Real World Implementation of Precision Medicine

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IGNITE
www.ignite-genomics.org

G2MC
www.nas.edu/G2MC
Disclosure Information

Geoffrey S Ginsburg MD PhD

I have the following financial relationships to disclose

- Consultant/Advisor/Board Member for:
  Omicia, Pappas Ventures, Alere, Interleukin Genetics, CardioDx
- Grant/Research support from:
  NHGRI, NHLBI, NCI, DARPA, USAMRIID, Gates Foundation, US Air Force, Henry Jackson Foundation, Singulex, IBIS Biosciences
- Stockholder in: CardioDx, Alere
- Employee of: Duke University

No Conflicts with the Current Presentation
The Challenge

Using genomic information about an individual to optimize their clinical care

Human Genome Project

Precision Medicine & Health
The (Non-Linear) Genomics Translation Research Cycle

Population Health

Discovery

Knowledge Integration

Human Application

Evaluation & Evidence Generation

T0

T1

T2

T3

T4

Basic, Clinical & Population Sciences

Effectiveness & Outcomes Research

Health care & Prevention Programs

Evidence based Recommendation or Policy

Implementation Science

Khoury MJ et al, AJPH, 2012
Early Precision Medicine: 1961 “Factors of Risk”

Factors of Risk in the Development of Coronary Heart Disease—Six-Year Follow-up Experience

Kannel WB et al.
November 1961

- High blood pressure
- Increased cholesterol
- Smoking
- Diabetes
- Family history
- Male sex

(Failure of) Implementation of CVD Risk Calculators

• Primary Care Physicians
  – only 13% had read guidelines carefully
  – only 17% used a CHD risk calculator
  “a large variability in knowledge, beliefs, and practice patterns among practicing family physicians”

• Barriers
  – Lack of knowledge
  – Distrust in validity
  – Time consuming


Lung Cancer: Molecular Guided Therapy

> 50% of non-small cell lung cancers have actionable mutations, but < 20% of non-small cell lung cancer patients are tested for EGFR in the USA (Lynch, Genet Med 2013)
Genomics Translation: Funding Priorities for Evidence or Implementation?

1.8% of NCI Funded Grants are T2 or beyond

Puggal, Circ Cardiovasc Genet. 2013

1% of NHLBI Funded Genetics Grants are T2 or beyond

Schully, Public Health Genomics 2010
Payer Adoption of Oncotype DX®: Not All Payers are Alike
## COVERAGE INCONSISTENCIES FOR SAMPLE DIAGNOSTICS (2010)*

<table>
<thead>
<tr>
<th>Innovative Test Examples</th>
<th>FDA Cleared?</th>
<th>Positive Coverage Policies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Aetna</td>
</tr>
<tr>
<td>AlloMap</td>
<td>Yes</td>
<td>✓</td>
</tr>
<tr>
<td>Oncotype DX (breast Cancer)</td>
<td>No</td>
<td>✓</td>
</tr>
<tr>
<td>MammaPrint</td>
<td>Yes</td>
<td>✓</td>
</tr>
<tr>
<td>Pathwork Tissue of Origin</td>
<td>Yes</td>
<td>✓</td>
</tr>
<tr>
<td>BRACAnalysis</td>
<td>No</td>
<td>✓</td>
</tr>
<tr>
<td>OVA1</td>
<td>Yes</td>
<td>✓</td>
</tr>
<tr>
<td>KRAS (colorectal cancer)</td>
<td>No</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Note: All of these tests are offered as LDTs. The information in this table was current as of the publication of the source report in 2010, and has not been updated to reflect the most current information.

• Much more happening than anticipated
• Largely in isolation
• Key barriers:
  • Lack of evidence
  • Interpretation of variants
  • Lack of expertise
  • Lack of standards
  • EMR integration
  • Financial model needed
electronic MEdical Records and GEnomecs (eMERGE) Network (https://emerge.mc.vanderbilt.edu/)
Decision Support for Clopidogrel

Clopidogrel Poor Metabolizer Rules

Genetic testing has been performed and indicates this patient is at risk for inadequate anti-platelet response to clopidogrel (Plavix) therapy. This patient has been tested for CYP2C19 variants, and the presence of the *2/*2 genotype has identified this patient as a poor metabolizer of clopidogrel. Poor metabolizers treated with clopidogrel at normal doses exhibit higher rates of stent thrombosis/other cardiovascular events.

