Cleveland Clinic Foundation
Personalized Health Care Summit
Sept. 20, 2011

Societal Issues and Their Impact on Personalized Health Care

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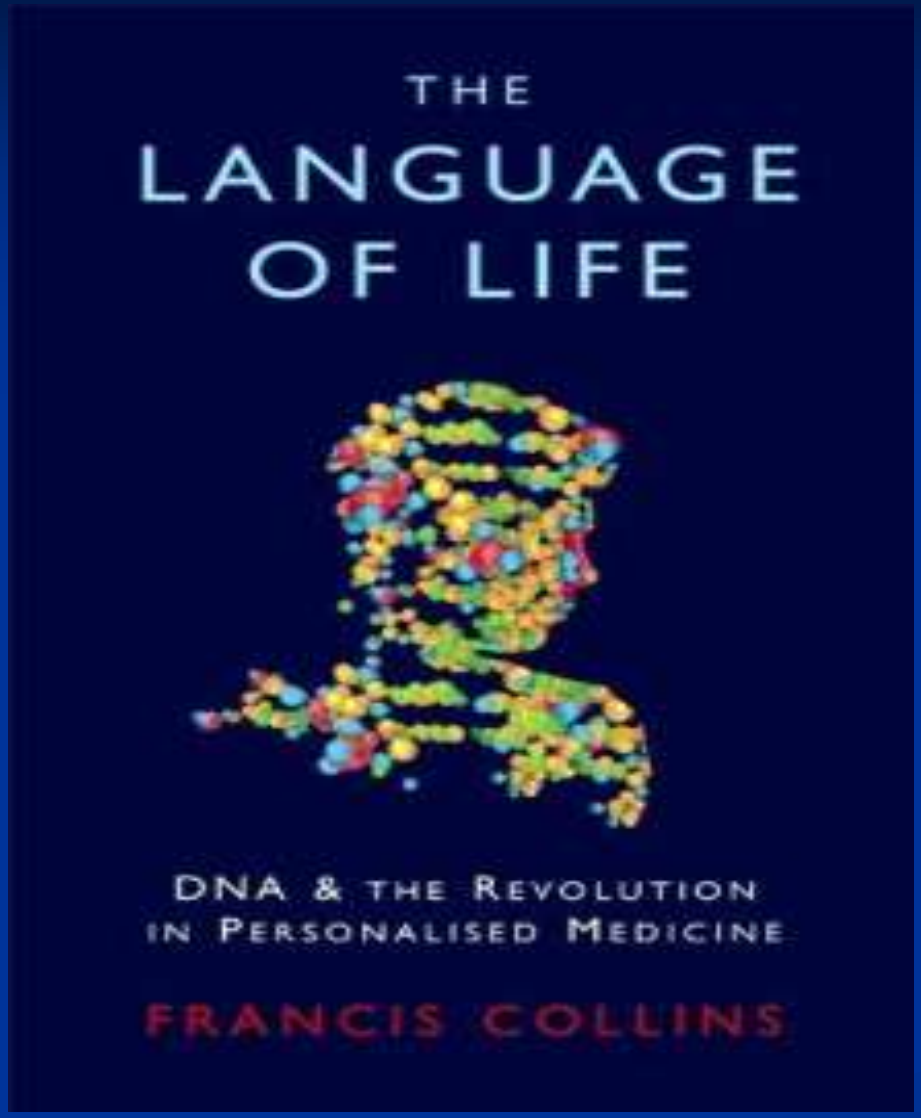

"We are on the leading edge of a true revolution in medicine, one that promises to transform the traditional "one size fits all" approach into a much more powerful strategy that considers each individual as unique and as having special characteristics that should guide an approach to staying healthy"

(Collins 2010: xxiv).

Societal Issues Impeding the Revolution

- U.S. economic woes
- Translational pipeline bottlenecks
- health care system needs
- low prof./public genetic literacy levels
- high prof./public "resistance to change"

Societal issues that will impact PHC *after* the revolution

- I..e., ways in which different social inclinations and issues could distort the trajectory of PHC, once the transitional coalition has to get serious about defining its priorities and goals.

- Why look ahead? Practicing what we preach, re: risk assessment, early detection, pre-emptive problem-solving!

“Anticipating Personal Genomic Medicine: Impact and Implications”
NIH R01 HG005277

Eric Juengst, UNC

Rick Settersten, OSU

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Michelle McGowan, CWRU

CGREAL

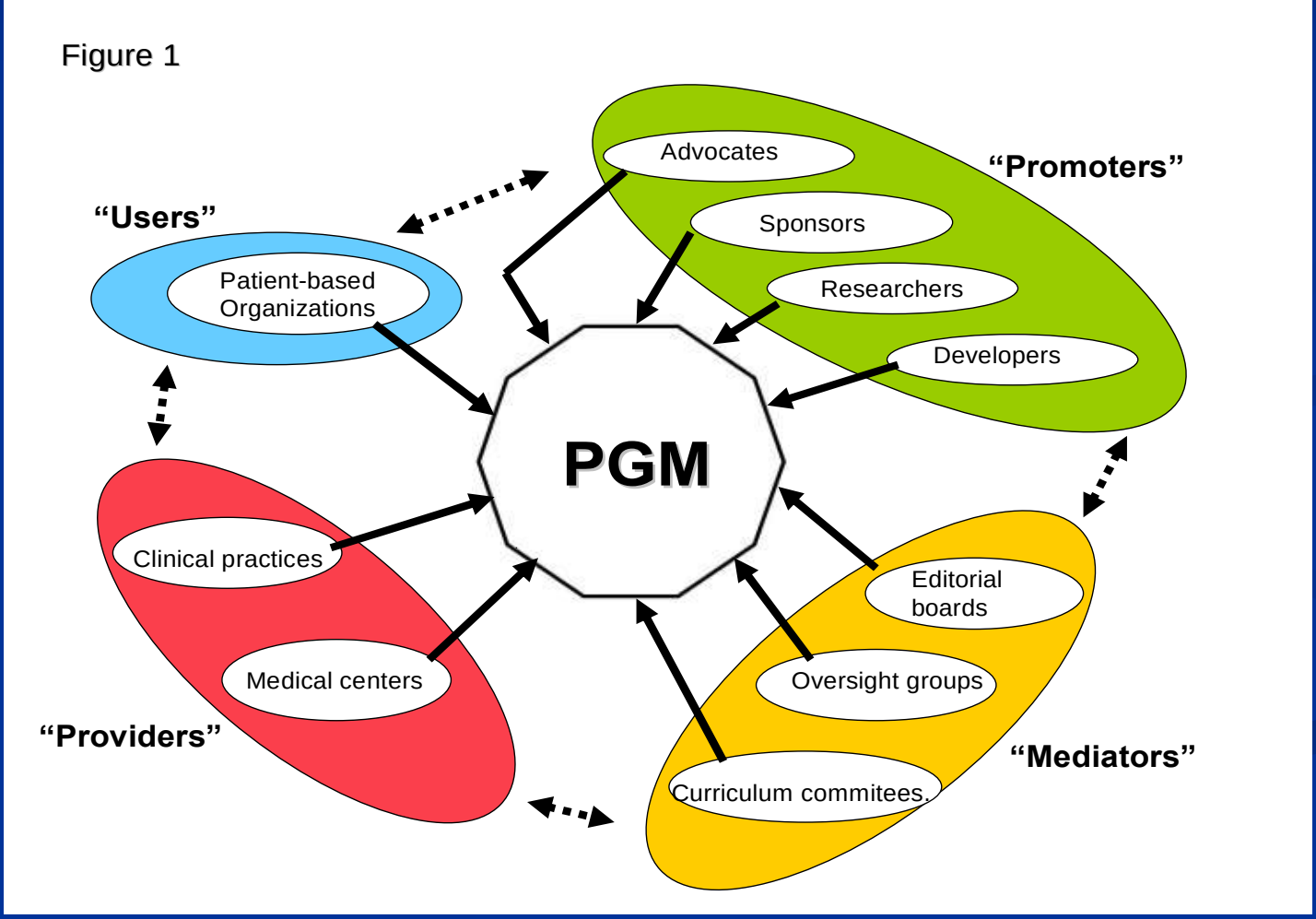
The Center for Genetic Research Ethics and Law

