



New Approaches to Medication Adherence Monitoring and Management

Innovations to Empower Patients, Support Differentiated
Care and Improve Health Outcomes: The Future Is Now

March 14, 2019



DISCLOSURES

- I am/have been funded by the Bill & Melinda Gates Foundation.
- I am/have been a paid consultant for WHO, Novartis, Bill & Melinda Gates Foundation, Medicines for All Institute, Unitaid, and the Stop TB Partnership.
- I have no conflicts of interest to declare.

EXECUTIVE SUMMARY

- Medication adherence is increasingly recognized as a major barrier to positive health outcomes.
- There is a wide range of digital technologies available to help address these adherence challenges.
- These technologies are increasingly:
 - Well accepted by patients (and providers),
 - Affordable,
 - Scalable,
 - Patient-centered,
 - Integrated/integratable, and
 - Evidence-based
- TB has led the way in evaluating, scaling, and utilizing these technologies in clinical practice.
- If we can use adherence technologies to inform and enable differentiated care with TB patients in the slums in Mumbai, where won't they work?
- What are we waiting for?



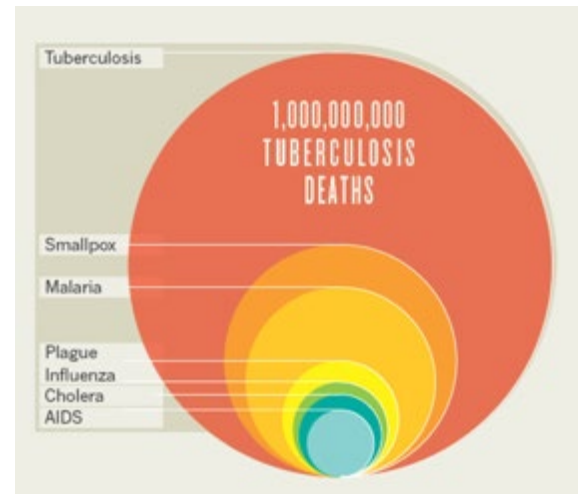


Tuberculosis Case Study



PROBLEM STATEMENT AND THEORY OF CHANGE

1. Current regimens likely to dominate for the next decade
2. Growing evidence that current regimens are *less forgiving for dosing gaps* than previously recognized
3. Current regimens underperform in programmatic settings, relative to clinical trials

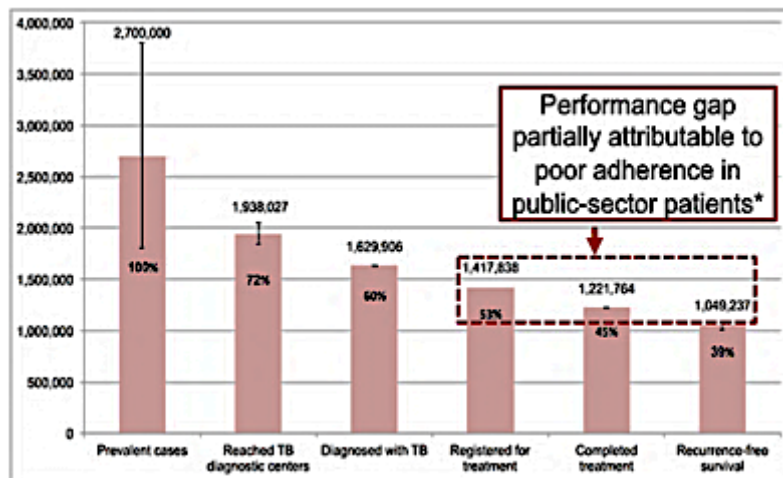


Infectious disease deaths. Macmillan Publishers Ltd: Nature. Paulson T. Epidemiology: a mortal foe. Nature 2013;502(7470):S2-3, copyright 2013

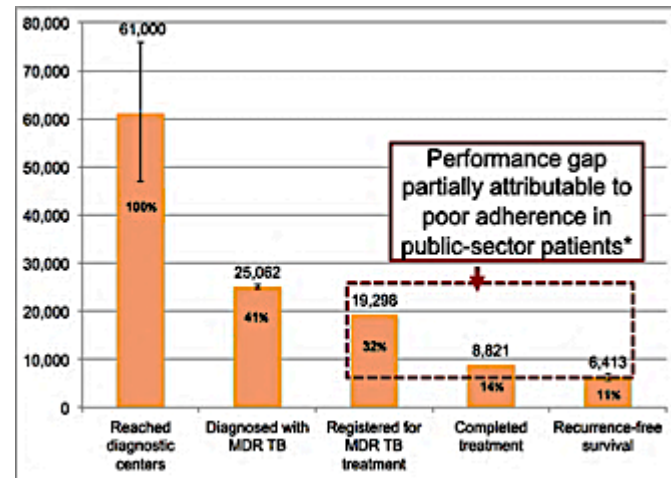
ADHERENCE: INDIA PROBLEM STATEMENT

Can we improve current regimen performance globally by closing gaps in treatment-half of cascade of care, with adherence tools and systems?

All Forms Of TB



MDR-TB



* Gap For Privately-treated Patients Not Well Defined But Expected To Be Greater

WHY IS ADHERENCE SO HARD IN TB?

- Dosing is VERY complicated and confusing.
- Treatments are long (6 and 18 months).
- Other factors: patients become asymptomatic early in treatment, side effects, stigma.
- DOT is expensive, resource-intensive, and highly burdensome on patients.
- As a result, most TB patients in high burden regions are self-administering.
- Baseline adherence for self-administering patients appears to be sub-optimal/poor.



