

***Personalized Medicine: Impact on Patients, Physicians
and Genetic Counselors***

Mountain States Genetics Foundation
25th Annual Education Conference

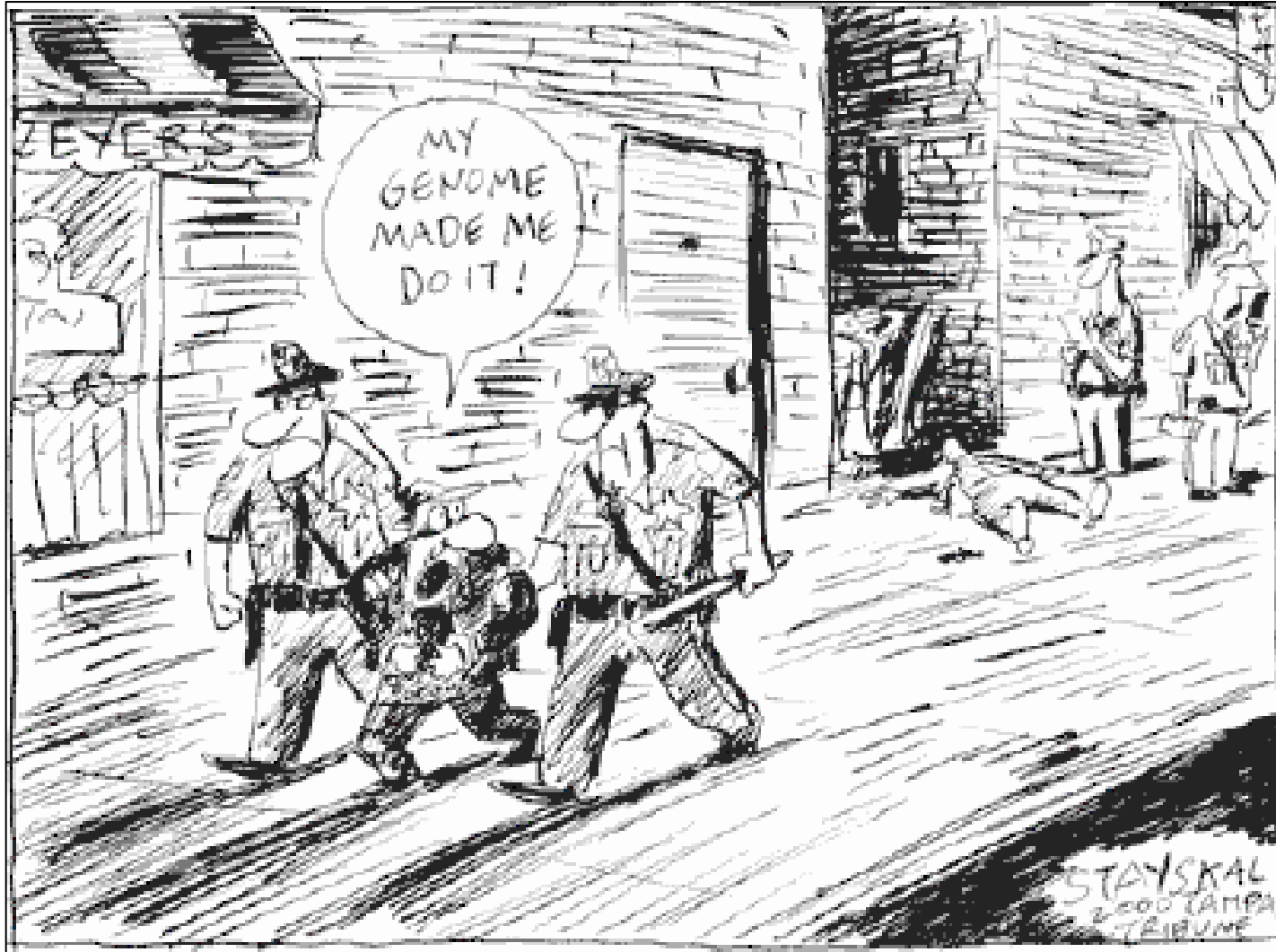
Mike Murray, MD
Brigham and Women's Hospital
Harvard Medical School
July 17th 2009

Disclosure

**Grant from
Genzyme Corporation**

The Impact of Personalized Medicine

- Personalized Medicine is the concept that managing a patient's health should be based on the individual patient's specific characteristics, including age, gender, height/weight, diet, environment, etc.
- Personalized medicine the concept that information about a patient's genotype or gene expression profile could be used to further tailor medical care to an individual's needs.



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The Impact of Personalized Medicine

- **Voices outside of the clinical and research genetics arena are asking:**
- **Voices inside of the clinical and research genetics arena are asking:**

The Impact of Personalized Medicine

- **Voices outside of the clinical and research genetics arena are asking:**
- **What is the holdup?**
- **Voices inside of the clinical and research genetics arena are asking:**

The Impact of Personalized Medicine

- **Voices outside of the clinical and research genetics arena are asking:**
- **What is the holdup?**

- **Voices inside of the clinical and research genetics arena are asking:**
- **What is the rush?**

So how does ...

