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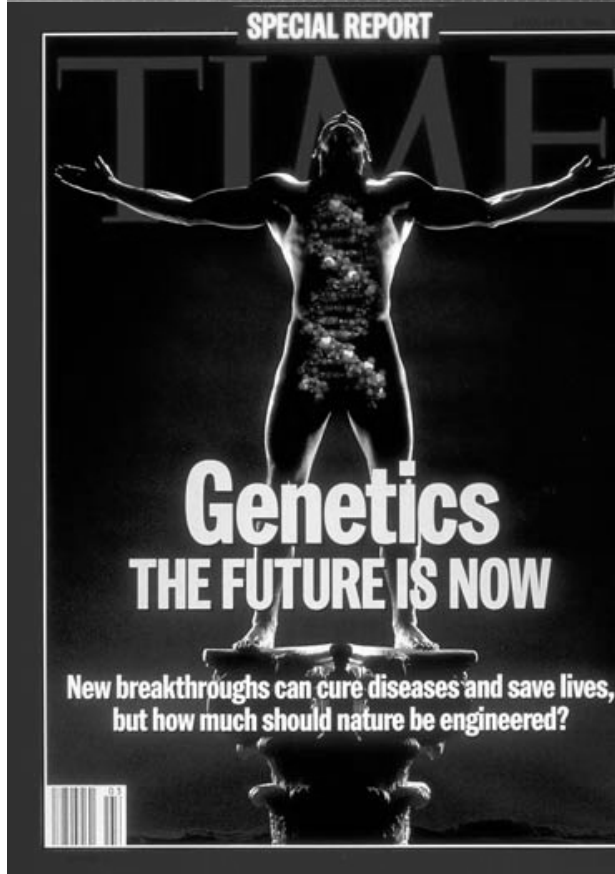
# Challenges to Widespread Adoption of Pharmacogenetics