Typical DS-TB medication: no dosing or other patient instructions

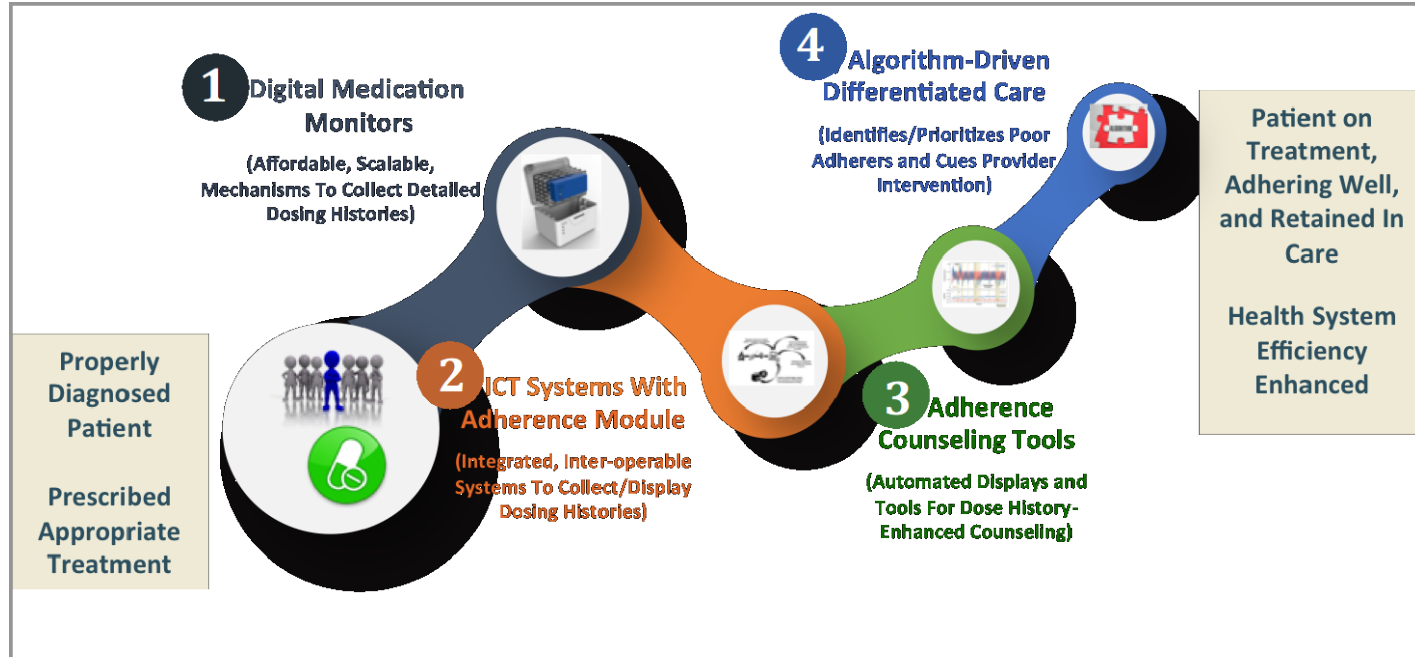


One month of MDR-TB medication: high pill burden and dosing complexity

PATIENT-CENTRIC OBSERVATION AND DIFFERENTIATED CARE

Critical Enabler: Highly Accurate, Detailed Dosing Histories Pragmatically, Affordably Compiled

- 1 TB medications are provided in/with a digital medication monitor, which provides visual and audible dosing and refill reminders.
- 2 The monitors are integrated with ICT systems to deliver dosing histories to providers and health systems.
- 3 Dosing histories are used to tailor counseling based on a patient's specific medication-taking behavior.
- 4 Dosing histories are used to inform and enable differentiated care, targeting poor adherers for more intensive management



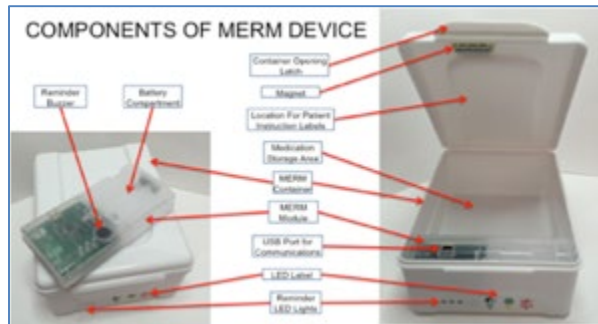
ISSUES: Challenging Treatment Settings and Patient Populations. VERY Inexpensive Treatments

ENABLING DIGITAL ADHERENCE TECHNOLOGIES



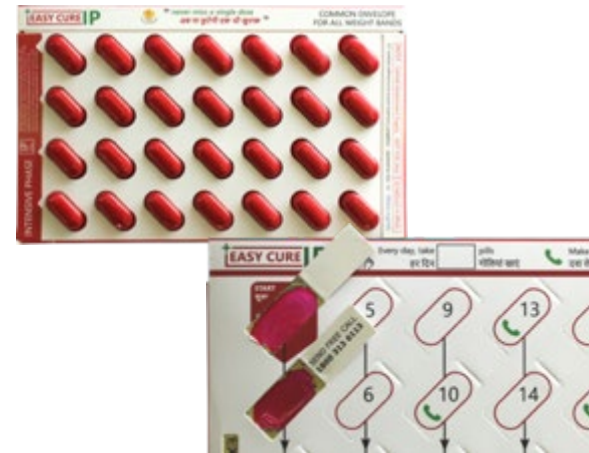
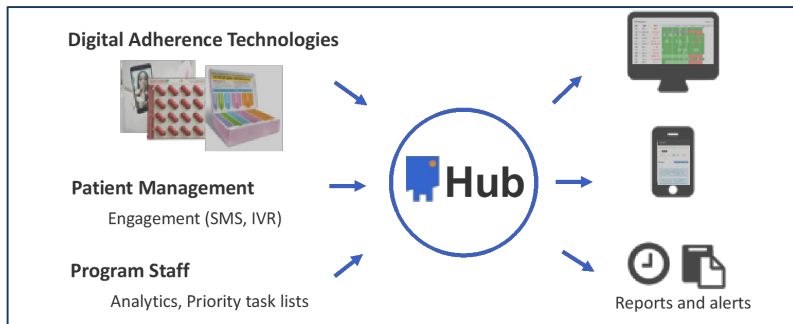
Everwell

