Will Precision Medicine Improve Population Health?

Yes, But….

Muin J. Khoury MD, PhD

Office of Public Health Genomics

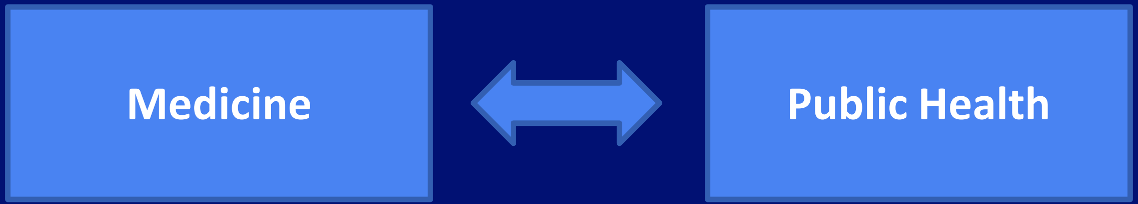
Centers for Disease Control and Prevention

Precision Medicine and Public Health

4 Themes

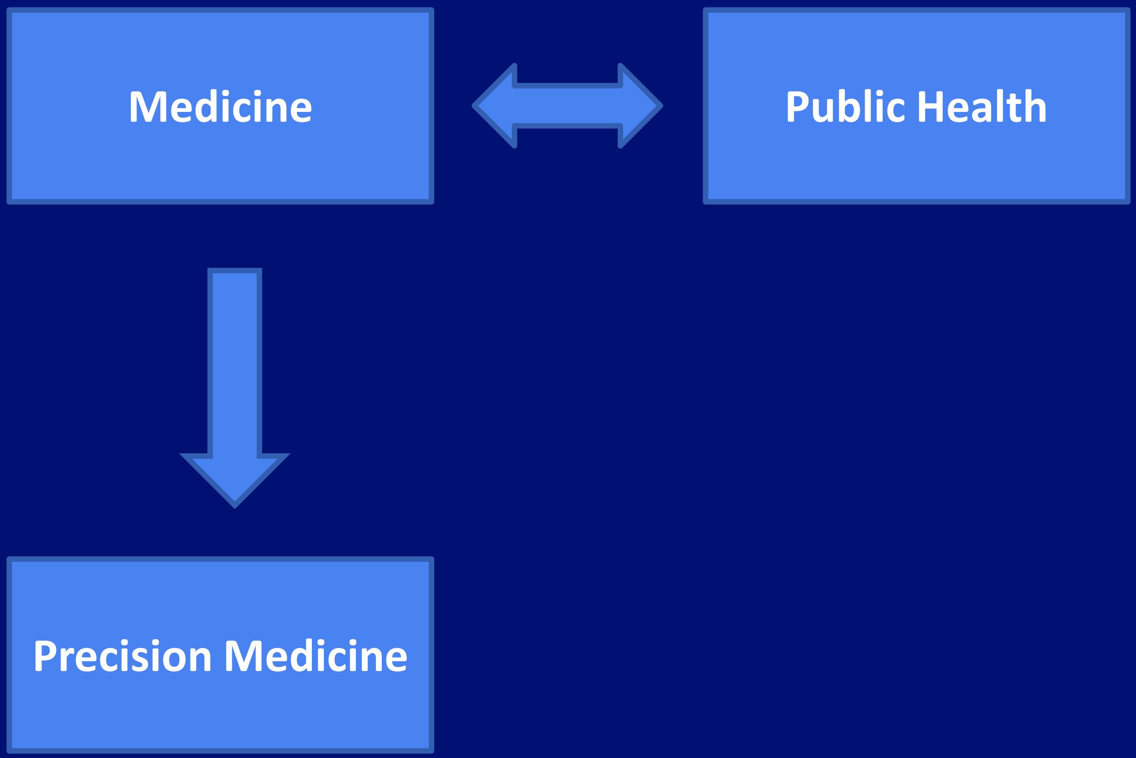
Medicine and Public Health:

Theme I. We Need Both to Improve Population Health

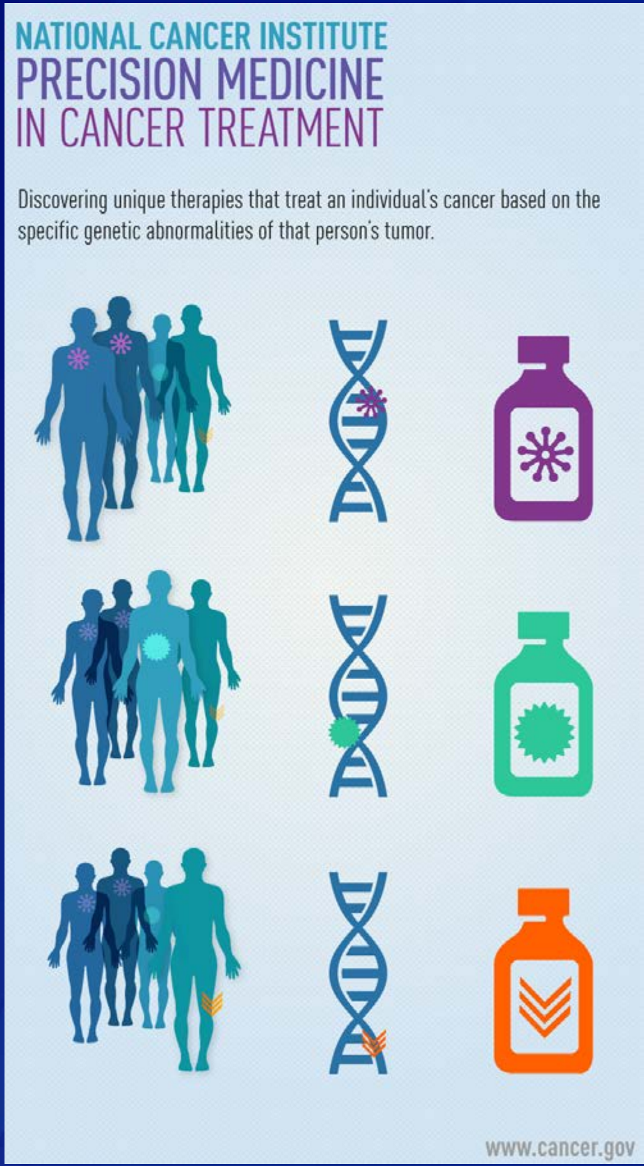


Precision Medicine and Public Health:

Theme I. We Need Both to Improve Population Health

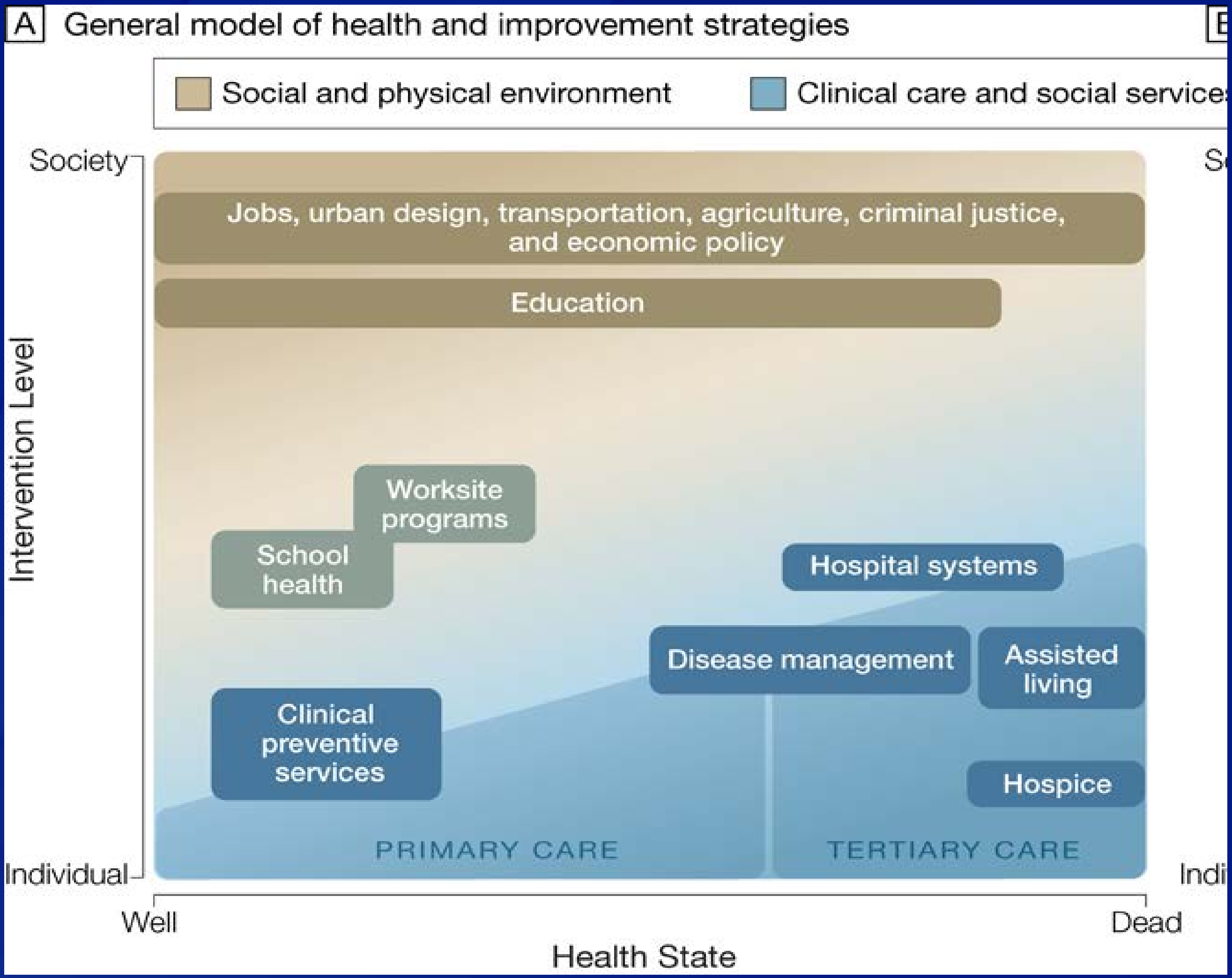


What is Precision Medicine?