- **A Rare Genetic Syndrome**
- **A Nobel Laureate**
- **And an Incomplete understanding of available data**

**make clear some of the issues facing us with regard to
personalized medicine in July 2009**

A Rare Genetic Syndrome

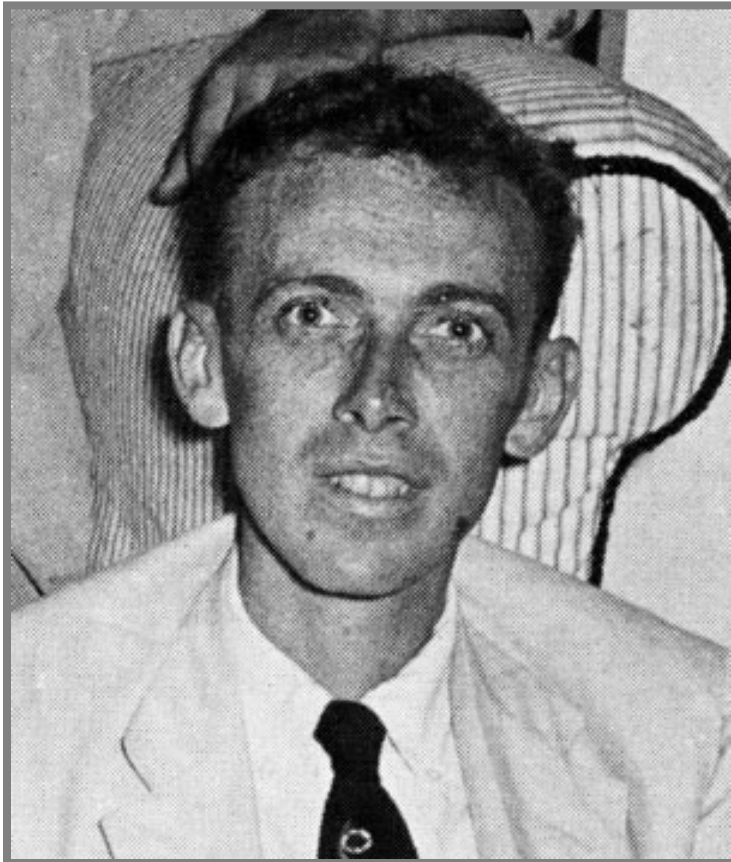
COCKAYNE SYNDROME

- **Autosomal Recessive**
- **Postnatal growth failure (height and weight <5th centile by age 2 years)**
- **Progressive neurologic dysfunction manifested as early developmental delay followed by progressive behavioral and intellectual deterioration**
- **Death by age 6-7 years**
- **Death from pneumonia**

A Rare Genetic Syndrome

**Among patients with Cockayne syndrome,
approximately 80% have mutations in the ERCC6
gene**

James D. Watson – Nobel Prize Winner (1928-)



James Watson's – "Disease Causing" Mutations

<u>Disease</u>	<u>Gene</u>	<u>Mutated Alleles</u>	<u>Disease Present</u>
COCKAYNE SYNDROME	ERCC6	2 *	No *
USHER SYNDROME	MYO7A	2 *	No *
GLYCOGEN STORAGE DISEASE VII	PFKM	2 *	No *
CONGENITAL NIGHT BLINDNESS	PDE6B	1 *	No *

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* Presumed

ERCC6 Gene Testing in Two Patients

Child with:

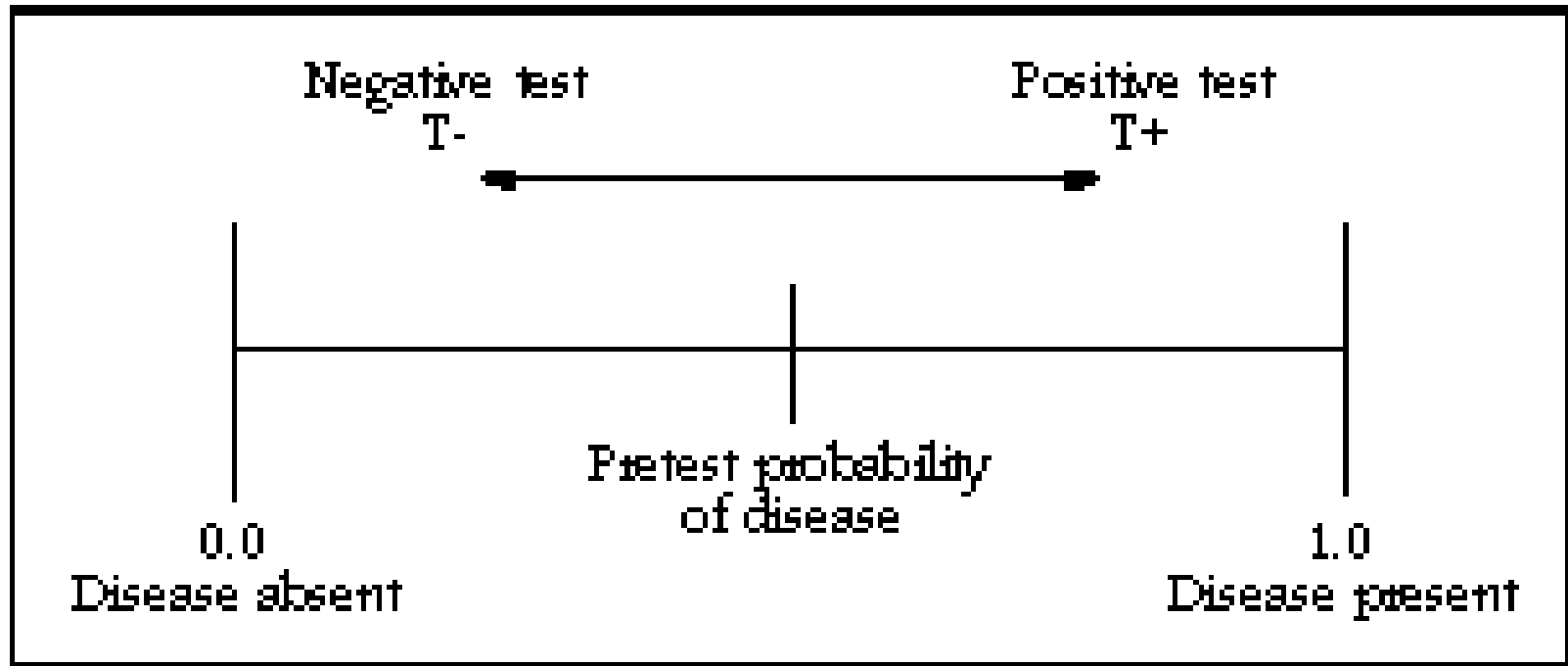
- Postnatal growth failure (height and weight <5th centile by age 2 years)
- Progressive neurologic dysfunction manifested as early developmental delay followed by progressive behavioral and intellectual deterioration
- Death by age 6-7 years
- Death from pneumonia