Integrated, Globally Scaled Solutions For Patient-Centered Adherence Management



evriMED from Wisepill Technologies

- Designed for low-patient burden, patients without access to phones
- DS, DR, LTBI versions
- Less than \$15 per patient



99DOTS

- Designed for ultras low-cost and scalability
- Can be used with standard feature phones, shared phones, land lines
- Less than \$4 per patient



DOSE HISTORY INFORMED DIFFERENTIATED CARE IN INDIA

October 30:
Patient registered on 99DOTS
Given counseling and wrapped medications



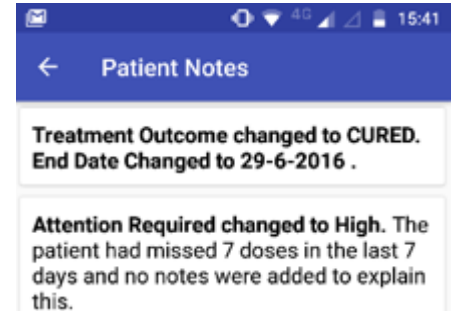
**[0000]
Please
take pills**

For 13 days, the patient receives automated SMS reminders and they have perfect calling adherence.

Starting on November 13, the patient stops calling despite the automated reminders. Their local health care staff are alerted by SMS and their adherence is reflected in the dashboard as missed doses as a high priority case for follow up.

The health care staff reaches out to the patient and found out the patient had some adverse reactions to the medication, and therefore had stopped taking medication. The staff encouraged the patient on the importance of adherence and made a note in the dashboard.

After the counseling, the patient started calling again daily and successfully completed treatment and was cured. Their overall adherence was 94%.



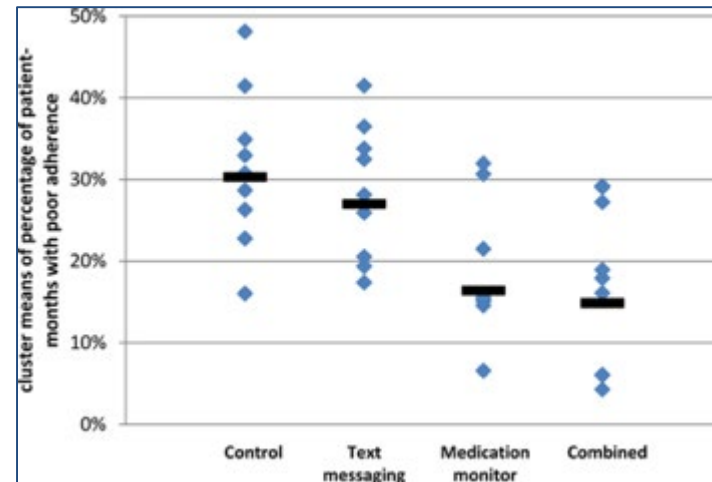
Patient adherence calendar

MEDICATION MONITOR EVIDENCE BASE

Evaluative criteria	Description
Feasibility	<ul style="list-style-type: none"> Formal usability assessment conducted (432 patients) in 2012. <i>Published -- Chin J Antituberculosis. 2012; 34:419–424.</i> January, 2017: deployment across 3 provinces (75,000 patients) as standard of care.
Acceptance / Burden	<ul style="list-style-type: none"> Formal usability study (50 patients, 10 providers) conducted in 2016. <i>Trials 201819:398</i> https://doi.org/10.1186/s13063-018-2650-3
Accuracy	<ul style="list-style-type: none"> 432 patient study in china compared monitor records with random urine tests. <i>Published -- China J Antituberculosis. 2012;34:419–424.</i>
Effectiveness (Adherence Enhancement)	<ul style="list-style-type: none"> Adherence effect demonstrated in 4500 patient RCT. <i>Published -- Liu et al, PLoS Medicine (2015)</i>
Effectiveness (Recurrence-Free Survival)	<ul style="list-style-type: none"> Health outcomes-oriented RCT in process. Xiaoqiu Liu (China CDC) Principal investigator. 3800 patients, 24 clusters. <i>Trial Registry -- http://www.isrctn.com/ISRCTN35812455</i>
Cost Effectiveness	<ul style="list-style-type: none"> In Process: Anna Vassal (LSH&TM) Principal Investigator. In connection with Current RCT. <i>Trial Registry -- http://www.isrctn.com/ISRCTN35812455</i>

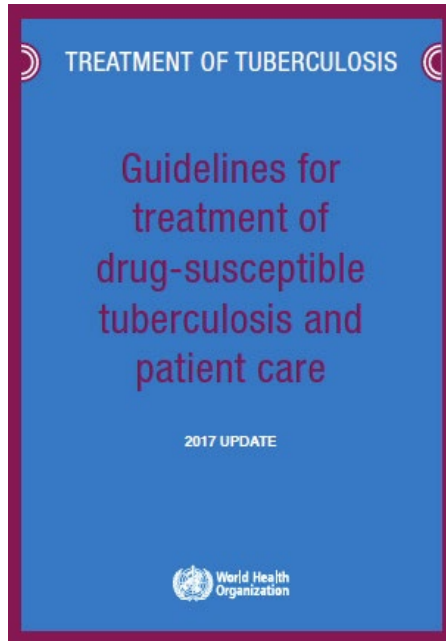
Adherence Effect: China-Based Cluster Randomized Trial

RCT (36 clusters, n = 4,173) China 2011-12



Liu et al, PLoS Medicine (2015)

WHO SHOWING GROWING CONFIDENCE & SUPPORT



“ As treatment supervision alone is not likely to be sufficient to ensure good TB treatment outcomes, additional treatment adherence interventions need to be provided.”

