



New Approaches to Medication Adherence Monitoring and Management

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

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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?

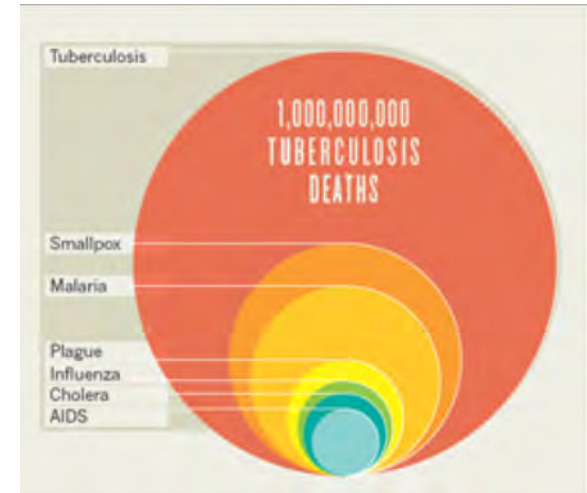


Tuberculosis Case Study



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



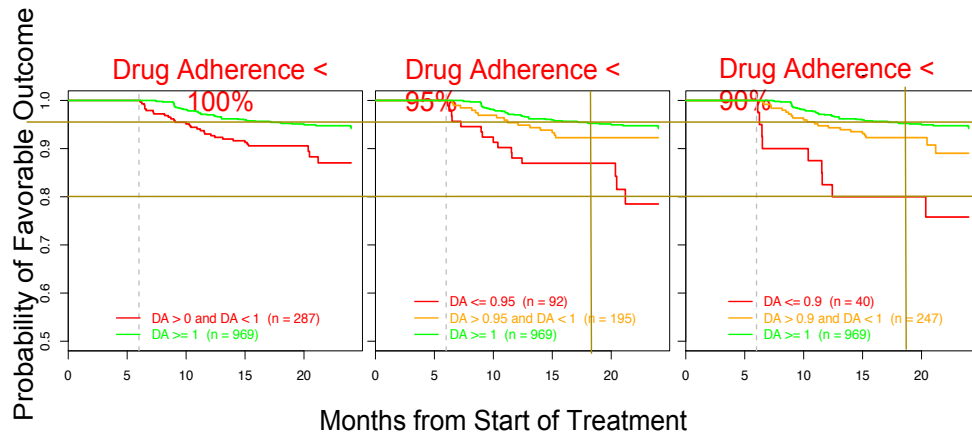
Infectious disease deaths. Macmillan Publishers Ltd: Nature. Paulson T. Epidemiology: a mortal foe. Nature 2013;502(7470):S2-3, copyright 2013

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.

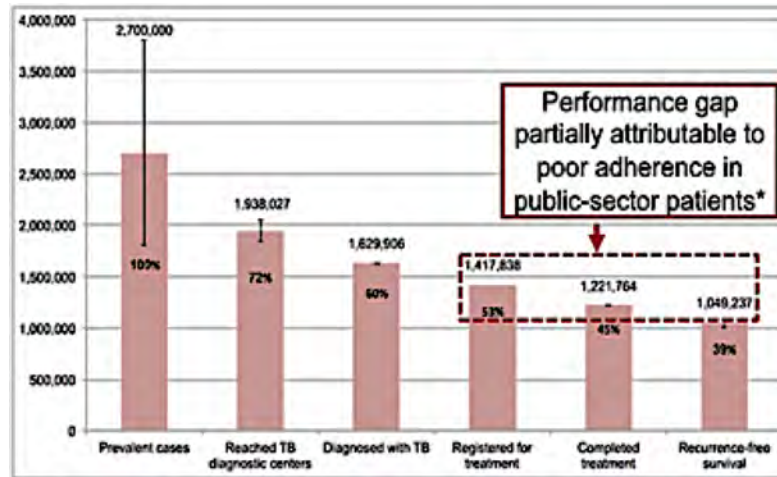
Source: Nature Medicine, 2018, Volume 24, Number 11,
Page 1708, Marjorie Z. Imperial, Rada M. Savic, et al.