*Thane Kreiner, PhD*  
*Senior Vice President, Corporate Affairs*

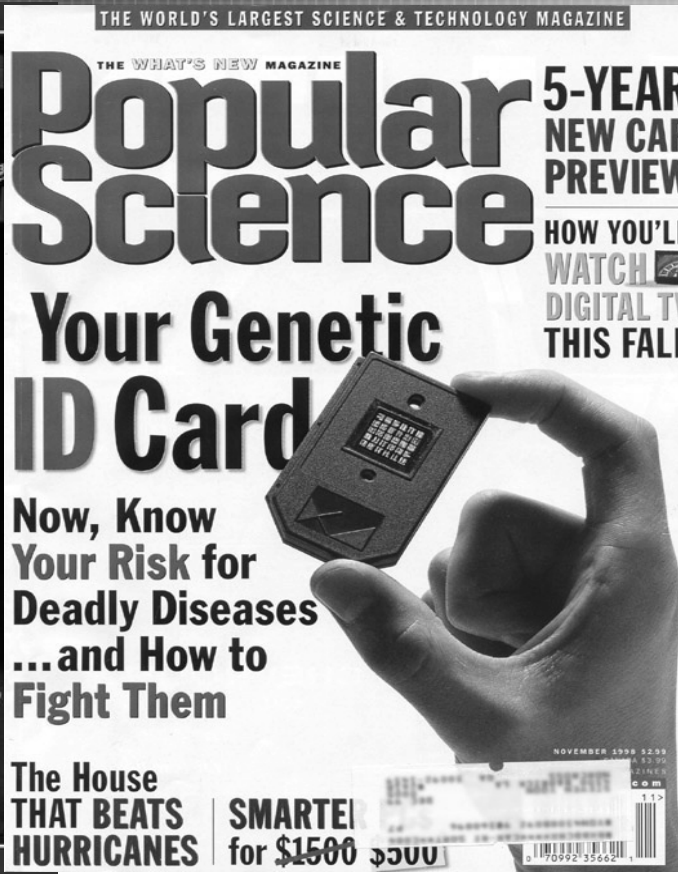


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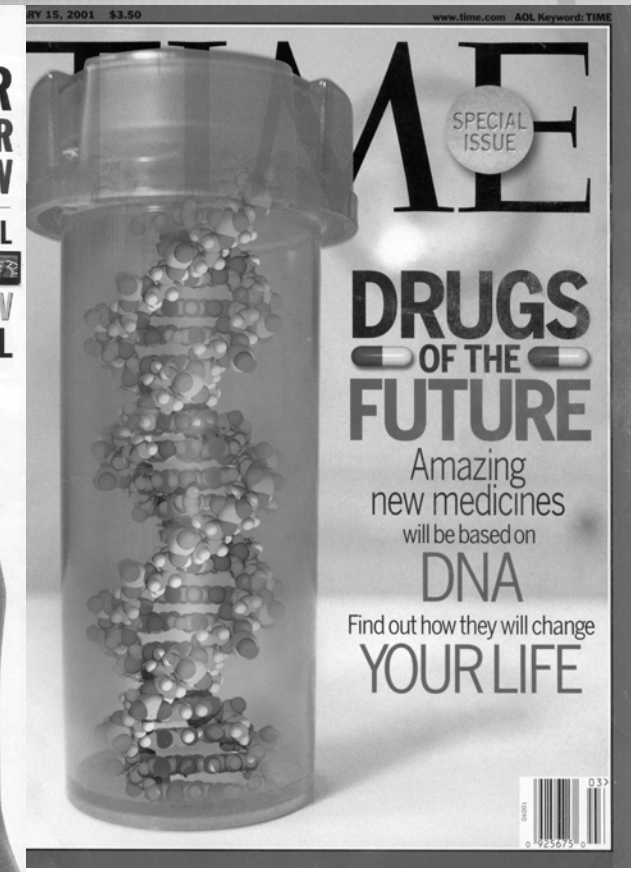
# Challenge: Unrealistic Expectations



1994



1998



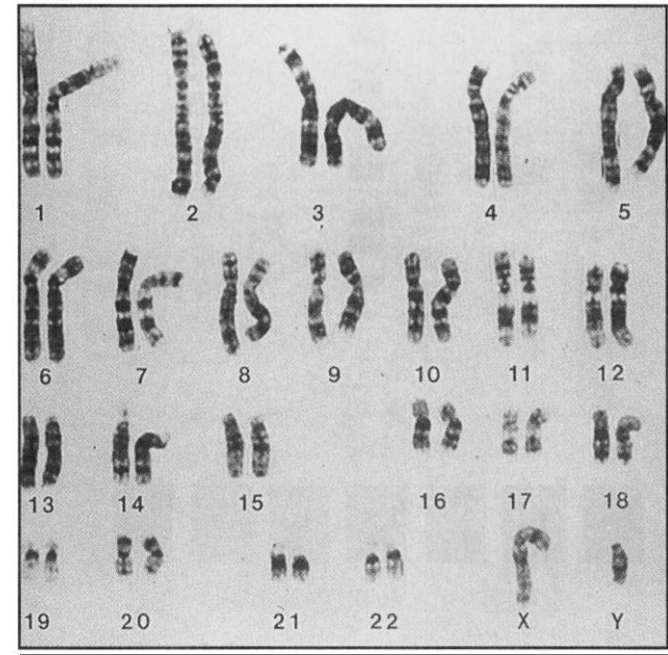
2001



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# Genomes are Information Intensive

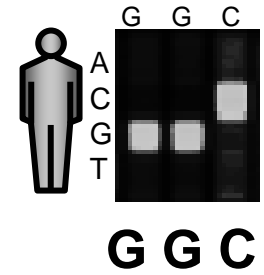
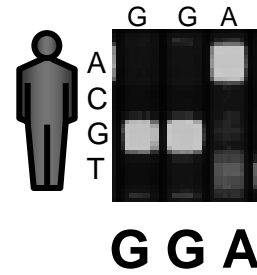
- 3.4B DNA bases
- 22,000 +/- “genes”
- Splice variants
- Polymorphisms
- “Dark matter”
- Methylation