**WHO DS-TB
Guidelines, 2017**

“ The evidence also showed that when patients receiving treatment adherence interventions (e.g. different combinations of patient education, staff education, material support, psychological support, tracer and use of medication monitor) in conjunction with DOT or SAT, the treatment outcomes were significantly improved compared to DOT or SAT alone.”

WHO DS-TB Guidelines, 2017

WHO Has Acknowledged:

- Adherence Interventions Are Necessary To Ensure Positive Treatment Outcomes
- Adherence Interventions Significantly Improve Treatment Outcomes For Directly Observed And Self-Administering Patients

SCALE UP OF DIGITAL ADHERENCE TECH IN TB CARE



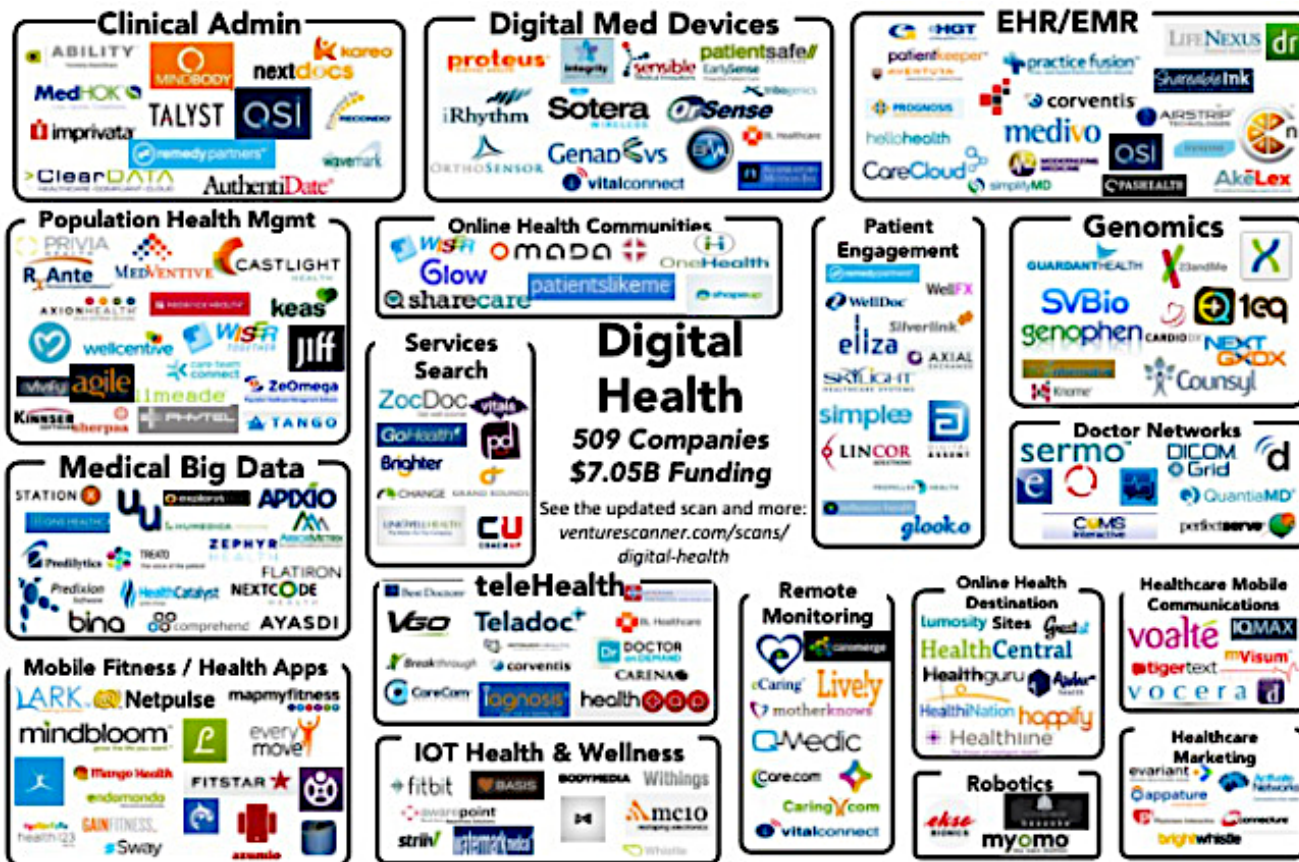
Adopted As Standard of Care In China and India. Evaluations, Demonstrations, and Scale-Up Planning Underway In 13 Additional Countries, Involving Over 100,000 DS, DR, and LTBI Patients