80 year old with:

- Nobel Prize and
- None of the findings in the left panel

Pretest Probability for COCKAYNE Syndrome?

Pretest probability of disease



BARBARA SCHEROKMAN, MD Selecting and interpreting Tests
<http://xnet.kp.org/permanentejournal/fall97pj/tests.html#>

Laboratory Test With 95% Sensitivity And 95% Specificity

Pretest Probability %	99	80	50	20	1
Positive Predictive Value %	99.9	99	95	83	16
Negative Predictive Value %	16	83	95	99	99.9

A test is most informative when the pretest probability of disease is between 40% and 60%.

Most positive test results will be proved false when testing a patient who has a low probability of having the disease.

In other words, as the pretest probability of disease falls, the predictive value of a positive test also falls and the predictive value of a negative test rises.

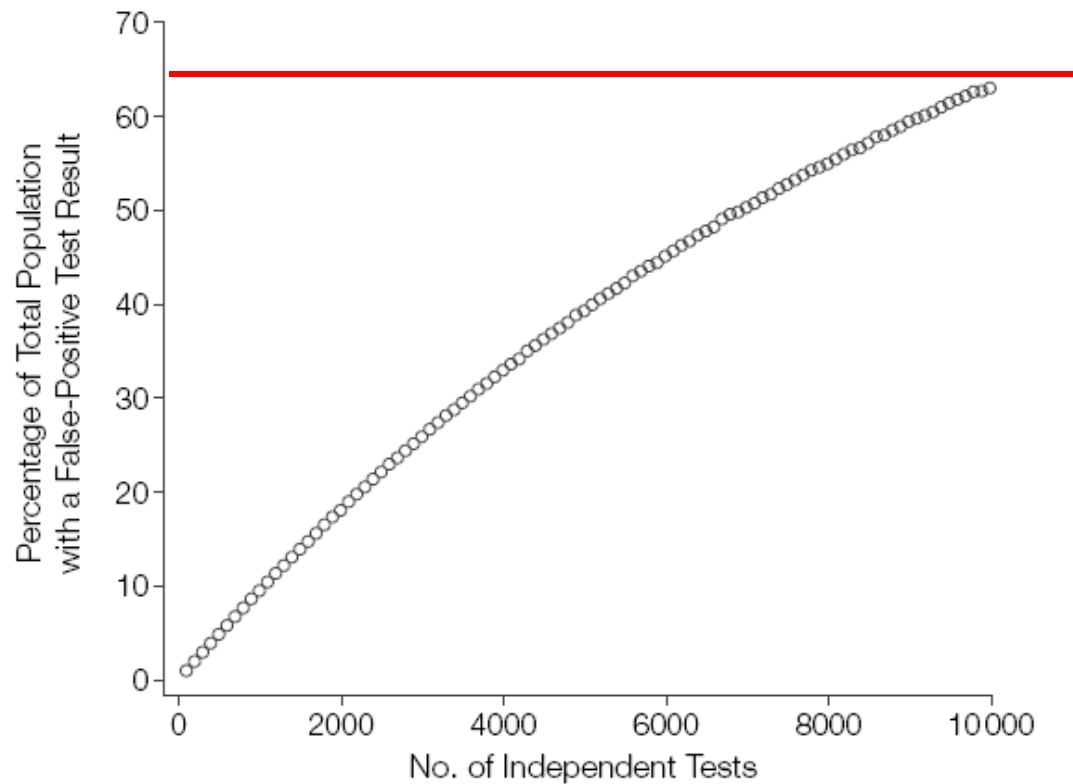
The Incidentalome: A Threat to Genomic Medicine

Isaac S. Kohane; Daniel R. Masys; Russ B. Altman

JAMA. 2006;296(2):212-215 (doi:10.1001/jama.296.2.212)

<http://jama.ama-assn.org/cgi/content/full/296/2/212>

Figure. Percentage of Total Population With a False-Positive Test Result



Avoiding the Pitfalls of the INCIDENTALOME

- Know the disease prevalence of all diseases with genetic basis within each population.
- Point of care information needs to be available to clinicians in order to interpret incidental genomic findings
- Clinicians need to be educated in the rational interpretation of genetic findings (avoid genetic determinism and understand environmental influences).
- Experts must determine whether genome wide testing, no matter how cost-effective has a role in clinical settings or if targeted testing is more appropriate.

Context Matters in Personalized Medicine

- Most Genetic Variation cannot be explained in 2009

The Impact of Personalized Medicine

- [1] What is the context in which DNA sequence analysis was obtained?
- [2] What is known about the specific change noted in a relevant clinical context?
- [3] Where does the rubber meet the road?