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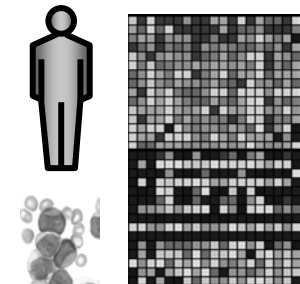
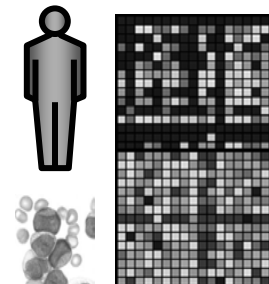
# Genetic Information Analysis



DNA Analysis

DNA

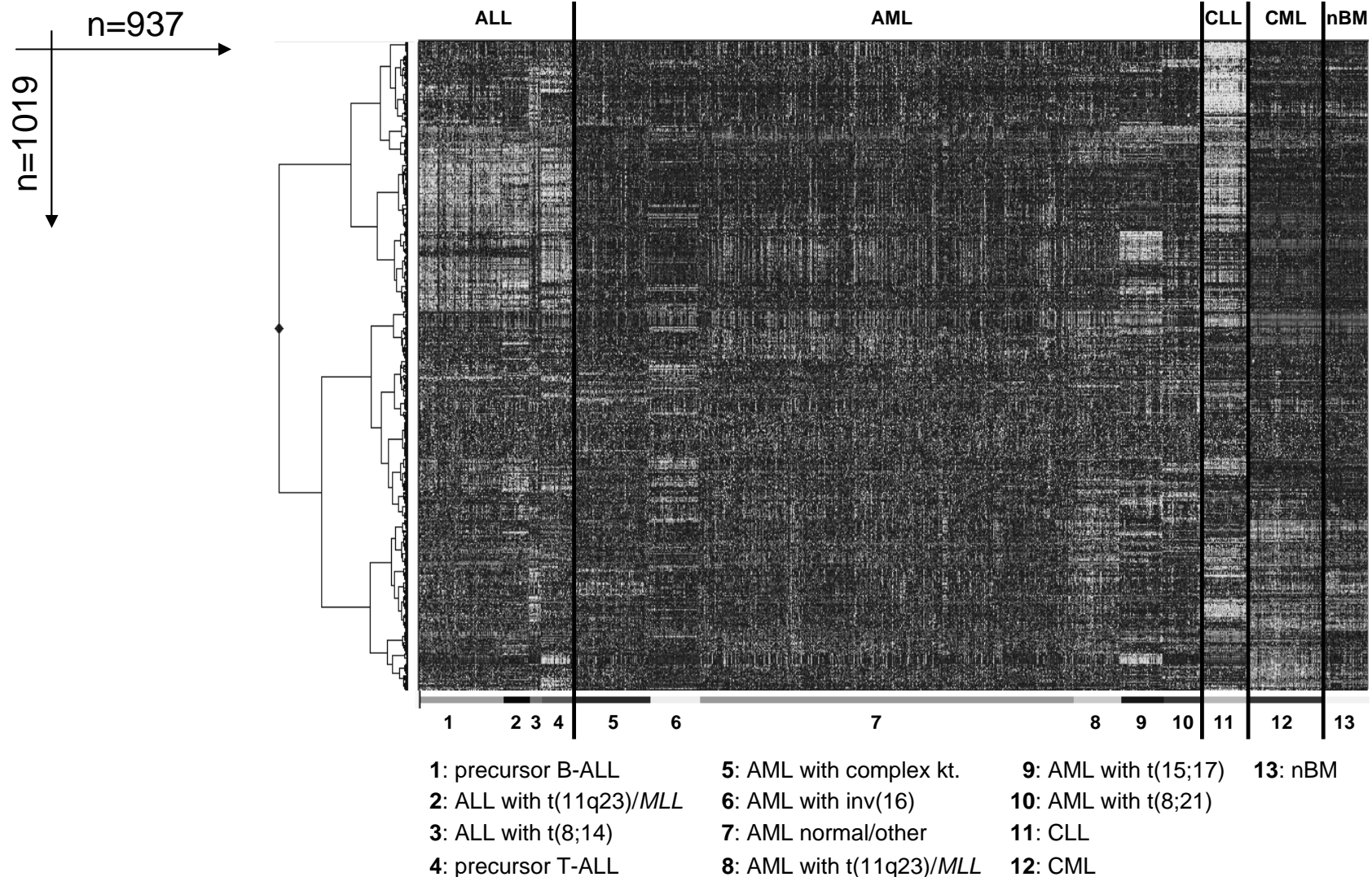
RNA



RNA Analysis

Eukaryotic Cell

# Distinct Gene Expression Patterns in 12 Clinically Relevant Leukemia Subtypes



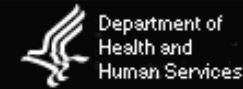


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# Challenge: Regulatory Paradigms



U.S. Food and Drug Administration



国家食品药品监督管理局

STATE FOOD AND DRUG ADMINISTRATION



CE

PMDEC

国立医薬品食品衛生研究所  
医薬品医療機器審査センター  
Pharmaceuticals and Medical Devices Evaluation Center

