Genomic Medicine Implementation in Diverse Healthcare Settings and Populations

A Public Health Perspective

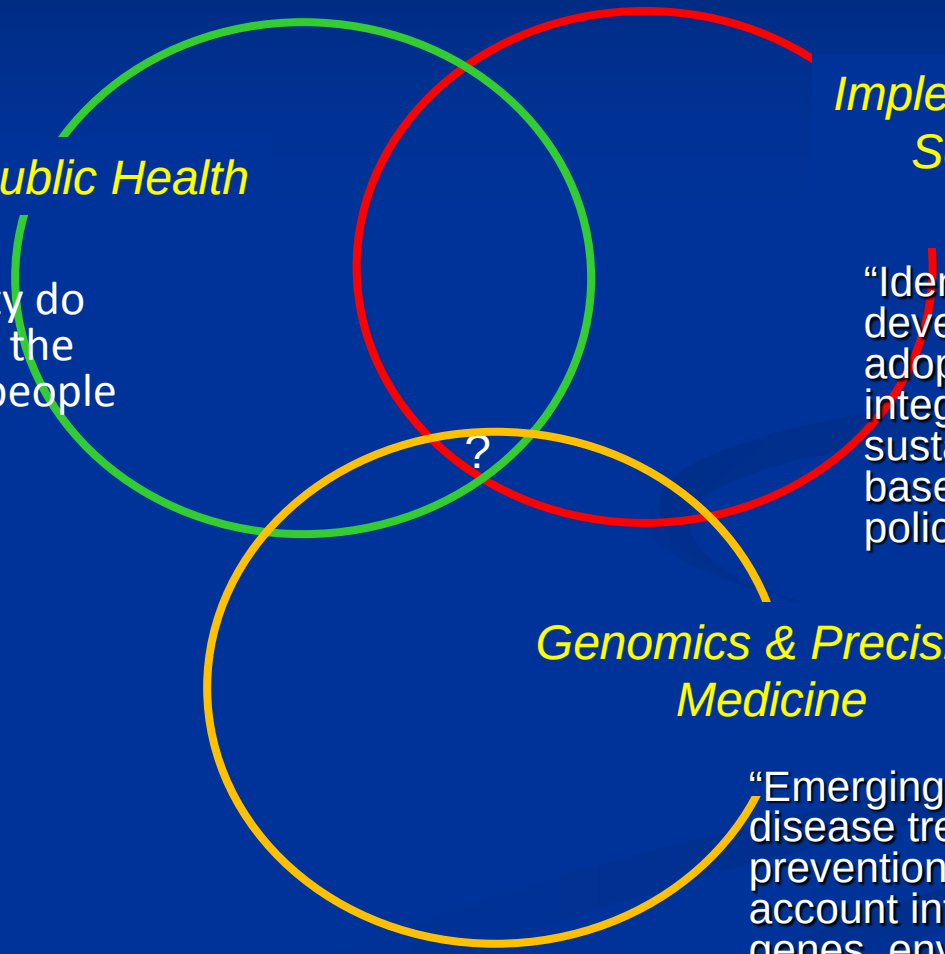
Muin J. Khoury MD, PhD

CDC Office of Public Health Genomics

Outline

- Exploring the Intersection of Genomic (and Precision) Medicine, Implementation Science, and Public Health
- Public Health Genomics and Cancer: Case Study
- The Genomics and Population Health Action Collaborative (of the NASEM Roundtable on Genomics & Precision Health)

Epidemiology, Implementation Science and Precision Medicine: A Growing Intersection

