

Source: Connect.Parkinson study
We conducted remote assessments with 50 participants in 23 states in 3 months

**Results**
- All study participants with self-reported PD were judged by neurologists to have PD (k=1.00)
- Also had high level of agreement for age of onset (k=0.97) and presence of family history (k=0.85)
- 95% of participants indicated interest in future virtual research visits
- This study sets the stage for larger scale studies targeting genetic sub-populations

Source: Digital Health available at: http://dhj.sagepub.com/content/1/2055207615592998
We performed a similar study with Fox Trial Finder and connected remotely to over 160 participants in 39 states.
This study provided some valuable insights

Virtual research visits

**Methods**
• Fox Trial Finder participants provided consent by phone, completed baseline surveys, downloaded video conferencing software, and received a web camera.
• After a test connection, participants underwent a remotely assessed cognition and had a virtual research visit to:

  (1) Review their history
  (2) Perform MDS-UPDRS (modified to exclude assessments of rigidity and balance).
  (3) Confirm whether PD was the most likely diagnosis,
  (4) Solicit feedback on their experience

**Results**
• 81.4% individuals from 39 states completed the visits

• On average, participants were:
  (1) 61.6 years old
  (2) Had Parkinson disease for 8.0 years
  (3) Scored 26.5 on the Montreal Cognitive Assessment
  (4) Had modified UPDRS motor score of 22.8.
  (5) Parkinson disease was most likely diagnosis in 97.0% of cases.

• Overall satisfaction with the visits was 79% (satisfied or very satisfied) among neurologists and 93% among participants.
To help stem the productivity decline, change is needed

Characteristics of 20th vs 21st century clinical trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>20th Century</th>
<th>21st Century</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Randomized, double-blind, parallel-group, placebo-controlled trial</td>
<td>Randomized, double-blind, parallel-group, placebo-controlled trial using adaptive designs</td>
</tr>
<tr>
<td>Study population</td>
<td>All comers with a given disease</td>
<td>Individuals selected based on phenotypic and genetic results</td>
</tr>
<tr>
<td>Study recruitment</td>
<td>Clinical practices</td>
<td>Global clinical trial registries and social networks organized by</td>
</tr>
<tr>
<td>Trial visits</td>
<td>In person and audio calls</td>
<td>In person and audio and video calls</td>
</tr>
<tr>
<td>Data management</td>
<td>Paper and electronic forms</td>
<td>Electronic forms</td>
</tr>
<tr>
<td>Participant feedback</td>
<td>Limited, delayed</td>
<td>Almost universal, approximately real time</td>
</tr>
<tr>
<td>Outcome measures</td>
<td>Insensitive</td>
<td>Sensitive</td>
</tr>
<tr>
<td></td>
<td>Episodic</td>
<td>Frequent or continuous</td>
</tr>
<tr>
<td></td>
<td>Subjective</td>
<td>Objective</td>
</tr>
<tr>
<td></td>
<td>Provider centered</td>
<td>Patient centered</td>
</tr>
<tr>
<td></td>
<td>In clinic</td>
<td>Remote</td>
</tr>
<tr>
<td></td>
<td>Unidimensional</td>
<td>Multidimensional</td>
</tr>
</tbody>
</table>

Clinical trials increasingly use novel measures

Accelerometers in a CHF trial

Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction

Margaret M. Redfield, M.D., Kevin J. Anstrom, Ph.D., James A. Levine, M.D.,
Gabe A. Koepp, M.H.A., Barry A. Borlaug, M.D., Horng H. Chen, M.D.,
Martin M. LeWinter, M.D., Susan M. Joseph, M.D., Sanjiv J. Shah, M.D.,
Marc J. Semigran, M.D., G. Michael Felker, M.D., Robert T. Cole, M.D.,
Gordon R. Reeves, M.D., Ryan J. Tedford, M.D., W.H. Wilson Tang, M.D.,
Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Monica R. Shah, M.D.,
and Eugene Braunwald, M.D., for the NHLBI Heart Failure Clinical Research Network