TIME's Best Invention of 2008

Invention of the Year

1. The Retail DNA Test

By Anita Hamilton

Before meeting with Anne Wojcicki, co-founder of a consumer gene-testing service called 23andMe, I know just three things about her: she's pregnant, she's married to Google's Sergey Brin,

ARTICLE TOOLS

- Print
- Email
- Sphere
- AddThis
- RSS
- Yahoo! Buzz



The Re-casting of “consumer genetics”

- ... it is simply privately-funded “Population Screening”

World Health Organization (WHO) criteria for "Population Screening"
[from Wilson and Junger 1968]

- (1) Addresses an important health problem.
- (2) There is an accepted treatment.
- (3) There are facilities for diagnosis and treatment available.
- (4) There is a recognizable latent or early symptomatic state.
- (5) There is a suitable test or examination.
- (6) The test or examination should be acceptable to the population.
- (7) The natural history of the condition, including development from latent to declared disease, should be adequately understood.
- (8) There is an agreed policy on whom to treat as patients.
- (9) The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- (10) Case-finding should be a continuing process and not a "once and for all" project.

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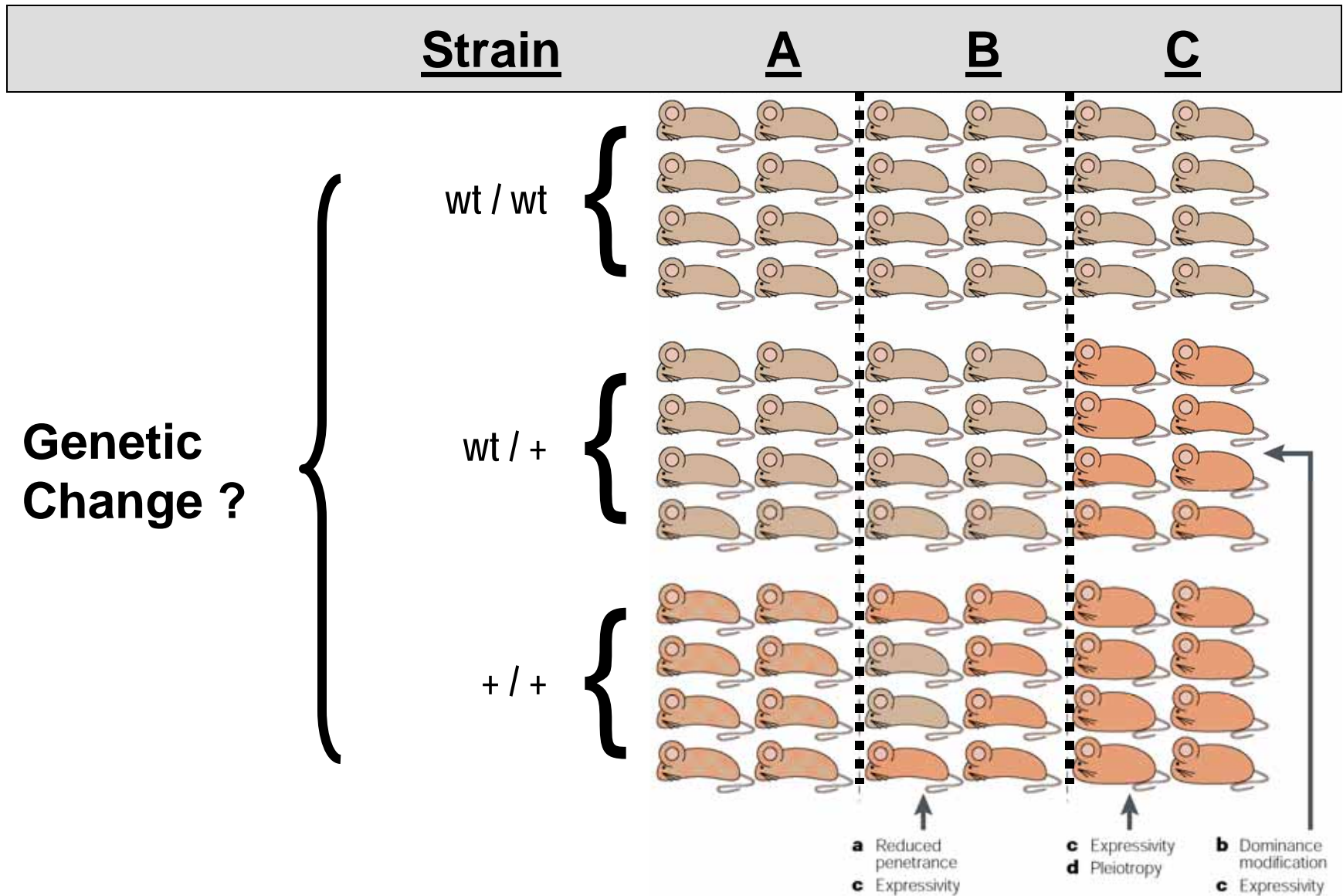
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The Impact of Personalized Medicine

- [1] What is the context in which DNA sequence analysis was obtained?
- [2] What is known about the specific change noted in a relevant clinical context?
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The same genetic change in two different mice, can have different effects depending on the strain of the mouse



The same genetic change in two different people, can have different effects depending on the family history



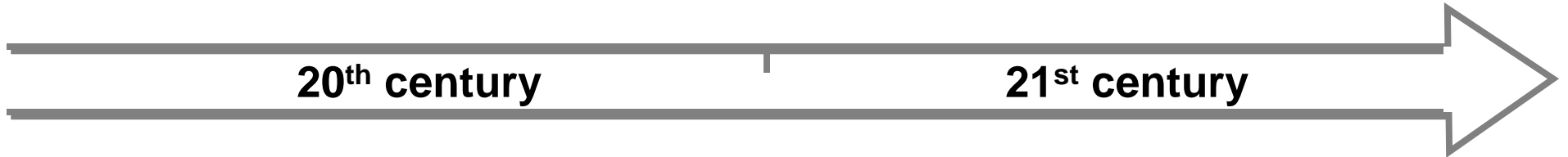
Why is Family Health History Part of Health Care?