Case Western Reserve University/Cleveland Clinic Foundation

www.cgreal.org

NIH/NHGRI P50-HG-003390

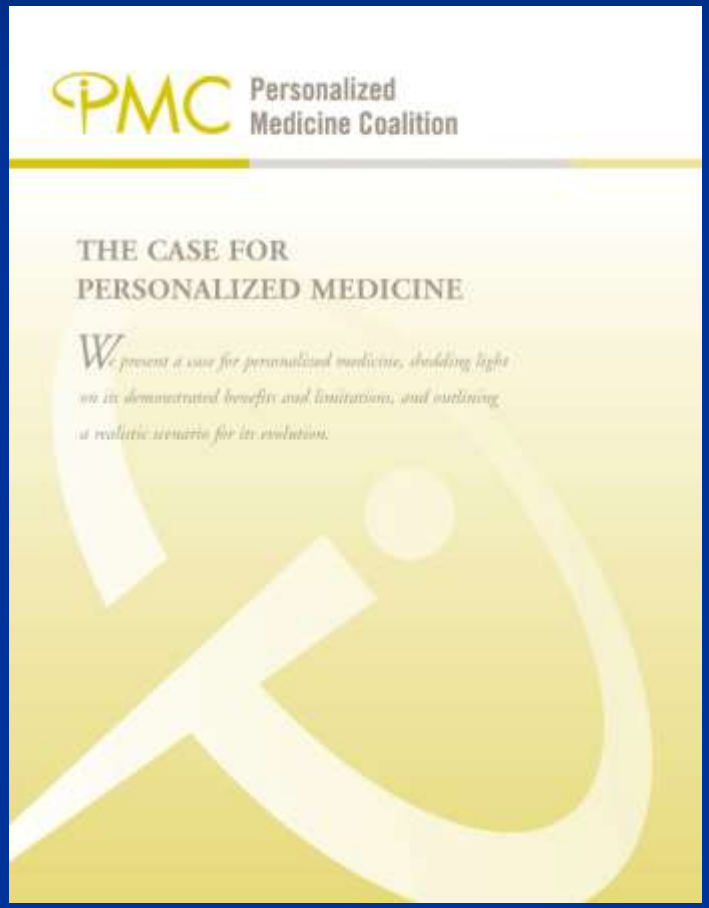
Stakeholders Shaping thel Definition of Personalized Genomic Medicine as a parardigm for health care



The polyvalent plurality of PGM's pluses and pros , according to its promoters

- *Thus, personalized healthcare promises to be predictive, preventive, and pre-emptive, with the potential to transform current healthcare into a value-based, patient-centric healthcare system."*

(Xu et al. *PM*, 2008: 457, emphasis added)



- "Healthcare today is in crisis: it is expensive, reactive, inefficient, and focused largely on one size fits all treatments for events of late stage disease. *The answer is personalized, predictive, preventive and participatory medicine* ."

(PMC 2009: 6, emphasis added)

- Predictive
  - Proactive, through risk profiling and forecasting
- Preventive
  - Pre-emptive, through early detection and intervention
- Personalized
  - Precisely-targeted, "individualized" via molecular identity
- Participatory
  - Patient-centered, empowering patients to take responsibility

Aristotle says that all virtues sit on a spectrum between correlative vices:

Cowardice…….Courage…….Fool-hardiness

Given the social context in which PGM is emerging, what potential vices flank the four virtues of PGM?

i.e., What cultural temptations and social susceptibilities should the proponents of PGM be on guard against?

The Virtue of Prediction

Ultimately, the results of the HGP ... will profoundly alter our approach to medical care, from treating disease that is already advanced to a preventative mode focused on identification of individual risk. This should permit early initiation of changes in lifestyle and medical surveillance, preventing individuals from becoming ill in the first place .

Guyer, M. and Collins F.C.: 1993, '**The Human Genome Project and the Future of Medicine**', American Journal of Diseases of Children 147, pp. 1145-1152.

Thanks to genomic research and microarray technologies:

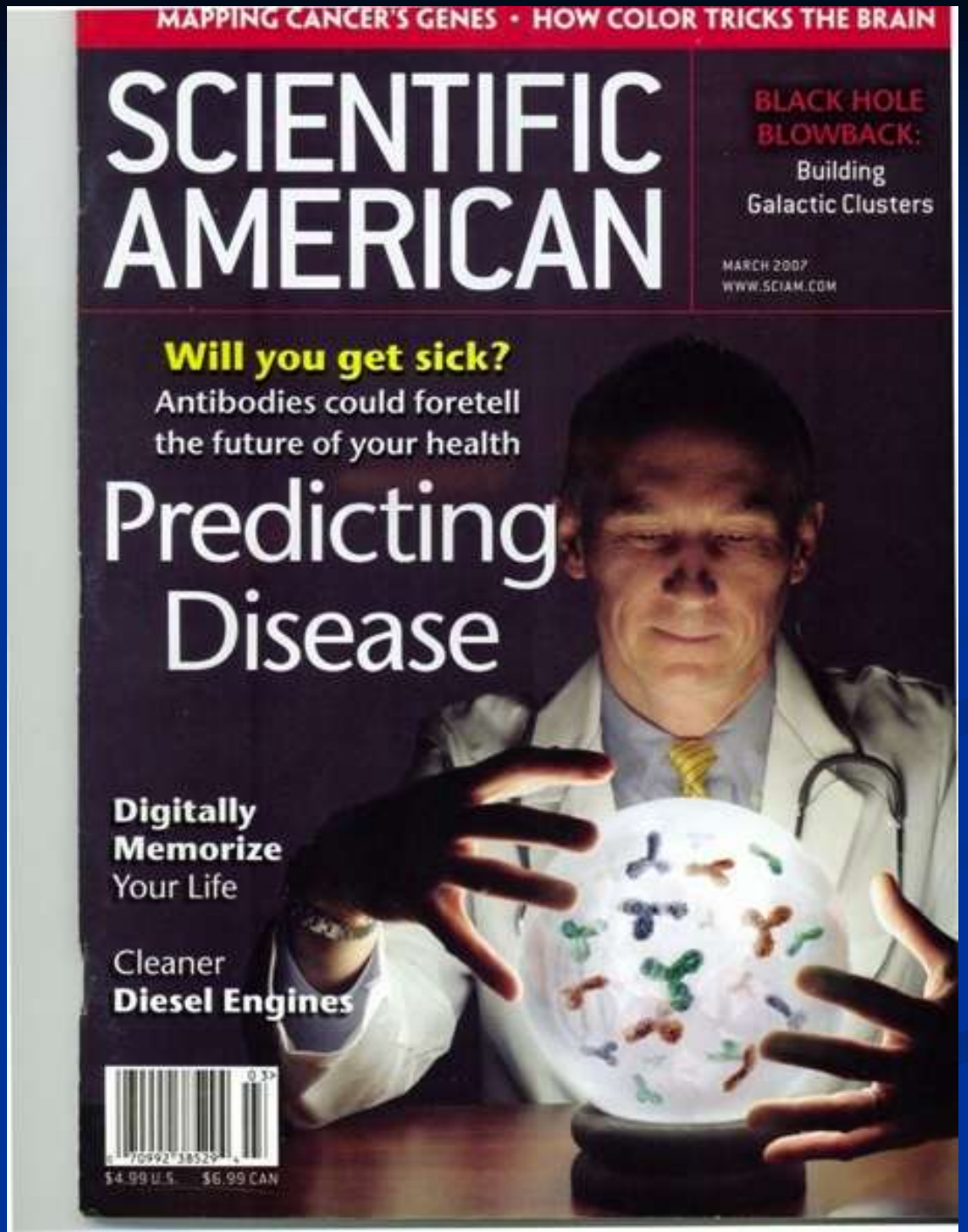
- Expanded panels (10-100 genes)
- Multiplex testing (100-1000 mutations)
- Genome-wide scanning (1K-100,000 snps)
- Medical Sequencing (100K – 3 billion nucleotides)
- Lots of statistical associations between all of the above and health risks.

Kohane, Masys, Altman, 2006: "The Incidentalome: A Threat to Genomic Medicine" *JAMA* 296:212

- "If the risk associated with the finding was established in a population with a high prevalence of disease, the rate of false positive results when testing in a population with a lower rate of disease will be much higher."
- For 10K independent tests, even with sensitivity of 100% and false positive of .01, 60% of population will get false positive reports.
- Even for the true positive mutations, not all will lead to clinical disease.

Kohane, Masys, Altman, "The Incidentalome: A Threat to Genomic Medicine" *JAMA* 296(2006):212

- "The application of comprehensive genotype and functional genomic measurements across the general population is likely to yield unexpected incidental findings for nearly everyone."


MAPPING CANCER'S GENES • HOW COLOR TRICKS THE BRAIN
SCIENTIFIC AMERICAN
BLACK HOLE BLOWBACK:
Building Galactic Clusters
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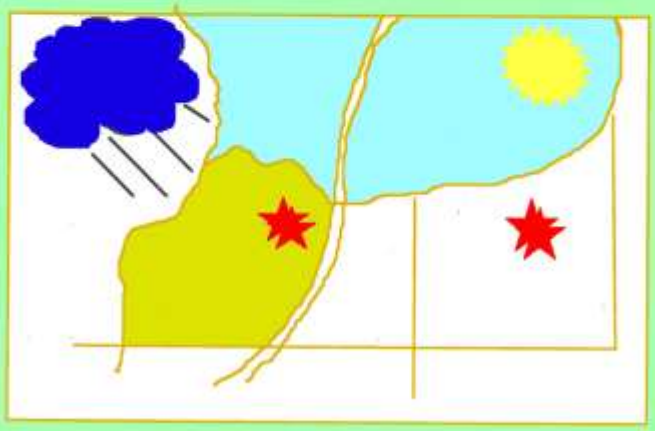
“Most genetic measurements only shift the probability of an outcome, which often depends on other environmental triggers and chance.” Kohane et al.



The identification of people at potential risk of dementia with a view to early therapeutic intervention is important, because it may lessen distress for both patient and family, minimize the risk of accidents, prolong autonomy, and perhaps even ultimately prevent the onset of the dementing process itself

Ritchie & Touchon, 2000.

Emergence of "MCI" as a clinical entity

- Petersen, et.al., "Aging, Memory and mild cognitive impairment," 1997
- Ritchie and Touchon, "Mild cognitive impairment: conceptual basis and current nosological status" Lancet, 2000.
- Morris, et. al. "Mild cognitive impairment represents early-stage AD", 2001.
- Collie and Maruff, "An analysis of systems for classifying mild cognitive impairment in older people," 2002
- St. John, et. al., "Cognitive scores, even within the normal range, predict death and institutionalization, 2002.
- Tuokko, et. al., "Five year follow-up of cognitive impairment with no dementia," 2003.
- Davis and Rockwood, "Conceptualization of mild cognitive impairment: a review," 2004.
- Rivas-Vazquez, et. al, "Mild cognitive impairment: new neuropsychological and pharmacological target" 2004

Cortex Pharmaceuticals:

Announcing deal which will allow them

"to participate in the accelerated development of a 'proof of principle' trial in MCI, an enormous market which blurs with the even more ubiquitous "age-related cognitive decline" which we all experience from age forty on.

Establishing consensual criteria for MCI disorder and its assessment opens the door for Cortex to sidestep the traffic jam in the AD drug arena, one which continues to invoke contention as to etiology and optimal treatment strategies.

If Ampakines continue to show safe positive effects upon memory and attention, the 'greying' population of the US and Europe would present an enormous potential market."

The temptations of medicalization

- Legitimizes medical attention and intervention
- Reinforces inclination to overly deterministic interpretations of genomic risk data.
- But…. Reframes risks as pathologies
- Creates psychosocial burden of “at risk” role.

Aaah!

Hmm.

Eeek?

Predictive → Medicalization → Stigmatization

The virtue of preventive care

- “An ounce of prevention is worth a pound of cure.”
- I.e., personalized prevention benefits from the “common knowledge” that prevention is more effective and less expensive than treatment in addressing peoples’ health problems.

Once personalized genomic medicine becomes standard medical practice for adults, the logic of providing physicians with this powerful tool earlier and earlier in the patient's life may prove to be inescapable.

Even if cancers, for example, are relatively rare in children and adolescents, why wait until adulthood to uncover susceptibilities and vulnerabilities that could well be countered by changes in diet and life habits (to say nothing of prophylactic therapies) at and early age?

President's Council on Bioethics, "The Changing Moral Focus of Newborn Screening" Dec., 2008.

"**Primary prevention genetic services** are services intended to prevent a birth defect, genetic disorder or disease before it occurs. Genetic counseling is a form of primary prevention. Genetic counseling provides couples with information about their pregnancy and reproductive risks and pregnancy options.