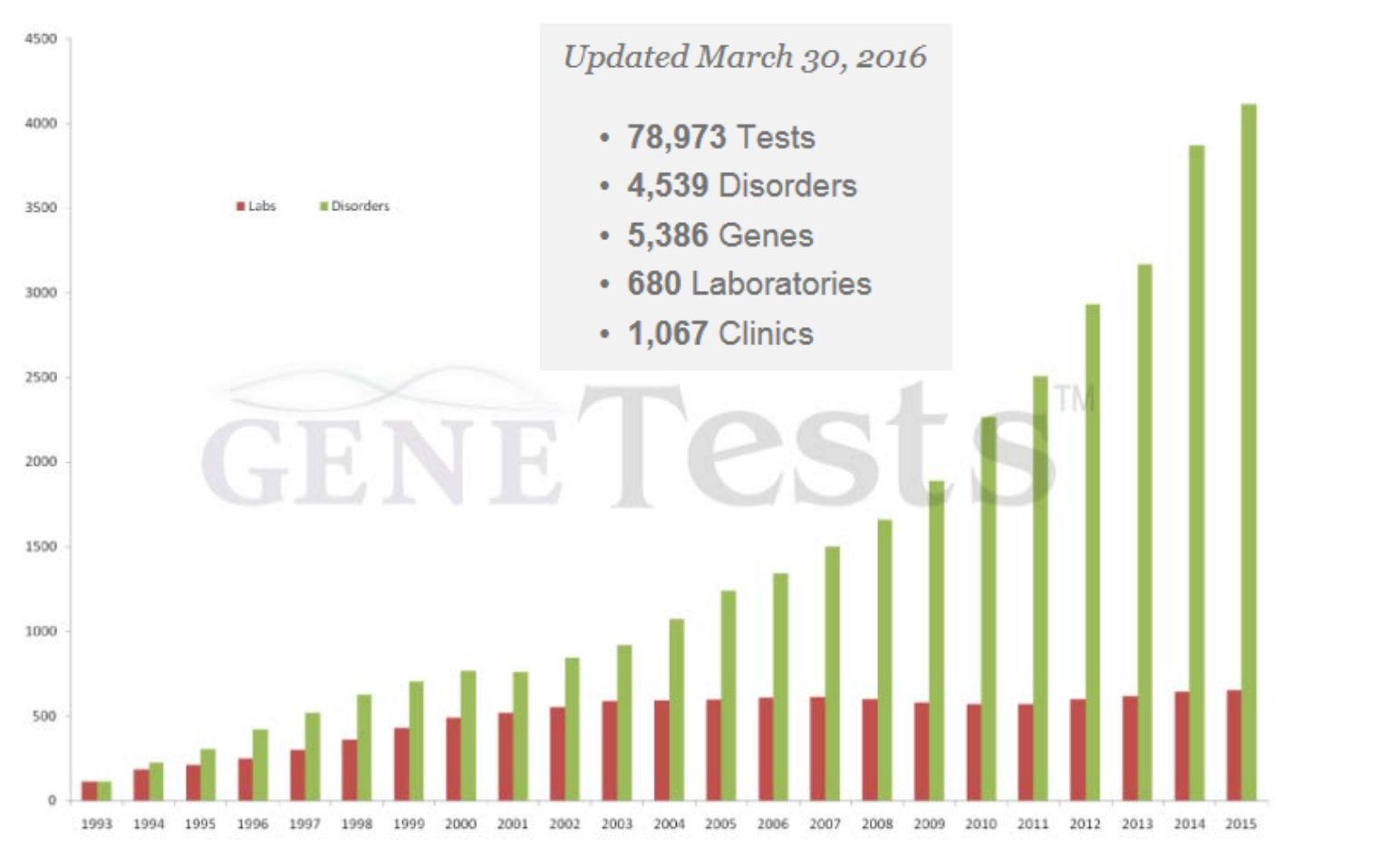


"What we as a society do collectively to assure the conditions in which people can be healthy."

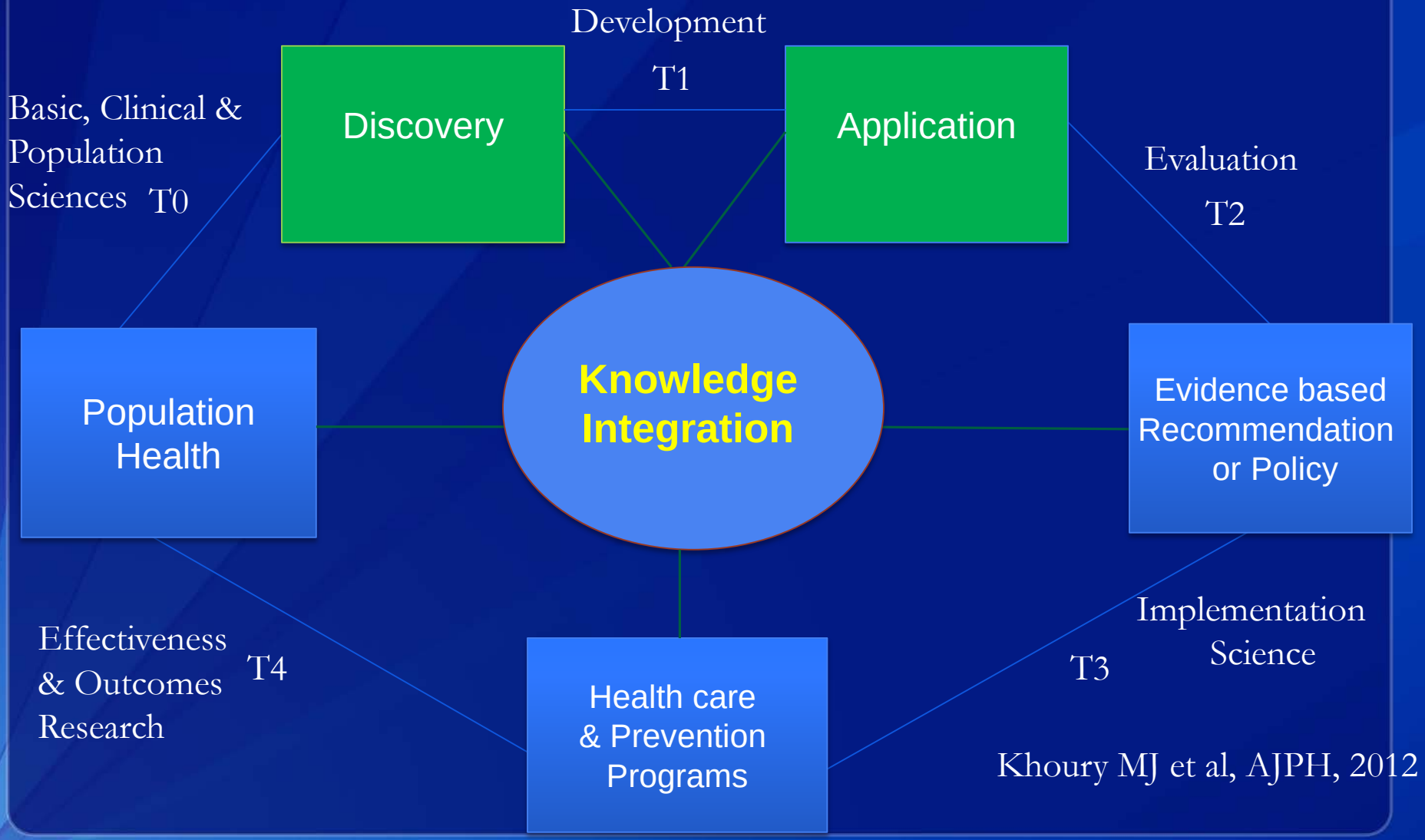
"Identify, understand, and develop to increase adoption, adaptation, integration, scale-up and sustainability of evidence-based interventions, tools, policies, and guidelines"

