



# Real World Implementation of Precision Medicine

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**IGNITE**  
[www.ignite-genomics.org](http://www.ignite-genomics.org)

**G2MC**  
[www.nas.edu/G2MC](http://www.nas.edu/G2MC)

# Disclosure Information

*Geoffrey S Ginsburg MD PhD*

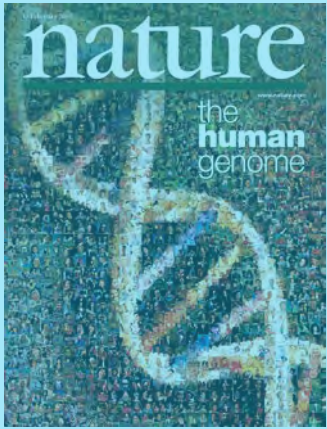
**I have the following financial relationships to disclose**

- Consultant/Advisor/Board Member for:  
Omicia, Pappas Ventures, Alere, Interleukin Genetics, CardioDx
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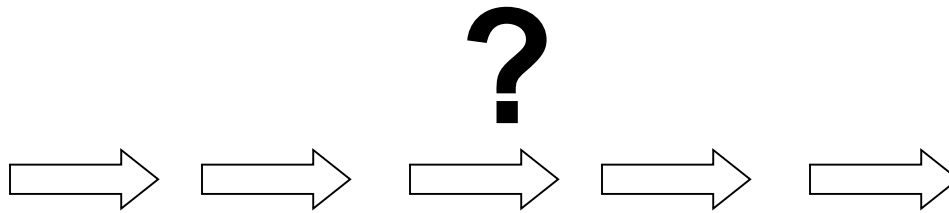
***No Conflicts with the Current Presentation***