- Companion diagnostics
- Patterns as analytes
- Low risk, high benefit

# Challenge: Gene Patents

- DNA sequence patents of doubtful validity
- Gene patents create transaction costs and stifle useful innovation
- At least 18% of genes patented: “surprisingly high” (*Science* 310: 239-240, 23 September, 2005)



## The ethics of patenting DNA

a discussion paper

NUFFIELD  
COUNCIL ON  
BIOETHICS

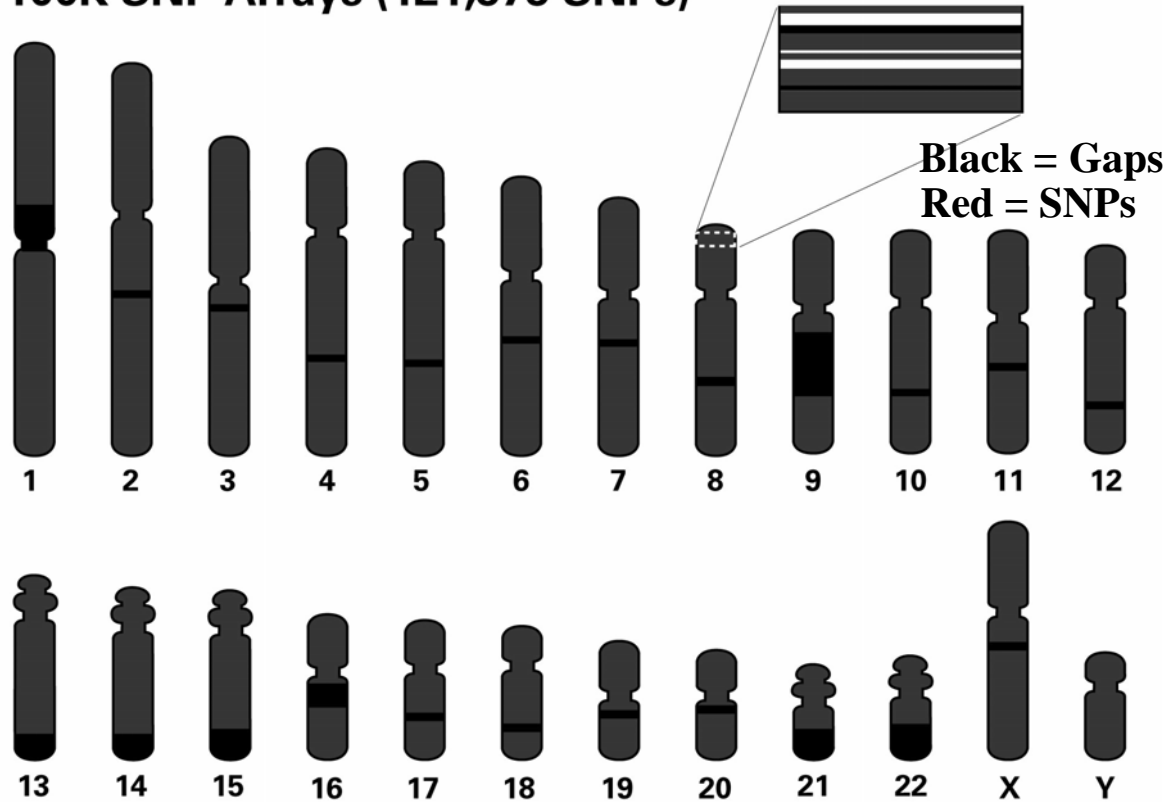
- Future patents on DNA sequences should be the exception
- Distinguish uses: basic research, diagnostics, therapeutics
- Create mechanisms to deal with extant gene patents, e.g., pools