Treatment modification is recommended:
- Prescribe prasugrel (EFFIENT) 10mg daily and stop clopidogrel (PLAVIX) startdate, 10 AM

Due to increased risk of bleeding, prasugrel should not be given to patients:
- that have a history of stroke or transient ischemic attack
- that are greater than 75 years of age
- whose body weight is less than 60 kg

Click here for more information

If prasugrel (EFFIENT) not selected, please choose desired action:
- Increase maintenance dose of clopidogrel (PLAVIX) 150 mg daily, startdate, 10AM
- Maintain requested daily dose of clopidogrel (PLAVIX) 75 mg daily, startdate, 10AM

Click here for more information

NOTE: The Vanderbilt P&T Committee has recommended that prasugrel (if not contraindicated) should replace clopidogrel for poor metabolizers; if this is not possible consider doubling the standard dose of clopidogrel (or, use standard dose clopidogrel). However, there is not a national consensus on drug/dose guidance in this population.

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To develop standards for integrating genomic patient data with other types of healthcare data in the EHR so that it becomes routine to deliver that information to providers and patients for patient care and to enable healthcare systems to generate evidence.
DIGITizE: Standards for Genetic Information Integration into the EHR

- Government Agencies
- Providers
- Laboratories
- EMR Vendors
- Patients Representatives
- Standards Organizations

Establishing Connectivity and Pharmacogenomic Clinical Decision Support Rules to Protect Patients Carrying HLA-B*57:01 and TPMT Variants
An Implementation Guide

12/1/2015
Displaying and Integrating Genetic Information Through the EHR Action Collaborative (DIGITizE AC)
Version 1.0

- Rational
- LOINC Transfer Codes
- Suggested Rules

• Expand and link existing genomic medicine efforts
• Develop implementation methods, in diverse settings and populations
• Contribute to evidence base regarding outcomes of incorporating genomic information into clinical care
• Disseminate best practices for genomic medicine implementation, diffusion, and sustainability
Duke University – Geoffrey Ginsburg, M.D., Ph.D
  Lori Orlando, M.D. (Family History and Coordinating Center)

Mount Sinai School of Medicine – Carol Horowitz, M.D.
  (Hypertension and CKD)

University of Florida – Julie Johnson, Ph.D.
  (Pharmacogenomics)

National Human Genome Research Institute

Vanderbilt University – Joshua Denny, M.D.,
  Mia Levy M.D. (Pharmacogenomics)

University of Maryland – Toni Pollin, Ph.D. (Diabetes)

Indiana University – Todd Skaar, Ph.D., Paul Dexter, M.D. (Pharmacogenomics)
6 Pilot Demonstration Projects
Developing Implementation and Effectiveness Outcomes

Primary Care or Specialty Care Patient

- Family History (80+ conditions)
- Pharmacogenetics (Antiplatelet Agents, Pain, HCV)
- Targeted Cancer Therapies
- Genetic Risk (Apo L1, MODY)

Pragmatic Trials

Genomics-Guided

Standard of Care

Outcome

Outcome

Patient, Provider, System and Economic Outcomes
New Family Health History Platform (MeTree™)

Patient entry from home or clinic

Data sent to medical record, processed and report generated

Prepare with worksheet to talk with relatives

Contact available for questions or problems

Appointment

New research

Algorithms updated

New recommendation

Disease risk

Patient values

Physician recommendation

Healthcare Plan
SMART on FHIR®:
Medical apps that integrate into diverse EHR systems at the point of care
## Implementation Stages

<table>
<thead>
<tr>
<th>Pre-Implementation</th>
<th>Implementation</th>
<th>Post-Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Identify current practice patterns</td>
<td>• Assess implementation integrity (used as intended)</td>
<td>• Assess acceptance and satisfaction for stakeholders</td>
</tr>
<tr>
<td>• Identify barriers &amp; facilitators</td>
<td>• Assess implementation exposure (used at intervention sites)</td>
<td>• Assess clinical impact for all stakeholders</td>
</tr>
<tr>
<td>• Assess feasibility</td>
<td>• Identify explanations and solutions for low integrity or intensity</td>
<td>• Adapt and finalize implementation strategy</td>
</tr>
<tr>
<td>• Establish implementation plan</td>
<td>• Modify implementation plan</td>
<td>• Assess impact of final implementation strategy</td>
</tr>
</tbody>
</table>

## IGNITE: Implementation Outcomes and Measures

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model Reach</td>
<td>Representativeness of patient population to general population</td>
</tr>
<tr>
<td>Model Adoption</td>
<td>Representativeness of clinics agreeing to participate</td>
</tr>
<tr>
<td>Implementation Integrity</td>
<td>% time intervention used as intended</td>
</tr>
<tr>
<td>Implementation Exposure</td>
<td>% time intervention used</td>
</tr>
<tr>
<td>Maintenance and Sustainability</td>
<td>Cost to Implement Cost/Effectiveness</td>
</tr>
</tbody>
</table>