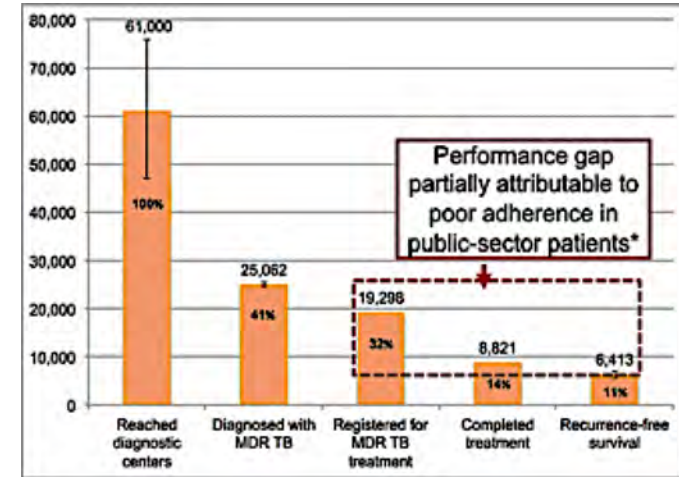
ADHERENCE: INDIA PROBLEM STATEMENT

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

WHAT IS THE PROBLEM THAT NEEDS TO BE SOLVED?

- Proper medication adherence (including persistence) is essential in TB treatment.
- Significant adherence challenges exist in resource-limited settings.
- DOT is expensive, resource-intensive, and highly burdensome on patients.
- DOT is increasingly not practiced:
 - In China, 52% of patients self-administer, 27% are observed by family members, and only 20% are observed by health workers.*
 - In India, the “private sector” accounts for at least 50% of TB patients – all of whom self-administer.
- Baseline adherence for self-administering patients appears to be sub-optimal/poor.