- **Traditional Role**
- **New Role (since ~1995)**
- **Coming Role**

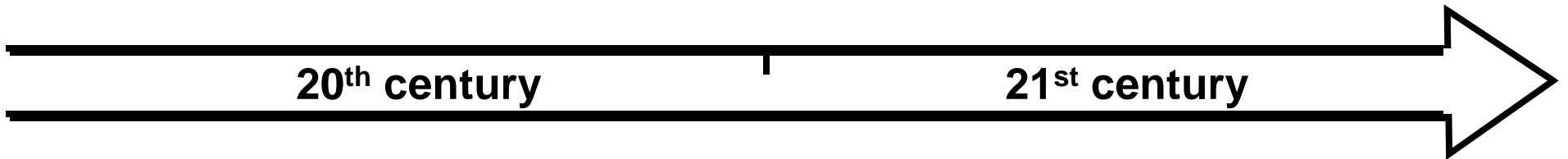
**The Traditional Role of
Family Health History
in Health Care**

20th century

21st century



The Traditional Role of Family Health History in Health Care



The Traditional Role of Family Health History in Health Care

Predict who is at risk

20th century

21st century

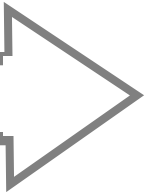
Used as a proxy for genetic code information

A New Role of Family Health History in Health Care

Predict who is at risk

20th century

21st century



A New Role of Family Health History in Health Care

Predict who is at risk

Decide who to Gene Test

20th century

21st century

Used as a proxy for genetic code information

The Next Role of Family Health History in Health Care

Predict who is at risk

Decide who to Gene Test

20th century

21st century

~~Used as a proxy for genetic code information~~

The Next Role of Family Health History in Health Care

Predict who is at risk

Decide who to Gene Test

20th century

21st century

~~*Used as a proxy for genetic code information*~~
Used to put genetic code information into context

The Next Role of Family Health History in Health Care

Predict who is at risk

Decide who to Gene Test

20th century

21st century

~~Used as a proxy for genetic code information~~
Used to put genetic code information into context

The Next Role of Family Health History in Health Care

Predict who is at risk

Decide who to Gene Test

Personalize Genetic Info

20th century

21st century

~~*Used as a proxy for genetic code information*~~

Used to put genetic code information into context

The same genetic change in two different people, can have different effects depending on the family history



The Impact of Personalized Medicine

- [1] What is the context in which DNA sequence analysis was obtained?
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The Impact of Personalized Medicine

A test for a DNA sequence variant will need to do some or all of the following in order to change the practice of medicine:

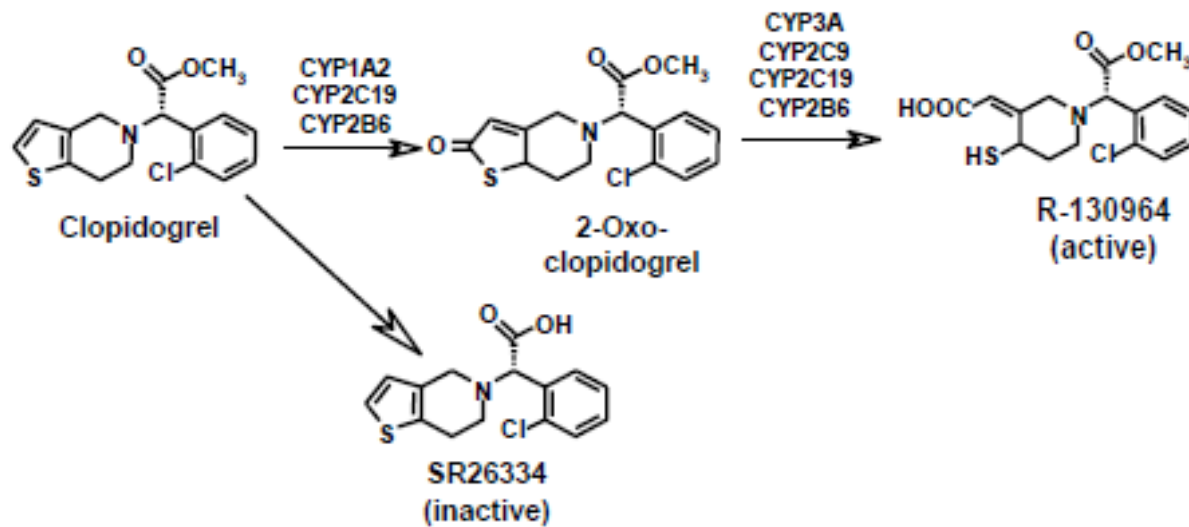
- [1] independently and more accurately predict disease
- [2] substantially and reliably modulate risk prediction
- [3] replace or supplement non-genetic markers in a cost-effective manner
- [4] predict risk earlier in life or earlier in disease
- [5] guide targeted intervention

Clopidogrel (Plavix®)

- Across the spectrum of acute coronary syndromes and in patients undergoing percutaneous coronary interventions (PCI) with stenting, dual antiplatelet therapy with aspirin and clopidogrel, a thienopyridine inhibitor of the platelet P2Y₁₂ adenosine diphosphate (ADP) receptor, is the standard of care.
- However, the pharmacodynamic response to clopidogrel has substantial interpatient variability
- Patients with coronary disease with lesser degrees of platelet inhibition in response to clopidogrel appear to be at increased risk for cardiovascular events.