"Emerging approach to disease treatment & prevention that takes into account information on genes, environment & lifestyles"

Numerous Genomic Tests are Available



An Expanded Genomics Translation Cycle (<1% of Publications are T2+)



Khoury MJ et al, AJPH, 2012

Genomics & Health Impact Update

ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

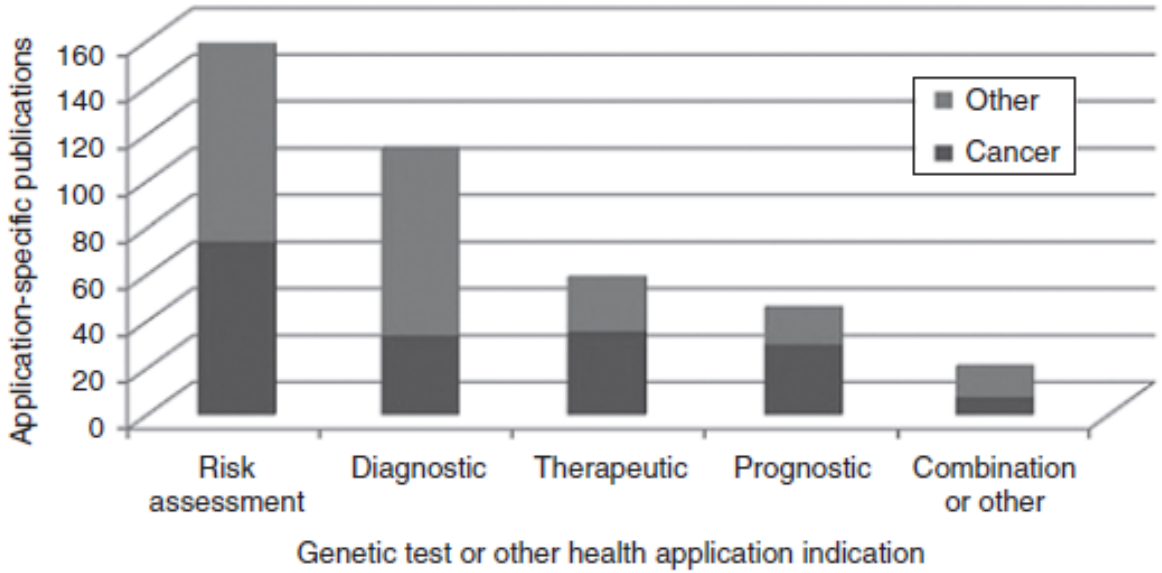
Horizon scanning for translational genomic research beyond bench to bedside

Mindy Clyne, MHS[1,2], Sheri D. Schully, PhD[2], W. David Dotson, PhD[3], Michael P. Douglas, MS[3,4], Marta Gwinn, MD, MPH[3,4], Katherine Kolor, PhD[3], Anja Wulf [3,5], M. Scott Bowen, MPH[3] and Muin J. Khoury, MD, PhD[2,3]

Purpose: The dizzying pace of genomic discoveries is leading to an increasing number of clinical applications. In this report, we provide a method for horizon scanning and 1 year data on translational research beyond bench to bedside to assess the validity, utility, implementation, and outcomes of such applications.

Methods: We compiled cross-sectional results of ongoing horizon

Results: Most articles (62%) addressed a specific genomic test or other health application; almost half of these (n = 180) were related to cancer. We estimate that these publications account for 0.5% of reported human genomics and genetics research during the same time.



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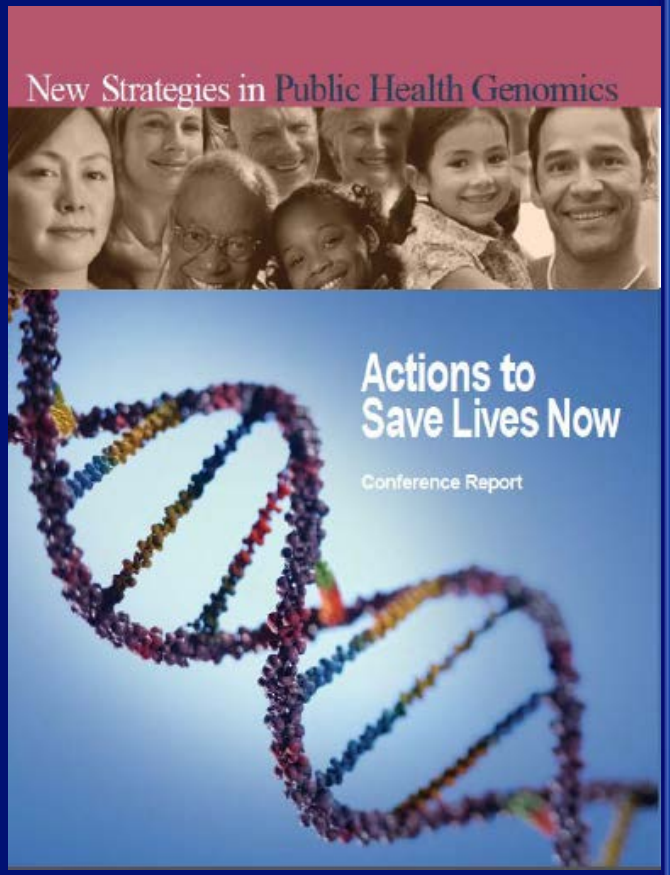
CDC Evidence-based Classification of Genomic Tests:
A Growing Number of Applications Ready for Prime Time