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

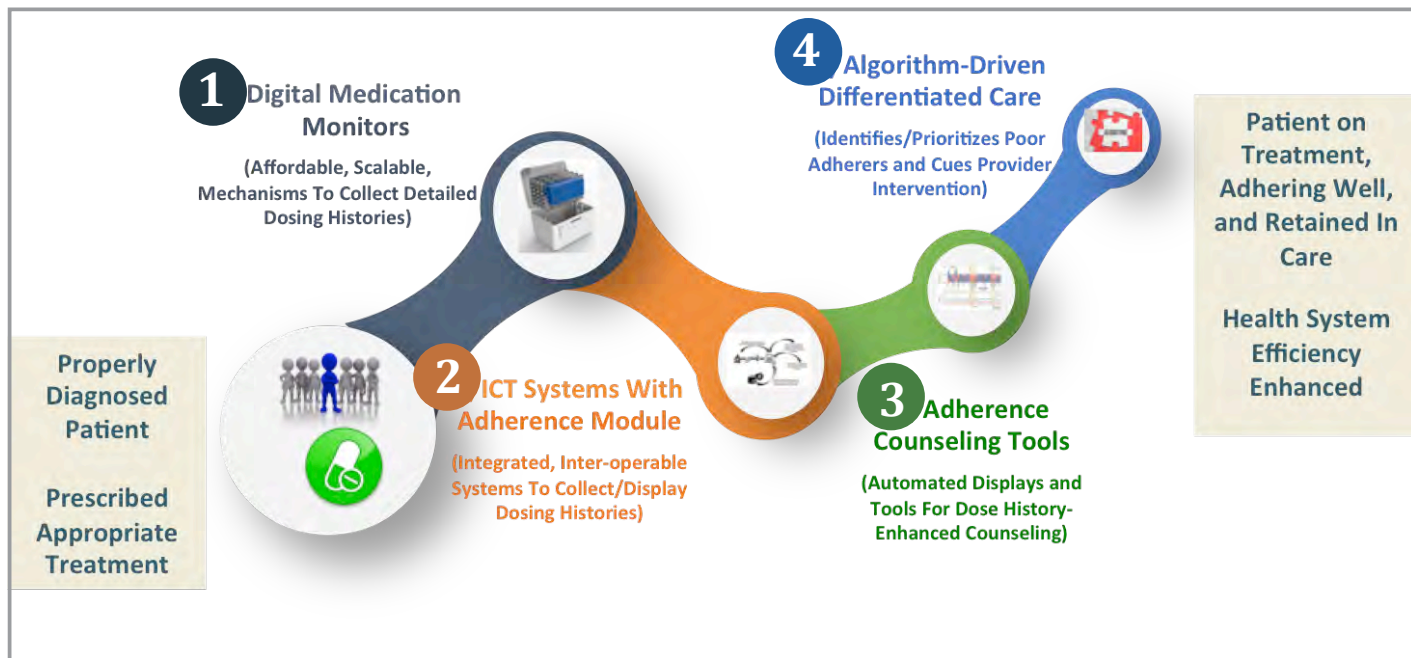


One month of MDR-TB medication: high pill burden and dosing complexity

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

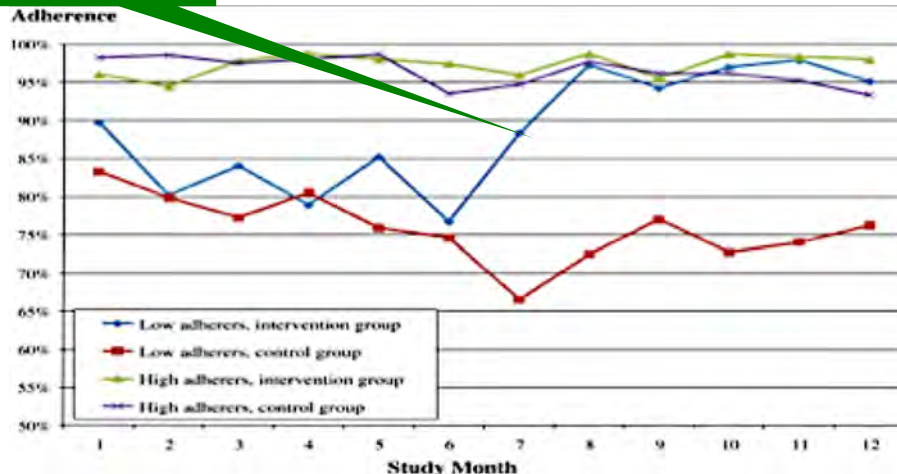


ISSUES: Challenging Treatment Settings and Patient Populations. VERY Inexpensive Treatments

EXPECTED IMPACT OF THIS APPROACH

Impact on EM-
Enabled Counseling

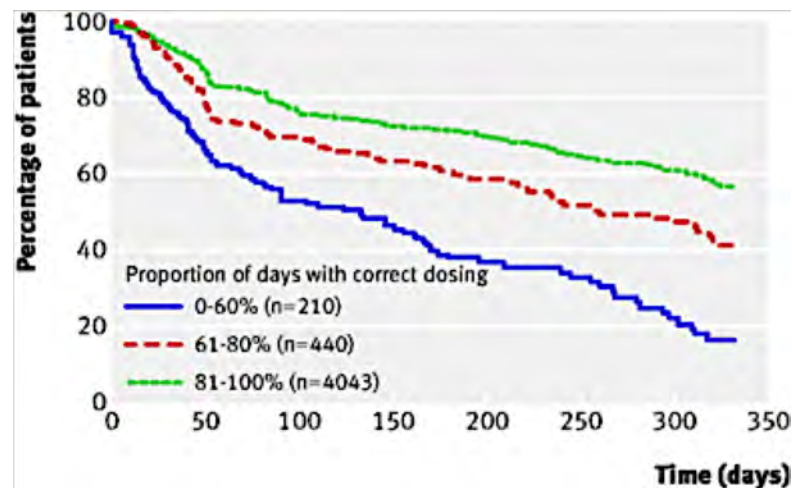
Impact On Dosing Implementation



“... 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.



ENABLING DIGITAL ADHERENCE TECHNOLOGIES



Everwell

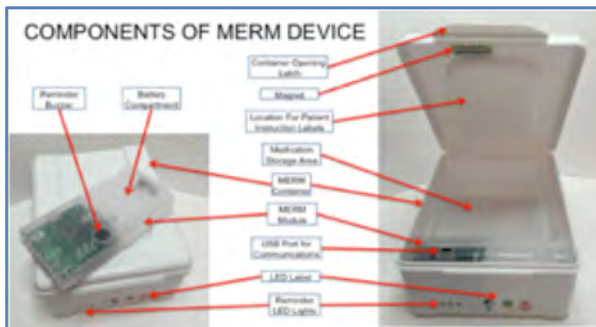
Integrated, Globally Scaled Solutions For Patient-Centered Adherence Management

Digital Adherence Technologies



Patient Management
Engagement (SMS, IVR)