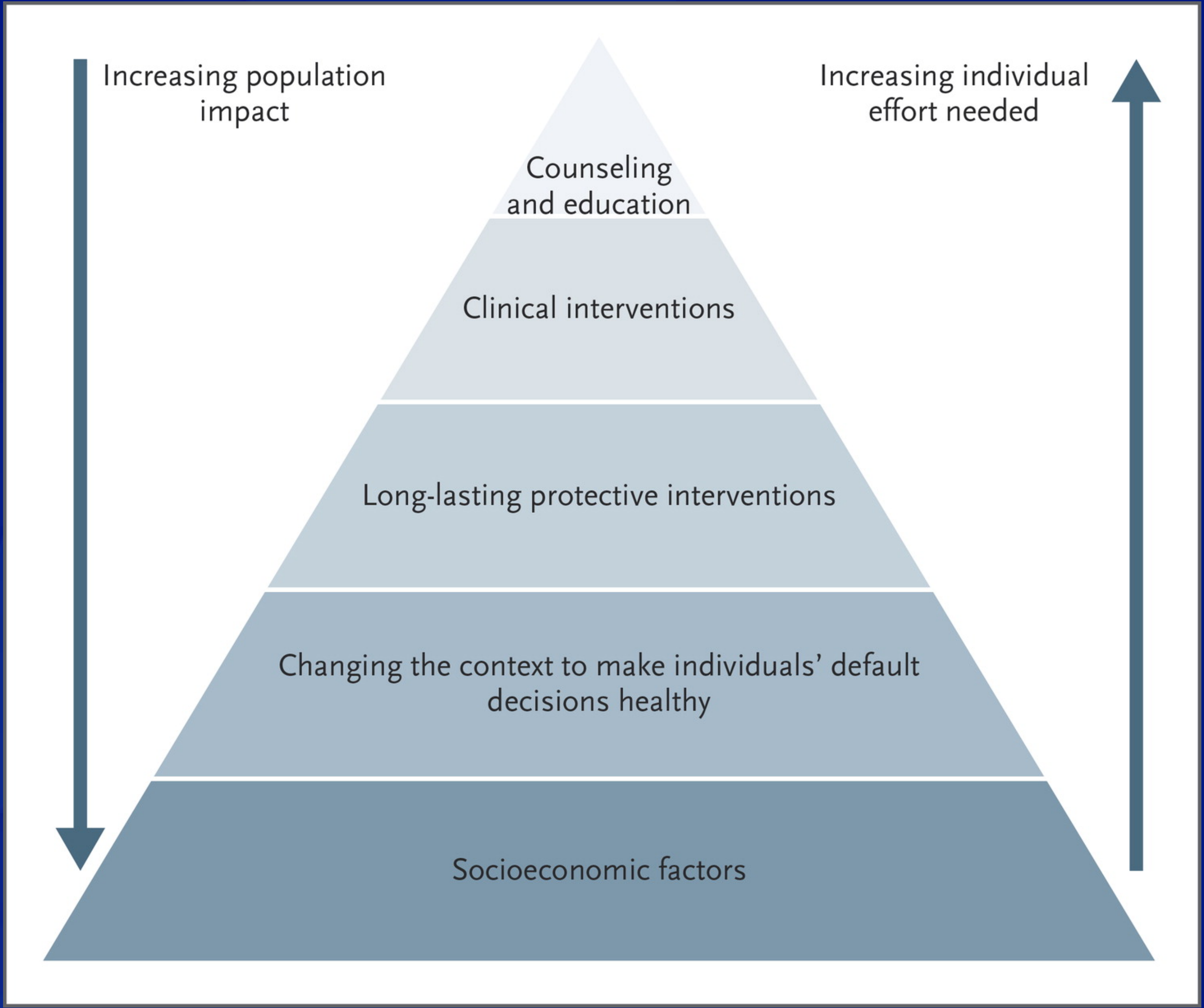
An emerging approach for disease <u>prevention</u> and treatment that takes into account variations in genes, <u>environment,</u> and <u>lifestyle</u>

Spectrum of Health & Strategies to Improve It: Individual and Population Approaches



Fielding, J. E. et al. JAMA 2011;305:2110-2111

The Health Impact Pyramid

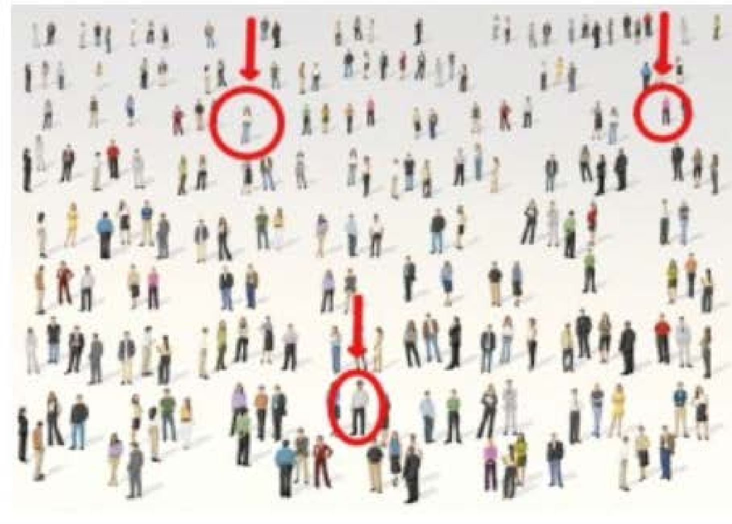


Frieden TR. N Engl J Med 2015;373:1748-1754.

Precision Medicine and Public Health: We Need Both!

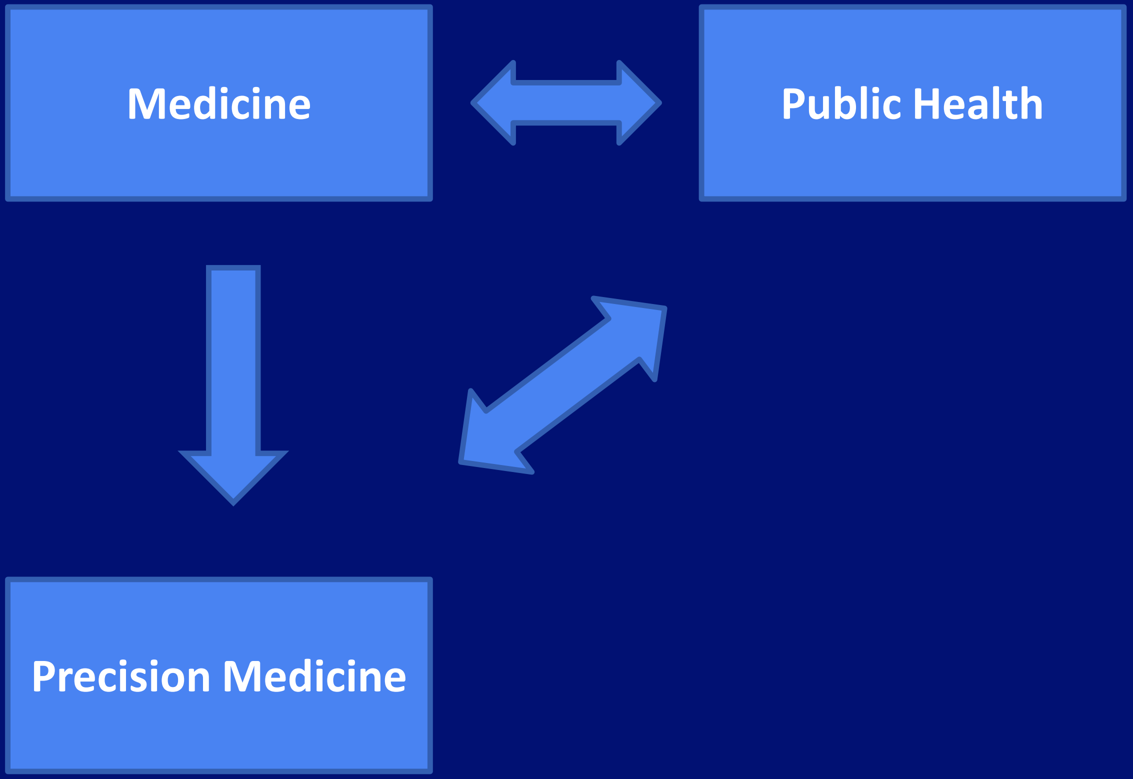
Precision Medicine vs. Public Health: a False Dichotomy?