Tier 1	Supported by a base of synthesized evidence for implementation in practice	e.g., Newborn Screening, HBOC, Lynch syndrome, Familial Hypercholesterolemia
Tier 2	Synthesized evidence is insufficient to support routine implementation in practice; may provide information for informed decision making	e.g., many pharmacogenomic tests
Tier 3	Evidence-based recommendations against use, or no relevant synthesized evidence identified; not ready for routine implementation in practice	e.g., direct-to-consumer personal genomic tests

Dotson WD, Douglas MP, Kolor K, et al. Clin Pharmacol Ther. 2014 Apr; 95(4): 394–402.
List of applications by level of evidence on CDC Public Health Genomics Knowledge Base website:
https://phgkb.cdc.gov/GAPPKB/topicStartPage.do

CDC Selected Emerging Tier 1 Genomic Applications

- Familial Hypercholesterolemia, Hereditary Breast and Ovarian Cancer, Lynch Syndrome
- 2 million people in the US
- Many don't know they have it
- Effective interventions reduce mortality
- Evidence-based recommendations
  - Familial Hypercholesterolemia
    - NICE Cascade screening
  - Hereditary Breast and Ovarian Cancer
    - USPSTF high risk approach
  - Lynch Syndrome
    - EGAPP universal colorectal cancer screening



Public Health Grand Rounds

Cancer and Family History: Using Genomics for Prevention

Tuesday, April 19, 2016 at 1 pm EDT

The risk factors for cancer are many and varied, and inherited genetic mutations play a major role in 5 to 10% of all cancers. When these mutations are identified early, patients are able to work with their healthcare providers to take crucial steps toward care and treatment. Many of those affected by genetic cancer syndromes don't know that genetic testing is an option.

BRCA1 Counseling/Testing Recommendations of the U.S. Preventive Services Task Force (USPSTF, 2013)

- **The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with one of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (*BRCA1* or *BRCA2*). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing.**
  Grade: B Recommendation.

- **The USPSTF recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes.**
  Grade: D Recommendation.

EGAPP Lynch Summary Statement

Genetics in Medicine Jan 2009

"The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found sufficient evidence to recommend offering genetic testing for Lynch syndrome to individuals with newly diagnosed colorectal cancer (CRC) to reduce morbidity and mortality in relatives.

Evidence to Practice

EGAPP

Evaluation of Genomic Applications in Practice and Prevention

Partnerships Needed to Address Challenges in Genomics Implementation

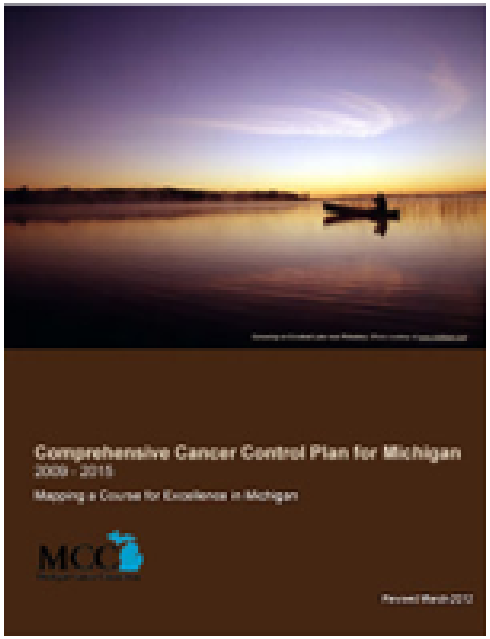
- Provider and public education
- Healthcare system limitations
- Evidence-based policy
- Population health impact data
- Laboratory quality
- Health disparities

An interactive web resource with unique areas for consumers and healthcare providers

Launched in 2014

Know:BRCA

Using State Cancer Registries for Surveillance of Cancer Genetic Services & Outcomes

