THE PATH TO GENOMIC MEDICINE: AN IMPLEMENTATION CHALLENGE

Lori A. Orlando, MD MHS
POTENTIAL TO CHANGE THE HEALTHCARE PARADIGM

From https://en.wikipedia.org/wiki/Metabolomics

Source: R. Snyderman. (Adapted with permission.)
IT IS NOT WITHOUT RISKS

Eugenics
Determinism

GATTACA 1997
REAL QUESTION IS: HOW TO IMPLEMENT?

CHALLENGES

- Complex
- Interventions vary widely
- Context dependent
- Highly diverse stakeholders
Implementations without structure provide no guidance on implementation in other settings—

- Lack generalizability
- Lack sustainability
EXAMPLE: CENTRAL LINE INFECTIONS

- Peter Pronovost’s ICU checklist (NEJM 2006)
- 108 ICUs in Michigan
- Catheter related infections decreased by 80% at all sites
HOW YOU GET TO OUTCOMES IS IMPORTANT
HOW YOU GET TO OUTCOMES IS IMPORTANT
CONSOLIDATED FRAMEWORK FOR IMPLEMENTATION RESEARCH (CFIR)

Overall:
26 constructs
13 sub-constructs

www.dissemination-implementation.org/
**Interventions**

*Purpose*: Evaluate Disease risk, Dx, Prognosis, Therapy

*Type*: Family history, SNP-panel, targeted, whole genome, exome sequencing, cascade

*Comparator*: none, usual care, another intervention

*Education*: patient, family, provider

*Return of Results*: By clinicians, genetic counselors, lay persons

**PHYSICAL CONTEXT**

**Medical**: Access, available quality of care

**Built Environment**: Housing, poverty, crime, walkability, pollution, food

**Unequal Distribution of Resources**: Money, Public Policy, Systems, Education

**MEDICAL CONTEXT**

**Setting Type**: in/outpatient, academic/community, rural/urban, private/safety

**Health Systems**: patient population (#/year, payor mix, EHR type, race/ethnicity, SES)

**Implementation Climate**: Readiness, access to resources & information, compatibility with workflow, leader engagement, tension for change

**PROCESSSES**

**Communication**: Patient, family, provider, lab (nature and quality)

**Laboratory**: Quality metrics, turn around, structural variant calling, ROR process

**OUTER SETTING**

**Inner Setting**

**INNER SETTING**

**IMPLEMENTATION PROCESS**

Select steps taken to facilitate uptake using expert recomm. for implementing change study choices (in sparks)

**OUTCOMES**

**Clinical Utility**: Actionability of intervention Diagnostic yield Health Status, QOL, Morbidity Mortality Patient uptake of intervention recs Provider uptake of intervention recs Patient achieves study endpoint

**Psychological Utility**: health behaviors, anxiety, distress, depression

**Pragmatic Utility**: Life and reproductive planning

**Intervention Adoption**: Patient (reach) Uptake by clinic, health system, provider (adoption) Adherence to intervention

**Social Utility & Maintenance**: Healthcare Utilization Effectiveness >6 months Sustained delivery of intervention Uptake by payors Cost effectiveness

**INTERMEDIATE OUTCOMES (RESULTS)**

Biological/Clinal: Processes and markers

1° & 2° Findings: Pathogenicity, findings, Iterative phenotyping, Follow up

**STAKEHOLDER ENGAGEMENT**
**EX. IMPLEMENT RISK ASSESSMENT PROGRAM**

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<th>Inner Setting</th>
<th>Potential Mitigating Factors</th>
<th>Individuals</th>
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### Stakeholder Engagement

- **Clinical Utility**: Actionability of intervention
  - Diagnostic yield
  - Health Status, QOL, Morbidity
  - Mortality
  - Patient uptake of intervention needs
  - Provider uptake of intervention needs
  - Patient achieves study endpoint
- **Psychological Utility**: health behaviors, anxiety, distress, depression
- **Prognostic Utility**: Life and reproductive planning
- **Intervention Adoption**: Patient (reach)
  - Uptake by clinic, health system, provider (adoption)
  - Adherence to intervention
- **Social Utility & Maintenance**: Healthcare Utilization
  - Effectiveness ≥6 months
  - Sustained delivery of intervention
  - Uptake by payors
  - Cost effectiveness
- **INTERMEDIATE OUTCOMES (RESULTS)**
  - Biological/Clinical: Processes and markers
    - Pathogenicity, findings, iterative: genotyping, follow up

### Implementation Process

- Select steps taken to facilitate uptake using expert recomm. for implementing change, study choices (in sparks)
KEY CHALLENGES FOR GENOMIC MEDICINE

There are many but will highlight 4 areas:

1) Intervention complexity
2) Disparities
3) Data (type and ownership)
4) Implementation outcomes
INTERVENTION COMPLEXITY

- Family health history, genotyping, WES/WGS?
  - Current guidelines recommend using FHH to guide testing
  - ~50% with pathogenic BRCA do not meet testing criteria
  - New knowledge makes genotyping results outdated in few years
  - Monogenic highly pathogenic variants are not 100% penetrant (why?)