Posted on September 28, 2015 by Ron Zimmern, PHG Foundation and Muin J. Khoury, Office of Public Health Genomics, Centers for Disease Control and Prevention



The recent focus on precision medicine has attracted criticism from the public health community that firmly believes that health is determined by far more than health care, and that more sophisticated medical technologies may not adequately address important determinants of population health. There is no argument that a focus on the wider environmental, structural and social determinants of health is of the greatest importance for improving the health of populations and addressing health disparities. However, we wonder whether a contrast between public health practice and precision medicine is a false dichotomy. Improving the health of populations requires a multifaceted approach that includes access to quality health care and diverse disease prevention efforts. Already public health programs are using the power of genomics and molecular tools in the investigation and control of infectious disease outbreaks. For common chronic diseases, evidence is accumulating for targeting preventive actions that incorporate genomics.

Precision Medicine and Public Health:
Theme II. Implementing What We Already Know



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 benefit. 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

JAMA 2015

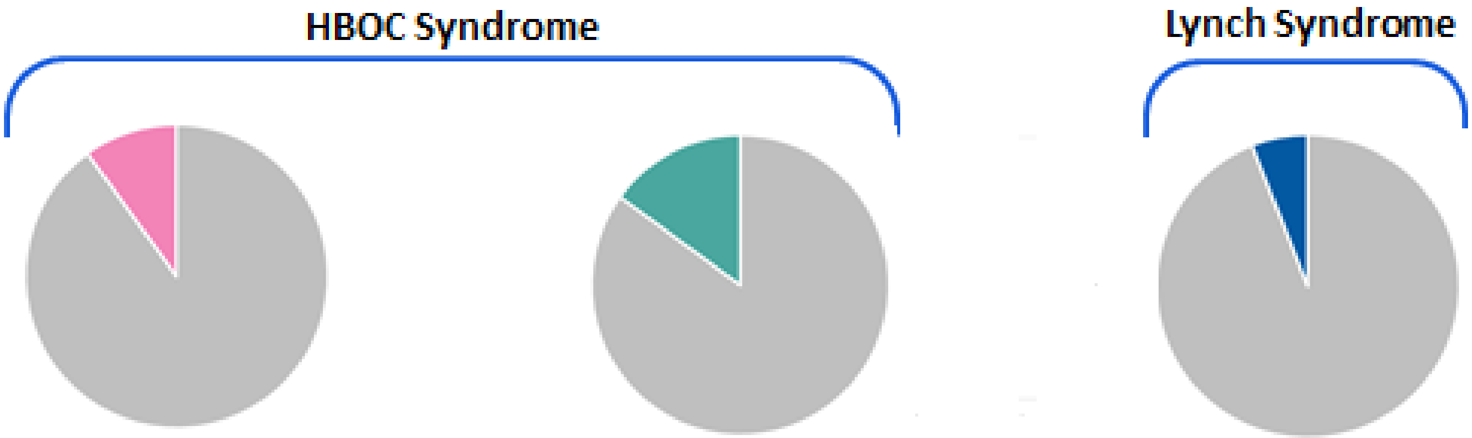
CDC Evidence-based Classification of Genomic Tests

Tier 1	Supported by a base of synthesized evidence for implementation in practice	e.g., HBOC, Lynch syndrome, newborn screening
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

Selected Cancers Associated with Hereditary Syndromes



Up to 10% or approximately 22,000 cases of breast cancer each year

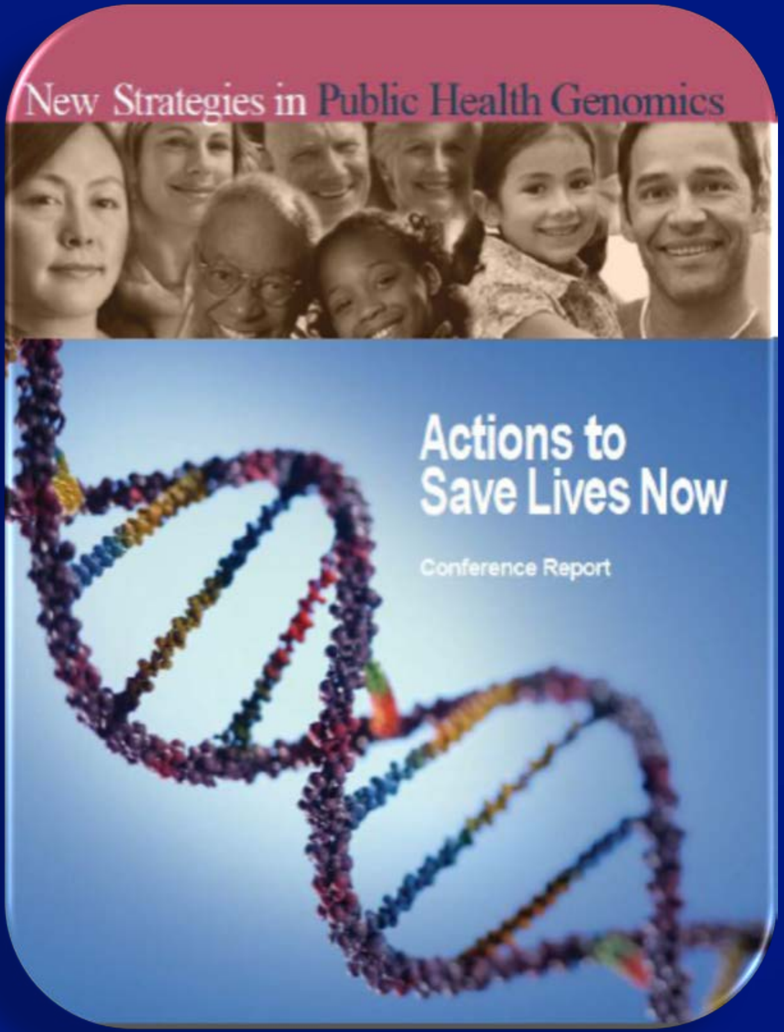
15% or approximately 3,000 cases of ovarian cancer each year

Up to 3-5% or approximately 4,000 cases of colorectal cancer each year

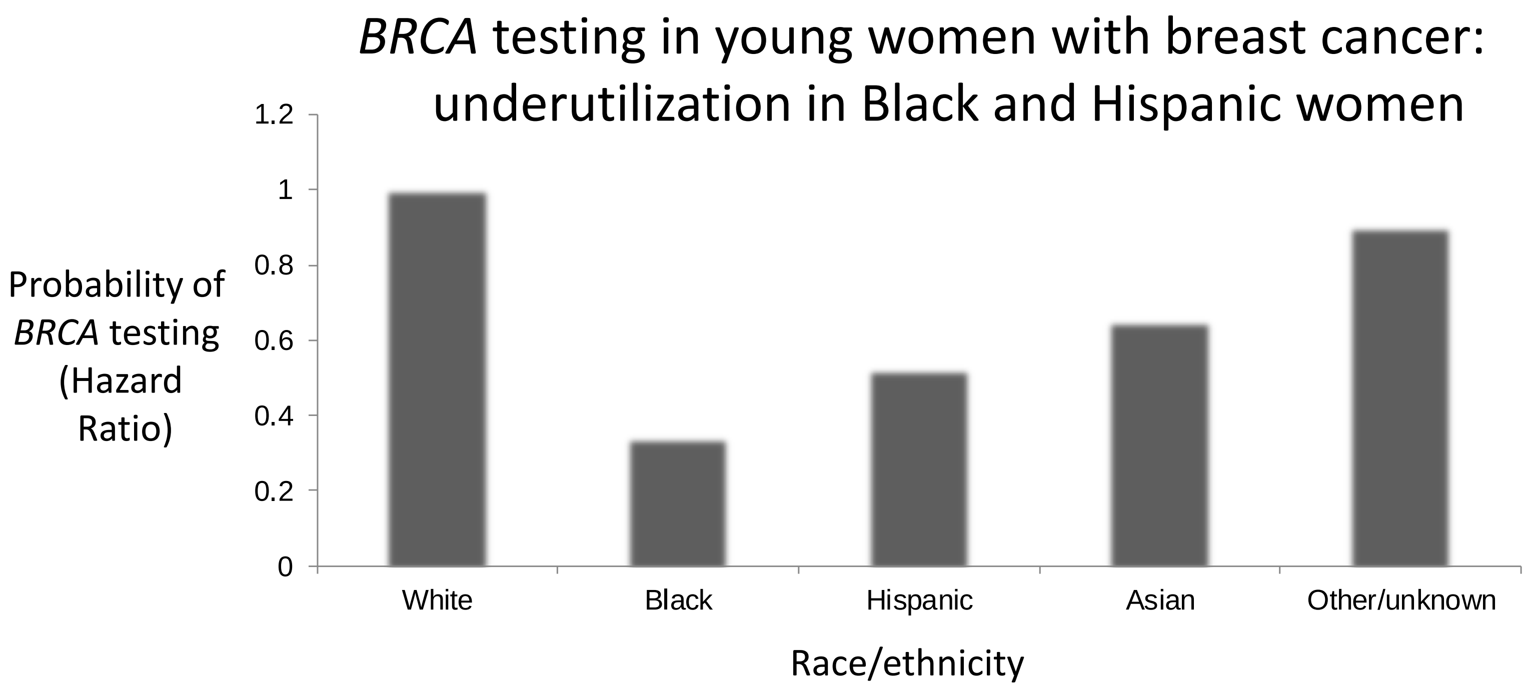
Campeau PM, Foulkes WD, Tischkowitz MD. Human Genetics 2008; 124(1):31–42.
Pal T, Permuth-Wey J, Betts JA, et al. Cancer 2005; 104(12):2807–16.
Hampel H, Frankel WL, Martin E, et al. J Clin Oncol 2008; 26 (35): 5783-8.