# The Challenge

**Using genomic information about an individual to optimize their clinical care**

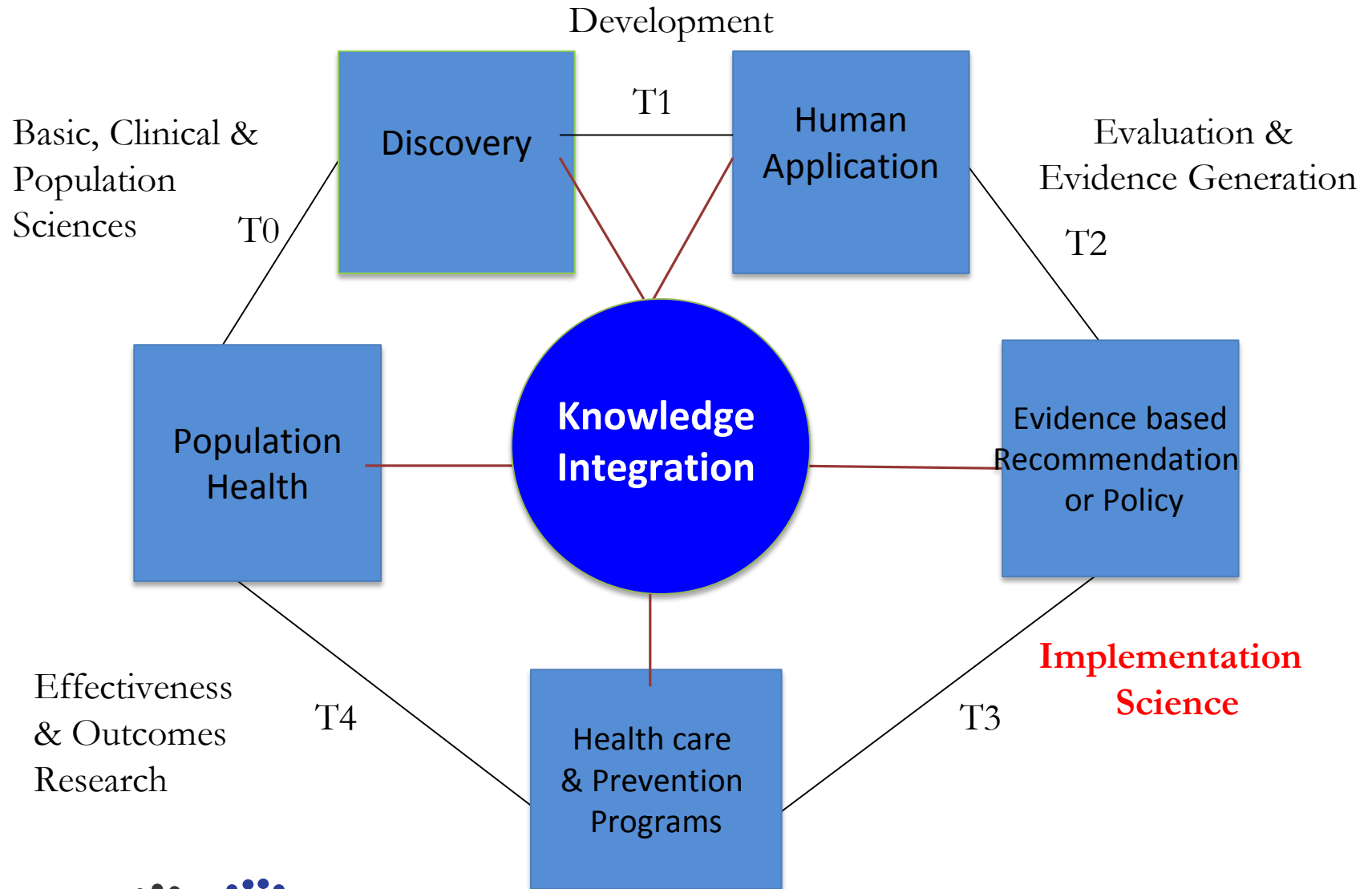


Human  
Genome  
Project



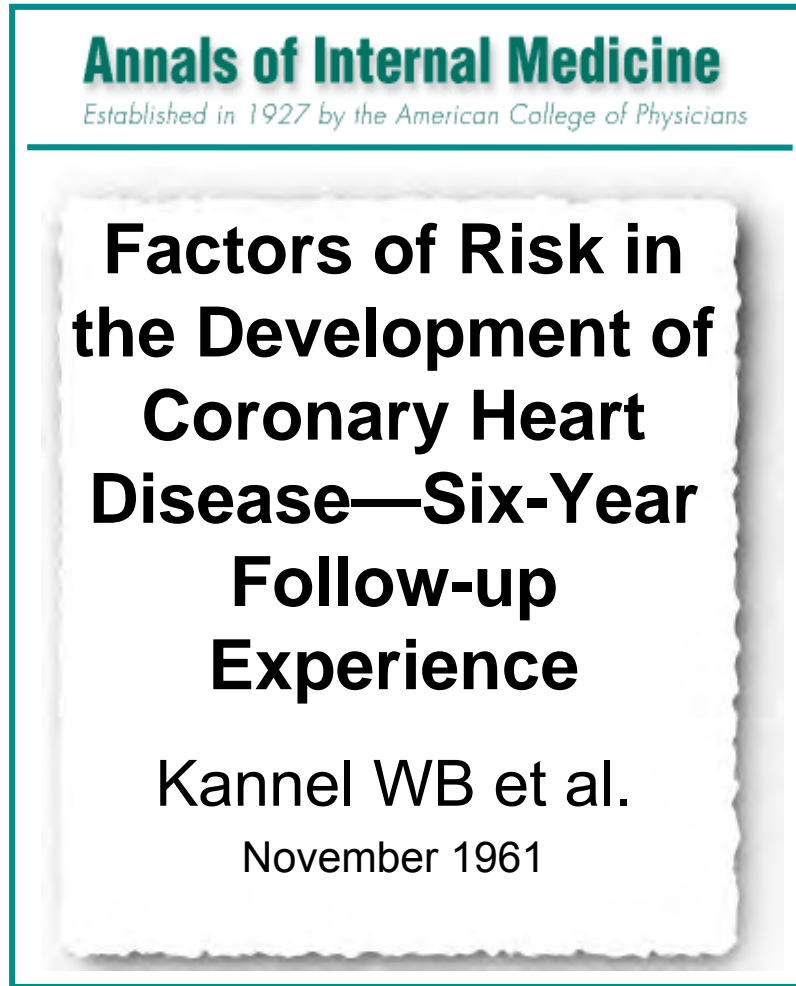
Precision  
Medicine &  
Health

# The (Non-Linear) Genomics Translation Research Cycle



# Early Precision Medicine: 1961

## “Factors of Risk”



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

Source: Kannel WB et al. *Ann Intern Med* 1961;55:33–50.

# (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

Eaton CB, *J Am Board Fam Med* 2006; 19:46–53.

Eichler K, *BMC Fam Pract* 2007; 8:1.

# Lung Cancer: Molecular Guided Therapy

Lapatinib/Temsirolimus

Erlotinib  
Second generation EGFR TKI

■ EGFR

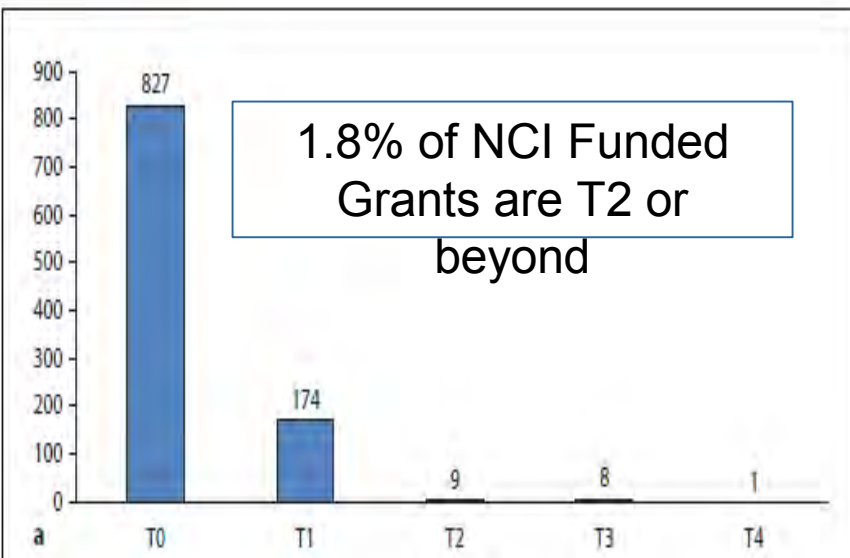
**> 50% of non-small cell lung cancers have actionable mutations, but < 20% of non-small cell lung cancer patients are tested for EGFR in the USA** (Lynch, Genet Med

