Access-by-Design: Making Biologics Available to All

Dr. Stacy L. Springs
Senior Director of Programs,
MIT Center for Biomedical Innovation
Executive Director, MIT BioMAN and CAACB

WCBP Conference 2019
Plenary Session 6: Global Access - Transformative Technology
Wednesday, January 30 2019
The Mayflower Hotel, Washington, D.C
Outline

Global burden of non-communicable disease

BioACCESS at MIT

Research to enable Access-by-Design
Non-communicable diseases cause >70% of deaths globally

WHO, 2016
Disproportional number of new NCD cases are in LMICs

% of total deaths due to NCDs, both sexes and all ages
1990-2015 with 2025 projections

IHME, 2017

- High Income
- Upper-Middle Income
- Lower-Middle Income
- Low Income
44% of NCD-related deaths are premature (<70 years old) and considered to be preventable

Global NCD Deaths disaggregated by age

- NCD Deaths (below 70 years)
- NCD Deaths (above 70 years)

WHO, 2016
87% of premature NCD-related deaths are in LMICs

Global NCD Deaths disaggregated by age

Disproportionate burden in Low & Middle Income Countries

WHO, 2016

Distribution of NCD-related premature deaths (2015)

- High Income Countries
- Low-and-Middle Income Countries
WHO Global Action for preventing/controlling NCDs

25% relative reduction in overall mortality due to NCDs (especially premature deaths) by 2025

80% availability of the affordable basic technologies and essential medicines, including generics, for NCDs in both public and private facilities by 2025

Examples of Initiatives aimed at increasing access:

Action to realize the commitments made is inadequate and the current level of progress is insufficient to meet targets.

“The world is reaching an inflection point…a paradigm shift is needed to do things differently to address obstacles in a new development era.”

Report of the UN Secretary-General on NCDs, 2018
Biologics are effective therapies for many NCDs

<table>
<thead>
<tr>
<th>Disease</th>
<th>Standard of Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell lymphoma</td>
<td>Rituximab (Rituxan) *</td>
</tr>
<tr>
<td>HER2 positive breast cancer</td>
<td>Trastuzumab (Herceptin) *</td>
</tr>
<tr>
<td>Various tumors (anti-VEGF)</td>
<td>Bevacizumab (Avastin) *</td>
</tr>
<tr>
<td>Macular Degeneration</td>
<td>Ranibizumab (Lucentis)</td>
</tr>
<tr>
<td>Diabetes (all type I, some type II)</td>
<td>Insulin *</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>Factor VIII *</td>
</tr>
<tr>
<td>Cervical Cancer (prophylactic)</td>
<td>HPV Vaccine *</td>
</tr>
</tbody>
</table>

* On WHO Model List of Essential Medicines (March 2017)
MIT Center for Biomedical Innovation

MISSION: to improve global health by overcoming obstacles to the development and implementation of biomedical innovation

GLOBAL HEALTH DELIVERY SYSTEM

Drug Discovery → Clinical Development & Manufacturing of New Drugs → Distribution & Global Delivery → Marketing & Reimbursement Policy → Drug Use Optimization & Clinical Care

BioMAN: BioMANufacturing Program
CAACB: Consortium on Anthrax Agent Containment in Biomanufacturing
FoCUS: Financing and Reimbursement of Cures in the US
MIT Center for Biomedical Innovation
Mission of BioACCESS

To enable global access to biotherapeutics through:

• Collecting data and building tools to identify systematic barriers
• Developing innovations and testing their potential impact
• Empowering a new generation of leaders to meet the challenges ahead

Administering meningitis vaccine in Burkina Faso
Credit: Compassion International
Building a **BioACCESS** community

- **Multidisciplinary** approach to achieving access-by-design
- **Convening** faculty from around the MIT campus and surrounding institutions

Jónas Jónasson  
Operations Management, MIT

Sara Fisher Ellison  
Economics, MIT

Veronika Wirtz  
Global Health, BU

Reuben Domike  
Manufacturing Technology, BYU

Amy Moran-Thomas  
Anthropology, MIT

Rajeev Ram  
Electrical Engineering, MIT
Key components of Access-by-Design

• Evidence-based learning
  • Identifying systematic barriers impeding access
  • Learning from successes and failures in small molecule / vaccines access
  • Modeling future scenarios