Available Adherence Technologies



AN EXPLOSION IN DIGITAL HEALTH TECHNOLOGIES

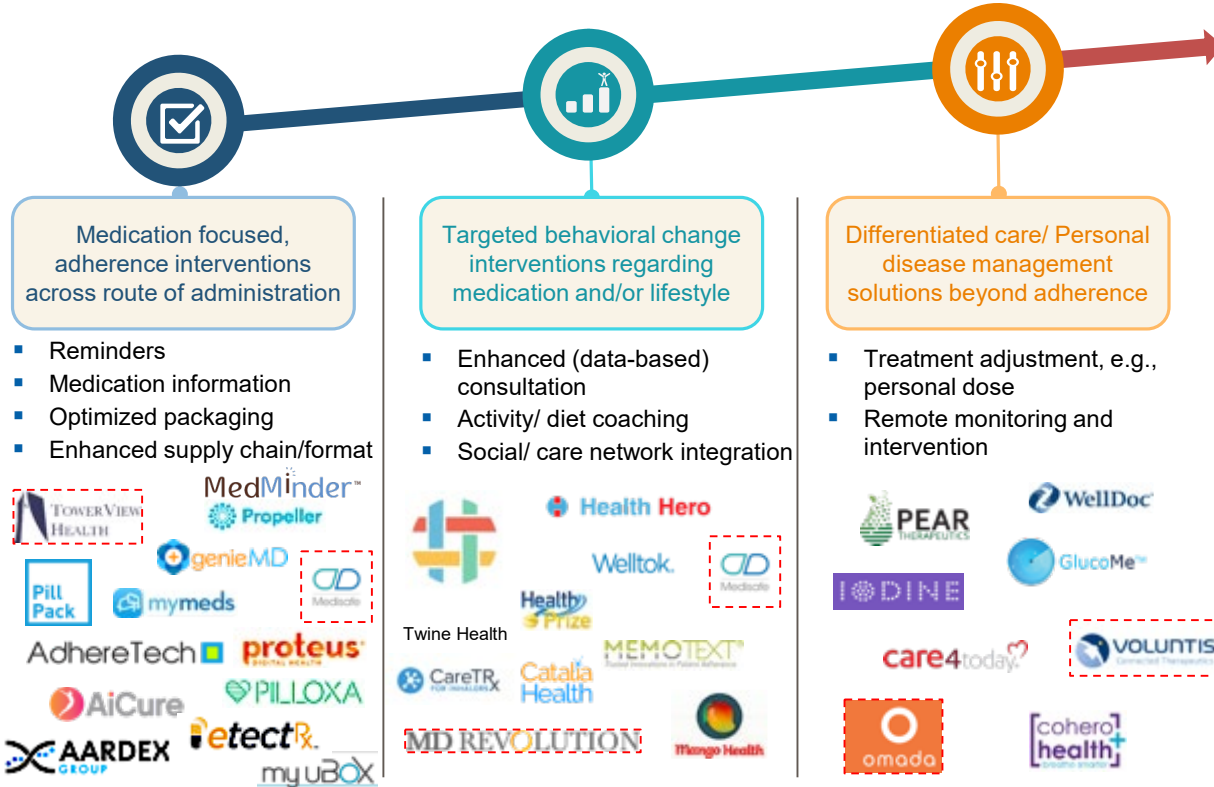


AND IN ADHERENCE TECHNOLOGIES AS WELL

Intervention capabilities

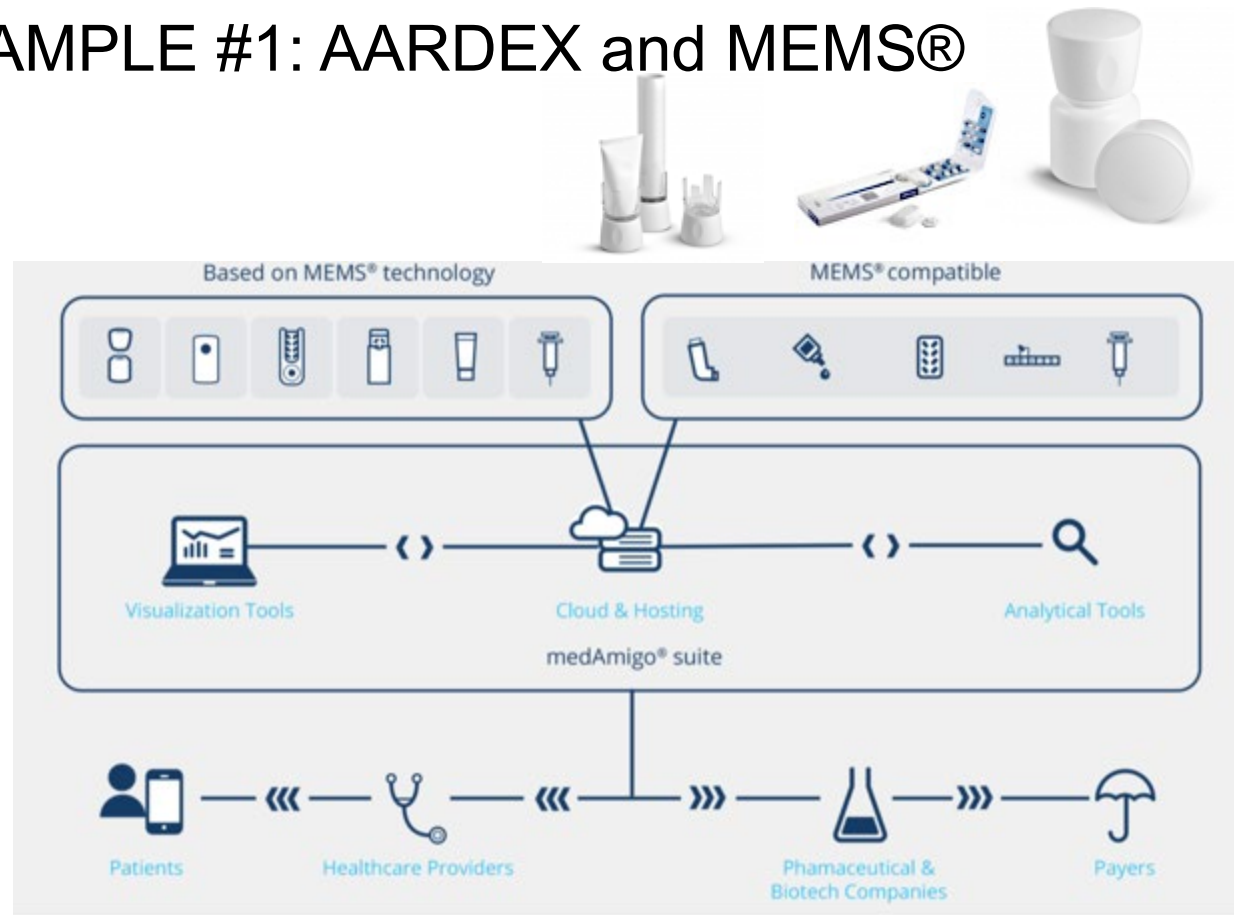
Typical applications

Examples



NOTEWORTHY EXAMPLE #1: AARDEX and MEMS®

- MEMS® technology recognized as the “gold standard” for adherence monitoring in clinical trials
 - Used in more than 70 countries
 - Used by more than 1,000,000 patients
 - Published in more than 750 peer-reviewed journals
 - Long battery life
 - Low patient burden
 - Proven to be strongly correlated with medication ingestion
- MEMS® technology incorporated into different package formats for monitoring across route of administration
- Can be incorporated into folding carton packaging for additional patient instructions/dosing support
- Users operate within the AARDEX medAmigo® system. Only MEMS® technology and MEMS® compatible devices are supported.