2013)

Crizotinib vs. Chemotherapy

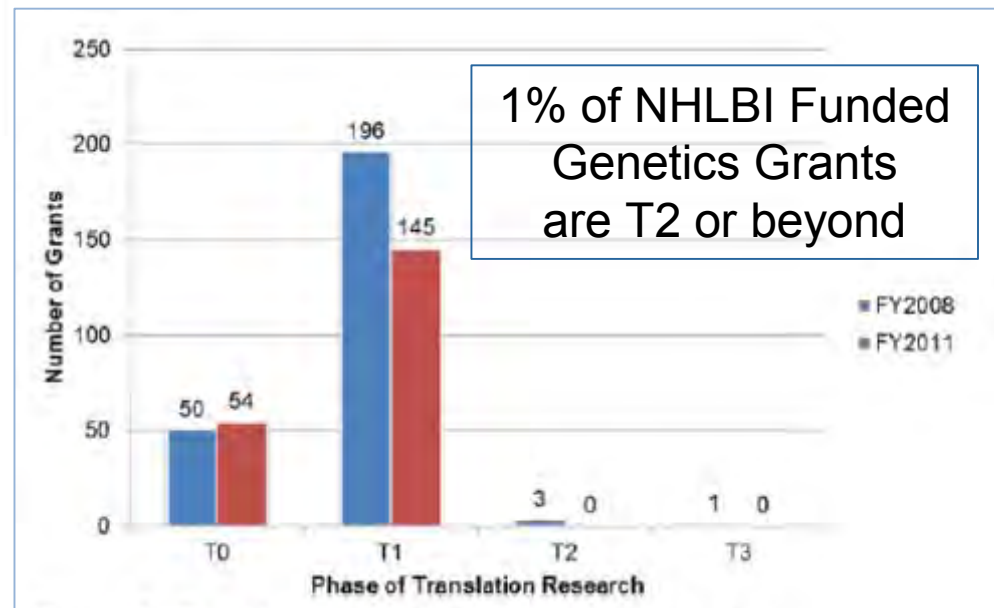
Crizotinib, 2<sup>nd</sup> Generation ALK Inhibitors