Selected Tier 1 Cancer Genomic Applications:

- Autosomal dominant disorders with adult onset
- Relatively common (collectively >1 million people in the US)
- Most people not ascertained or managed by health care
- Evidence of disparities
- Effective interventions that reduce mortality
- Involves family history and cascading interventions
- Can be integrated into public health programs with strong healthcare collaborations

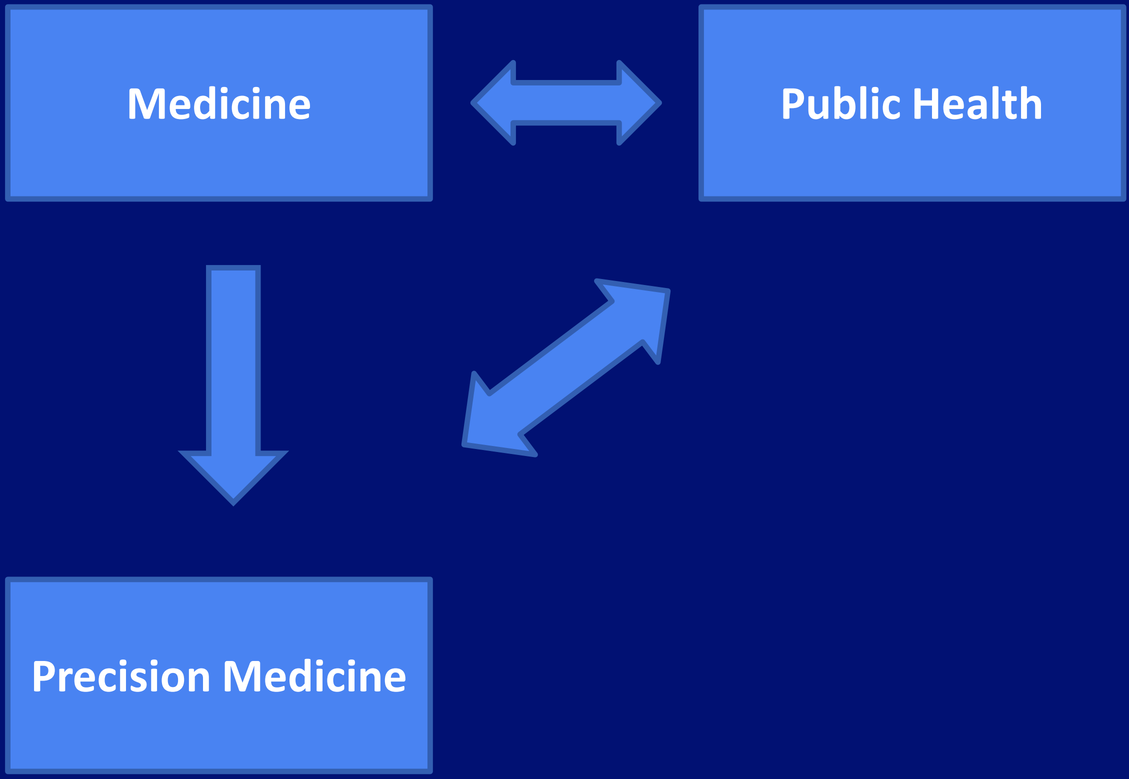


Disparities in Implementation of BRCA Testing



Levy DE, Byfield SD, Comstock CB, et al. Genet Med. 2011 Apr;13(4):349-55.

Precision Medicine and Public Health: Theme III. Role of Public Health Sciences in Developing and Implementing New Knowledge



A Vision for the Future of Medicine
Why We Need Public Health Sciences?

Table 1. Results of Genetic Testing in a Hypothetical Patient in 2010.

A 23 year old man named John

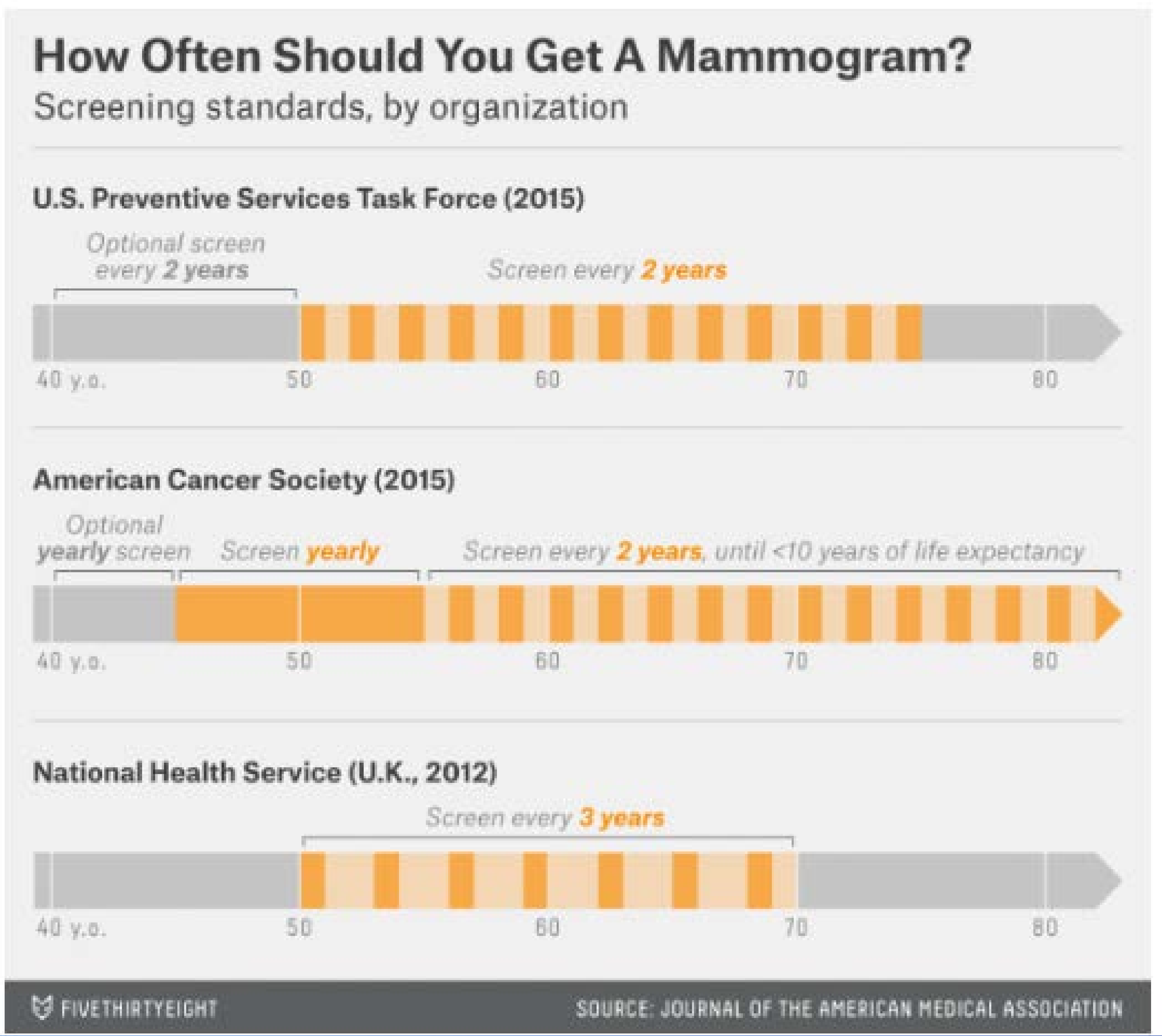
Condition	Genes Involved*	Relative Risk	Lifetime Risk (%)
Reduced risk			
Prostate cancer	*HPC1, HPC2, HPC3*	0.4	7
Alzheimer's disease	*APOE, FAD3, XAD*	0.3	10
Elevated risk			
Coronary artery disease	*APOB, CETP*	2.5	70
Colon cancer	*FCC4, APC*	4	23
Lung cancer	*NAT2*	6	40

Collins FC, NEJM 1999

Where do we get these numbers? (hint, epidemiology)

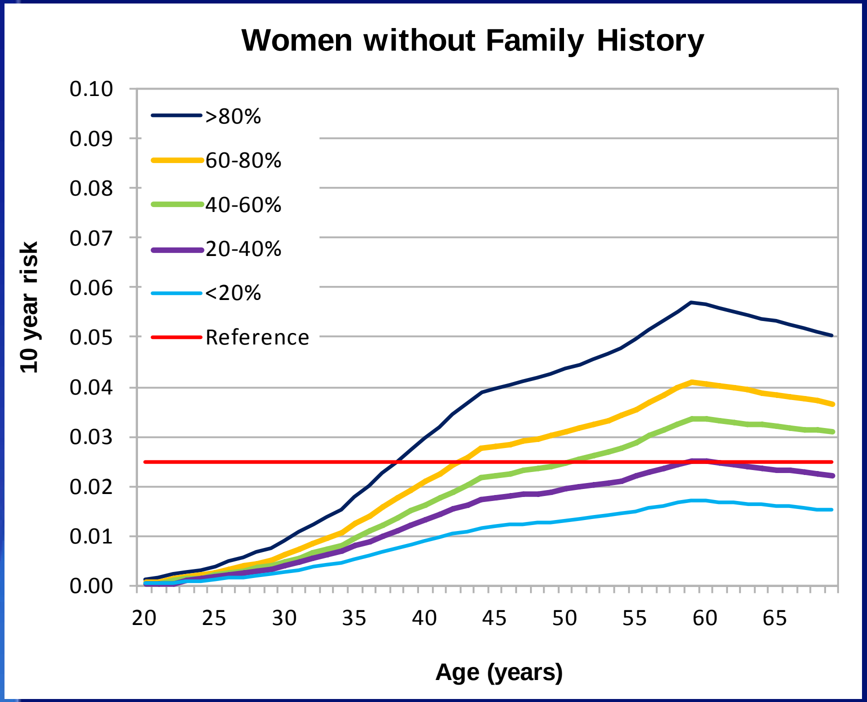
What do we do with these numbers?