Program Staff
Analytics, Priority task lists



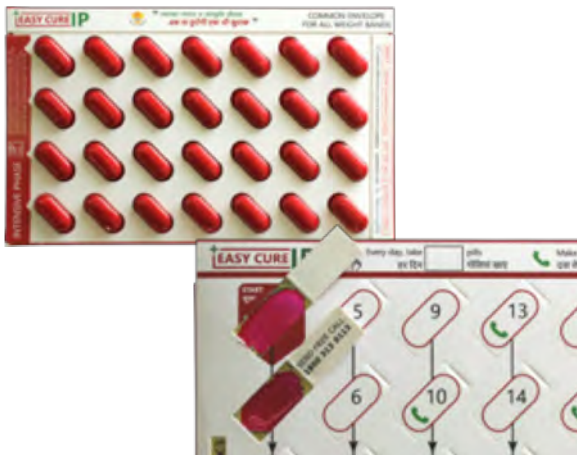
evriMED from Wisepill Technologies

- 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



THE ARCADY GROUP

DOSE HISTORY INFORMED DIFFERENTIATED CARE IN INDIA

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

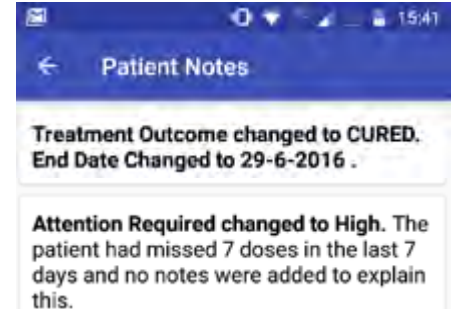


**[0000]
Please
take pills**

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

EVALUATION CRITERIA FOR DIGITAL ADHERENCE TECH

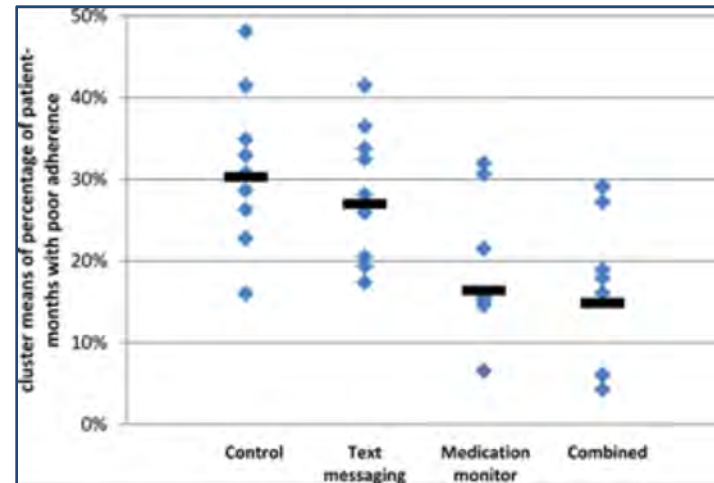
Evaluative criteria	Description
Feasibility	<ul style="list-style-type: none">Relative ease of implementation and operation of the technology within existing health systems, technology infrastructure, and supply chains.
Acceptance / Burden	<ul style="list-style-type: none">Relative satisfaction of patients 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.

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 2018</i>19:398 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

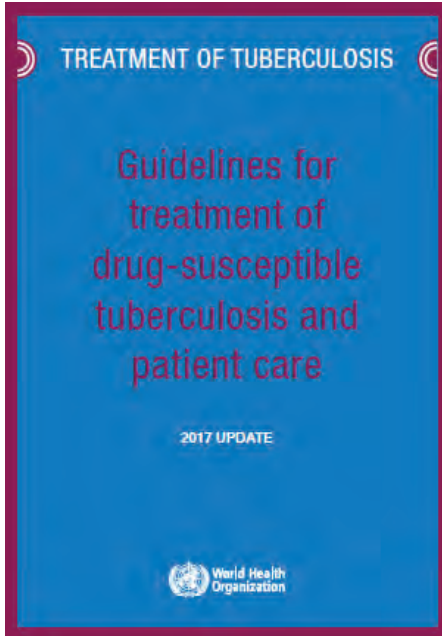
RCT (36 clusters, n = 4,173) China 2011-12