# Genomics Translation: Funding Priorities for Evidence or Implementation ?



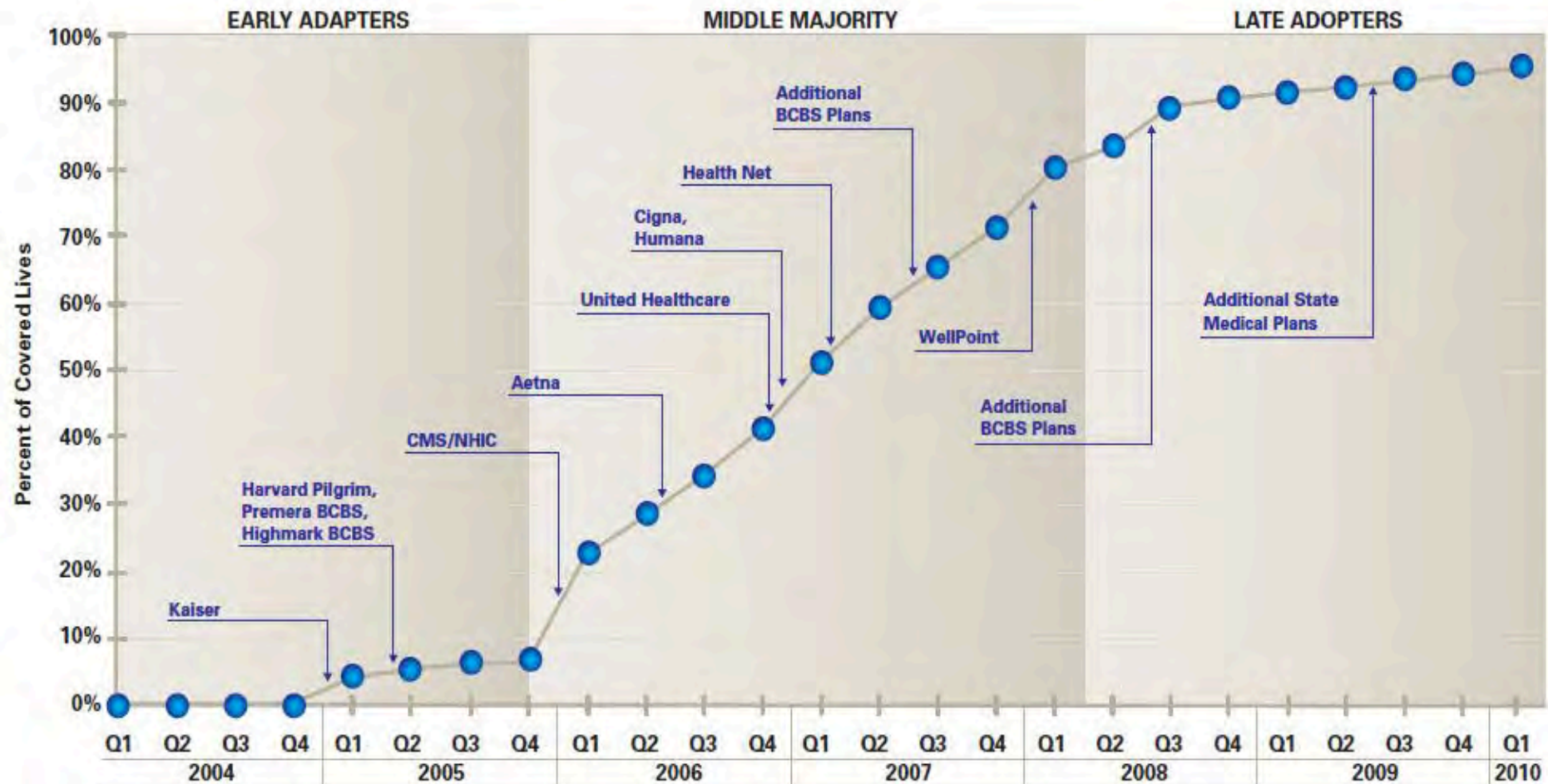
Schully, Public Health Genomics 2010

Puggal, Circ Cardiovasc Genet. 2013





# Payer Adoption of Oncotype DX®: Not All Payers are Alike



## COVERAGE INCONSISTENCIES FOR SAMPLE DIAGNOSTICS (2010)\*

Innovative Test Examples	FDA Cleared?	Positive Coverage Policies			
		Aetna	Regional CMS	Cigna	Regional BCBS
<b>AlloMap</b>	Yes		✓		
<b>Oncotype DX (breast Cancer)</b>	No	✓	✓	✓	✓
<b>MammaPrint</b>	Yes		✓		
<b>Pathwork Tissue of Origin</b>	Yes				
<b>BRACAnalysis</b>	No	✓	✓	✓	✓
<b>OVA1</b>	Yes		✓		✓
<b>KRAS (colorectal cancer)</b>	No	✓	✓	✓	✓

\*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.

Source: BIO and Health Advances Report: The Reimbursement Landscape for Novel Diagnostics: Current Limitations, Real-World Impact, and Proposed Solutions. 2010.