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# Whole Genome SNP Analysis: 10K, 100K, 500K SNPs

## 100K SNP Arrays (121,575 SNPs)

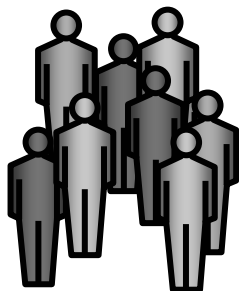


**Genome-wide coverage enables association  
of human traits with genetic loci**



# Multiple Sclerosis

- Multiple sclerosis is a chronic autoimmune disease that affects the central nervous system
  - Wide range and type of symptoms
  - “Flare-ups” are unpredictable
  - Genetic & environmental components to disorder
- Studied by Daniel Cohen at the Serono Research Institute



**1,800 MS patients  
600 controls**

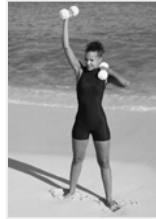


**Each run on  
100K SNP set**



**Identification of  
80 genes  
involved in MS**

# Challenge: Environmental Effects v. Genetic Determinism



Exercise



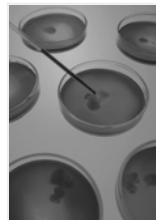
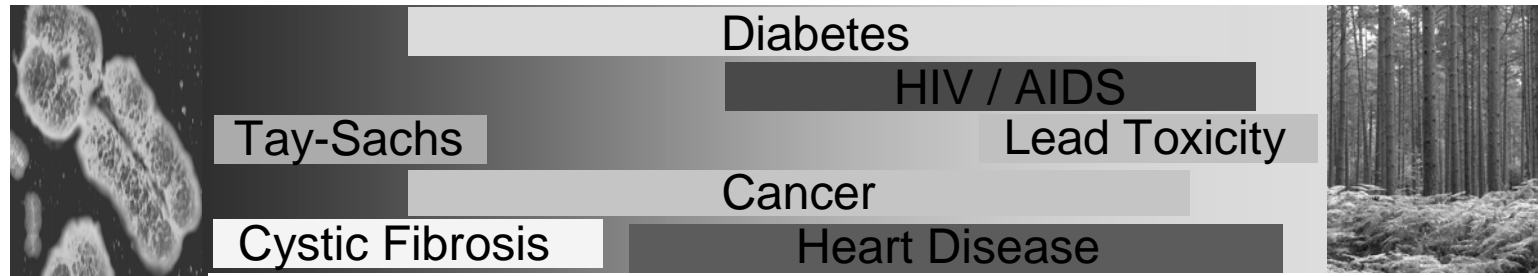
Diet