Clopidogrel (Plavix®)

Supplemental Figure 1. Schematic Representation of the Metabolic Activation Pathway for Clopidogrel



CYP2C19

(cytochrome P450, family 2, subfamily C, polypeptide 19)

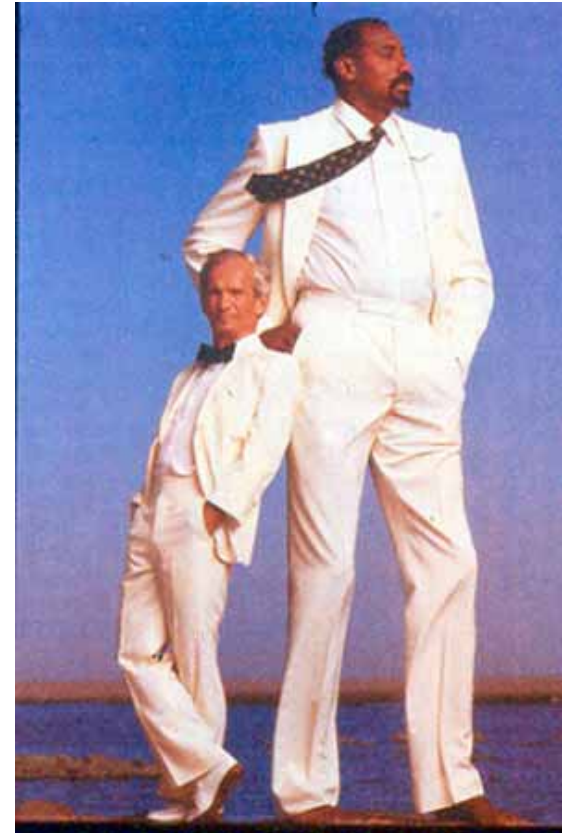
- Polymorphism within this gene is associated with variable metabolism of mephenytoin (designated EM and PM)
- Poor metabolizers (PM) of mephenytoin, which represent approximately 13-23% of Asians and 3-5% of Caucasians

The Impact of Personalized Medicine

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Genetic Variation Matters in the Practice of Medicine



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Genetic Variation Matters in the Practice of Medicine

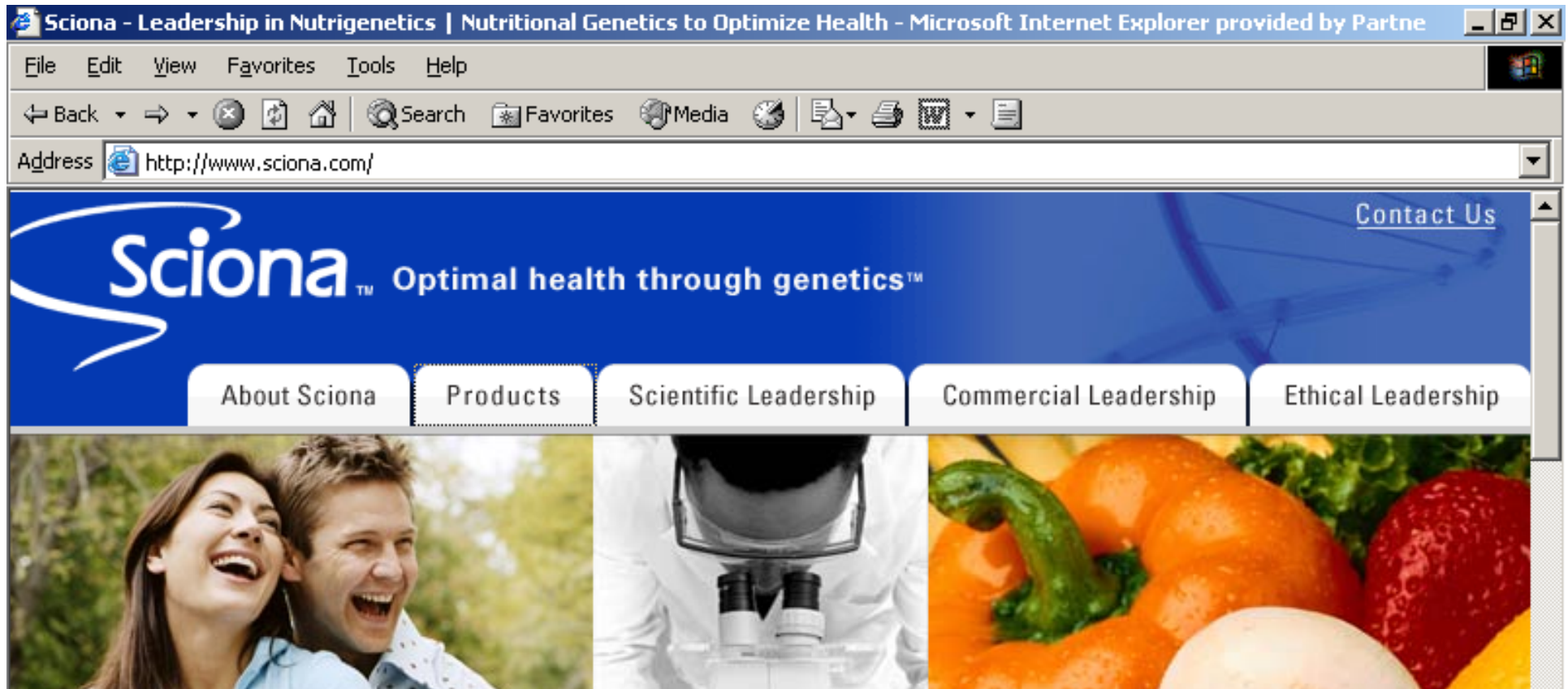
In 2009 our technology and has brought us to this Current Paradox:

- While we can identify and name the genetic variations.
- There are relatively few examples where we know what to do about the variation.