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

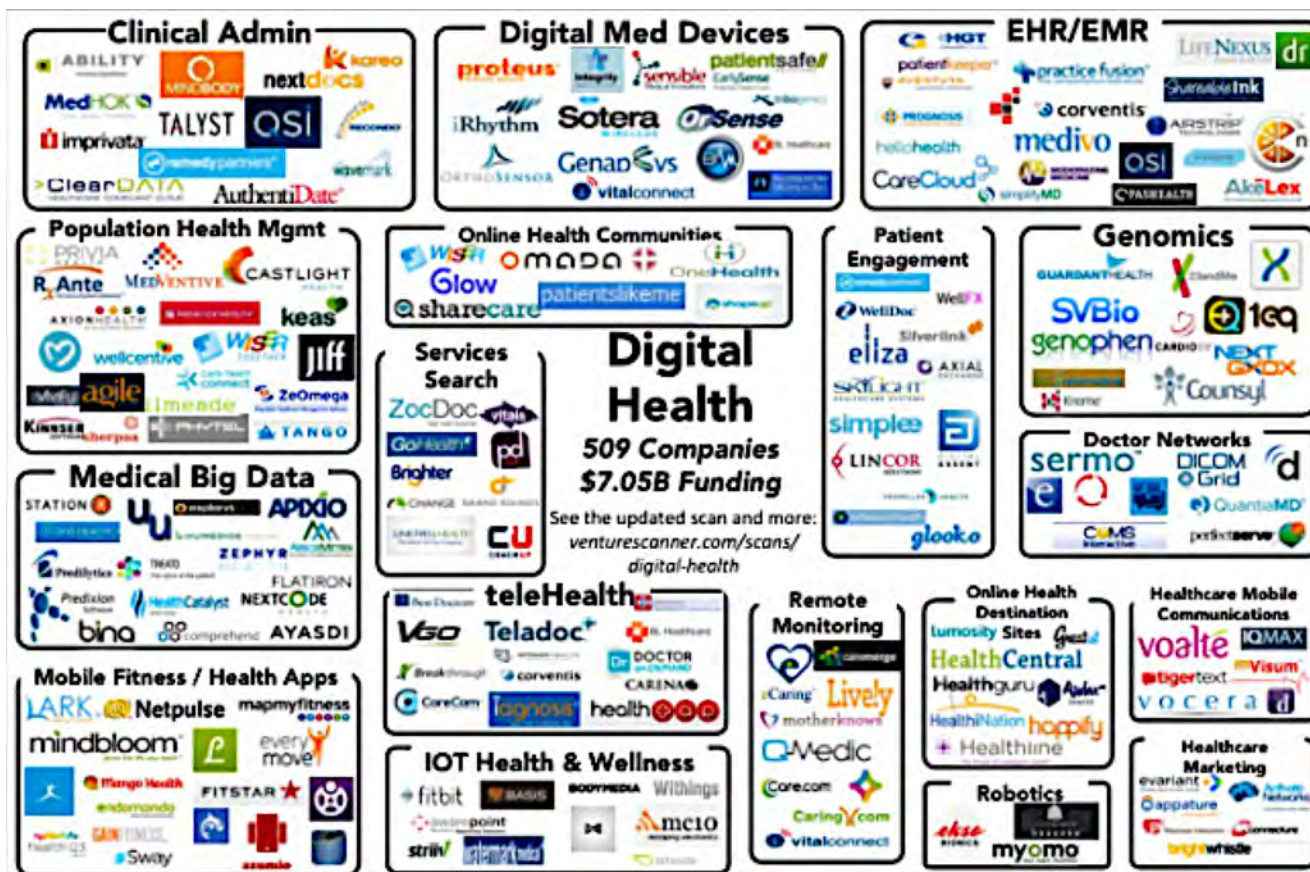


Adopted As Standard of Care In China and India. Evaluations, Demonstrations, and Scale-Up Planning Underway In 13 Additional Countries, Involving Over 100,000 DS, DR, and LTBI Patients