Mixture of Survey, EMR, and Qualitative data
IGNITE: Effectiveness Outcomes

<table>
<thead>
<tr>
<th>Category</th>
<th>Patient</th>
<th>Provider</th>
<th>System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emotional</strong></td>
<td>SF-12 (quality of life)</td>
<td>Satisfaction</td>
<td>Staff satisfaction</td>
</tr>
<tr>
<td></td>
<td>Patient Activation Measure</td>
<td>Knowledge</td>
<td>Organizational readiness to change (ORCA)</td>
</tr>
<tr>
<td></td>
<td>Prochaska Stage of Change</td>
<td>Barriers to Model use</td>
<td>Implementation climate</td>
</tr>
<tr>
<td></td>
<td>Satisfaction and anxiety</td>
<td>Concur with CDS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quality of clinical encounter</td>
<td>Quality clinical encounter</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Barriers to Model use</td>
<td>Quality CDS for care</td>
<td></td>
</tr>
<tr>
<td><strong>Behavioral</strong></td>
<td>Medication adherence (Morisky)</td>
<td>Discussion of prevention</td>
<td>Work flow/processes</td>
</tr>
<tr>
<td></td>
<td>% exercising (Stanford Brief Activity)</td>
<td>Discussion of risk</td>
<td>Implementation policies and practices</td>
</tr>
<tr>
<td></td>
<td>% eating 3 servings fruits/veggies per day (Rapid Food Screener)</td>
<td>% time CDS output used (uptake)</td>
<td>Implementation climate</td>
</tr>
<tr>
<td></td>
<td>% smoking</td>
<td>% adherence to CDS</td>
<td>Intervention values and task fit</td>
</tr>
<tr>
<td></td>
<td>% ideal BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Implemented provider rec (uptake)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Biological</strong></td>
<td>Demographics</td>
<td>FHH documentation &amp; counseling</td>
<td>% completion MeTree™</td>
</tr>
<tr>
<td></td>
<td>FHH</td>
<td></td>
<td>time to complete FHH</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>Laboratory Data (i.e. LDL)</td>
<td>Disease control goals met</td>
<td>% high risk patients</td>
</tr>
<tr>
<td></td>
<td>Screening tests performed</td>
<td>Referrals made</td>
<td>% w/ risk based screening</td>
</tr>
<tr>
<td></td>
<td>Screening complications</td>
<td></td>
<td>% w/ screening compl.</td>
</tr>
<tr>
<td></td>
<td>Vital Signs, Weight and BMI</td>
<td></td>
<td>% w/ disease at goal</td>
</tr>
<tr>
<td></td>
<td>Number of medications</td>
<td></td>
<td>Visit length/Wait times</td>
</tr>
<tr>
<td><strong>Financial</strong></td>
<td>Socio-economic status</td>
<td></td>
<td>Office/ ER visits, hospitalizations</td>
</tr>
<tr>
<td></td>
<td>Medication costs</td>
<td></td>
<td>Model resource needs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Impact on family members</td>
</tr>
</tbody>
</table>

Mixture of EMR (blue) and survey data
IGNITE: Common Challenges and Solutions

1) Clinician knowledge
   - all projects developed educational materials and conducted educational meetings for clinicians

2) Integration with the electronic health record
   - health system level adoption of genomic standards
   - development of clinical decision support and access

3) Engaging diverse patient and clinician populations
   - Forming genomics medicine advisory board to represent stakeholders and involve them in every step

3) Recruiting patients
   - actively involve patients in implementation (e.g., a patient advisory board to develop educational materials) and develop materials to inform patients about questions to ask their clinician or payer

Sperber et al – in preparation
The IGNITE Toolbox

To disseminate best practices in the implementation of genomic medicine

www.ignite-genomics.org
Global Genomic Medicine Collaborative (G2MC)

Global implementation of genomic medicine: We are not alone


• > 35 nations
• Explore synergies, redundancies, collaborative opportunities for implementation of genomics into medicine
• Opportunities to advance the genome sciences as an agenda to impact global health

Sci Trans Med 2015
G2MC 2015: Large Scale Genomics Initiatives

- Genomics England
  - 100,000 genomes (Linked to NHS EMR data)
- Geisinger - Regeneron (USA)
  - 100,000 genomes (Linked to EPIC EMR data)
- Genome Qatar
  - 300,000 Qatari genomes (Linked to CERNER EMR data)
- Estonian Genome Project
  - 52,000 genomes (Linked to health care data)
- The US Precision Medicine Initiative
  - ? 1,000,000 Genomes (Linked to EMR and mHealth data)
- Initiating efforts in Korea, Malaysia, Scotland, Singapore
A Grand Challenge... for Implementation of Genomic Medicine

Using genomic information about individuals to optimize clinical care and population health

Evidence Generation/Economic Models
Data Sharing/Security
Implementation Incentives
Workforce Development
Participant Engagement/Trust

Precision Medicine & Population Health

Millions of Genomes

Applied Genomics & Precision Medicine

Global Genomic Medicine Collaborative

IGNITE: Implementing Genomics In practiCExE
Questions?

Please submit your question in the Q&A feature on the right of the interface. Type and press submit.