Secondary prevention genetic services are services intended to prevent the unfavorable sequelae of an existing disorder or genotype. Newborn screening is a classic example of secondary prevention.

Tertiary prevention genetic services are services aimed at ameliorating the unfavorable consequences of existing disorders, through enabling services such as parent-to-parent support and empowerment."

Kaye, et. al., "Integrating genetic services into public health: guidance for state and territorial programs" *Community Genetics* 1(2001): 175-196.

Genotypic vs. Phenotypic Prevention

- Genotypic prevention:
  - preventing the intergenerational transmission of disease genes (e.g., prenatal testing).

- Phenotypic prevention:
  - preventing the expression of a genetic disease in an individual (e.g., newborn screening).

Protect Your Child From 100+ Genetic Diseases

Order Now

Each year, millions of unsuspecting couples are at risk for conceiving a child with a serious genetic disease, such as cystic fibrosis, spinal muscular atrophy, or Tay-Sachs disease.

While these diseases cannot be cured, with the Universal Genetic Test they can now be *prevented*. The test is recommended for both men and women and tests for diseases common to every ethnic group, for maximum safety.

Learn more about each of the diseases covered by the test below.

Full Disease List

ABCC8-Related Hyperinsulinism
Achondrogenesis Type 1B
Achromatopsia
Alkaptonuria
Alpha-1 Antitrypsin Deficiency
Andermann Syndrome
ARSACS
Aspartylglycosaminuria
Ataxia With Vitamin E Deficiency
Ataxia-Telangiectasia
Autosomal Recessive Polycystic Kidney Disease
Bardet-Biedl Syndrome, BBS1-Related
Bardet-Biedl Syndrome, BBS10-Related
Beta Thalassemia
Biotinidase Deficiency
Bloom Syndrome
Canavan Disease
Carnitine Palmitoyltransferase IA Deficiency
Carnitine Palmitoyltransferase II Deficiency
Herlitz Junctional Epidermolysis Bullosa, LAMC2-Related
Hexosaminidase A Deficiency
HFE-Associated Hereditary Hemochromatosis
Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency
Hurler Syndrome
Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome
Hypophosphatasia, Autosomal Recessive
Inclusion Body Myopathy 2
Infantile Refsum Disease
Isovaleric Acidemia
Krabbe Disease
Leigh Syndrome, French-Canadian Type
Limb-Girdle Muscular Dystrophy Type 2E
Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency
Maple Syrup Urine Disease Type 1B
Maple Syrup Urine Disease Type 3
Medium Chain Acyl-CoA Dehydrogenase Deficiency
Metachromatic Leukodystrophy
Mucolipidosis IV

The temptation of cost effectiveness

- What about when an ounce of genotypic prevention is worth a pound of phenotypic prevention?

- I.e., prenatal screennng for Fragile X syndrome, etc.

Aaah! Hmm. Eeek?

Predictive → Medicalization → Stigmatization

Preventive → Genotypic Prevention → Eugenics

The Virtue of Personalization

Personalized medicine is often described as the right treatment for the right person at the right time. This emerging sciencee has the potential to truly customize healthcare to the patient, enabling providers to match drugs to patients based on their genetic profiles, identify which health conditions an individual is susceptible to, and to determine how a given patient will respond to treatment.

As a result, personalized medicine can eliminate unnecessary treatments, minimize potential adverse events, and ultimately improve patient outcomes.

G. McDougall and M. Rosamond,
PWC View: Personalized medicine and health sciences 13., p3.

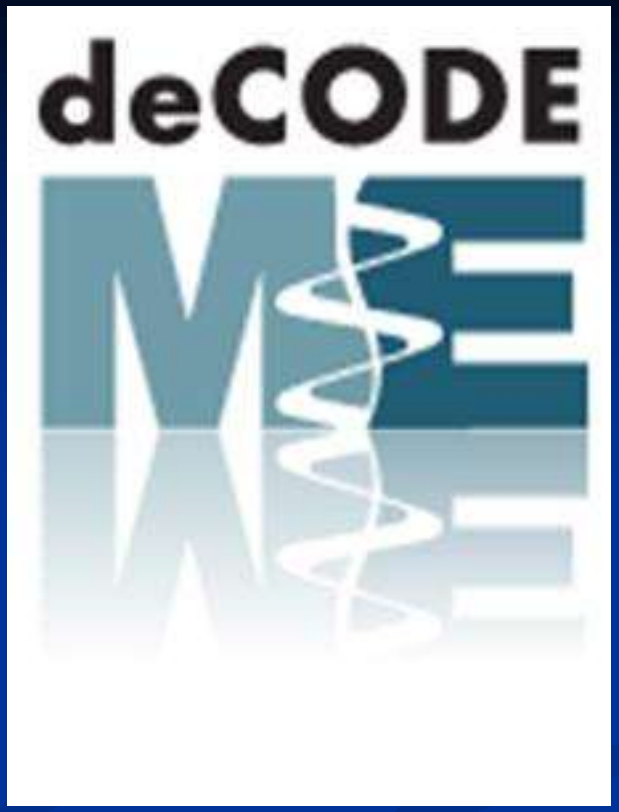
The Risk of Simplistic Reductionism

"For thousands of years mankind has always wanted to know; who are we? Where do we come from? And what makes us unique? Now thanks to advances in DNA and genetics we can start to answer some of these questions.

Your DNA determines who and what you are. No one has ever had the same DNA as you; it is the source of your uniqueness."

(www.DNAWorldwide.com, 2008)


Knome


deCODE
ME


mycellf
the science of you


23andMe

Commentary

The twin questions of personalized medicine: who are you and whom do you most resemble?

Isaac S Kohane

Address: Harvard Medical School, 10 Shattuck Street, Boston, MA 02115, USA.

Email: Isaac_kohane@harvard.edu

Published: 20 January 2009

Genome Medicine 2009, **1**:4 (doi:10.1186/gm4)

The electronic version of this article is the complete one and can be found online at http://genomemedicine.com/content/1/1/4