ABSTRACT

METHODS
In this multicenter, double-blind, crossover study, 110 patients with heart failure and a preserved ejection fraction were randomly assigned to a 6-week dose-escalation regimen of isosorbide mononitrate (from 30 mg to 60 mg to 120 mg once daily) or placebo, with subsequent crossover to the other group for 6 weeks. The primary end point was the daily activity level, quantified as the average daily accelerometer units during the 120-mg phase, as assessed by patient-worn accelerometers. Secondary end points included hours of activity per day during the 120-mg phase, daily accelerometer units during all three dose regimens, quality-of-life scores, 6-minute walk distance, and levels of N-terminal pro–brain natriuretic peptide (NT-proBNP).

Movement disorders have external manifestations that smartphones can assess.

**Figure 1:** Picture of Android smartphone and software application.

**Figure 2:** Procedure for collecting voice recordings, finger tapping, and passive sensor data from gait and postural sway test.

Smartphones can distinguish those with PD from those without

Gait and posture tests in Parkinson disease

Source: Parkinsonism and Related Disorders 2015 (epub ahead of print)
We have recently launched a 2000 person smartphone study in PD

Two new studies in which you can participate!

**Smartphone Data:** A new study for people with, and without, Parkinson's, in collaboration with the University of Rochester Medical Center. You will need an Android smartphone, please enroll to contribute data collected by your smartphone to this exciting new project.

**Electronic Consent for Smartphone-PD**

You may read and complete this consent form on any of your internet-enabled devices (e.g. desktop or laptop computer, tablet, smartphone, etc.).

Please complete the following to enroll in the SMARTPHONE-PD Study. If you choose not to participate, there will be no penalty to you. A blank copy of this consent form can be downloaded from this attachment for your review prior to providing consent. Please keep this copy for your records.

Attachment: [SmartphonePD RSRB 50772 Consent Form 7_16.pdf](https://foxtrialfinder.michaeljfox.org/trial/3861/)
Smartphones allow for global participation anytime anywhere

Geographical representation of study participants (N=653)
Participants have produced nearly 100,000 hours of high fidelity and high frequency data over 6 months.

“Where today people surf the Web and check their e-mail on their cell phones, tomorrow they will be checking their vital signs.”

-Eric Topol
Data are captured remotely from the smartphone and transferred to a secure server and then analyzed.

Architecture of the Android smartphone application.

Source: IEEE Journal of Biomedical and Health Informatics (under review)
The signal from the smartphone sensors can be quite sensitive in response to drugs

Sample accelerometry tracing in three dimensions

Source: IEEE Journal of Biomedical and Health Informatics (under review)
Pharma companies are incorporating such devices into early stage development.

Roche app measures Parkinson's disease fluctuations

“This could be the first time that such an app has been used to measure disease and symptom severity in a medicine development program in Parkinson’s disease.”

In March 2015 Apple announced the release of smartphone applications for medical research

mPower smartphone application for Parkinson disease
Researchers are leveraging these apps to reach large populations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Name of the app (lead organization)</th>
<th>Participants enrolled as of 10/5/15</th>
<th>Functionality of the app</th>
</tr>
</thead>
</table>
| Asthma                     | Asthma Health (Mount Sinai)          | 7,770                               | • Surveys  
• Structured tasks, including electronic diary of symptoms and triggers  
• Passive monitoring of activity and local air quality  
• Daily maintenance medication reminders  
• Educational information                                                                                                                                                                                                                                                                  |
| Breast cancer              | Share the Journey (Sage Bionetworks) | 2,508                               | • Surveys to assess cognitive changes, changes in mood, fatigue, sleep patterns and exercise  
• Randomization to daily expressive diary and exercise motivation  
• Passive monitoring of movement, exercise and typing patterns  
• Educational information                                                                                                                                                                                                                                                                  |
| Cardiovascular disease     | My Heart Counts (Stanford)           | 44,841                              | • Surveys  
• Passive monitoring of physical activity through phone or wearables  
• Structured tasks, including assessments of fitness and guideline-based-cardiovascular risk scores                                                                                                                                                                                                                                          |
| Diabetes                   | GlucoSuccess (Massachusetts General Hospital) | 5,595                               | • Surveys on sleep, diabetes care, quality of life  
• Blood glucose tracking (from device or manual entry)  
• Food logging  
• Passive monitoring of physical activity through phone or wearables  
• Insights relating users’ blood glucose levels with health behaviors                                                                                                                                                                                                                      |
| Parkinson disease          | mPower (Sage Bionetworks)            | 15,340                              | • Surveys  
• Structured tasks, including assessments of voice, motor speed, memory, gait, and posture  
• Passive monitoring of activity and mobility                                                                                                                                                                                                                                           |

