# Toxicogenethics: Ethical Issues at the Intersection of Genetics and Toxicology

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#### **Overview**

- Toxicogenomics and "familiar" ethical challenges
  - Questions about how researchers should present the promise and limitations of these new areas of research to the public
  - Informed consent and future uses of stored biological materials
  - Potential misapplications of genomic information or technologies
- Other "newer" ethical issues
  - The geneticization of environmental hazards and its implications for assignments of responsibility for poor health outcomes
  - Are existing science policy mechanisms adequate for defining and responding to ethical and social challenges posed by toxicogenomics?

### **Applications of Toxicogenomic Tools**

Toxicogenomic tools could be applied in three main areas relevant to environmental regulation:

- To identify individuals and subgroups at increased risk of disease (biomarkers of susceptibility)
- To identify persons exposed to an environmental hazard and/or assess the level of their exposure (biomarkers of exposure)
- To identify early disease processes before phenotypic changes are evident (biomarkers of early clinical effect)

### The Promise of Toxicogenomics

- 1. Cheaper way to assess the toxicity of chemicals, drugs, cosmetics, and environmental agents
- 2. Improve understanding of mechanisms of toxicity
- 3. Provide more precise estimates of exposure levels
- 4. Measure biological effects earlier, perhaps before evidence of toxicity
- 5. Identify unknown toxins (gene-expression and "toxic fingerprints")
- 6. Identify individuals and subpopulations with increased sensitivity to chemicals, pharmaceuticals, cosmetics, etc.
- 7. Reduce number of animals used to evaluate chemical toxicity
- 8. Assist in setting regulatory standards

### **Descriptions of Toxicogenomics**

"... will likely contribute answers to some of toxicology's most fundamental questions."

"Toxicologists Brace for Genomics Revolution"

"... will have a dramatic impact on toxicology ..."

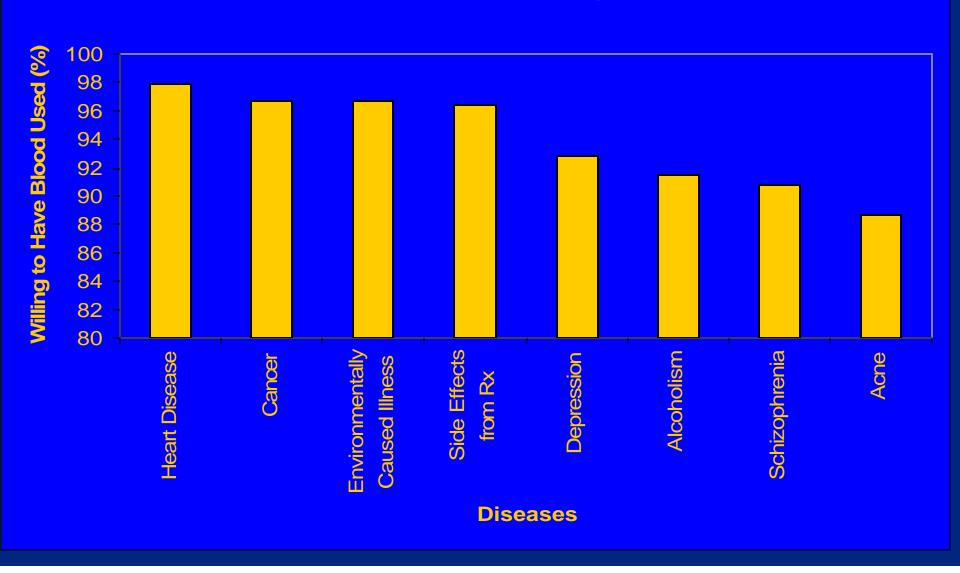
"... promises new insights into mechanisms of drug action and toxicity."

"... a unique opportunity to dramatically improve the predictive power of safety assessment and to accelerate the drug development process."

"Toxicogenomics is not a promise for the future, it is a tool that is available to us now ..."

"... a tool of unprecedented power for use in toxicology ... "

### Donor Attitudes Regarding the use of Stored Biological Materials for Genetic Research on Specific Conditions



### Potential Discrimatory Threats: New Twists of Familiar Issues

- The effects of environmental-response genes often depend upon the level of exposure, time of exposure, presence or absence or concurrent exposures, and variation in other sensitivity genes.
  - The biological implications of variation in these genes often is unclear (and far more complicated than familiar examples of genetic tests).
- The effects of environmental-response genes may be altered by changes in behavior or environmental conditions.
- Variation in environmental-response genes is much more common than the genetic variation associated with rare "disease genes".