# First Genomic Medicine Meeting Report

- 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

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Open

Teri A

M

Murr

Davi

Michael

Alan R

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MD<sup>15</sup>,

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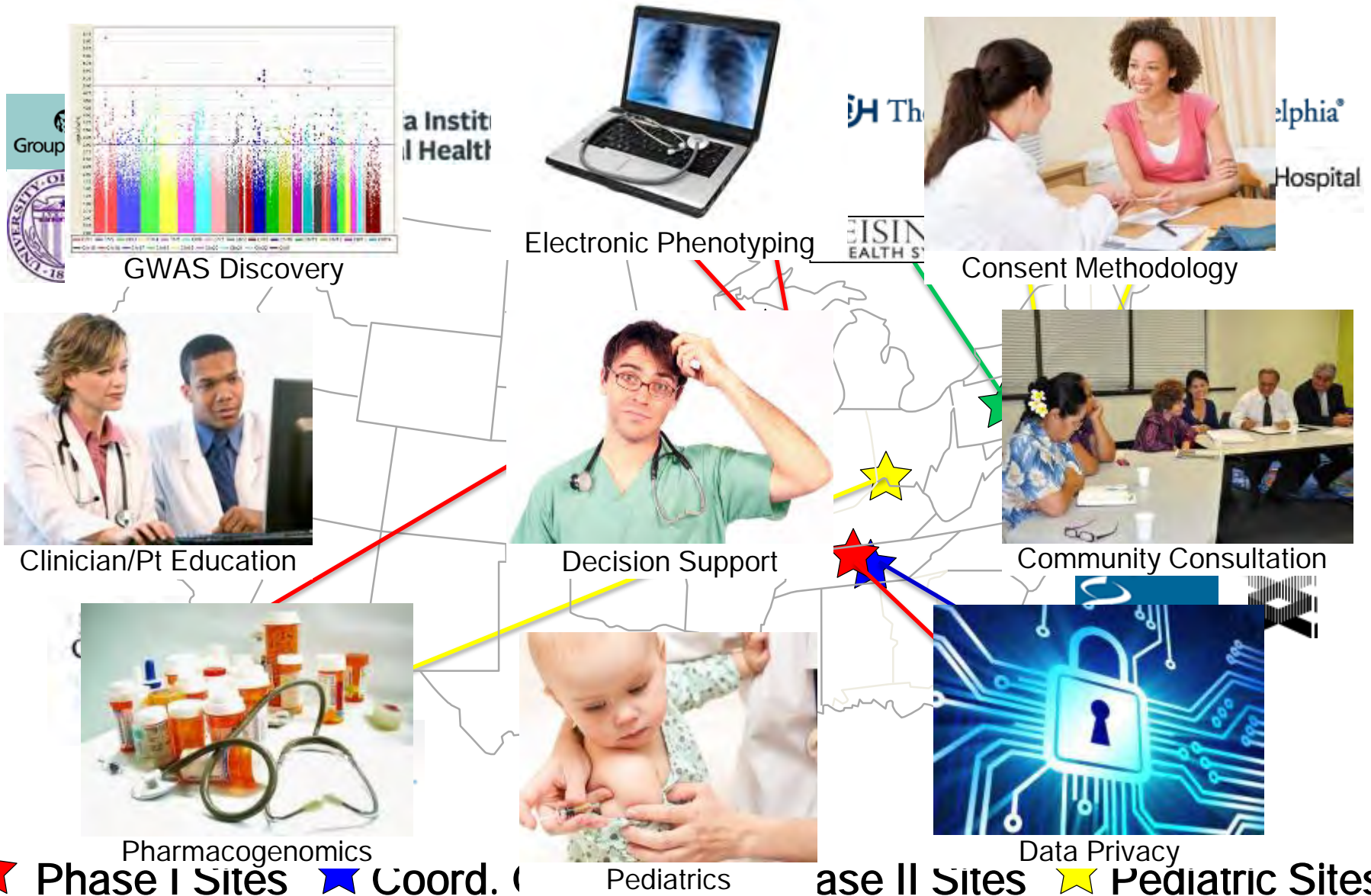
Although t

has long been anticipated, the pace of defining the risks and benefits of incorporating genomic findings into medical practice has been

interventions; and burden to patients and clinicians of assaying, reporting, intervening, and following up genomic findings. Key infrastructure needs



# electronic Medical Records and Genomics (eMERGE) Network (<https://emerge.mc.vanderbilt.edu/>)



# Decision Support for Clopidogrel

 HBO Popup

**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 \*\*\* Not known; please check StarPanel
- 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

☐ Contraindicated

☐ Expected effects (e.g. nuisance bleeding)

☐ Patient preference

☐ Other

Click here for [more information](#)

Cancel

Order

**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.

Back

Home

Close

**ABOUT HMD**

**REPORTS**

**ACTIVITIES**

**MEETINGS**

**ACTION COLLABORATIVES**

## **DIGITizE: Displaying and Integrating Genetic Information Through the EHR**

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

<http://www.pgrn.org/pgx-news/announcing-digitize-implementation-guide>



RESEARCH ARTICLE

Open Access



# The IGNITE network: a model for genomic medicine implementation and research

Kristin Wiisanen Weitzel<sup>1</sup>, Madeline Alexander<sup>2</sup>, Barbara A. Bernhardt<sup>3</sup>, Neil Calman<sup>4</sup>, David J. Carey<sup>5</sup>, Larisa H. Cavallari<sup>1</sup>, Julie R. Field<sup>6</sup>, Diane Hauser<sup>4</sup>, Heather A. Junkins<sup>7</sup>, Phillip A. Levin<sup>8</sup>, Kenneth Levy<sup>9</sup>, Ebony B. Madden<sup>7</sup>, Teri A. Manolio<sup>7</sup>, Jacqueline Odgis<sup>7</sup>, Lori A. Orlando<sup>10,19</sup>, Reed Pyeritz<sup>3</sup>, R. Ryanne Wu<sup>10,19</sup>, Alan R. Shuldiner<sup>11,12</sup>, Erwin P. Bottinger<sup>13</sup>, Joshua C. Denny<sup>14,15</sup>, Paul R. Dexter<sup>9</sup>, David A. Flockhart<sup>9\*</sup>, Carol R. Horowitz<sup>16</sup>, Julie A. Johnson<sup>1</sup>, Stephen E. Kimmel<sup>2,17</sup>, Mia A. Levy<sup>18</sup>, Toni I. Pollin<sup>11</sup>, Geoffrey S. Ginsburg<sup>19\*</sup> and on behalf of the IGNITE Network

- 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



\* IGNITE Principal Site

★ New sites



● 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)