Drugs

## Genetics

## Environment



Infectious Disease



Lifestyle Choices



Exposures

## Challenge: Potential for Discrimination



- Burlington Northern began secret genetic testing of its workforce in 2000, hoping to prove a “pre-existing condition” and avoid paying workers’ compensation costs.
- The EEOC sued for discrimination based upon predictive genetic testing
- Case settled in 2002 with Burlington Northern paying \$2.2 million to the workers

- Strong nondiscrimination legislation for insurance and employment
  - National (passed in U.S. Senate, awaiting House action)
  - International standards?
- Changes in health care systems may be necessary
  - Remove incentive to discriminate
  - Ensure equitable access

# Human Diversity: each variant arose only once



	A	A	A	A	A	A	A	A	A	A
1	T	G	G	G	G	G	T	G	T	
	C	C	C	C	C	C	C	C	C	C
	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
	T	T	T	T	T	T	T	T	T	T
1000	G	C	G	G	C	G	G	G	G	G
	A	A	A	A	A	A	A	A	A	A
	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
	G	G	G	G	G	G	G	G	G	G
2000	C	C	A	A	C	A	C	A	A	C



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# African Ancestry



## AFRICAN ANCESTRY

**TRACE  
YOUR  
DNA**

Do you wonder what part of Africa you share ancestry with? We can tell you.

Would you like to have a personal connection with an African country? We can help you.

Now there is a new tool to help your family trace its genealogy. African Ancestry uses current advances in genetic technology to provide a bridge to the past for people of African descent.

### TRACE YOUR MATERNAL ANCESTRY

You can find out whether your maternal line has African ancestry with a simple and easy test of your mitochondrial DNA. Click here to learn about the MatriClan™ Test Kit.

### TRACE YOUR PATERNAL ANCESTRY

You can find out whether your paternal line has African ancestry with a simple and easy test of male Y-chromosome DNA. Click here to learn about the PatriClan™ Test Kit.



**Save \$40.00!!!**

Order our Family Package



PatriClan Test Kit \$349

MatriClan Test Kit \$349

- One (1) MatriClan Kit
- One (1) PatriClan Kit

# Challenge: Confounding Race and Genetics

- BiDil (hydralazine/isosorbide) is the first drug approved by the FDA for a specific “racial” group (African Americans)
- 43% increase in 1 year survival rates for African Americans
  - How much African American?
  - Socio-economic factors and lack of access to quality health care are most often cited for the increased rate of heart disease in African Americans
- Lack of consistent terminology in the literature
  - Confounding of continent of origin with social constructs



- **Analyze contributing genetic factors**
- **Focus on the highest return interventions**



Diagnosics

**You could never know this just by looking at a patient.**  
*A breakthrough test to help you better select and dose many widely prescribed drugs.*



- Ultra-rapid metabolizer
- Extensive metabolizer
- Intermediate metabolizer
- Poor metabolizer



Imagine a tool with the insight to help you select the appropriate drug at the best dose for each patient. Introducing the AmpliChip CYP450 Test—the world's first and only CE-IVD chip-based test.\*

This new test performs robust, accurate, and reliable analysis of two CYP450 genes (CYP2D6 and CYP2C19) that play a major role in the metabolism of many widely prescribed drugs. Never before has such a tiny chip provided this type of analysis for routine clinical use.

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AmpliChip is a trademark of a member of the Roche Group.  
\* Not currently available for IVU use in the United States.

  
**AMPLICHIP**  
Know. Now.



Diagnosics

**Know more about patients than they could ever tell you.**  
*A breakthrough test to help you better select and dose many widely prescribed drugs.*



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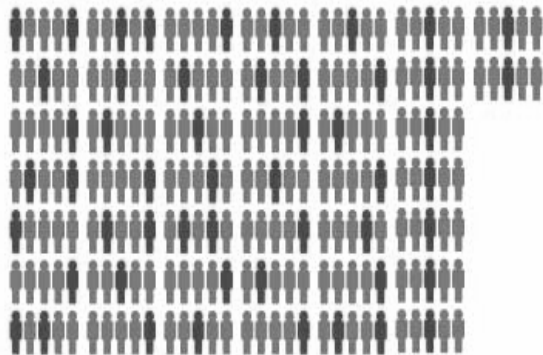
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AmpliChip is a trademark of a member of the Roche Group.  
\* Not currently available for IVU use in the United States.