NOTEWORTHY EXAMPLE #2: AiCure

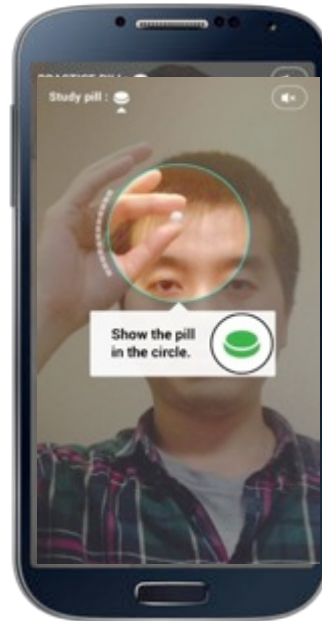


• Positives:

- Verifies the **right pill** has been **ingested** by the **right patient**
- Unlike VOT, no “video review” is required – verification is automatic
- Unlike VOT, image not actually being broadcast – an electronic “tick mark” is generated
- Works with multiple pills and with existing packaging formats
- Thoroughly evaluated – largely in clinical trials

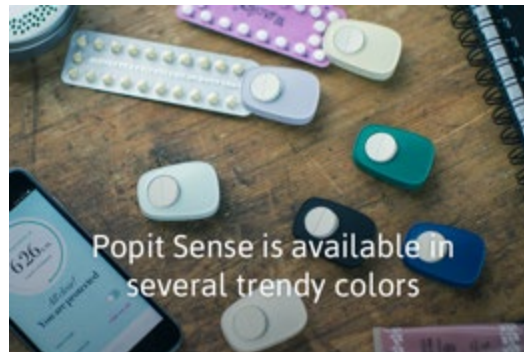
• Remaining questions:

- As yet, largely untested in clinical practice settings
- Outside of clinical trials, will patients accept this level of patient burden?



NOTEWORTHY EXAMPLE #3: POPIT

- Fills a huge gap for adherence technologies for “blistered” (as opposed to loose fill) medications.
- Uses sensor technology attached to standard blister sheets to detect pill expression/adherence
- Three different types of sensors (accelerometer and heat to determine medication in hand, sound recognition to verify pill expression) used to achieve high level of accuracy.
- Bluetooth connection to phone captures and transmits dosing history and permits reminders and alerts.
- Relatively inexpensive -- **\$49**.
- EU approved. No USA approvals to date.



NOTEWORTHY TECHNOLOGY #4: INGESTIBLE SENSORS

• Positives:

- Highly accurate
- Low patient burden
- Ideal for multi-pill treatments
- Regulatory environment surprisingly favorable
- Manufacturability has progressed well

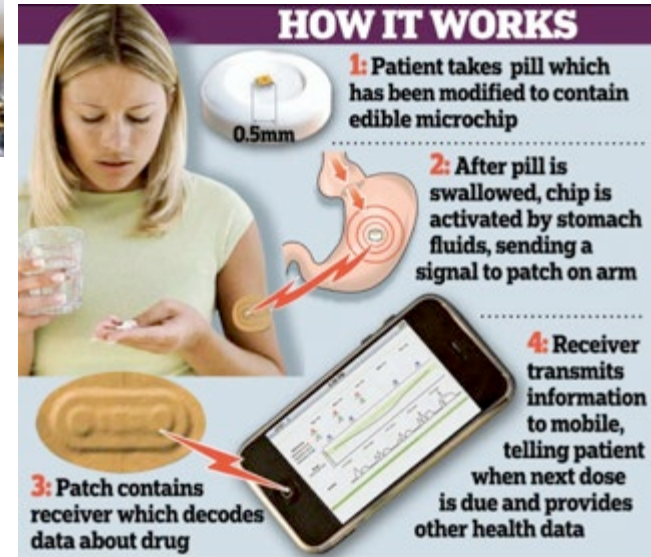
• Remaining questions:

- Expensive (etectRx may change that)
- Patch is a challenge from patient acceptance perspective
- Is this much accuracy required/worth it?