• Systems evaluation & optimization
  • Re-envisioning product development for access in LMICs
  • Optimize benefit/risk for all stakeholders in the system
  • Patient-centered product profiles for resource-limited settings

• Mens et Manus (technology development projects)
  • Leverage the best of MIT’s Schools of Science, Engineering and Management to develop disruptive solutions in technology, manufacturing, supply chain management and policy
Impact of manufacturing models on global supply security

**Centralized**
- 1 site in 1 region

**De-centralized**
- n sites in 1 region

**Distributed**
- n sites in n regions

**Point-of-Care**
- DIY – district/clinic level

---

**Business drivers**
- First-to-enter emerging markets
- Compulsory in-country manufacturing
- Flexibility to respond to changing demand
- Invest in local biotech industry to boost economy
- Reduce supply dependence

**Technology drivers**
- (Semi-) continuous systems
- Process intensification / automation
- Single-use technology

Emerging manufacturing platforms
- Just
- UNIVERCELLS
- ultra
Economic evaluation of manufacturing innovations

Design Options

Manufacturing mAb

- # of Facilities
  - Centralized
  - Decentralized
  - Distributed
- Bioreactor Type
  - Stainless Steel
  - Disposables
- Facility Function
  - Drug Substance
  - Drug Product
- Process Parameters
  - Drug Substance + Product

Simulating Scenarios

- Cost Estimation
- Country Readiness
- Financial Risk Forecasting

Evaluating Tradeoffs

- Option A
- Option B
- Option C

Criteria for evaluation:
- COGs & 10-yr NPC
- Time to market
- Supply security
- Technology transfer
- Other factors (e.g., geographic proximity of facilities)
Integrated, whole-of-system approach to access

**DEMAND-SIDE OF BIOLOGICS ACCESS**
- Screening
- Prevention
- Diagnosis

**SUPPLY-SIDE OF BIOLOGICS ACCESS**
- Manufacturing
- Supply Chain
- R&D

**TREATMENT**
- Proper Use
- Adherence

*Dynamic socioeconomic, political, and environmental context*
Advances in Diagnostic Technology to Support Global Access

Dr. Rajeev Ram

Professor of Electrical Engineering and Computer Science, MIT

WCBP Conference 2019
Plenary Session 6: Global Access - Transformative Technology
Wednesday, January 30 2019
The Mayflower Hotel, Washington, D.C
## Requirements for high impact diagnostics in the developing world

http://www.nature.com/diagnostics

<table>
<thead>
<tr>
<th>Health-care setting (personnel)</th>
<th>Summary of resources and capabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>No laboratory infrastructure</td>
<td>No electricity or clean water available; no temperature control; venipuncture required before patient</td>
</tr>
<tr>
<td>Minimal laboratory infrastructure</td>
<td>No reliable electricity and clean water; minimal temperature control; room temperature required before</td>
</tr>
<tr>
<td>Moderate to advanced laboratory infrastructure</td>
<td>Dependable electricity and clean water available; room temperature required; storage available; time</td>
</tr>
</tbody>
</table>

### Characteristics of the ideal diagnostic test for the developing world: ASSURED

- **Affordable** by those at risk of infection.
- **Sensitive** (few false-negative results).
- **Specific** (few false-positive results).
- **User-friendly** (simple to perform by persons with little training).
- **Rapid** treatment at the first visit and robust use without the need for special storage.
- **Equipment-free** (that is, no large electricity-dependent instruments needed to perform the test; note that portable handheld battery-operated devices are acceptable, which differs from the criterion of the original authors).
- **Delivered** to those who need it.
**Undiagnosed Diabetes**

Proportion of early deaths, undiagnosed diabetes and number of diabetes per region.

![Diagram showing the proportion of diabetes cases undiagnosed by region.](IDF DIABETES ATLAS Eighth edition 2017)
Deeper Dive: Diagnosing Diabetes