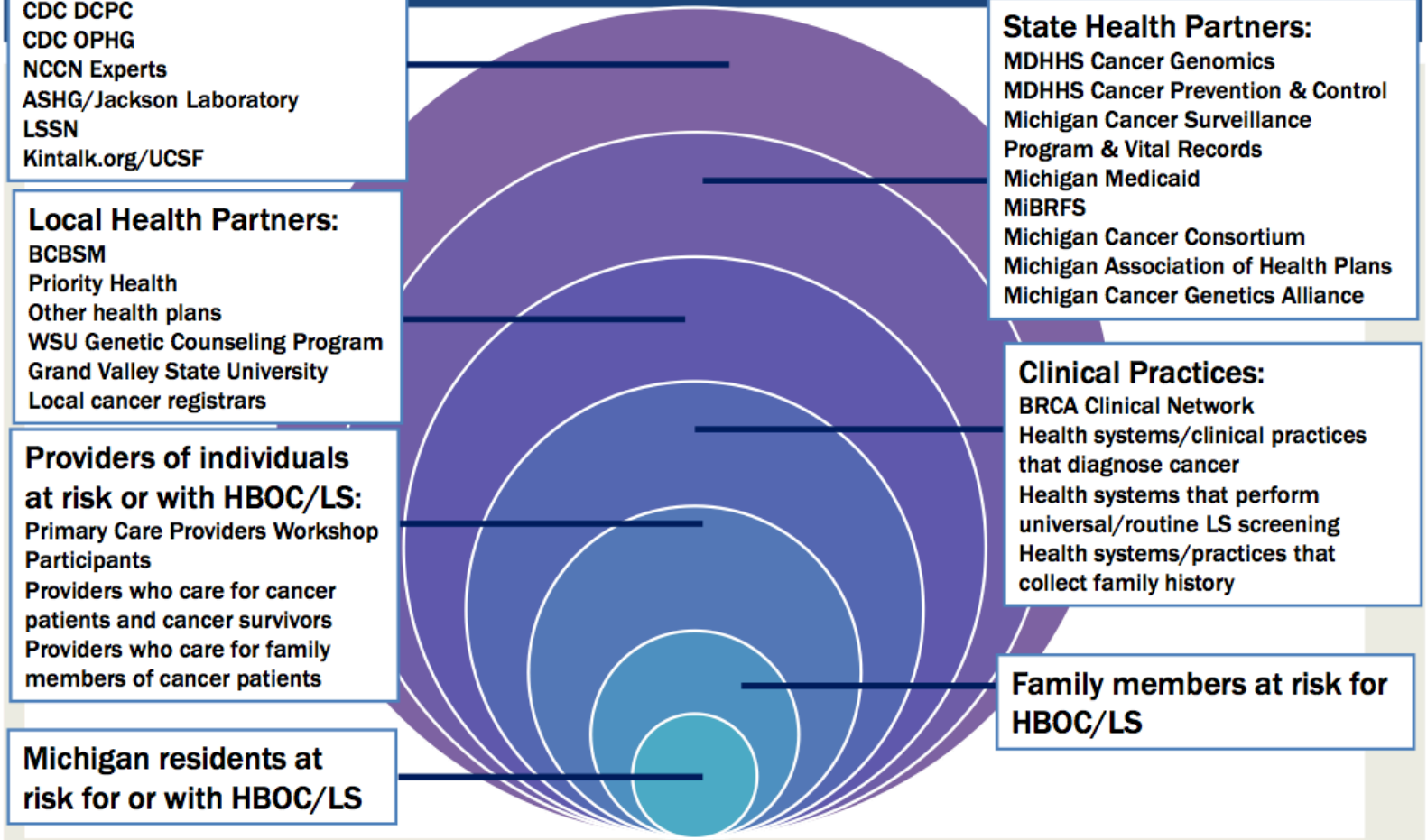


Genomics Goal

- Increase availability of cancer-related genetic information to the Michigan public and decrease barriers to risk-appropriate services

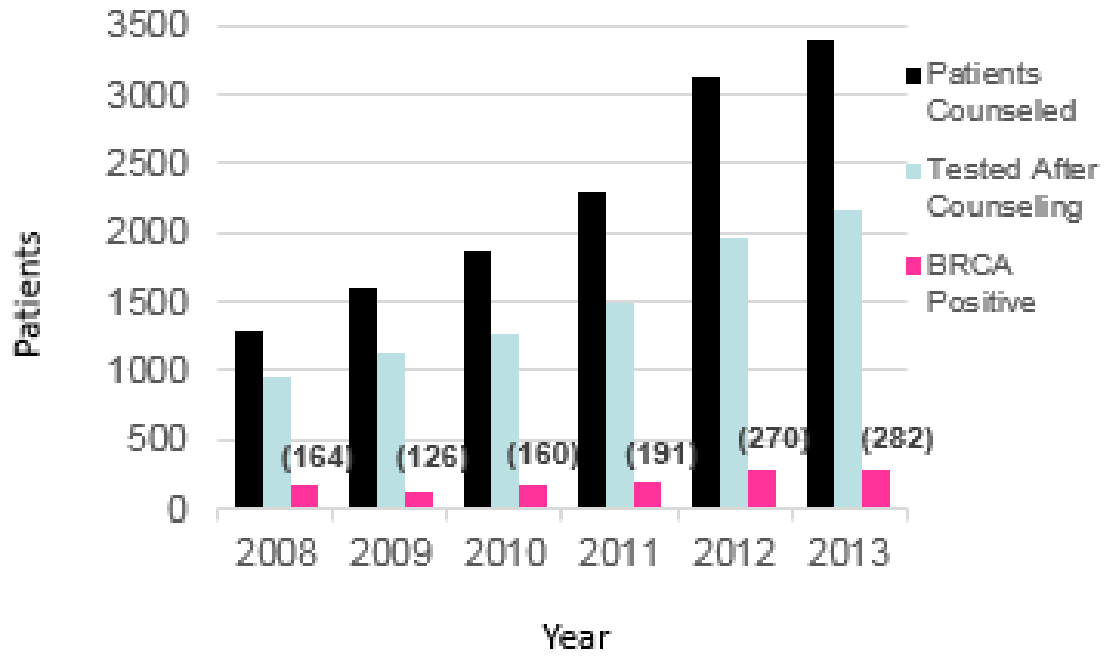
- Examine potential cases at risk for HBOC or Lynch syndrome
- Disseminate data to healthcare systems and providers to reinforce educational messages

MULTI-LEVEL & MULTIDISCIPLINARY PARTNERS



Taplin et al, Multilevel Intervention Clinical-Public Health Collaboration, 2011

Michigan Population Data Related to *BRCA* Counseling Access and Referrals



- Black women less likely than other women to use cancer genetic services

Uptake of Genetic Testing by Relatives of Lynch Syndrome Probands: A Systematic Review