Wilt Chamberlain
Willie Shoemaker

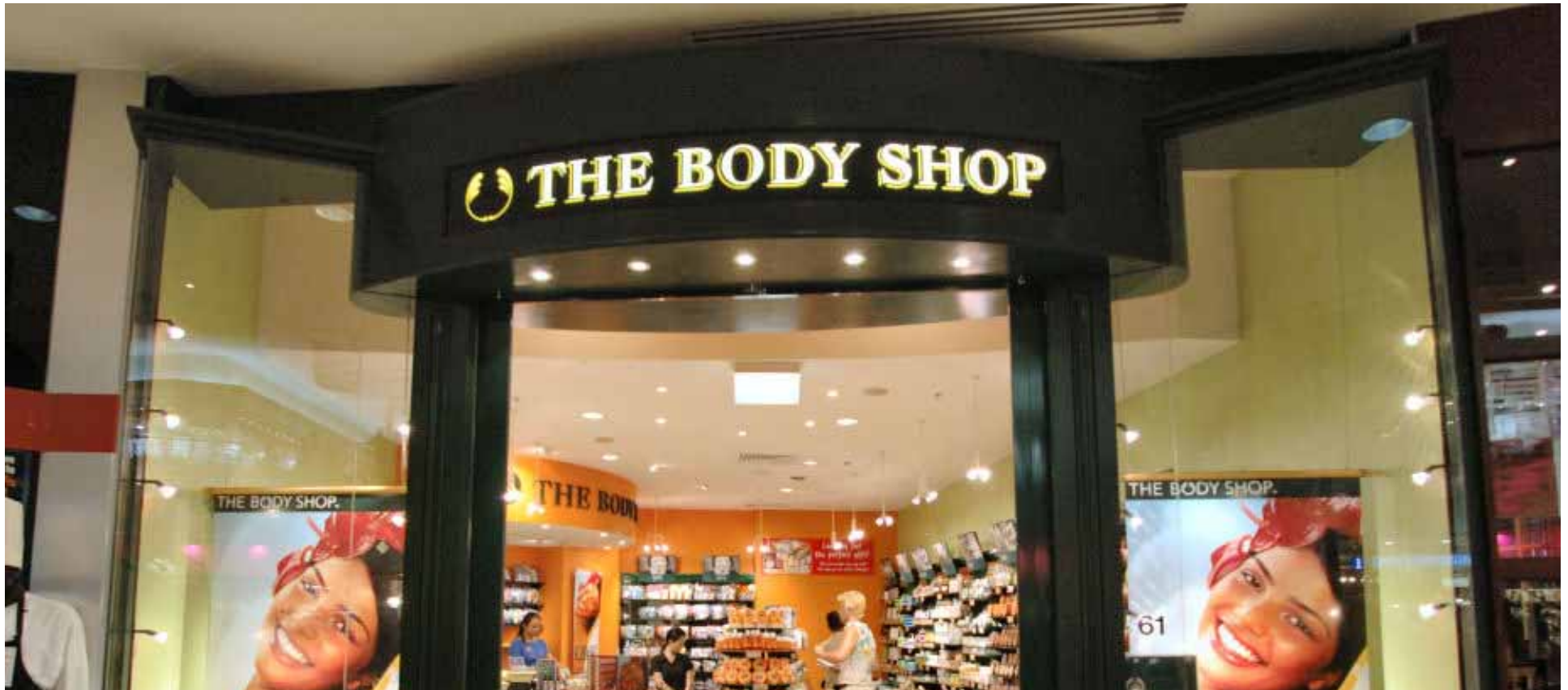




BODY BENEFITS™

“Small differences in your genes can influence how well your body metabolises foods, utilises nutrients and excretes damaging toxins, all of which can affect your general state of health. By finding out if you have any of these small variations, Body Benefits nutrition can provide you with specific dietary information that cannot be obtained from any other source.”

Sciona Web site, accessed Dec 29, 2002



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THE BODY SHOP

THE BODY SHOP.



GET GORGEOUS!