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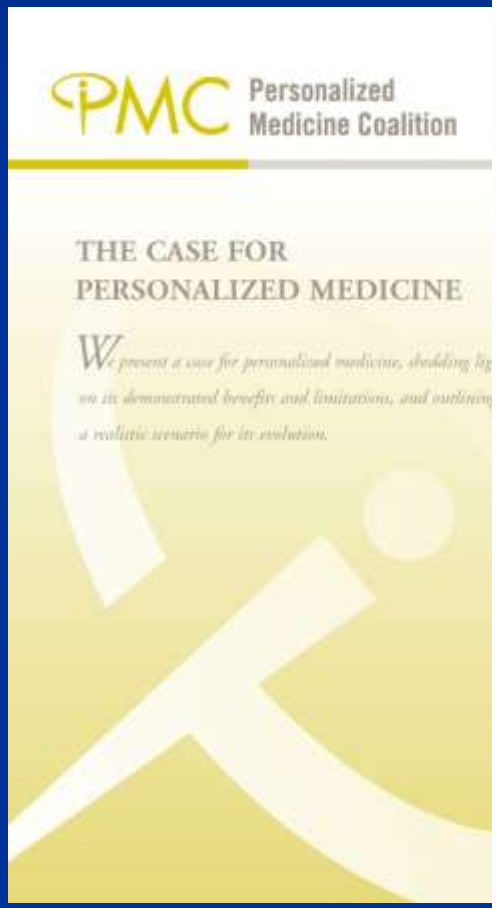
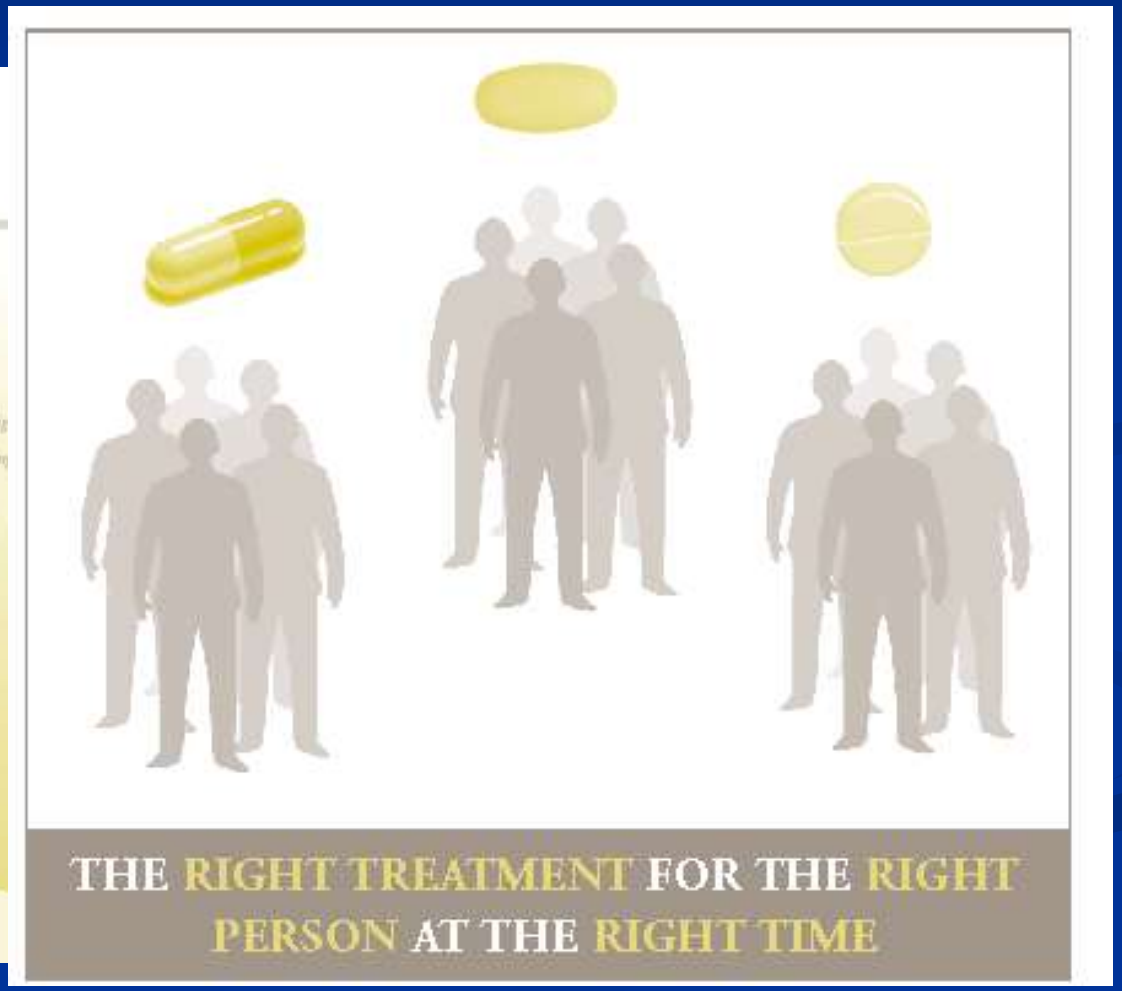
Abstract

Personalized medicine is typically described as the use of molecular or genetic characteristics to customize therapy. This perspective at best provides an incomplete model of the patient and at worst can lead to grossly inappropriate practices. Personalization of medicine requires two characterizations: a well-grounded understanding of who the patient is and an equally robust understanding of the subpopulation that most resembles that patient in the context of the decisions at hand. These characterizations are readily represented probabilistically and can be used to drive decision-making in a rational manner that maximizes the positive outcomes for the patient.

The Risk of Using Social Categories as Risk Bins





The limitation in trying to reach the goal of having a unique medicine for every individual for every disease is that it is simply not practical. It's not practical from a research perspective nor is it practical from a pharmaceutical or diagnostic perspective.

The reality of how patients behave is that they do respond differently, and these responses can be organized into groups. The first step to improving healthcare is to identify what those groups look like, how to cluster individuals within a group and then manage the behavior in terms of the clinical response of that group both for diagnosis and treatment.

If we can't get to treating patients in groups, then the hope of driving it even further into a personalized – completely personalized type of medication is going to be well beyond our reach.

http://www.strategicmedicine.com/index.php/stratified-medicine

NitroMed Inc. | BiDil for Treatment of Heart Failure in African Americans - Microsoft Internet Explorer

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BiDil® | Pain and Inflammation | Restenosis | Other Programs

BiDil® for Treatment of Heart Failure in African Americans

Heart failure, or end-stage cardiovascular disease, affects approximately five million Americans. There is no cure for this disease, and more than 50% of patients die within five years of diagnosis. Studies indicate that African Americans suffer a disproportionate incidence of cardiovascular disease. With respect to heart failure, they are affected at a rate almost twice the rate of the corresponding white population and are more likely to die from it at a younger age. This dramatic ethnic difference in health outcomes has been attributed to a variety of factors, including access to medical care, management of heart failure and socioeconomic factors. Recent analyses of heart failure clinical trials, however, show that the mortality rate and the hospitalization rate for African Americans is significantly higher than for non-African Americans, even after adjustment for such factors. Based on data from the U.S. census bureau and the Centers

Heart Failure

The A-HeFT Coalition

Maintaining a commitment of shared beliefs

- African Americans are disproportionately affected by heart failure
- New clinical data on race and medicine is needed
- African Americans are under represented in clinical trials
- A-HeFT is a landmark trial that provides an important opportunity to collect data

Committed to improving cardiovascular

Internet

Start 3:43 PM

Genetic Background of Patients from a University Medical Center in Manhattan: Implications for Personalized Medicine

Bamidele O. Tayo[1]*, Marie Teil[2], Liping Tong[1], Huaizhen Qin[3], Gregory Khitrov[2], Weijia Zhang[2], Quinbin Song[2], Omri Gottesman[2], Xiaofeng Zhu[3], Alexandre C. Pereira[4], Richard S. Cooper[1], Erwin P. Bottinger[2]*

1 Department of Preventive Medicine and Epidemiology, Loyola University Chicago Stritch School of Medicine, Maywood, Illinois, United States of America, **2** Charles R. Bronfman Institute for Personalized Medicine, Mount Sinai School of Medicine, New York, New York, United States of America, **3** Department of Biostatistics and Epidemiology, Case Western University, Cleveland, Ohio, United States of America, **4** University of Sao Paulo Medical School, Sao Paulo, Brazil

Abstract

Background: The rapid progress currently being made in genomic science has created interest in potential clinical applications; however, formal translational research has been limited thus far. Studies of population genetics have demonstrated substantial variation in allele frequencies and haplotype structure at loci of medical relevance and the genetic background of patient cohorts may often be complex.