Cascade genetic testing in Lynch syndrome: room for improvement

Kory Jasperson

Genetic testing in relatives of individuals with Lynch syndrome is of utmost importance for targeted screening and prevention. A recent systematic review suggests that the uptake of testing in at-risk relatives is inadequate and therefore the cost-effectiveness of Lynch syndrome testing is questionable. The result

Jasperson, K. *Nat. Rev. Gastroenterol. Hepatol.* adva
doi:10.1038/nrgastro.2013.122

CLINICAL GASTROENTERO & HEPATOLOGY 2013

The Evaluation of Genomic Applications i
Practice and Prevention (EGAPP) Workin
Group (EWG) in 2009 established tha
there was "sufficient evidence to recom
mend offering genetic testing for Lync
syndrome to individuals with newly diag

VOLUME 31 · NUMBER 20 · JULY 10 2013

JOURNAL OF CLINICAL ONCOLOGY

E D I T O R I A L

Population-Based Universal Screening for Lynch Syndrome: Ready, Set… How?

Joanne Ngeow and Charis Eng, *Cleveland Clinic Genomic Medicine Institute, Cleveland, OH*

See accompanying article on page 2554

Although the fields of health care and public health have many evidence-based innovations, the failure to implement health interventions that have been rigorously demonstrated to be cost effective hampers health care delivery.[1,2] The identification of individuals who are at increased risk of hereditary cancer allows for the possibility of heightened surveillance and early cancer detection, resulting in decreased disease-specific mortality.[3] Such data-driven identification and risk stratification to guide management is one of the foundations of value-based health care delivery.[4] However, it is not always easy to identify those in the general population who may be at increased risk

deficiency, defined as the presence of microsatellite instability (MSI) or loss of MMR protein expression (detected via immunohistochemistry [IHC]), which are the cellular hallmarks of this disorder.[8,15] Ward et al[5] explored a population-based approach by including all incident CRCs that were identified within their catchment area of 1.2 million residents in New South Wales, Australia. The study consisted of two phases. In the first phase, without obtaining patient consent, they identified all MMR-deficient cancers by IHC and assigned an a priori likelihood for LS as either low (both MLH1 loss and *BRAF* mutation) or high (all other cancers). Recommendations were sent to the treating

SPECIAL ARTICLE

Implementing screening for Lynch syndrome among patients with newly diagnosed with colorectal cancer: Summary of a public health/clinical collaborative meeting

Cecelia A. Bellcross, PhD, MS[1,2], Sara R. Bedrosian, BA, BFA[1], Elvan Daniels, MD, MPH[3], Debra Duquette, MS[4], Heather Hampel, MS[5], Kory Jasperson, MS[6], Djenaba A. Joseph, MD, MPH[7], Celia Kaye, MD, PhD[8], Ira Lubin, PhD[9], Laurence J. Meyer, PhD, MD[10], Michele Reyes, PhD, MS[1], Maren T. Scheuner, MD, MPH[11], Sheri D. Schully, PhD[12], Leigha Senter, MS[5], Sherri L. Stewart, PhD[7], Jeanette St. Pierre, MA, MPH[1], Judith Westman, MD[5], Paul Wise, MD[13], Vincent W. Yang, MD, PhD[14], and Muin J. Khoury, MD, PhD[1]

Abstract: Lynch syndrome is the most common cause of inherited colorectal cancer, accounting for approximately 3% of all colorectal cancer cases in the United States. In 2009, an evidence-based review process conducted by the independent Evaluation of Genomic Applications in Practice and Prevention Working Group resulted in a recommendation to offer genetic testing for Lynch syndrome to all individuals with newly diagnosed colorectal cancer, with the intent of reducing morbidity and mortality in family members. To explore issues surrounding implementation Lynch syndrome can potentially serve as a model to facilitate the development and implementation of population-level programs for evidence-based genomic medicine applications involving follow-up testing of at-risk relatives. Such endeavors will require multilevel and multidisciplinary approaches building on collaborative public health and clinical partnerships. ***Genet Med*** **2011:XX(X):000–000.**

Key Words: *genetic screening, colorectal cancer, Lynch syndrome, HNPCC, genetic testing*

Genetics in Medicine 2011

Lynch Syndrome Screening Network

Genomics and Health Impact Blog

A blog devoted to discussing best practices and questions about the role of genomics in disease prevention, health promotion and healthcare.

Making Universal Screening for Lynch Syndrome a Reality: The Lynch Syndrome Screening Network

Categories: colorectal cancer, genomics

March 22nd, 2012 11:35 am ET - Guest Blogger

Deb Duquette, MS, CGC, Sarah Mange, MPH- Michigan Department of Community Health
Cecelia Bellcross, PhD, MS- Emory University
Heather Hampel, MS, CGC- The Ohio State University
Kory Jasperson, MS, CGC- Huntsman Cancer Institute

Authors are all from the Lynch Syndrome Screening Network (LSSN) Founding Board of Directors

Every day, about 400 people in the United States are diagnosed with colorectal cancer. Approximately twelve of them have Lynch syndrome, a hereditary condition that increases the risk of colorectal cancer and other cancers. Identifying people with Lynch syndrome could have substantial health

Blog Categories
colorectal cancer
family history
genomics
heart disease
investigation
personal genomics
personalized medicine
pharmacogenomics
stroke