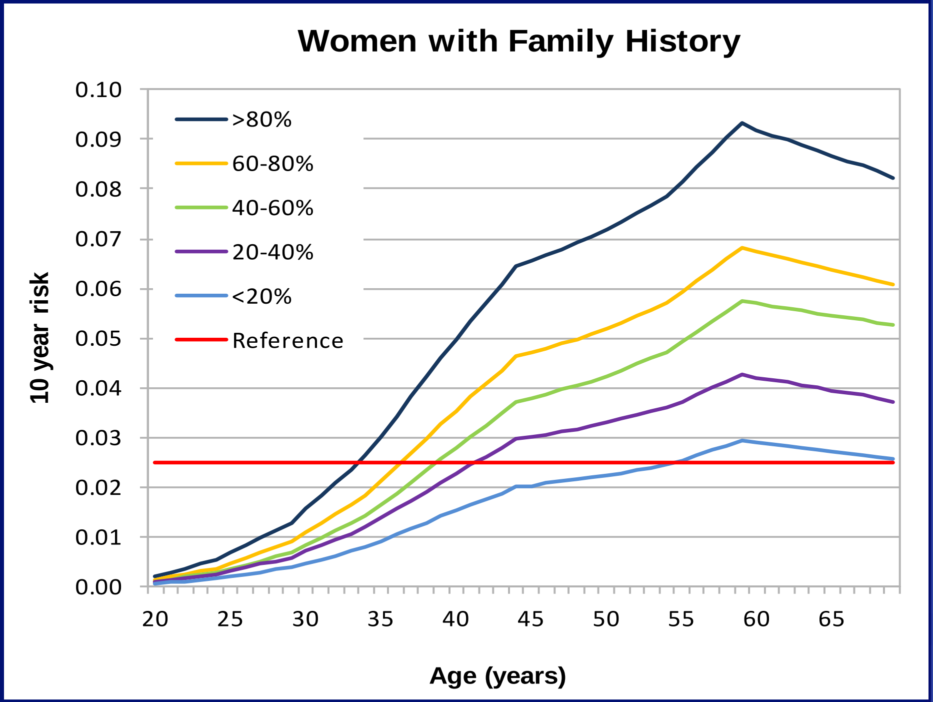
For Example


How Often Should You Get A Mammogram?
Screening standards, by organization
U.S. Preventive Services Task Force (2015)
Optional screen every 2 years
Screen every 2 years
40 y.o.
50
60
70
80
American Cancer Society (2015)
Optional yearly screen
Screen yearly
Screen every 2 years, until <10 years of life expectancy
40 y.o.
50
60
70
80
National Health Service (U.K., 2012)
Screen every 3 years
40 y.o.
50
60
70
80
FIVETHIRTYEIGHT
SOURCE: JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Can We Use Age and Polygenic Score in Breast Cancer Screening?

10-year absolute risk of developing breast cancer for women with and without family history by polygenic risk percentiles





Reference: 2.5% 10-year absolute risk for developing breast cancer corresponds to risk of UK women aged 47 , i.e. age of invitation to the UK NHS Breast Screening programme

Mavaddat et al. JNCI 2015: 107(5): djv036   ***From N Pashayan***

Public Health Sciences Needed to Fulfill Promise of Precision Medicine

- Epidemiology
- Behavioral, Communication and Social Sciences
- Health Care Delivery Research
- Implementation Science
- Economic Analysis: Cost Effectiveness & Beyond
- ELSI
- And many others

Investments in Public Health Genomic Sciences Beyond "Bench to Bedside" Are Limited

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, Ph...
Marta Gwinn, MD, MPH[3,4], Katherine Kolor, PhD[3], Anja Wulf...
and Muin J. Khoury, MD, PhD[2,3]

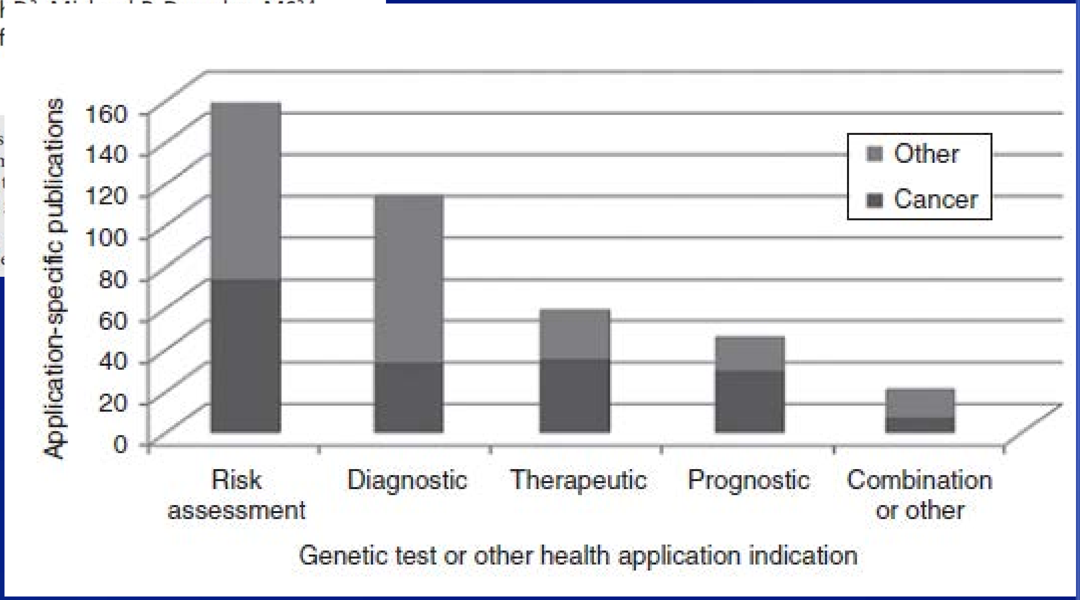
Purpose: The dizzying pace of genomic discoveries is leading to an increasing number of clinical applications. In this report, we provide a method for horizon scanning and 1 year data on translational research beyond bench to bedside to assess the validity, utility, implementation, and outcomes of such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

Methods: We compiled cross-sectional results of ongoing horizon ...

Results: Most articles ... health application; aln... cer. We estimate that ... human genomics and ...

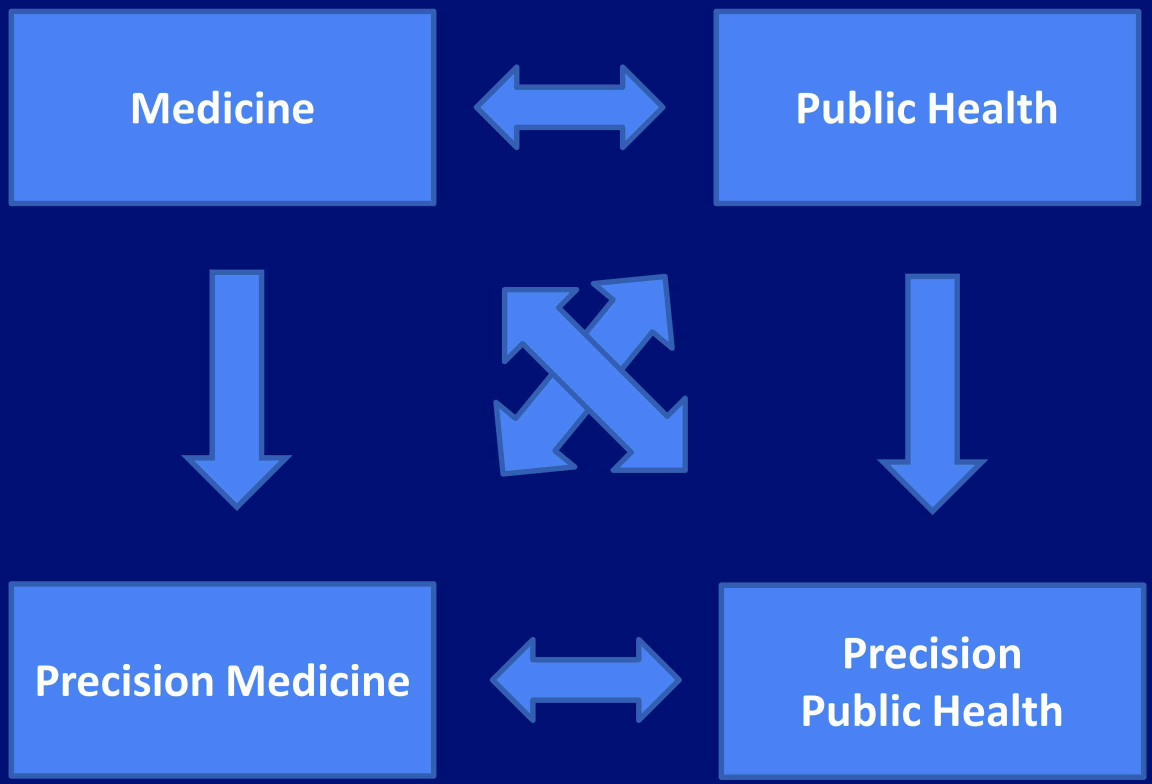
Conclusion: These ... the evolving knowle...