  
**AMPLICHIP**  
Know. Now.

**2M ADEs in US per year, 100,000 deaths, \$170 B**

# Challenge: Ascribing Appropriate Value

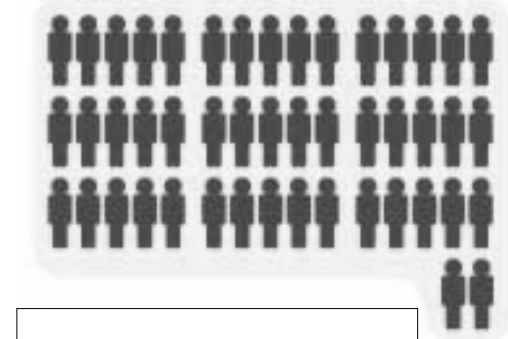
Herceptin approved in 1998: \$425 mi in sales in 2003



2,200 patients for 10 years  
(each person = 10 people)

Faster & Cheaper  
→

$\frac{3}{4}$  fewer patients  
5x faster



Trial conducted with 469  
patients in 1.6 years

- Getting to market
- Getting to market faster (longer economic life)
- Staying on the market (and avoiding litigation)
- Avoiding ADEs and ineffective prescriptions



# Challenge: Dynamics of Extant Healthcare Delivery Systems

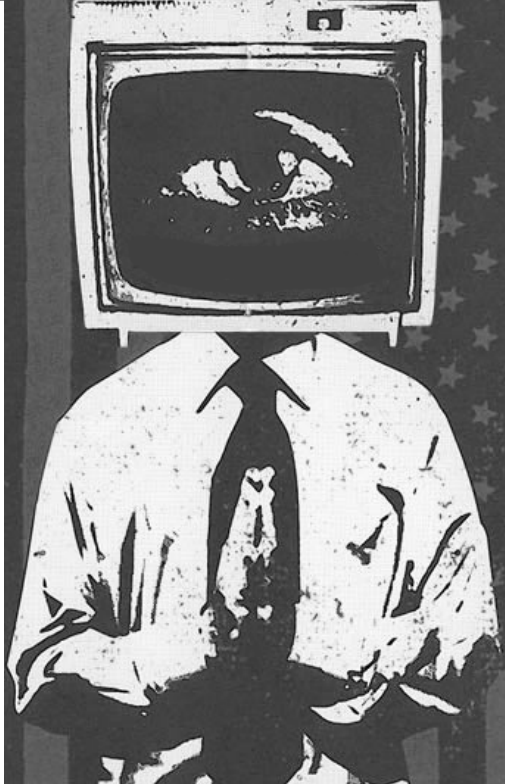
- US spends 15% of GDP on health care
  - Inefficient
  - Inequitable
  - Competition encourages cost-cutting, not investment

- Long-term health -> preventative medicine
  - PGx
  - Newborn screening (including PGx?)
  - Non-genetic interventions
- Include contribution of health to GDP



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# Challenge: Genetic Literacy