Available Adherence Technologies



AN EXPLOSION IN DIGITAL HEALTH TECHNOLOGIES

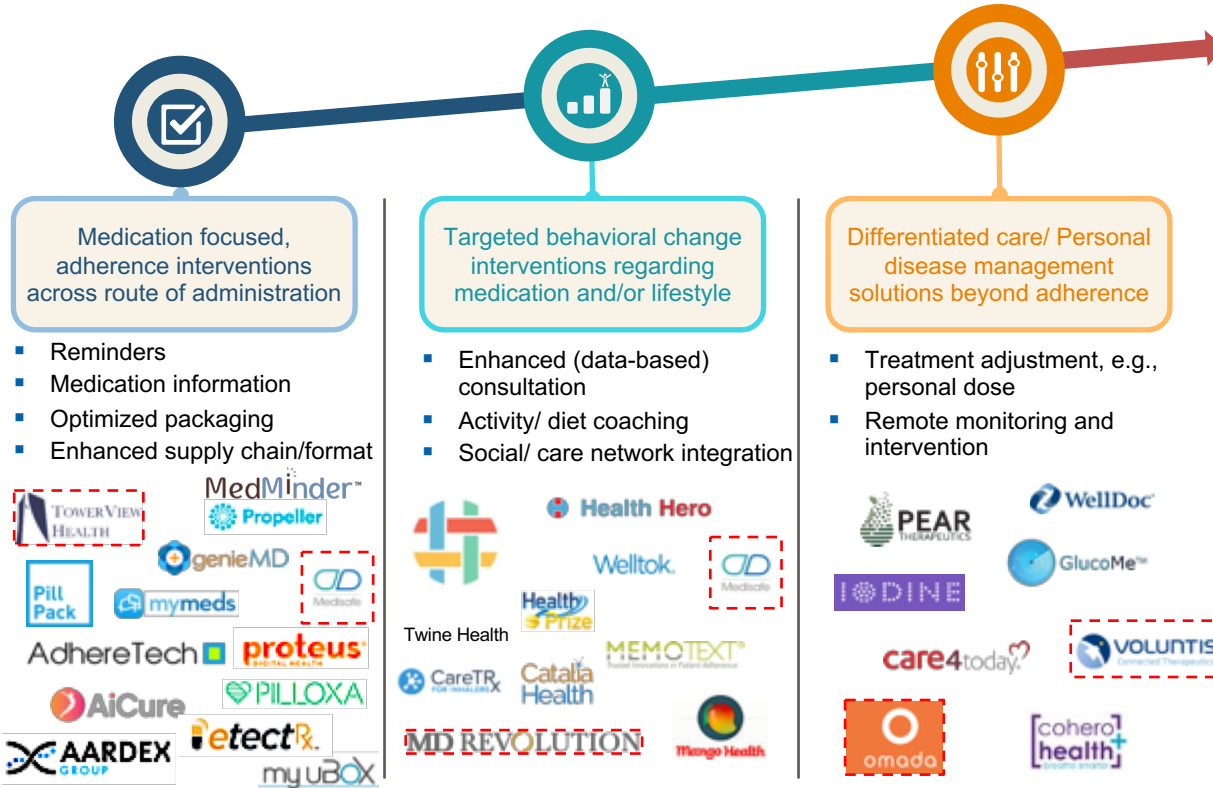


AND IN ADHERENCE TECHNOLOGIES AS WELL

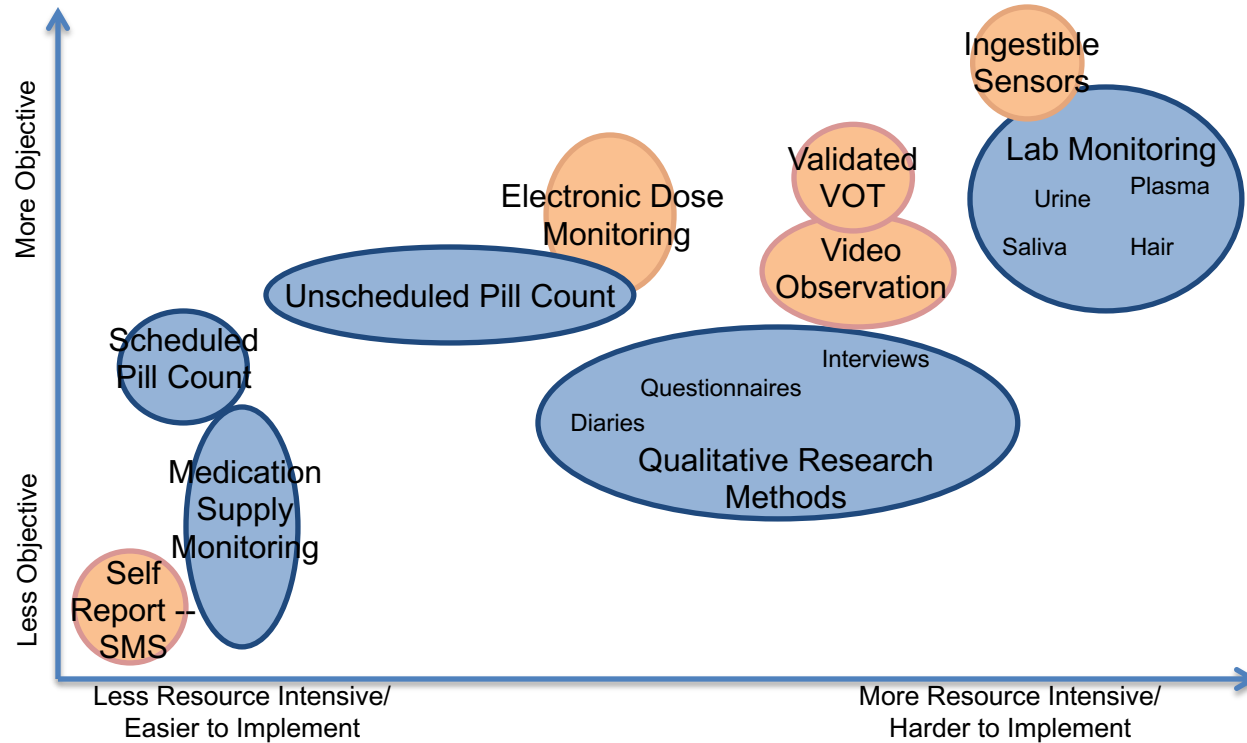
Intervention capabilities