Clyne, M et al, 2014

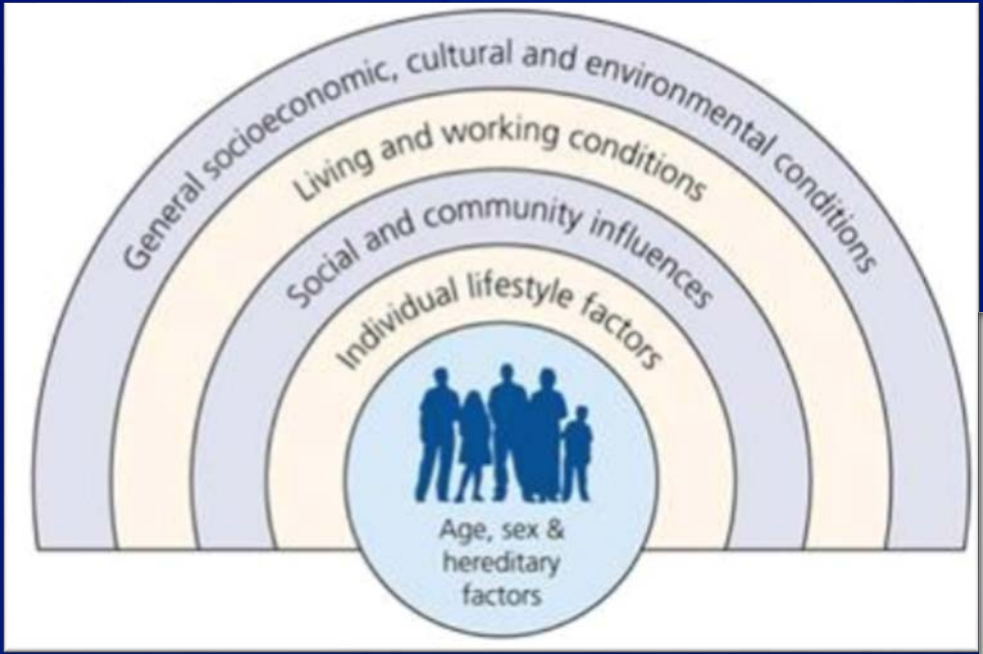


<1% of published genomics research is beyond "bench to bedside" and half of it is in cancer

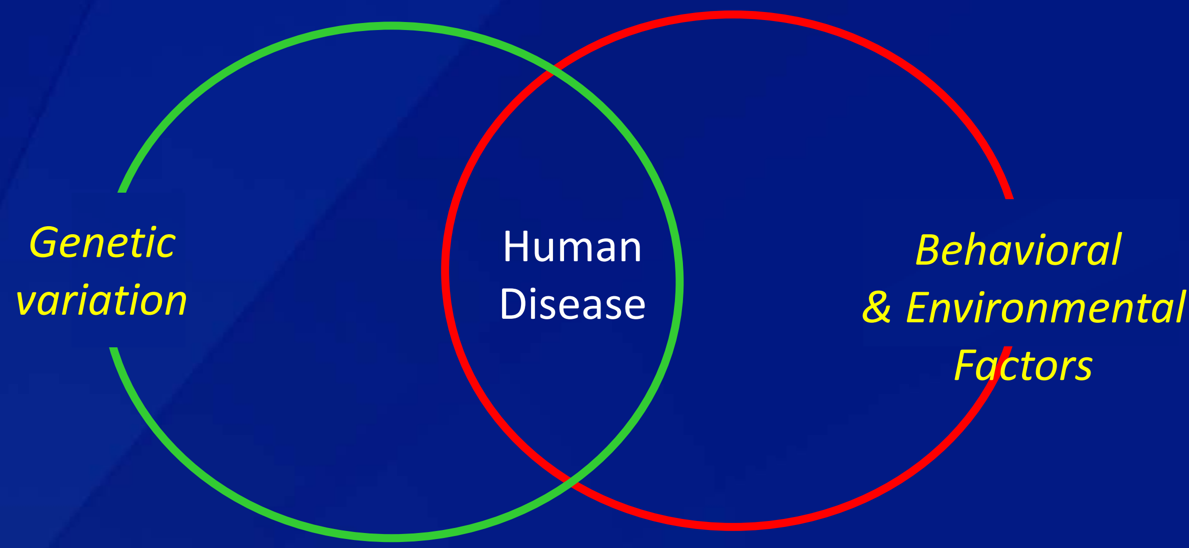
Precision Medicine and Public Health:
Theme IV. A New Era of "Precision Public Health"



Multi Level Determinants of Health



Genes, Behavior, Environment and Human Disease



Genetic Diseases: Mendelian disorders-PKU Example, 5000+ conditions, 5%-10% of human disease

“Complex” Diseases: heart disease, cancer, diabetes, environmental , behavioral & infectious agents – 90%-95% of human disease

Interactions Getting More Complex
What Genomes?

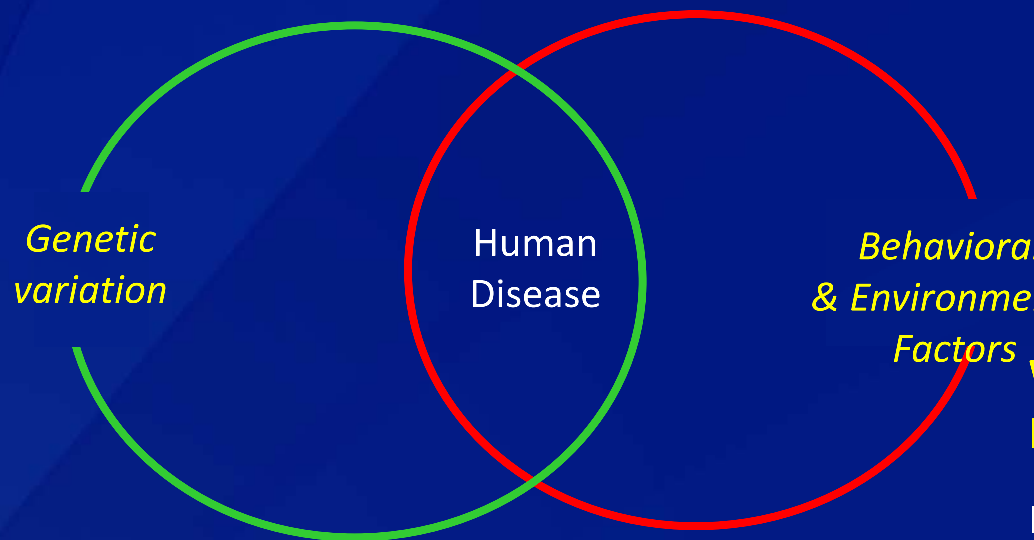
What Genome?

Inherited (germ)

Acquired (somatic)
(e.g. cancer)

Symbiotic
(microbiome)

Vectors



What Environments?

Infection

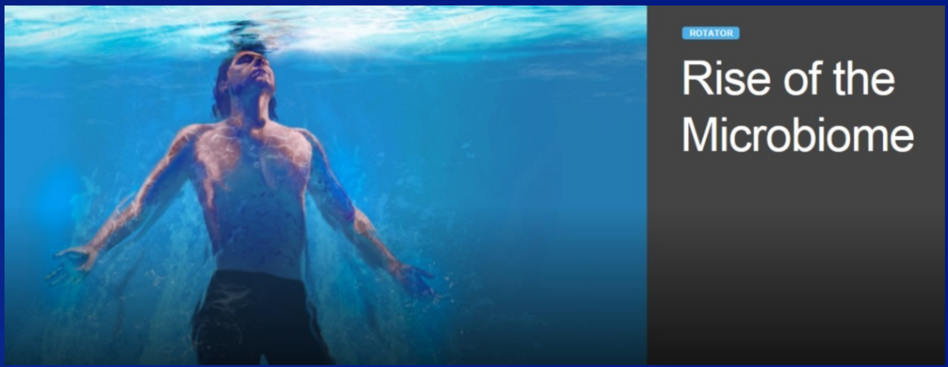
Chemicals

Physical agents

Diet

Behavioral

Social



Mayo Clinic Blog

Interaction Getting Even More Complex
Epigenetics: Life Course & Intergenerational