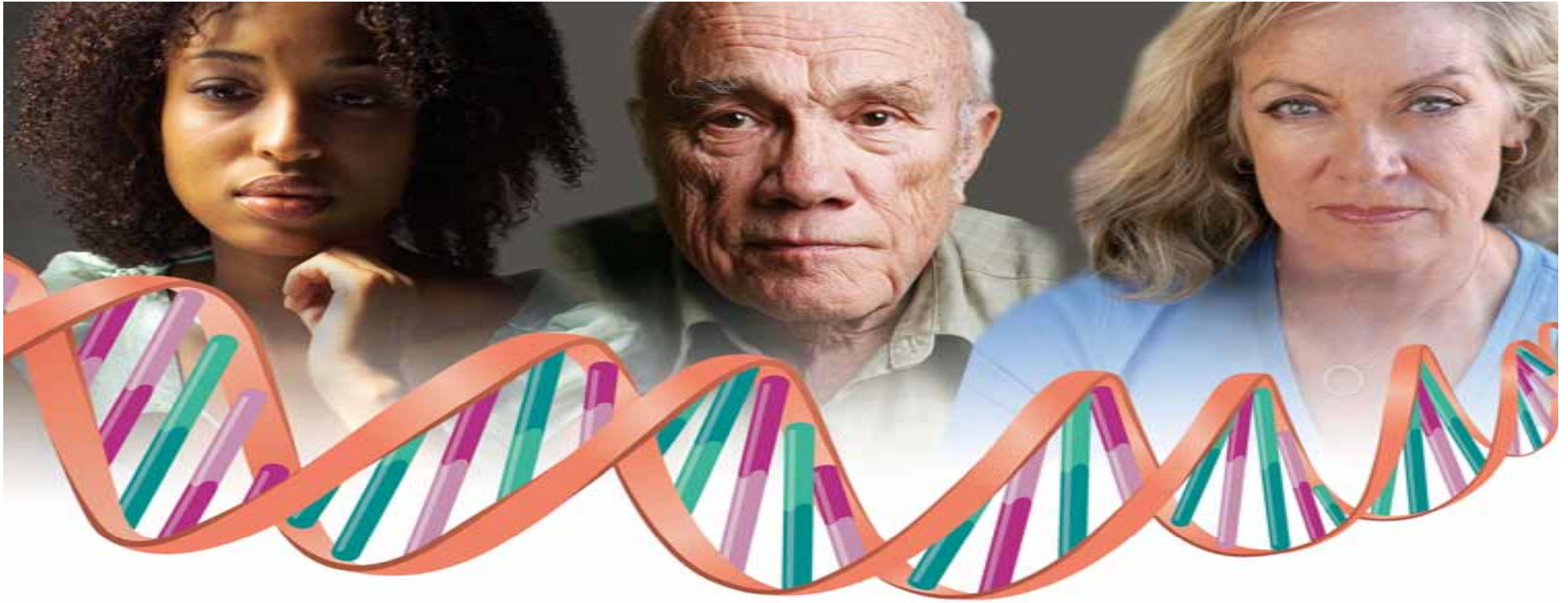
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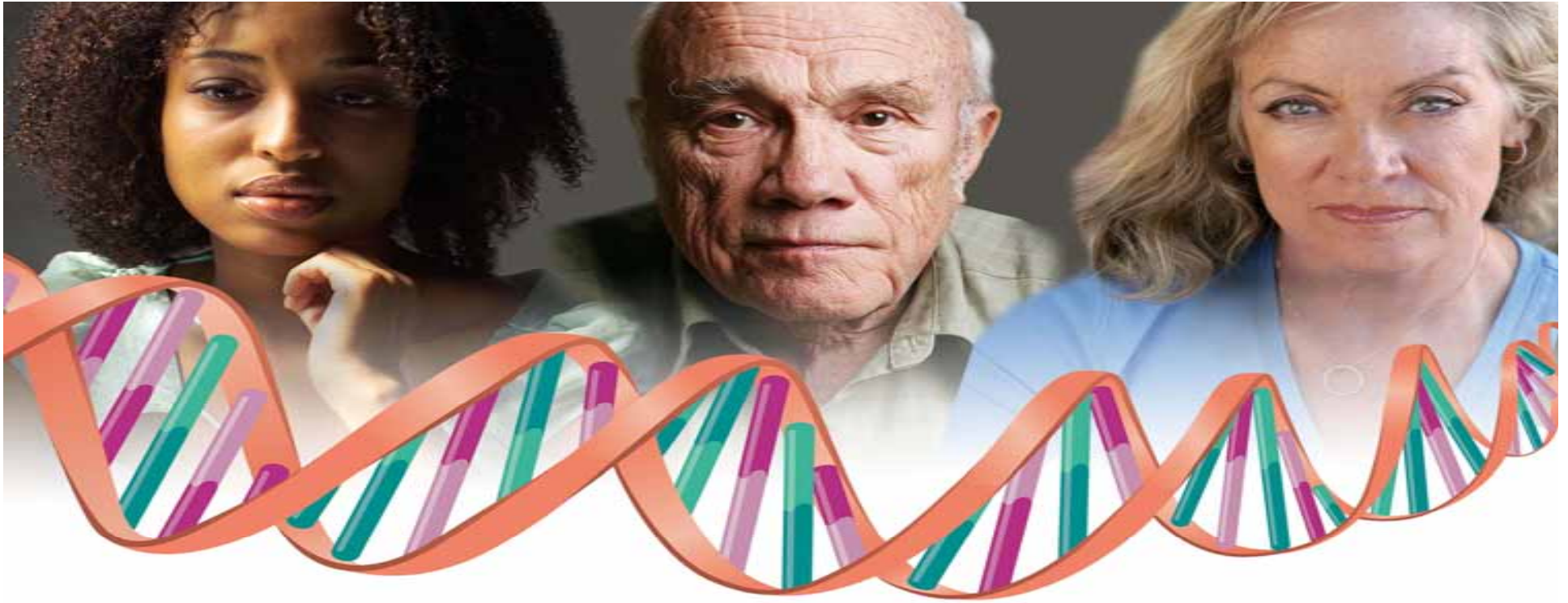
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GET GORGEOUS!





Personalized Medicine: What is the Impact on Patients, Physicians and Genetic Counselors that we should be striving for?



*Personalized Medicine: What is the Impact on Patients, Physicians
and Genetic Counselors that we should be striving for?*

Better and Cheaper Healthcare

The Genetic Basis of Adult Medicine

What the Primary Care Provider Needs to Know



October 2 – 4, 2009

The Fairmont Copley Plaza • Boston, MA

Course Director

Michael F. Murray, MD



Brigham and Women's Hospital
Department of Medicine
Division of Genetics

Harvard Medical School
Department of Continuing
Education



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Version 5.0

Boston Fairmont Copley October 2-4, 2009