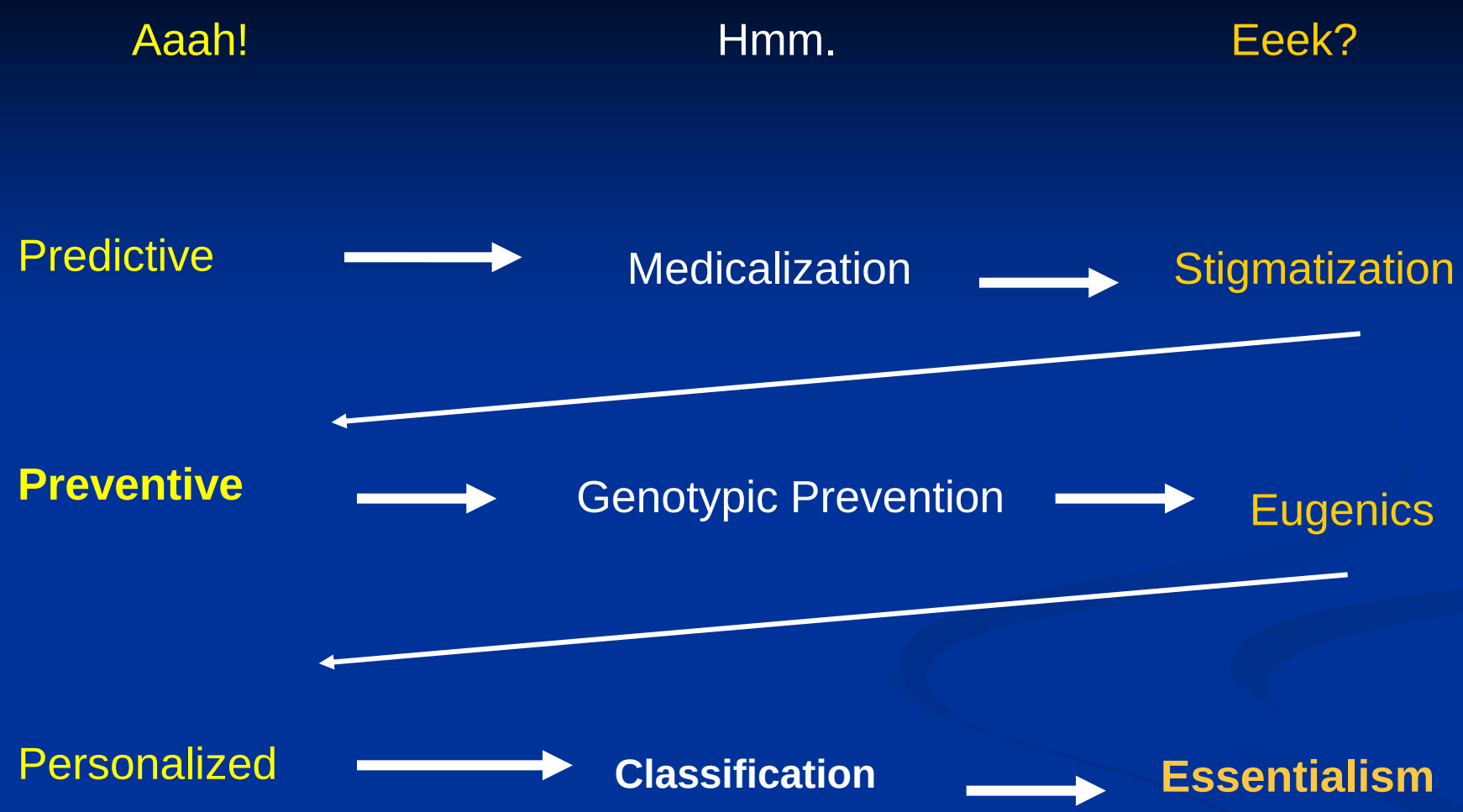
Methods and Findings: To describe the heterogeneity in an unselected clinical sample we used the Affymetrix 6.0 gene array chip to genotype self-identified European Americans (N = 326), African Americans (N = 324) and Hispanics (N = 327) from the medical practice of Mount Sinai Medical Center in Manhattan, NY. Additional data from US minority groups and Brazil were used for external comparison. Substantial variation in ancestral origin was observed for both African Americans and Hispanics; data from the latter group overlapped with both Mexican Americans and Brazilians in the external data sets. A pooled analysis of the African Americans and Hispanics from NY demonstrated a broad continuum of ancestral origin making classification by race/ethnicity uninformative. Selected loci harboring variants associated with medical traits and drug response confirmed substantial within- and between-group heterogeneity.

Conclusion: As a consequence of these complementary levels of heterogeneity group labels offered no guidance at the individual level. These findings demonstrate the complexity involved in clinical translation of the results from genome-wide association studies and suggest that in the genomic era conventional racial/ethnic labels are of little value.

PLoS ONE 6(5): e19166.

Temptations of genetic classification

- Encouraging essentialistic and deterministic inflation of the importance of genes in defining identity as patients
- Depersonalization of health care relationship by “binning” patients in reference groups defined by socially potent categories like race.