etectRx

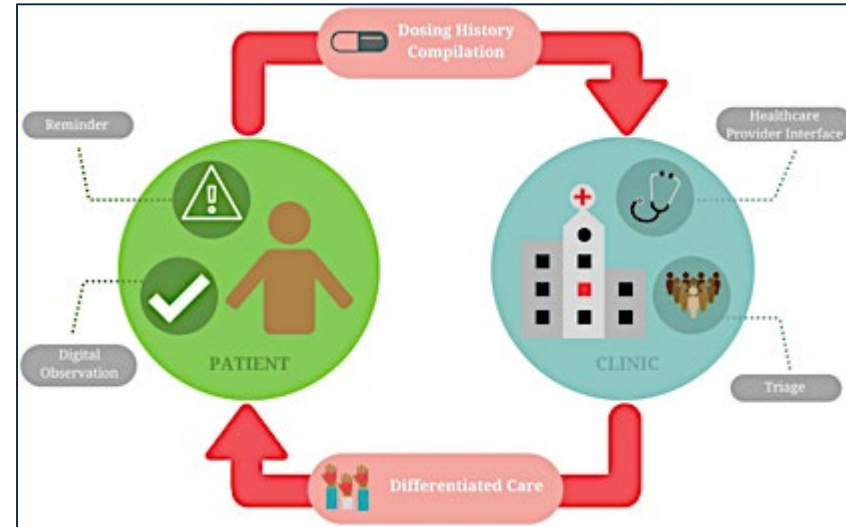
proteus[®]
DIGITAL HEALTH



KEY TRENDS – AND CONCLUSIONS

- Large number of capable, well-funded, adherence solutions are available.
- Evidence base for these solutions is growing rapidly.
- Several adherence solutions have achieved full integration with US specialty pharmacy players.
- Solutions are moving away from a “closed system” approach – integration is the emerging best practice.
- Payors and pharma are beginning to act, especially with respect to treatments that are relatively unforgiving.
- The cost of adherence technologies is falling . . . and will continue to do so.
- Global health (TB) has acted. For the US and EU, adherence technology-informed differentiated care still seems largely a “bridge too far.”

Emerging Standard of Care For TB Patients In High Burden Regions



“A Bridge Too Far” Still in the USA and EU

QUESTIONS?



APPENDIX?

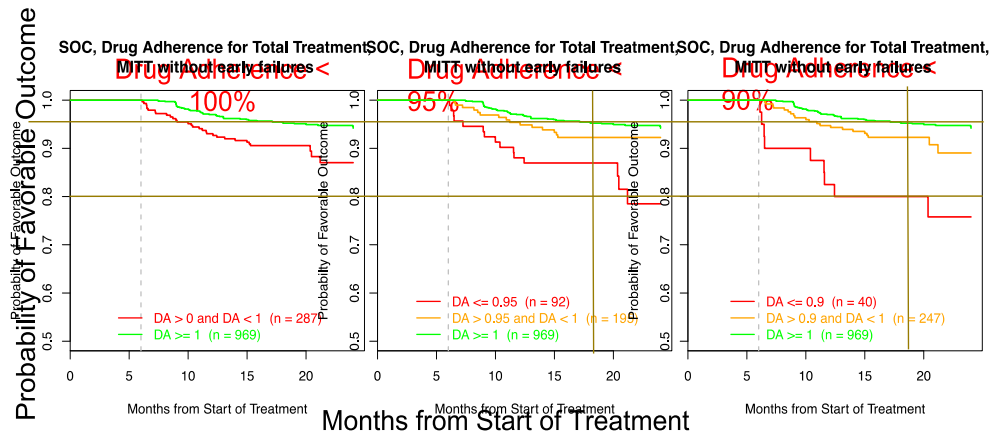


LINK: DOSING IMPLEMENTATION AND RECURRENT TB

Severity of non-adherence (in patients who “completed treatment”)	TB recurrence rate, 18 months after completing treatment
“Regular” adherence (Complete treatment within 8 months)	9%
“Irregular” adherence (Complete within 10 months)	15%
“Very irregular” adherence (Complete treatment within 12 months)	25%

Study of 534 smear + patients in India found a strong relationship between adherence and post-treatment TB recurrence.

Source: Thomas et al. Int J TB Lung Dis
2005; 9(5): 556-61⁶



TB patients taking HRZE with <90% adherence had 5.6 times increased risk of TB recurrence in a meta-analysis of the OFLOTUB, REMox, and Rifaquin trials.

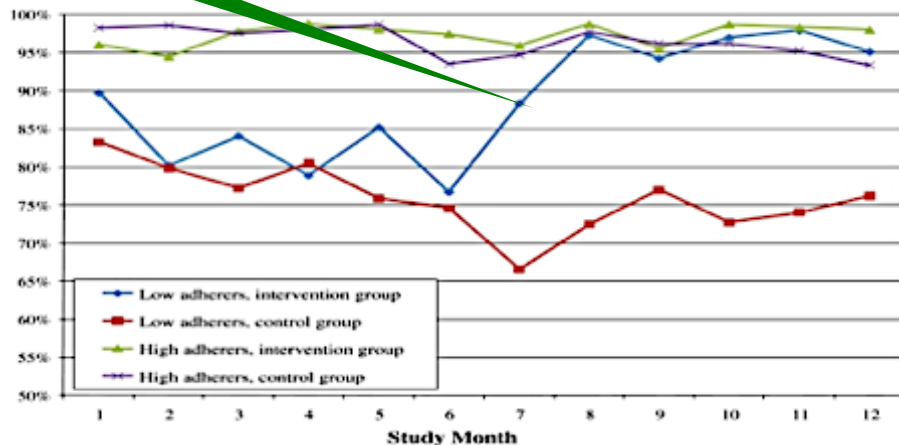
Source: Nature Medicine, 2018, Volume 24, Number 11,
Page 1708, Marjorie Z. Imperial, Rada M. Savic, et al.

EXPECTED IMPACT OF THIS APPROACH

Impact on EM-Enabled Counseling

Impact On Dosing Implementation

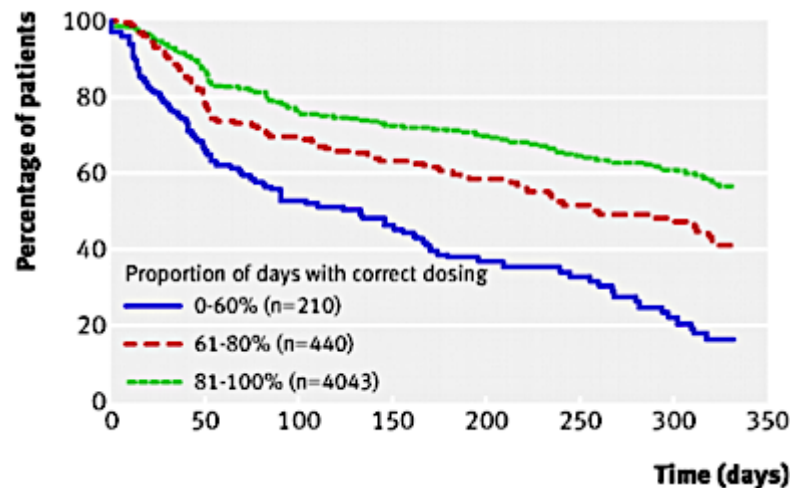
Adherence



“... a simple intervention involving monthly adherence counseling based on EDM feedback significantly improved mean adherence among Chinese ART patients. **We found an impact on adherence that was both very high — above the 95% threshold — and sustained**, with mean adherence above 95% throughout the 6-month intervention period.”