Typical applications

Examples



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



Sparse Sampling



Rich Sampling

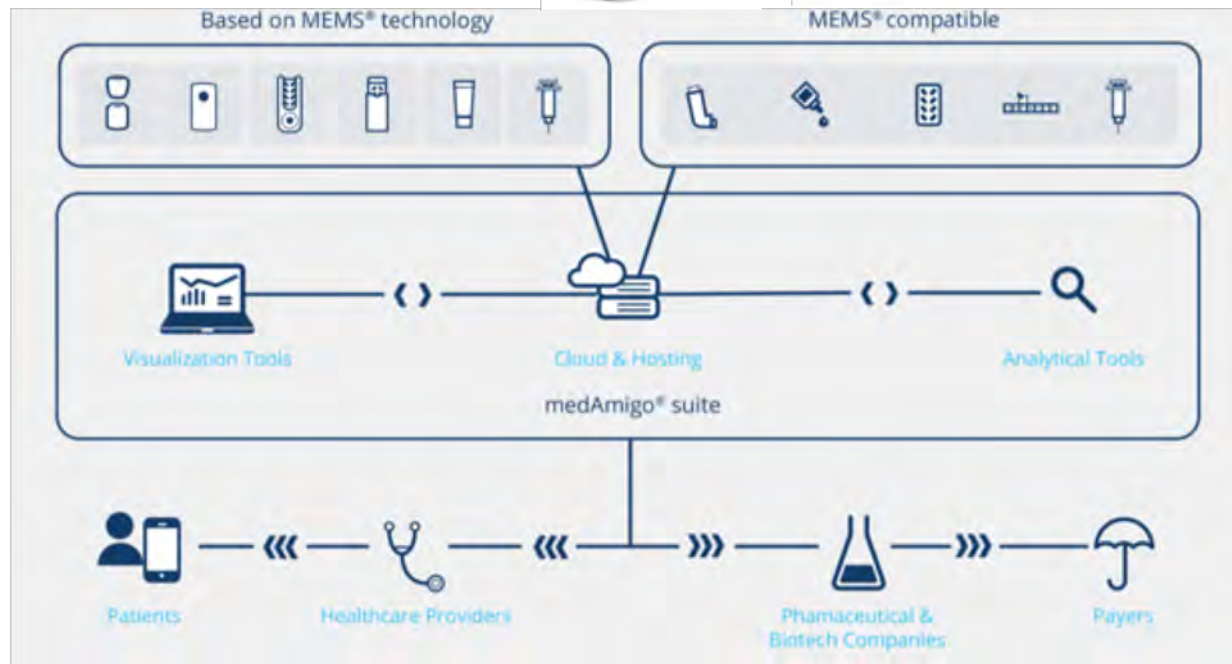
"Rich Sampling" refers to capture of daily, detailed dosing history.