**General Public**



**Medical Professionals**

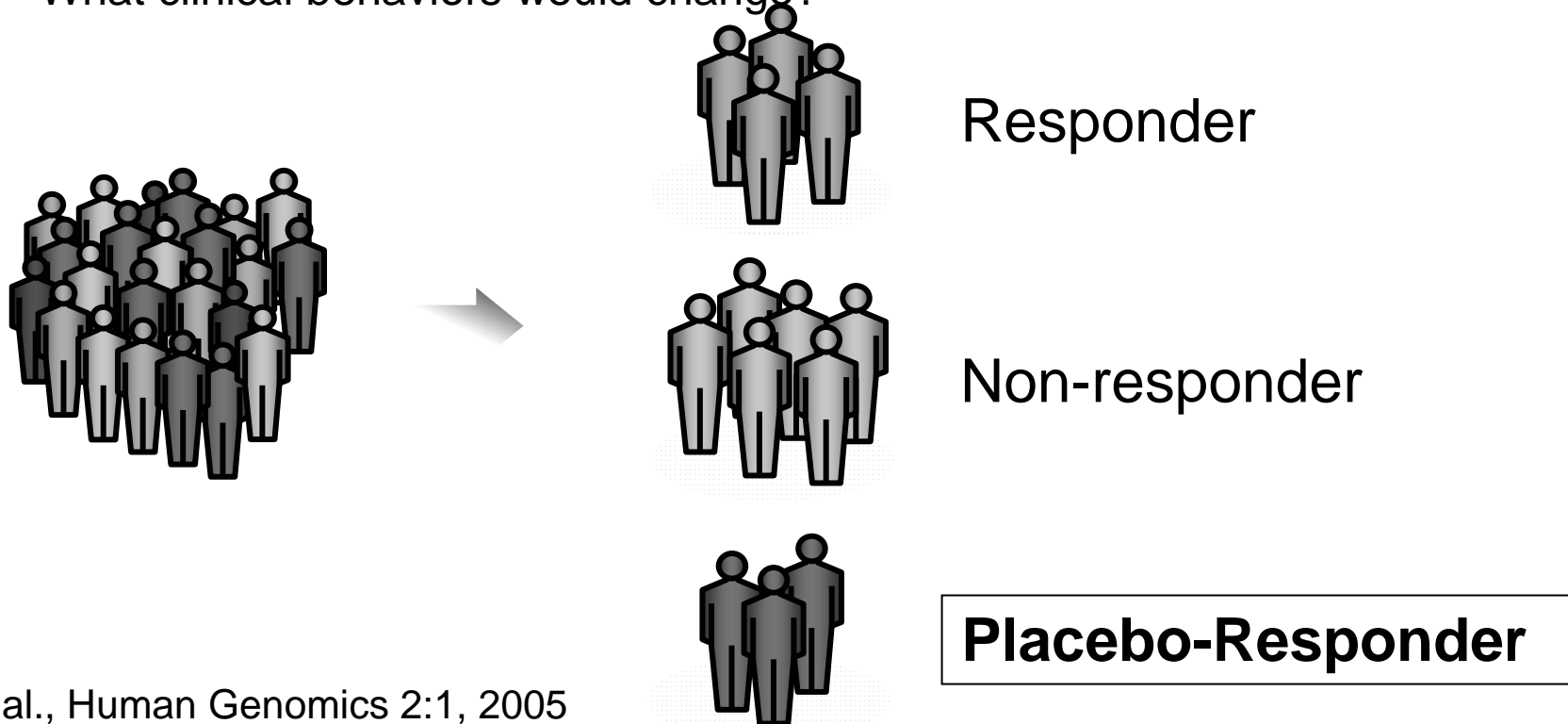


**The Next Generation**

- Reform medical education: no genetics exceptionalism
- Ensure equitable general education systems

# Placebo Effect & Pharmacogenetics

- What if a “non-responder” has a placebo response to a given drug?
  - e.g., antidepressants
- To test for placebo effect, must have at least 500 participants
  - Is this ethical?
  - What clinical behaviors would change?



# Challenge: Ethics of Eliminating Placebo Effect



# Challenges to the Widespread Adoption of PGx/Targeted Medicine

- Unrealistic expectations
- Regulatory paradigms
- Gene patents
- Environmental impacts/determinism
- Discrimination
- Confounding of race and genetics
- Ascribing appropriate value
- Healthcare delivery systems
- Genetic literacy
- Placebo effect

**Status quo?**

**Incremental change?**

**Frame shift?**



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# Q&A