### Analytic Validity

- Accuracy, precision, and reproducibility

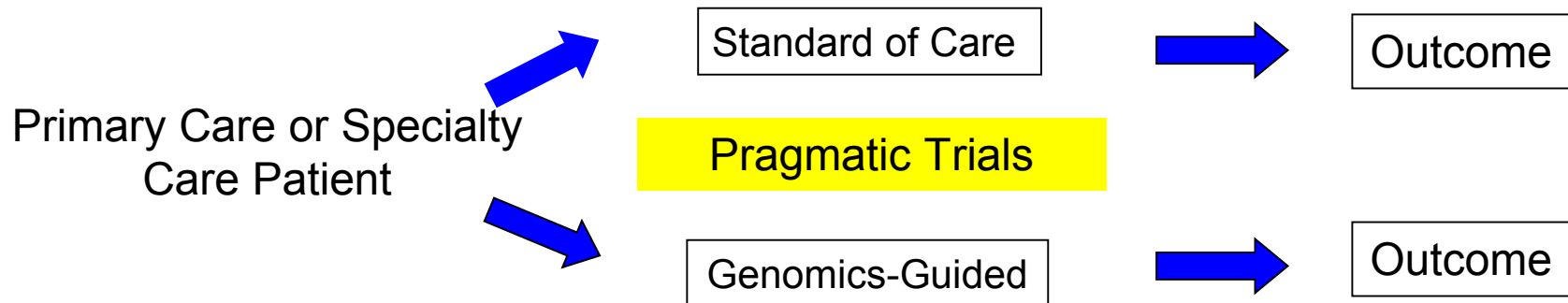
### Clinical Validity

- Association of the test result with clinical outcomes of interest

### Clinical Utility

- Evidence that test use influences physician decision-making and/or improves patient outcomes

# 6 Pilot Demonstration Projects Developing Implementation and Effectiveness Outcomes



**Family History (80+ conditions)**  
**Pharmacogenetics (Antiplatelet Agents, Pain, HCV)**

**Targeted Cancer Therapies**

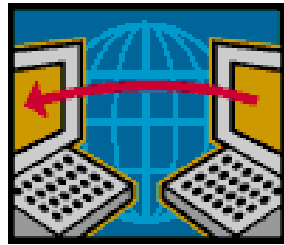
**Genetic Risk (Apo L1, MODY)**

*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



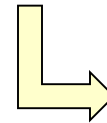
## Appointment



Patient-Physician

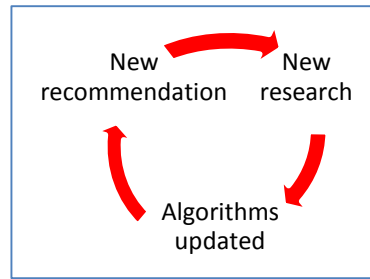
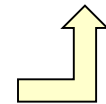


Healthcare  
Plan



Disease  
risk

Patient  
values



Prepare with  
worksheet to talk with  
relatives

Contact available for  
questions or problems

# SMART on FHIR®:

## Medical apps that integrate into diverse EHR systems at the point of care



Provider-Centric



- Open-source interface developed by HL7
- Endorsed by ONC and all major EHR vendors
- Familiar technology like REST and JSON (e.g., same as that used by Google, Facebook, etc.)
- Platform that incorporates FHIR to enable plug-and-play apps
- Incorporates OAuth 2.0 and standardized HTML5 and native apps



## White House Champions of Change *Precision Medicine*



- Family history is the most effective "genomic test"
  - One 1st-degree relative with CAD age < 50 doubles Framingham risk score
  - One 1st-degree relative with DM2 triples risk
  - Only way to identify many hereditary cancer and cardiovascular syndromes
- There is limited uptake of evidence-based risk stratified guidelines for disease prevention and early detection
  - <4% of charts reviewed had even 1 relative fully documented
  - Studies show that 40-80% of general population are at risk for at least one condition



# Implementation Stages

<u>Pre-Implementation</u>	<u>Implementation</u>	<u>Post-Implementation</u>
<ul style="list-style-type: none"><li>• <b>Identify current practice patterns</b></li></ul>	<ul style="list-style-type: none"><li>• Assess implementation integrity (used as intended)</li></ul>	<ul style="list-style-type: none"><li>• Assess acceptance and satisfaction for stakeholders</li></ul>
<ul style="list-style-type: none"><li>• <b>Identify barriers &amp; facilitators</b></li></ul>	<ul style="list-style-type: none"><li>• Assess implementation exposure (used at intervention sites)</li></ul>	<ul style="list-style-type: none"><li>• Assess clinical impact for all stakeholders</li></ul>
<ul style="list-style-type: none"><li>• <b>Assess feasibility</b></li></ul>	<ul style="list-style-type: none"><li>• Identify explanations and solutions for low integrity or intensity</li></ul>	<ul style="list-style-type: none"><li>• Adapt and finalize implementation strategy</li></ul>
<ul style="list-style-type: none"><li>• <b>Establish implementation plan</b></li></ul>	<ul style="list-style-type: none"><li>• Modify implementation plan</li></ul>	<ul style="list-style-type: none"><li>• Assess impact of final implementation strategy</li></ul>

Adapted from Smith J, editor. Evaluation Methods in Implementation Research: An introduction. Implementation Science Meeting; 2010.