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

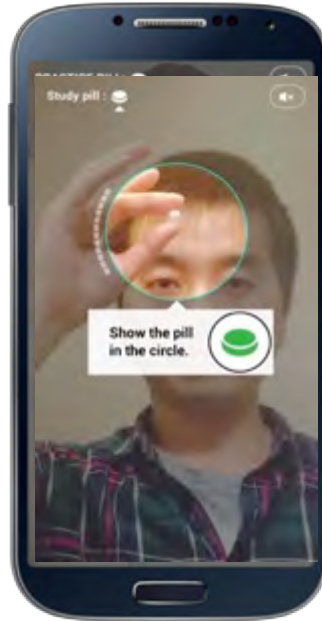


• Positives:

- 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

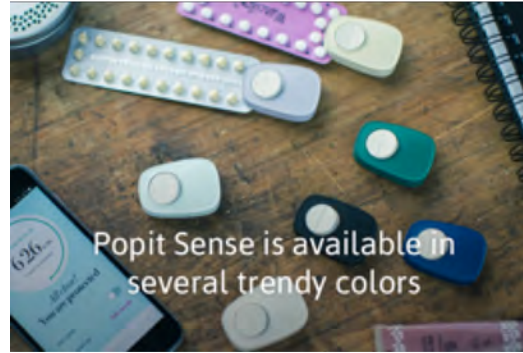
• Remaining questions:

- 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.



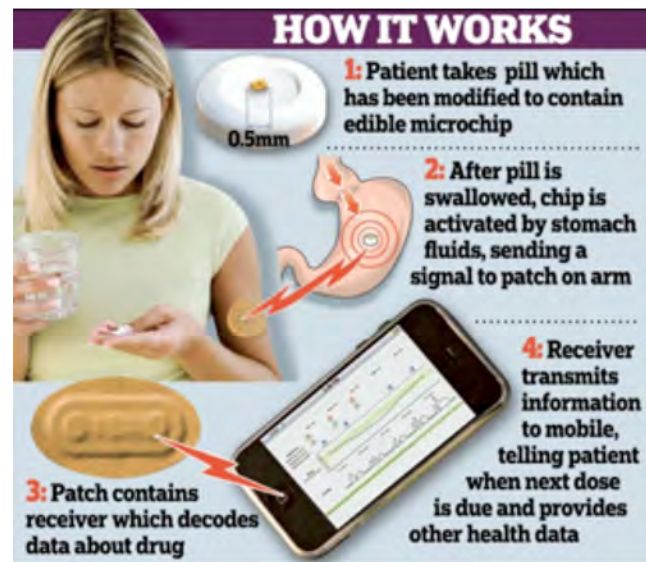
NOTEWORTHY TECHNOLOGY #4: INGESTIBLE SENSORS

• Positives:

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

• Remaining questions:

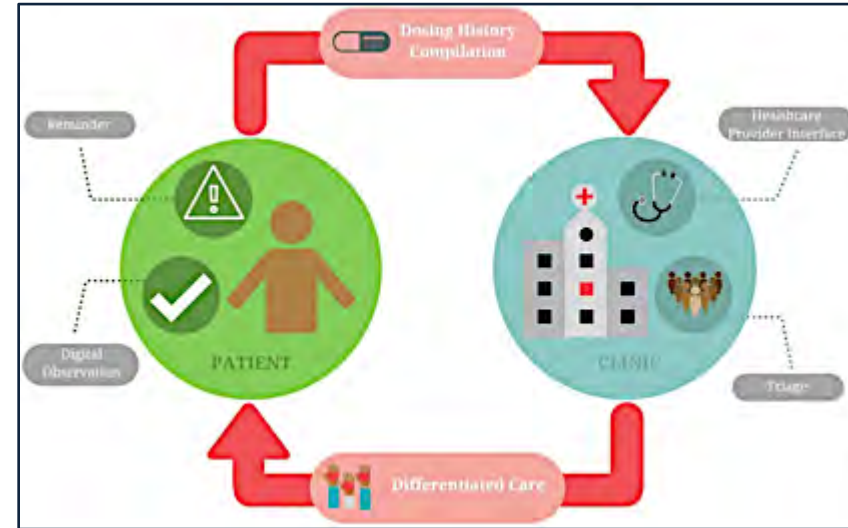
- Expensive (etectRx may change that)
- Patch is a challenge from patient acceptance perspective
- Is this much accuracy required/worth it?



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?