Sabin et al. AIDS Behavior, 2010.

Impact On Persistence



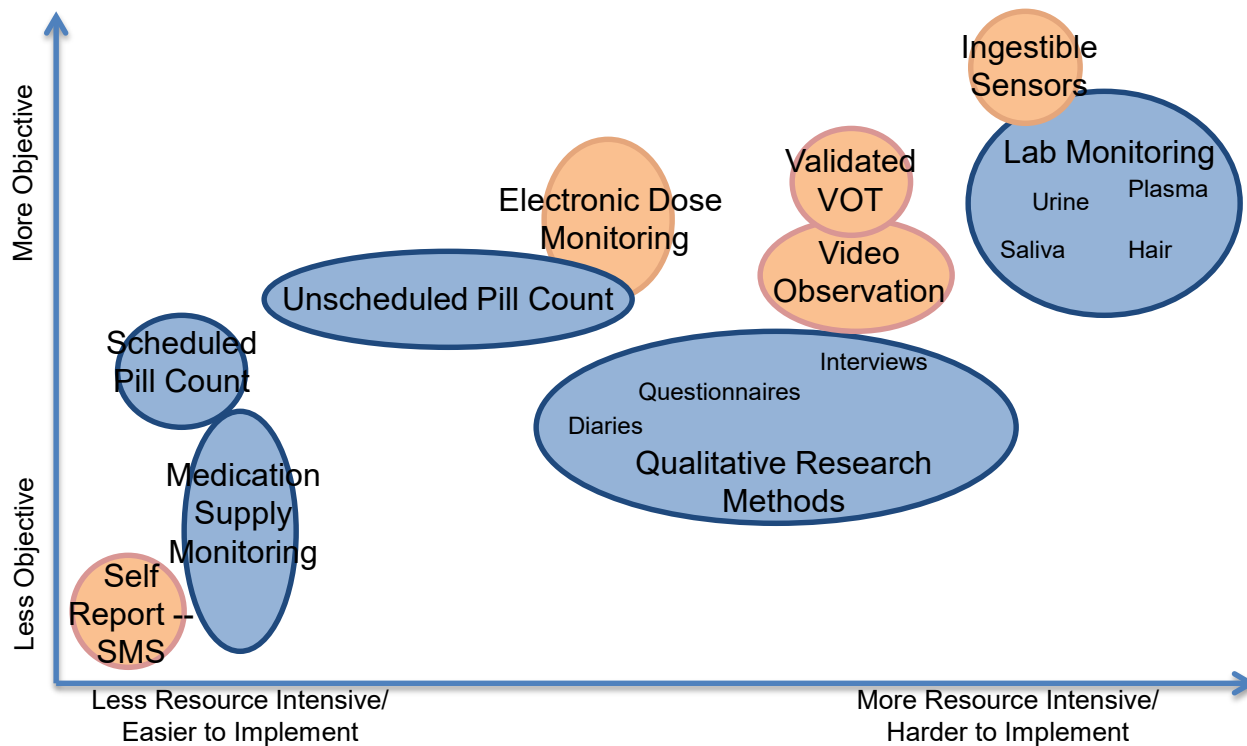
“The figure displays the estimates of persistence stratified by the degree of execution, clearly showing **that the better the execution, the longer the persistence**. The likelihood that a patient would discontinue treatment early was related to the quality of his/her daily execution of the dosing regimen.

Vrijens, B, BMJ. 2008; 336(7653): 1114.

EVALUATION CRITERIA FOR DIGITAL ADHERENCE TECH

Evaluative criteria	Description
Feasibility	<ul style="list-style-type: none">Relative ease of implementation and operation of the technology within existing health systems, technology infrastructure, and supply chains.
Acceptance / Burden	<ul style="list-style-type: none">Relative satisfaction of patients and providers with the technology.Should include an understanding of (i) cultural or other barriers to uptake (e.g. VDOT for women/girls), (ii) how this relative satisfaction changes over time, and (iii) how this burden affects both uptake and persistence with respect to the technology.
Accuracy	<ul style="list-style-type: none">For monitoring technologies, the extent to which the technology's "event" (e.g., self-reported medication ingestion) is correlated with actual event (e.g., medication ingestion).
Effectiveness (Adherence Enhancement)	<ul style="list-style-type: none">Extent to which the technology is able to generate or elicit the intended action, behavior, or event (e.g., improvement in average adherence).Should include information on the extent to which the effect persists over time.
Effectiveness (Recurrence-Free Survival)	<ul style="list-style-type: none">Extent to which the technology positively impacts treatment outcomes.Ideally, should be more than just WHO treatment outcomes – should reflect positive impact on relapse as compared to standard of care.
Cost Effectiveness	<ul style="list-style-type: none">An assessment of cost-effectiveness/comparative cost-effectiveness (mean and incremental costs per death and DALY averted) of the proposed technology-enabled intervention versus standard of care in the relevant context, i.e., disease burden, budget/costs of the resource-limited setting.

DOSING MEASUREMENT METHODS: ONE APPROACH



Evaluative Criteria

- **More objective/less objective:**
 - Bias or potential bias in adherence measurement
- **More resource intensive/harder to implement:**
 - Affordability
 - Patient burden
 - Cultural appropriateness
 - Technology/infrastructure fit



"Rich Sampling" refers to capture of daily, detailed dosing history.