# IGNITE: Implementation Outcomes and Measures

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

# IGNITE: Effectiveness Outcomes

	Patient	Provider	System
Emotional	<ul style="list-style-type: none"> <li>SF-12 (quality of life)</li> <li>Patient Activation Measure</li> <li>Prochaska Stage of Change</li> <li>Satisfaction and anxiety</li> <li>Quality of clinical encounter</li> <li>Barriers to Model use</li> </ul>	<ul style="list-style-type: none"> <li>Satisfaction</li> <li>Knowledge</li> <li>Barriers to Model use</li> <li>Concur with CDS</li> <li>Quality clinical encounter</li> <li>Quality CDS for care</li> </ul>	<ul style="list-style-type: none"> <li>Staff satisfaction</li> <li>Organizational readiness to change (ORCA)</li> <li>Implementation climate</li> </ul>
Behavioral	<ul style="list-style-type: none"> <li>Medication adherence (Morisky)</li> <li>% exercising (Stanford Brief Activity)</li> <li>% eating 3 servings fruits/veggies per day (Rapid Food Screener)</li> <li>% smoking</li> <li>% ideal BMI</li> <li>Implemented provider rec (uptake)</li> </ul>	<ul style="list-style-type: none"> <li>Discussion of prevention</li> <li>Discussion of risk</li> <li>% time CDS output used (uptake)</li> <li>% adherence to CDS</li> </ul>	<ul style="list-style-type: none"> <li>Work flow/processes</li> <li>Implementation policies and practices</li> <li>Implementation climate</li> <li>Intervention values and task fit</li> </ul>
Biological	<ul style="list-style-type: none"> <li>Demographics</li> <li>FHH</li> </ul>	<ul style="list-style-type: none"> <li>FHH documentation &amp; counseling</li> </ul>	<ul style="list-style-type: none"> <li>% completion MeTree™</li> <li>time to complete FHH</li> </ul>
Clinical	<ul style="list-style-type: none"> <li>Laboratory Data (i.e. LDL)</li> <li>Screening tests performed</li> <li>Screening complications</li> <li>Vital Signs, Weight and BMI</li> <li>Number of medications</li> </ul>	<ul style="list-style-type: none"> <li>Disease control goals met</li> <li>Referrals made</li> </ul>	<ul style="list-style-type: none"> <li>% high risk patients</li> <li>% w/ risk based screening</li> <li>% w/ screening compl.</li> <li>% w/ disease at goal</li> <li>Visit length/Wait times</li> </ul>
Financial	<ul style="list-style-type: none"> <li>Socio-economic status</li> <li>Medication costs</li> </ul>		<ul style="list-style-type: none"> <li>Office/ ER visits, hospitalizations</li> <li>Model resource needs</li> <li>Impact on family members</li> </ul>