**INITIAL lab glucose**
7.8 – 11.0 mmol/L

**random glucose**

**suitable for HbA1c?**

**NO**
- **fasting glucose**
  - not diabetic
  - ≤6.0
  - AND
  - 2-hr glucose
  - 6.1 – 6.9
  - OR
  - ≥7.0

**high risk**
- 7.8 – 11.0
- OR
- ≥11.1

**diabetes**
- 2-hr glucose

**YES**
- Abnormal red cell turnover
- Abnormal haemoglobin
- Renal disease
- Liver disease
- Pregnancy

**HbA1c**
- not diabetic
  - ≤41 mmol/mol
- high risk
  - 42 – 47 mmol/mol
- diabetes
  - ≥48 mmol/mol

**OGTT**

**Glucose bound to N-terminal valine of β-chain**

**Fasting glucose**
- ≤6.0
- AND
- 2-hr glucose
- 6.1 – 6.9
- OR
- 7.8 – 11.0
- OR
- ≥11.1

**OGTT**
- Diabetic
- Normal
HbA1c in the Field

The number of diabetes patients achieving optimal glycaemic control increased by 125%, while the number with very poor glycaemic control halved.

Costs ($7+/test) and supply chain for reagents becomes challenging.
Next Generation Instrumentation: Microfluidics

On-chip, aptamer-based sandwich assay for detection of glycated hemoglobins via magnetic beads

Jingjun Li, Ko-Wei Chang, Chih-Hung Wang, Ching-Hsuan Yang, Shu-Chu Shieh, Gwo-Rin Lee

Self-powered integrated microfluidic point-of-care low-cost enabling (SIMPLE) chip

Erh-Chia Yeh, Chi-Cheng Fu, Lucy Hu, Rohan Thakur, Jeffrey Feng, Luke P. Lee

Reduced the reagent consumption by 75%
Lessons from Glucose Test Strips

Cost to manufacture: ~ $0.15

Sale price in West: ~ $0.35-$1

Annual glucose testing/person: $80/yr

Medical Devices: Evidence and Research 2018:11 51–56

Glucose testing costs:
Senegal $2-2.5
Gambia $2-2.5
Mali $2.38

Non-Invasive Glucose Detection

Disruption in the diabetic device care market

“It should be noted that the performance of GlucoTrack is inferior to that of current SMBG and CGMs, mainly due to the indirect non-invasive nature of the measurement that subjects it to suffer from a relatively low signal-to-noise ratio. For this reason, GlucoTrack should not be used for diagnosis and medications intake or treatment decisions should not be based only on measurements obtained by it.”

Ultrasonic + Conductivity + Heat Capacity
<table>
<thead>
<tr>
<th>Disease</th>
<th>Group</th>
<th>Publication Year</th>
<th>Patient Number</th>
<th>Specificity (%)</th>
<th>Selectivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrett’s esophagus</td>
<td>Huang et al</td>
<td>2014</td>
<td>373</td>
<td>87 (high grade)</td>
<td>84.7</td>
</tr>
<tr>
<td>Cervical precancer</td>
<td>Mahadevan-Jansen et al.</td>
<td>2011</td>
<td>172</td>
<td>96.5 (dysplasia)</td>
<td>97.8</td>
</tr>
<tr>
<td>GI cancer</td>
<td>Huang et al</td>
<td>2011</td>
<td>164</td>
<td>92.5 (bevelled probe)</td>
<td>93.1 (bevelled probe)</td>
</tr>
<tr>
<td>GI cancer</td>
<td>Huang et al</td>
<td>2014</td>
<td>450</td>
<td>81.3 (prospective)</td>
<td>88.3</td>
</tr>
<tr>
<td>Oral cancer</td>
<td>Gupta et al</td>
<td>2014</td>
<td>199</td>
<td>96 (malignant)</td>
<td>99 (normal)</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>Zeng et al</td>
<td>2012</td>
<td>453</td>
<td>90 (cancer vs. benign)</td>
<td>64</td>
</tr>
</tbody>
</table>
Reagentless Blood Diagnostics: Raman Spectroscopy

Selected Known Raman Peaks in Serum

The Landscape is Changing Rapidly

Hardware
For low-value add, hardware needs to be cheap

cheap lasers

cheap sensors

Computation
Advances in data analysis
Requirements for high impact diagnostics in the developing world

http://www.nature.com/diagnostics

Characteristics of the ideal diagnostic test for the developing world: ASSURED

- Affordable by those at risk of infection.
- Sensitive (few false-negative results).
- Specific (few false-positive results).
- User-friendly (simple to perform by persons with little training).
- Rapid treatment at the first visit and robust use without the need for special storage.
- Equipment-free (that is, no large electricity-dependent instruments needed to perform the test; note that portable handheld battery-operated devices are acceptable, which differs from the criterion of the original authors).
- Delivered to those who need it