Aaah!
Hmm.
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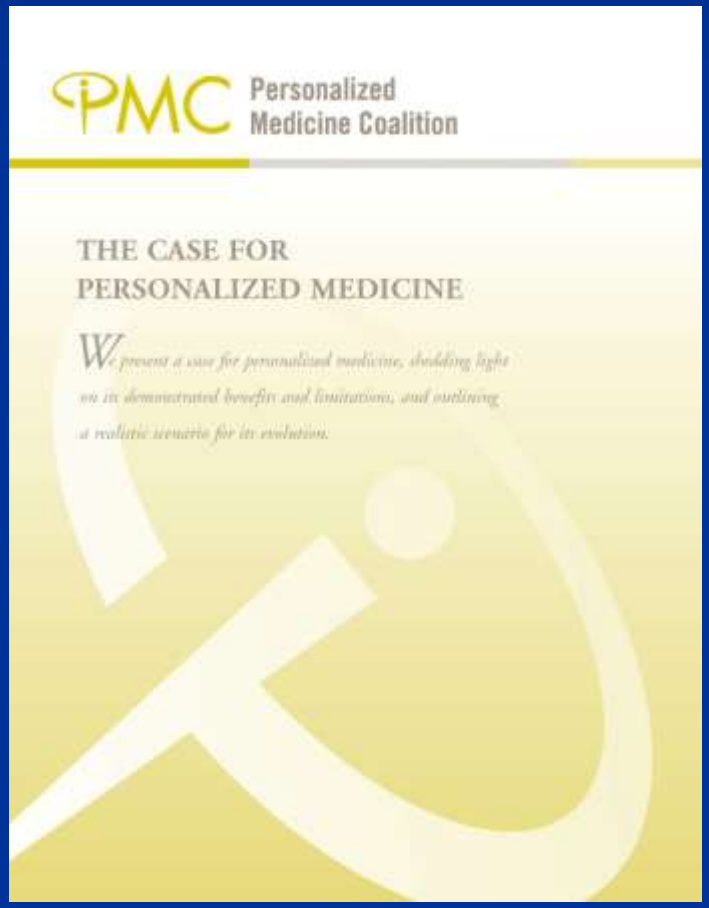
Predictive
Medicalization
Stigmatization
Preventive
Genotypic Prevention
Eugenics
Personalized
Classification
Essentialism

The Virtue of Participatory Care



As the Personalized Medicine Coalition stresses in describing PHC, "it is proactive and participatory, engaging patients in lifestyle choices and active health maintenance to compensate for genetic susceptibilities."

(PMC 2009: 2)

D-T-C marketing of PGM

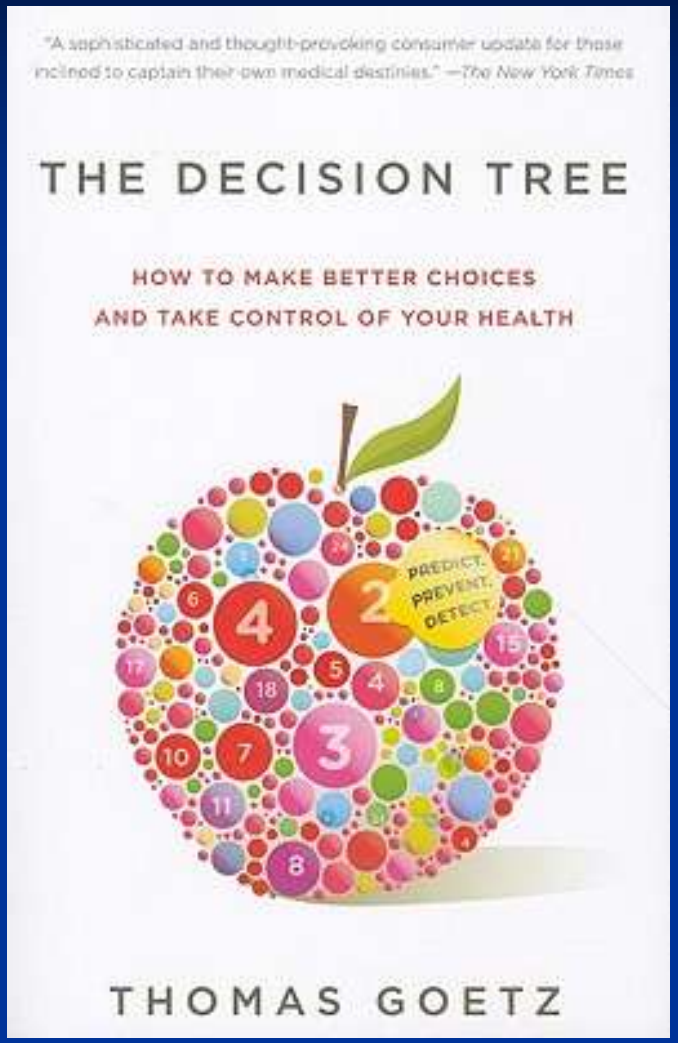
- Navigenics: "There's DNA. An then there's what you do with it. …revealing your genetic predisposition for important health conditions and empowering you with knowledge to help you take control of your future health."

(Navigenics 2009)

- DecodeMe: "getting to know your personal genome will empower you and provide you with a road map to improve your health."

(deCodeMe 2009)

A Moral Stand Against Paternalism?



- "Designating physicians as gatekeepers for genetic information isn't just disempowering -- it's basically sticking healthcare in a time capsule for a decade or more, until physicians get up to speed.
- This persistent paternalistic streak also reflects a lack of faith in the ever-more empowered patient, who is eagerly scouring the Internet for the latest research concerning their condition.
- Like it or not, patients are not going to stop trying to understand ourselves, and our health better. What our genomes might tell us is just one more piece of the puzzle."

(Goetz 2010)

http://www.huffingtonpost.com/thomas-goetz/dna-test-is-your-dna-dang_b_616568.html

Or Virtue of a necessity?

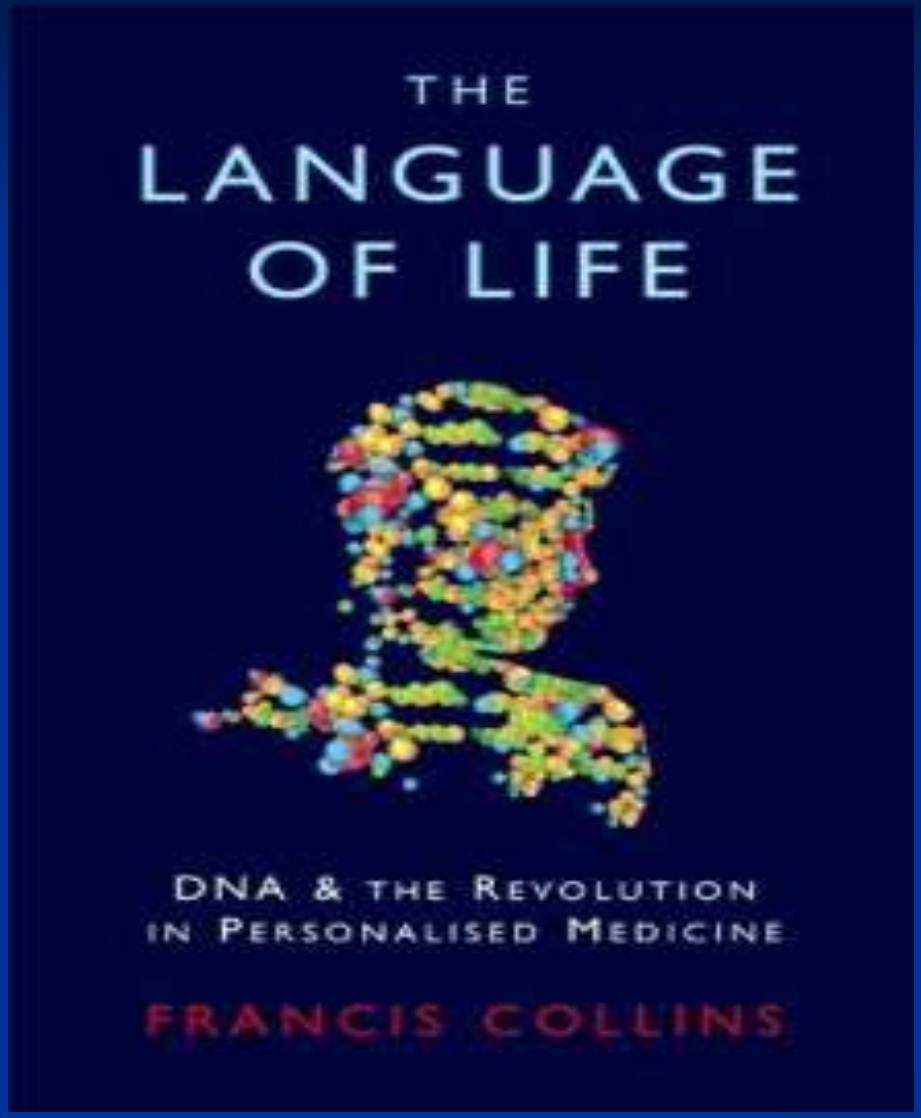
"Since being given the results of my test, my initial feelings of fear and depression have gradually been replaced by a sense of empowerment … 'There is no need to worry, providing you change your lifestyle' [the doctor] kept repeating. So that is what I have decided to do. I now have the greatest possible incentive to change my way of life."