Source: Academic Medicine (epub ahead of print)
mPower includes surveys, structured tests of cognition, speech, speeded taps, speed and gait
This technology is currently being used in clinical trials to capture objective measures of Parkinson disease.
We conducted a pilot study of wearable sensors in Huntington disease

Pilot study

• 15 individuals with Huntington disease and five unaffected family members
• Individuals wore five sensors (one for chest and one for each limb) in clinic and for one day at home
• Wore chest sensor at home for an additional six days
• Objective was to assess feasibility and ability to differentiate those with Huntington disease from controls
• Sponsored by Auspex/Teva Pharmaceuticals; sensors from BioSensics

We found significant differences in gait in the clinic and more differences at home

Analysis of gait features during walking test in clinic and at home*

<table>
<thead>
<tr>
<th>Feature</th>
<th>In Clinic</th>
<th>At Home</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n = 5)</td>
<td>HD (n = 15)</td>
</tr>
<tr>
<td></td>
<td>HD (n = 15)</td>
<td>Control (n = 7812)</td>
</tr>
<tr>
<td></td>
<td>HD (n = 6987)</td>
<td>p-value</td>
</tr>
<tr>
<td>Step time standard deviation (seconds)</td>
<td>0.03 ± 0.01</td>
<td>0.12 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>&lt;0.0001*</td>
<td>0.08 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>0.13 ± 0.05</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Maximum medial-lateral speed (meters/second)</td>
<td>0.46 ± 0.08</td>
<td>0.59 ± 0.15</td>
</tr>
<tr>
<td></td>
<td>0.091</td>
<td>0.53 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>0.66 ± 0.23</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Average medial-lateral speed (meters/second)</td>
<td>0.12 ± 0.02</td>
<td>0.18 ± 0.07</td>
</tr>
<tr>
<td></td>
<td>0.059</td>
<td>0.14 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>0.19 ± 0.06</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Maximum medial-lateral displacement (meters)</td>
<td>0.14 ± 0.04</td>
<td>0.21 ± 0.11</td>
</tr>
<tr>
<td></td>
<td>0.179</td>
<td>0.22 ± 0.11</td>
</tr>
<tr>
<td></td>
<td>0.27 ± 0.13</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Average medial-lateral displacement (meters)</td>
<td>0.06 ± 0.03</td>
<td>0.09 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>0.386</td>
<td>0.09 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>0.11 ± 0.08</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

* Walking test was the Timed Up and Go test

We have launched a pilot study to evaluate state of the art sensors for multiple neurological disorders

MC10 BioStampRC

Sensor-MD Overview:
• We are enrolling 40 participants
  • 10 with Parkinson disease
  • 10 with Huntington disease
  • 10 with prodromal Huntington disease
  • 10 without a movement disorder
• Participants will wear sensors on their 1) trunk; 2) arms; and 3) legs
• Aims of the study:
  • Feasibility
  • Ability to differentiate between groups
  • Ability to detect pharmacological response to treatment
  • Ability to generate novel insights

Source: http://www.mc10inc.com/our-products/biostamprc
Transforming face-to-face clinical research

- Individuals can accurately self-identify illnesses, sometimes using direct to consumer testing
- Individuals endorse ‘research from home’, and provide consent remotely
- Researchers endorse remote evaluations, but feel some constraints with technology
- Researchers in one location can access and evaluate potential participants in a national and perhaps global distribution
- The model of an academic clinical research site with a local reach is actively being ‘disrupted’ by central research sites with a global reach