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Applying an Implementation Science Approach to Genomic Medicine: Workshop Summary

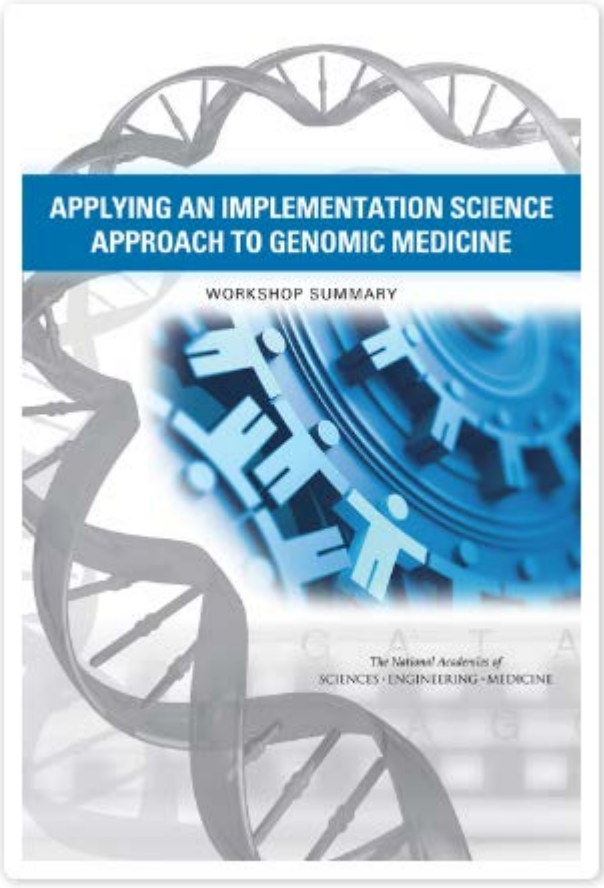
April 2016

The Road Ahead

Hybrid studies that examine effectiveness & implementation measures may reduce the amount of time it takes to integrate a research discovery in the clinic

Within existing implementation efforts, gather useful knowledge from case studies of "exceptional implementation" and failures

Leveraging existing health systems and networks, such as those at the state level, may be useful during implementation

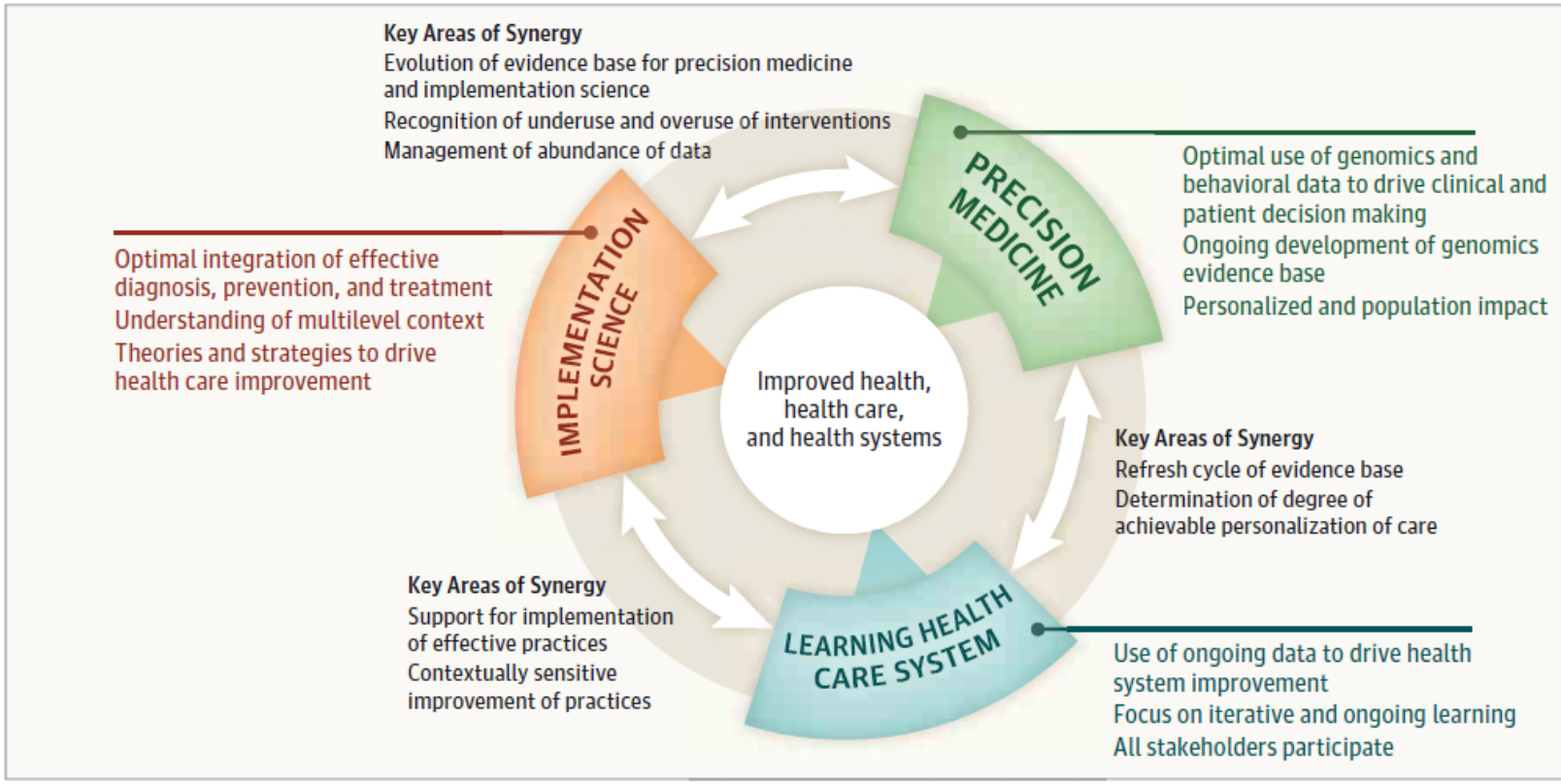


INNOVATIONS IN HEALTH CARE DELIVERY

Convergence of Implementation Science, Precision Medicine, and the Learning Health Care System