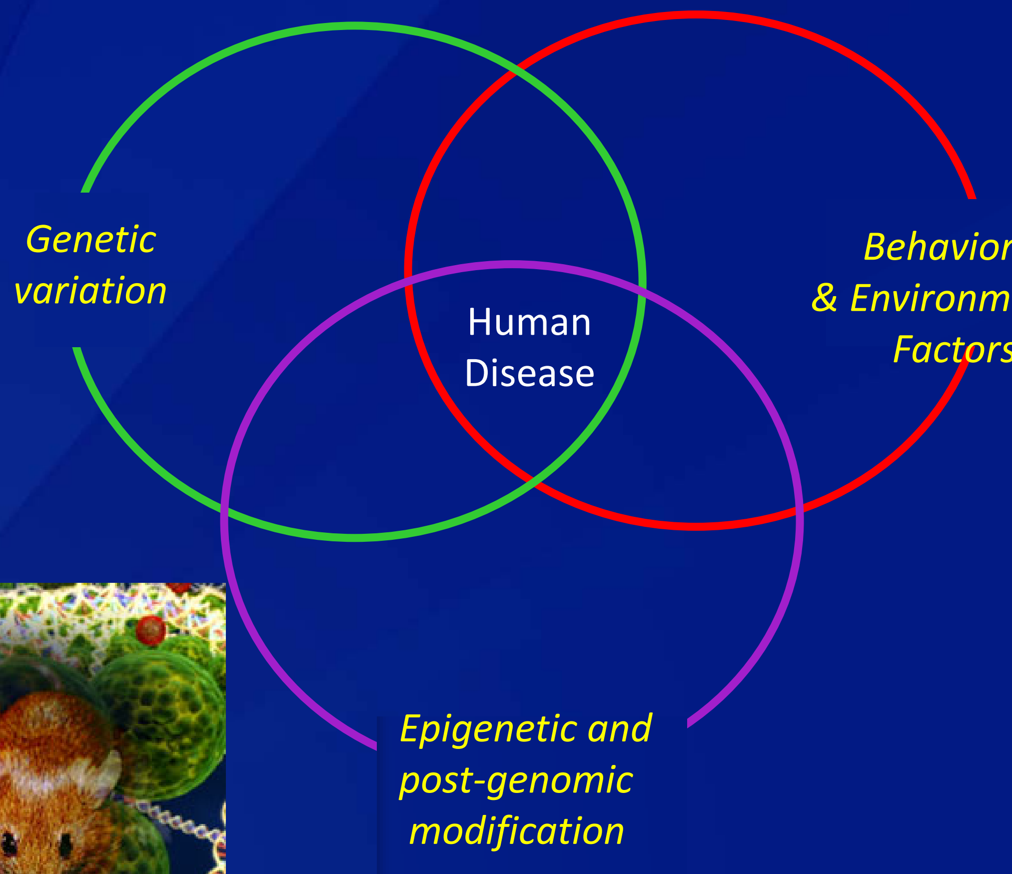
What Genome?

Inherited (germ)

Acquired (somatic)
(e.g. cancer)

Symbiotic
(microbiome)

Vectors



What Environments?

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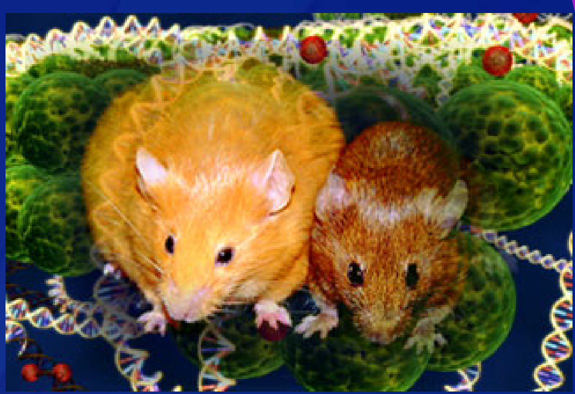
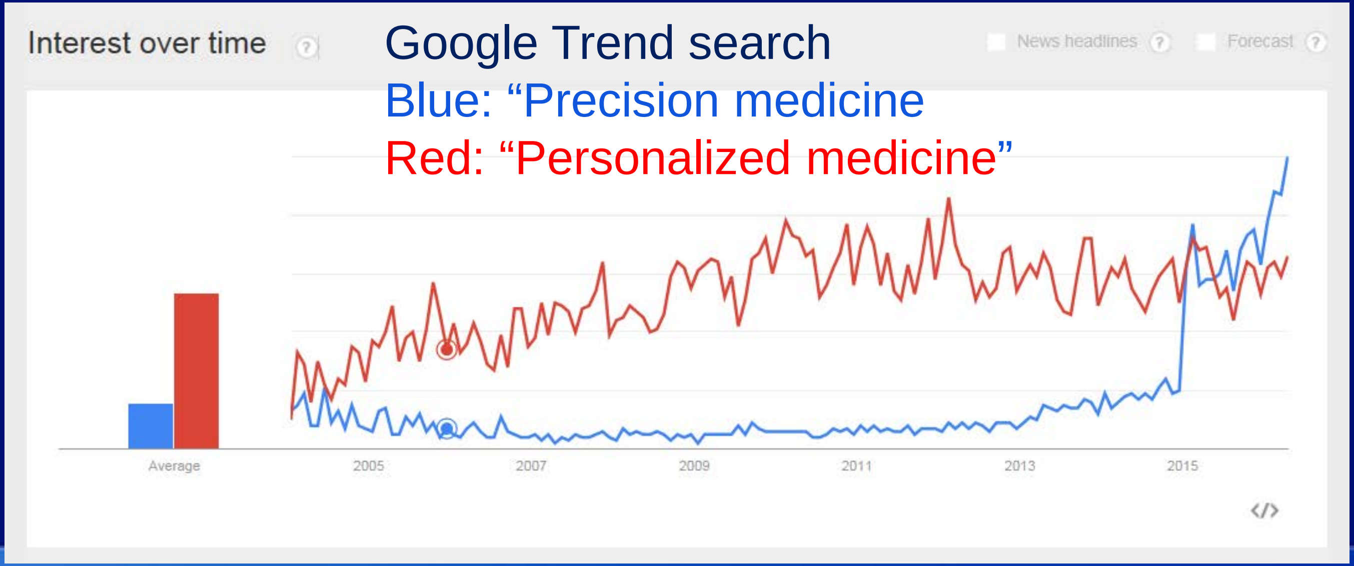


From Personalized Medicine to Precision Medicine & Precision Public Health: Words Matter

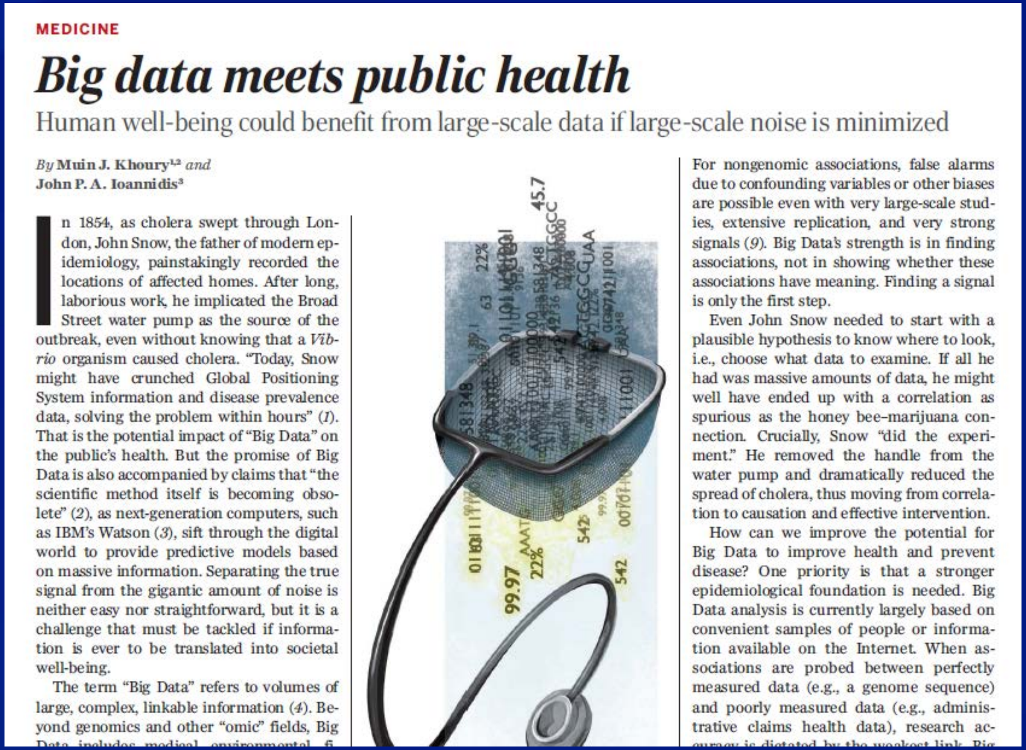
- Personalized Medicine: individualized but can be imprecise (e.g DTC genetic tests)
- Precision Medicine: provides biological & Environmental insights but its applications may be population-wide (e.g. statins)
- Can we use ALL determinants of health (from the micro to the macro) to develop analytic approaches to population health?



Can We Conduct Public Health Functions with More "Precision"?