Maitland (quoted in Harvey 2009: 372)

From rights to responsibilities

- "At DNA Direct, we believe that testing is about empowerment – your body and your health are ultimately your responsibility and your genes offer tremendous insight into personal, medical and lifestyle choices."

(Ryan Phelan, Founder & CEO of DNA Direct)



"The success of personalized medicine will come about only when we each take responsibility for our health. Health care providers can help, but they cannot drive your bus. Each chapter of this book has concluded with a list of things you can do now to take full advantage of the potential for personal empowerment. If you follow these recommendations, you will truly be on the leading edge of this new revolution. But the edge will keep moving, and so it will be essential to upgrade your own knowledge base periodically."

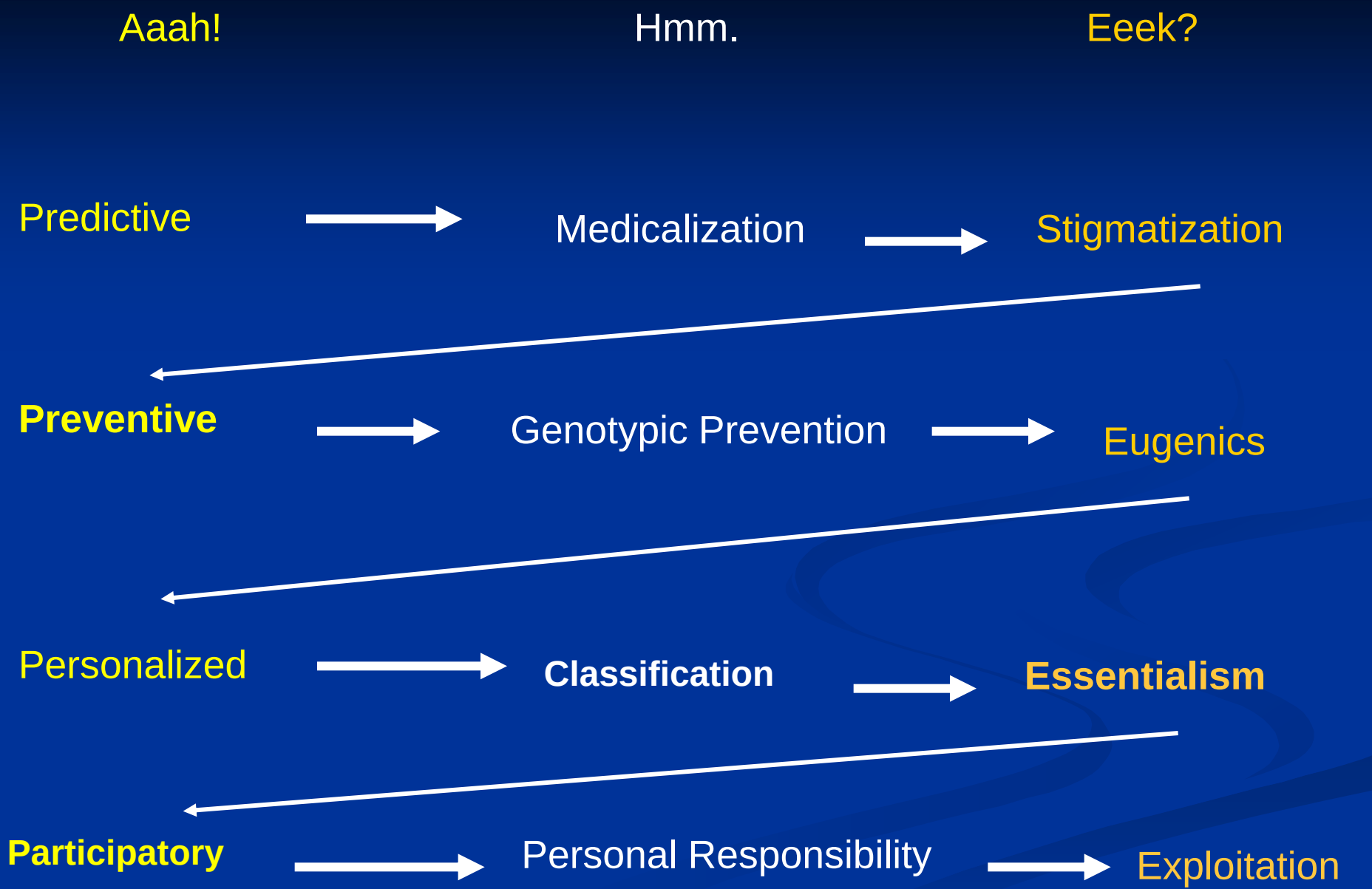
(Collins 2010: 278)

"As harsh as it sounds in an egalitarian society like ours, solidarity stops at a negative genetic test"

R. Porkorski, "Insurance Underwriting in the Genetic Era," *American Journal of Human Genetics*, January, 1999

The temptations of transferring responsibility

- Exploitation:
  - Take charge of your personal genome and put it on your charge card.
- Exculpation:
  - Take responsibility for your personal genome or we cannot take responsibility for the consequences.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Personalized
Classification
Essentialism
Participatory
Personal Responsibility
Exploitation

In Summary

- Most of the ELSI discussion of PHC has focused on the external constraints that challenge its success: provider education, test efficicy, social repercussions. But even the internal virtues of PHC require careful contextual attention:
- If PHC slides into medicalizing risk factors, it risks feeding the determinism that encourages stigmatization.
- If PHC is carried by the logic of prevention into reproductive settings, it risks resurrecting coercive eugenic practices.
- If PHC is allowed to buttress reductionistic thinking, it risks exacerbating individual and group forms of discrimination.
- If PHC serves only to transform social responsibilites for health care into individual responsibilities, it may exacerbate health care injustices rather than combat them.