- Who will collect the FHH?
- Who will analyze FHH to know when to test?
- Who will perform the testing and explain the testing to the patient?
- Who and how will results be documented and returned to patient?
PROPOSED FHH-BASED RISK ASSESSMENT

Patient entry from home or clinic *

Prepare with worksheet to talk with relatives

Contact available for questions or problems

Data sent to medical record, processed and report generated

New recommendation

New research

Algorithm updating

Appointment

Patient-Physician

Disease risk

Patient values

Physician recommendation

Healthcare Plan

*
## EX. IMPLEMENT RISK ASSESSMENT PROGRAM

### Interventions

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**Return of Results:**
- By: clinicians, genetic counselors, lay persons
- To: patient, family, provider
- How: in person, app, EHR, telemedicine
- What: Structure, content of report including what will be returned

**Characteristics:**
- Cost, relative advantage, evidence strength, adaptability, complexity

### Implementation Process

Select steps taken to facilitate uptake using expert recomm. for implementing change, study choices (in sparks)

### Outer Setting

**Physiological Context**

- **Medical**: Access, available quality of care
- **Built Environment**: Housing, poverty, crime, walkability, pollution, food

### Inner Setting

**Medical Context**

- **Setting Type**: In/outpatient, academic/community, rural/urban, private/safety
- **Health Systems**: Patient population (#/year, payer mix, EHR type, race/ethnicity, SES)

### Implementation Climate

- Readiness, access to resources & information, compatibility with workflow, leader engagement, tension for change

### Processes

- **Communication**: Patient, family, provider, lab (nature and quality)
- **Laboratory**: Quality metrics, turn around, structural variant calling, ROR process

### Potential Mitigating Factors

#### Individuals

**Patient Factors**

- **Social**: Social network, support, influence, engagement
- **Demographic**: Age, race/ethnicity, sex/gender, lang., literacy, numeracy, income, employment, education, insurance
- **Psychosocial**: Depression, stress, anxiety, self-efficacy, perceived racism, activation, cultural norms, family issues
- **Stressors/Resources**: Family, community, occupational, financial, behavioral

**Attitude, Understanding**: Genetic testing, return of results, about intervention, trust (in testing, results, providers), expected utility, preference for who returns results

**Biological/genetic makeup**: Family history, Health history, Ancestry

### Outcomes

**Clinical Utility**

- Actionability of intervention
- Diagnostic yield
- Health Status, QOL, Morbidity
- Mortality

**Provider uptake of intervention recs**

- Patient uptake of intervention recs
- Provider uptake of intervention recs
- Patient achieves study endpoint

**Psychological Utility**

- Health behaviors, anxiety, distress, depression

**Prognostic Utility**

- Life and reproductive planning

**Intervention Adoption**

- Patient (teach)
- Uptake by clinic, health system, provider (adoption)
- Adherence to intervention

**Social Utility & Maintenance**

- Healthcare Utilization
- Effectiveness >6 months
- Sustained delivery of intervention
- Uptake by payors
- Cost effectiveness

**Intermed. Outcomes (Results)**

- Biological/Cl inical: Processes and markers
- 1^e & 2^e Findings: Pathogenicity, findings, iterative: phenotyping, follow up
DISPARITIES

- Social determinants of health
- Trust
- Ancestry
- Insurance coverage
- Type of accessible medical providers and clinics
- Resources for performing testing or return of results

FHH IMPLEMENTATION ADAPTATION

Each step contains several implementation strategies that each site could select based upon their context.

1. Access to risk assessment via linkage from EMR, stand alone web server, phone
2. Testing via health system lab, mailed samples to lab, online servicing
3. Genetic counseling via GC or lay person trained in returning results, in person vs tele-counseling
### EX. IMPLEMENT RISK ASSESSMENT PROGRAM

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**Implementation Process**
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**Processes**
- Communication: Patient, family, provider, lab (nature and quality)
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**Intermed. Outcomes (Results)**
- Biological/Genetic: processes and markers 1st & 2nd findings: Pathogenicity, findings, iterative, phenotyping, follow up

**Stakeholder Engagement**
PATIENT DATA (RISK INFORMATION)

- Are risks interpreted differently if it is family history or DNA?
- Does sharing with relatives change for family history vs DNA?
- Do relatives react differently to family history vs DNA?
- Does it change their likelihood of acting on risk information?

Who prefers which method and how do we predict response?
PATIENTS SHOULD HAVE THE OPTION TO OWN THEIR DATA

Not all patients want their data but those who do, should

PHRs so far have been limited and dysfunctional
  • E-patient Dave in 2009 lead to Google Health’s closure in 2011

Advances in informatics and data standards
  • SMART – FHIR
  • Blockchain

Blockchain: Securing Internet of Medical Things (IoMT) - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Internet-of-Medical-Things-IoMT_figi_330883527 [accessed 21 Jun, 2019]
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**INTERIM OUTCOMES (RESULTS)**
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  - 1st & 2nd Findings: Pathogenicity, findings, iterative, phenotyping, follow up
OUTCOMES TO EVALUATE IMPACT

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End result: intervention helps 32% of those who could benefit from it

Context: will further mediate this impact (most likely for the worse)
Genomic Medicine has tremendous potential to transform healthcare for the better.

There are numerous pitfalls that could lead to misuse, misalignment, and the possibility of harm.

An implementation sciences framework can help anticipate, evaluate, and understand facilitators and barriers to clinical use of genomics and help guide optimal implementations that are tailored to the setting.