A New Model for Biomedical Research

Figure. Contributions of Implementation Science, Learning Health Care System, and Precision Medicine



Chambers D, Feero W, Khoury MJ, et al, JAMA, May 2016

The US Precision Medicine Initiative
Flying It While Building It!

VIEWPOINT

A Public Health Perspective on a National Precision Medicine Cohort
Balancing Long-term Knowledge Generation With Early Health Benefit

Muin J. Khoury, MD, PhD
Office of Public Health Genomics, Centers for Disease Control and Prevention, Atlanta, Georgia.

James P. Evans, MD, PhD
Department of Genetics, University of North Carolina, Chapel Hill; and Department of Medicine, University of North Carolina, Chapel Hill.

The new US precision medicine initiative[1] has been made possible by improvement and price reduction in genome sequencing, as well as advances in multiple sectors of biotechnology. The initiative includes 2 components: a focus on cancer intended to spur development of new targeted cancer treatments, and a proposal for establishing a national cohort of at least 1 million people to explore genetic and environmental determinants of health and disease. The success of this initiative requires a public health perspective to help ensure generalizability, assess methods of implementation, focus on prevention, and provide an appropriate balance between generation of long-term knowledge and short-term health gains.

Although precision medicine focuses on individualized efit. For example, improving access to smoking cessation assistance is a component of the highly successful public health efforts that have resulted in reductions in smoking over the past few decades. Recent data suggest that using genetically informed biomarkers of the speed with which people metabolize nicotine[2] could lead to personalized smoking cessation. Another example of precision prevention is changes in recommended screening schedules for people at increased risk of cancer, identified either by acquisition of family health history or through detection of those individuals who carry pathogenic mutations in high-risk cancer genes.

The proposed long-term investment in precision medicine comes at a time of increasing fiscal restraint and widespread recognition that the US health care system

Khoury MJ et al, JAMA, 2015

Implementation Science & Precision Medicine Cohort
"Tier 1" 56 Genes and their Variants

Genetics in Medicine, 2013

American College of Medical Genetics and Genomics

ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

Robert C. Green, MD, MPH[1,2], Jonathan S. Berg, MD, PhD[3], Wayne W. Grody, MD, PhD[4-6], Sarah S. Kalia, ScM, CGC[1], Bruce R. Korf, MD, PhD[7], Christa L. Martin, PhD, FACMG[8], Amy McGuire, JD, PhD[9], Robert L. Nussbaum, MD[10], Julianne M. O'Daniel, MS, CGC[11], Kelly E. Ormond, MS, CGC[12], Heidi L. Rehm, PhD, FACMG[2,13], Michael S. Watson, MS, PhD, FACMG[14], Marc S. Williams, MD, FACMG[15], Leslie G. Biesecker, MD[16]

[1]Division of Genetics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [2]Partners Healthcare Center for Personalized Genetic Medicine, Boston, Massachusetts, USA; [3]Department of Genetics, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina, USA; [4]Division of Medical Genetics, Department of Human Genetics, UCLA School of Medicine, Los Angeles, California, USA; [5]Division of Molecular Pathology, Department of Pathology & Laboratory Medicine, UCLA School of Medicine, Los Angeles, California, USA; [6]Division of Pediatric Genetics, Department of Pediatrics, UCLA School of Medicine, Los Angeles, California, USA; [7]Department of Genetics, University of Alabama, Birmingham, Alabama, USA; [8]Department of Human Genetics, Emory University School of Medicine, Atlanta, Georgia, USA; [9]Center for Medical Ethics and Health

Genomics and Population Health Action Collaborative of the NASEM Roundtable on Genomics & Precision Health

Work Product: Develop an online guide/toolkit for states interested in integrating genomics into population health programs.

Evidence Working Group

Chair: Ned Calonge

Work Stream 1:

- Using case studies (BRCA1/2 and Lynch syndrome) consider how genomic applications can reach 'Tier 1' level

Work Stream 2:

- Explore potential population health impact of implementing genomic applications in public health programs including modelling, population data and existing evidence

Implementation Working Group

Chair: Deb Duquette

Work Stream 1:

- Assess what factors determine 'genomics readiness' of states
- Perform qualitative interviews of state public health officials

Work Stream 2:

- Using principles of implementation science, design a set of common outcome metrics for public health genomics programs that are implementing genomic applications

NEW ADDITION: TOOL KIT FOR HEALTH SYSTEMS-IGNITE COLLABORATION

Summary

- A Widening Intersection Among Genomics (and Precision) Medicine, Implementation Science, and Public Health
- Cancer Continues to Serve as a Main Driver for Public Health Genomics Beyond Newborn Screening.
- Current Field is Still limited and We Need More Robust Collaboration at the Interface of Public Health & Healthcare