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

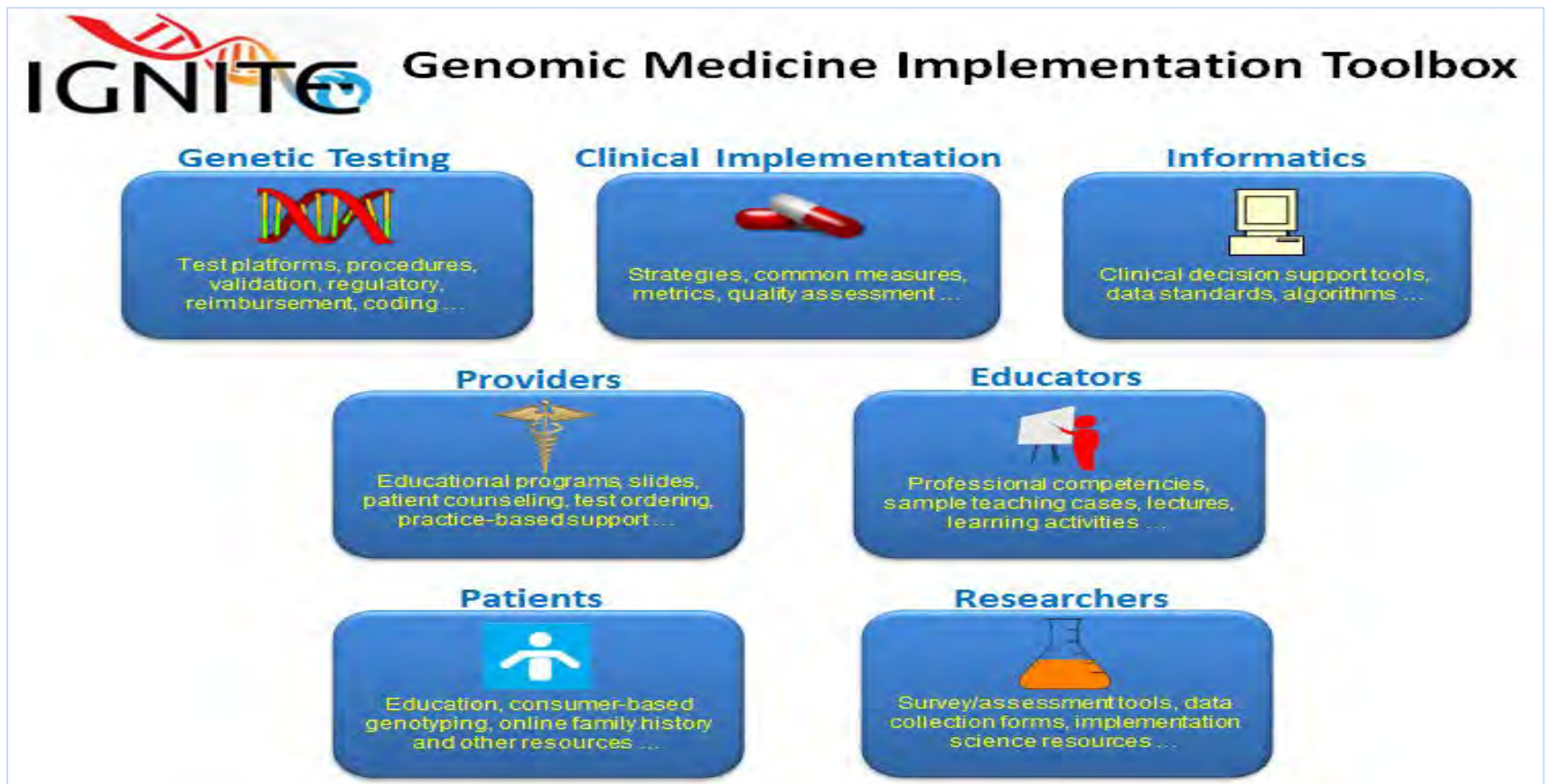
### 3) Recruiting patients

- 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



# The IGNITE Toolbox

To disseminate best practices in the  
implementation of genomic medicine



# Global Genomic Medicine Collaborative (G2MC)

## PERSPECTIVE

### POLICY

## Global implementation of genomic medicine: We are not alone

Teri A. Manolio,<sup>1\*</sup> Marc Abramowicz,<sup>2</sup> Fahd Al-Mulla,<sup>3</sup> Warwick Anderson,<sup>4</sup> Rudi Balling,<sup>5</sup> Adam C. Berger,<sup>6</sup> Steven Bleyl,<sup>7</sup> Aravinda Chakravarti,<sup>8</sup> Wasun Chantratita,<sup>9</sup> Rex L. Chisholm,<sup>10</sup> Vajira H. W. Dissanayake,<sup>11</sup> Michael Dunn,<sup>12</sup> Victor J. Dzau,<sup>13</sup> Bok-Ghee Han,<sup>14</sup> Tim Hubbard,<sup>15</sup> Anne Kolbe,<sup>16</sup> Bruce Korf,<sup>17</sup> Michiaki Kubo,<sup>18</sup> Paul Lasko,<sup>19</sup> Erkki Leego,<sup>20</sup> Surakameth Mahasirimongkol,<sup>21</sup> Partha P. Majumdar,<sup>22</sup> Gert Matthijs,<sup>23</sup> Howard L. McLeod,<sup>24</sup> Andres Metspalu,<sup>20</sup> Pierre Meulien,<sup>25</sup> Satoru Miyano,<sup>26</sup> Yaakov Naparstek,<sup>27</sup> P. Pearl O'Rourke,<sup>28</sup> George P. Patrinos,<sup>29</sup> Heidi L. Rehm,<sup>30</sup> Mary V. Relling,<sup>31</sup> Gad Rennert,<sup>32</sup> Laura Lyman Rodriguez,<sup>1</sup> Dan M. Roden,<sup>33</sup> Alan R. Shuldiner,<sup>34</sup> Sukdeb Sinha,<sup>35</sup> Patrick Tan,<sup>36</sup> Mats Ulfendahl,<sup>37</sup> Robyn Ward,<sup>38</sup> Marc S. Williams,<sup>39</sup> John E. L. Wong,<sup>40</sup> Eric D. Green,<sup>1</sup> Geoffrey S. Ginsburg,<sup>41\*</sup>

Sci Trans Med 2015

- > 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

# 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

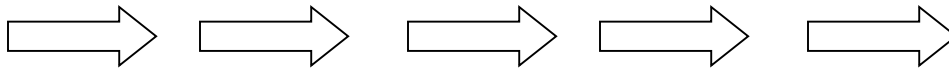
# A Grand Challenge... for Implementation of Genomic Medicine

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



Millions of  
Genomes

?



**Evidence Generation/Economic  
Models**

**Data Sharing/Security**

**Implementation Incentives**

**Workforce Development**

**Participant Engagement/Trust**



Precision  
Medicine &  
Population Health

# Questions?

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

**U.S. Department of Health and Human Services  
National Institutes of Health | National Cancer Institute**

<http://cancercontrol.cancer.gov/research-emphasis/precision-medicine.html>

**1-800-4-CANCER**

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