3 Core Public Health Functions

- Assessment
  - More "precision" in measuring population health problems
- Policy Development
  - Developing the right intervention for the right population
- Assurance
  - More "precision" in delivering interventions



MEDICINE

Big data meets public health

Human well-being could benefit from large-scale data if large-scale noise is minimized

By **Muin J. Khoury**[1,2] and **John P. A. Ioannidis**[3]

In 1854, as cholera swept through London, John Snow, the father of modern epidemiology, painstakingly recorded the locations of affected homes. After long, laborious work, he implicated the Broad Street water pump as the source of the outbreak, even without knowing that a *Vibrio* organism caused cholera. "Today, Snow might have crunched Global Positioning System information and disease prevalence data, solving the problem within hours" (*1*). That is the potential impact of "Big Data" on the public's health. But the promise of Big Data is also accompanied by claims that "the scientific method itself is becoming obsolete" (*2*), as next-generation computers, such as IBM's Watson (*3*), sift through the digital world to provide predictive models based on massive information. Separating the true signal from the gigantic amount of noise is neither easy nor straightforward, but it is a challenge that must be tackled if information is ever to be translated into societal well-being.

The term "Big Data" refers to volumes of large, complex, linkable information (*4*). Beyond genomics and other "omic" fields, Big

...

For nongenomic associations, false alarms due to confounding variables or other biases are possible even with very large-scale studies, extensive replication, and very strong signals (*9*). Big Data's strength is in finding associations, not in showing whether these associations have meaning. Finding a signal is only the first step.

Even John Snow needed to start with a plausible hypothesis to know where to look, i.e., choose what data to examine. If all he had was massive amounts of data, he might well have ended up with a correlation as spurious as the honey bee–marijuana connection. Crucially, Snow "did the experiment." He removed the handle from the water pump and dramatically reduced the spread of cholera, thus moving from correlation to causation and effective intervention.

How can we improve the potential for Big Data to improve health and prevent disease? One priority is that a stronger epidemiological foundation is needed. Big Data analysis is currently largely based on convenient samples of people or information available on the Internet. When associations are probed between perfectly measured data (e.g., a genome sequence) and poorly measured data (e.g., administrative claims health data), research ac-

Khoury & Ioannidis, Science 2014

Precision Public Health: Examples of Immediate Applications to Improve Population Health

Pathogen Genomics

Modernizing Surveillance, Informatics, Tracking (Data Science)

Targeting Prevention Efforts (beyond Genomics)

Precision Public Health for the Era of Precision Medicine

Muin J. Khoury, MD, PhD,[1,2] Michael F. Iademarco, MD, MPH,[1,3] William T. Riley, PhD[2]

The Precision Medicine Initiative[1] promises a new healthcare era. A proposed 1 million–person cohort could create a deeper understanding of disease causation. Improvements in quality of sequencing, reduction in price, and advances in "omic" fields and biotechnology promise a new era, variably labeled personalized or precision medicine. Although genomics is one driver of precision health care, other factors may be as important (e.g., health information technology).

Both excitement and skepticism met the announcement.[2] Public health experts are concerned about the disproportionate emphasis on genes, drugs, and disease, while neglecting strategies to address social determinants

evidentiary foundation for use. The following are examples of priority areas.

Role of Multidisciplinary Public Health Sciences

Though precision medicine focuses on individualized care, its success truly requires a population-based approach. To learn what interventions work for whom, data on each individual need to be compared with data from large, diverse numbers of people to identify population subgroups likely to respond differently to interventions. In addition, collecting information from

Khoury MJ, et al. AJPM, December 2015

Pathogen Genomics: Precision Medicine for Public Health

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

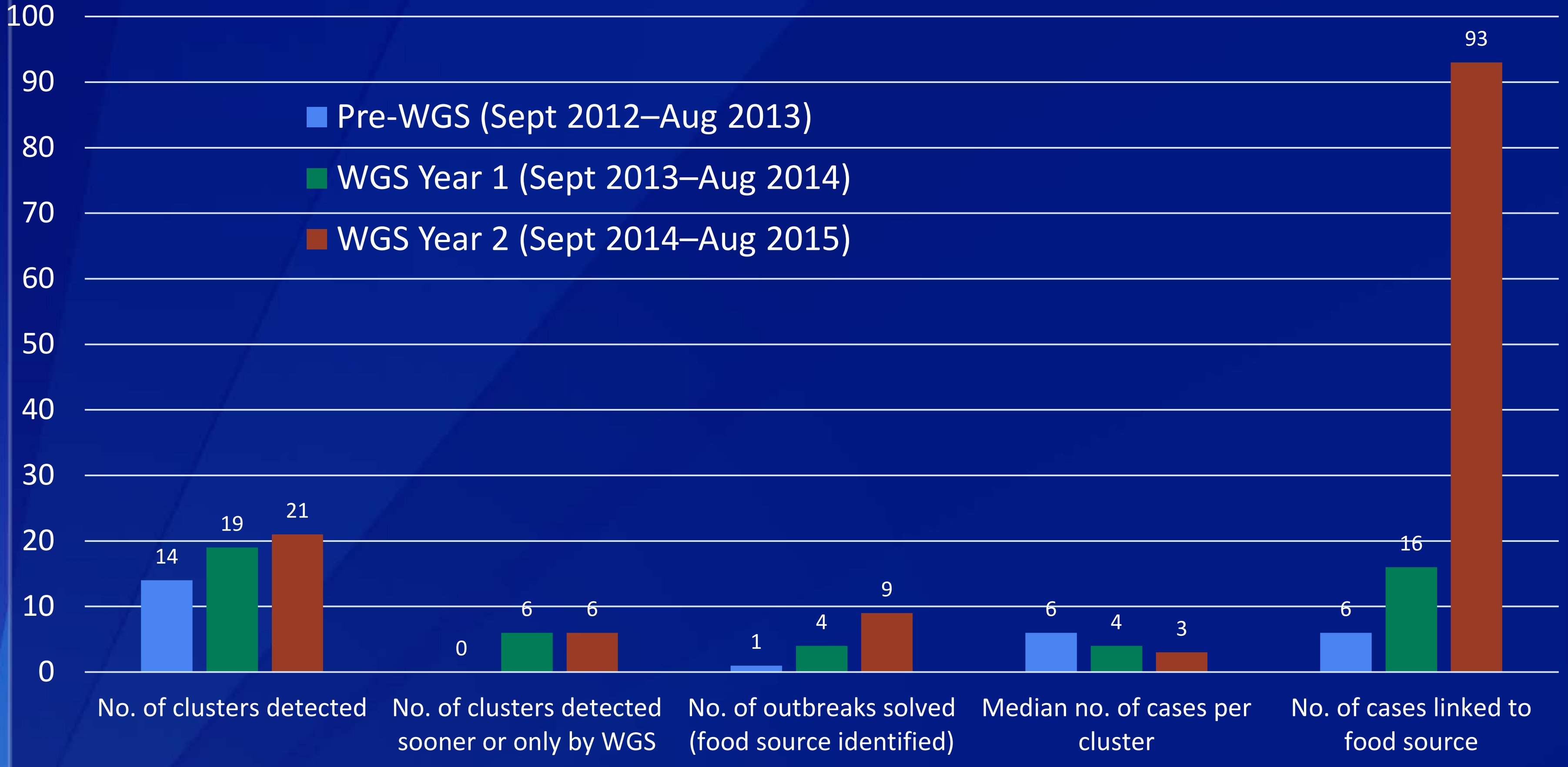
SEARCH

CDC A-Z INDEX

Advanced Molecular Detection (AMD)

Using molecular technologies to counter infections in patients and populations		
Application	**Patient care**	**Public health**
Pathogen identification	Rapid diagnosis	Outbreak detection
Antibiotic selection	Proper treatment	Effective antibiotic use guidelines
Vaccines	Better protection	Reduced burden of disease

Listeria Cluster Metrics Pre/Post WGS



From R. Khabbaz

From WGS to GPS

"As cholera swept through London in the mid-19th century, a physician named John Snow painstakingly drew a paper map indicating clusters of homes where the deadly waterborne infection had struck. In an iconic feat in public health history, he implicated the Broad Street pump as the source of the scourge—a founding event in modern epidemiology. Today, Snow might have crunched GPS information and disease prevalence data and solved the problem within hours"

http://www.hsph.harvard.edu/news/magazine/big-datas-big-visionary/?utm_source=SilverpopMailing&utm_medium=email&utm_campaign=Kiosk%2009.25.14_academic%20(1)&utm_content

What is Precision Public Health?

- “As a cancer doctor, I was part of this new targeted therapy, getting the right medicine to the right patient. So today, I’m interested in something I’d call precision public health. Can we bring that same innovation, that speed, that ability to use big data to the problems we’re trying to solve? That is not a one-cause passion. That is my wish: To bring all of this intellectual data, understanding and tracking of diseases to bear for things that affect the poor every bit as much as we have traditionally done for the rich.”

S. Desmond-Hellman, CEO Gates Foundation, Aspen Institute, December 2015

Conclusions
Precision Medicine and Precision Public Health- Two Peas in a Pod!

- We need both (precision) medicine and public health to improve population health
- Public health-medicine partnerships are needed to implement what we already know in precision medicine to save lives and reduce health disparities
- Public health sciences are needed to generate and implement new knowledge in precision medicine
- We are entering a new era of precision public health that is not just about "genes, drugs, and diseases"