#### **Summary of Statutes Regarding Discrimination on the Basis of Genetic Information**

State or District	Health Insurance	Life Insurance	Employment	Confidentiality
Alabama	Yes, for cancer only†			
Alaska	Yes:			
Arizona	Yes	Yes	Yes	Yes
Arkansas	Yes†‡		Yes	Yes
California	Yes¶	Yes[	Yes	Yes
Colorado	Yes	Yes		Yes
Connecticut	Yes‡		Yes[	Yes
Delaware	Yes		Yes§	Yes
District of Columbia	Yes‡			
Florida	Yes‡			Yes
Georgia	Yes			Yes¶
Hawaii	Yes†t§			
Idaho	Yes‡			
Illinois	Yes‡			Yes
Indiana	Yes†§			Yes
Iowa	Yes†‡		Yes†	
Kansas	Yes†§		Yes†	
Kentucky	Yes†‡			
Louisiana	Yes†		Yes	Yes
Maine	Yes‡	Yes	Yes†	
Maryland	Yes†	Yes	Yes†	
Massachusetts	Yes†	Yes	Yes	Yes
Michigan	Yes†		Yes†	
Minnesota	Yes†§		Yes†	
Mississippi				
Missouri	Yes†		Yes	Yes
Montana	Yes†‡¶	Yes		
Nebraska	Yes‡		Yes†	
Nevada	Yes†‡§		Yes†	Yes

Table 1. (Continued.)						
State or District	Health Insurance	Life Insurance	Employment	Confidential		
New Hampshire	Yes†	Yes	Yes	Yes		
New Jersey	Yes:	Yes	Yes	Yes		
New Mexico	Yes:			Yes¶		
New York	Yes		Yes	Yes		
North Carolina	Yes		Yes			
North Dakota	Yes‡			Yes		
Ohio	Yes†‡					
Oklahoma	Yes†‡		Yes†	Yes†		
Oregon	Yes		Yes†	Yes		
Pennsylvania						
Rhode Island	Yes		Yes			
South Carolina	Yes{			Yes		
South Dakota	Yes†‡		Yes	Yes		
Tennessee	Yes:					
Texas	Yes <sup>a</sup>		Yes	Yes¶		
Utah	Yes		Yes	Yes		
Vermont	Yes†	Yes	Yes†	Yes		
Virginia	Yes§		Yes			
Washington						
West Virginia	Yest					
Wisconsin	Yes†	Yes	Yes†			
Wyoming	Yes:					

Yes indicates that the state has enacted legislation concerning the use of genetic information in the indicated circum stance. This table was compiled in June 2003. Because these are areas of intense legislative activity, the laws change fi quently. In addition, the laws vary far more widely from state to state than can be reflected in a table such as this. This table is not intended to be a legal opinion about the coverage of these laws. Readers are encouraged to consult the law in their own states.

<sup>†</sup> Testing cannot be required.

<sup>\$\</sup>delta\text{ According to the statute, genetic information cannot be considered to indicate a preexisting condition in the absence symptoms.

The statute specifically addresses illnesses in family members.

The statute contains exemptions about the use of information for certain research and other purposes.
Testing can be required for certain purposes, such as evaluating workers' compensation claims or surveillance.

<sup>\*\*</sup> The statute permits testing to be required under certain circumstances.

### **New Discriminatory Challenges**

Since variability in sensitivity genes is common, but the biological implications of these genetic variants is often unclear, there is more opportunity for misuse of such genetic information (easy to find differences, difficult to interpret their meaning).

- Over time, will employers begin placing more emphasis on removing the "genetically vulnerable" worker instead of eliminating workplace hazards to which that worker may be sensitive?
- Chronic beryllium disease as a case study

### Testing Workers for Susceptibility to CBD

- Beryllium susceptibility testing bears little resemblance to the Burlington Northern case (or other historical precedents)
- Beryllium testing would appear to be a "best-case" scenario for testing workers for inherited susceptibility to occupational hazards (for all the reasons described above)

Nonetheless, the ethical issues here are more subtle than they may appear at first glance.

### **Proposed Testing Programs Around CBD**

#### Raises a very different set of ethical considerations:

- Voluntary testing
- Informed consent obtained before testing
- Testing done by independent laboratories; reimbursed by the employer in a confidential manner
- Results provided directly to individuals, management does not have access to individual results
- Counseling available to the worker upon request
- Genetic marker is well understood
- Intervention possible (exposure avoidance or medical monitoring)
- No collateral information associated with the marker
- Post-employment testing (not a screening tool to eliminate workers)

# Ethical Considerations in Testing Beryllium Workers for Gx Susceptibilities

- 1. Interpretive challenges
  - Low-moderate PPV; high NPV (individual reporting)
  - Prevalence of genetic essentialism/determinism (misinterpretation)
- 2. Protecting confidential information
  - Self-disclosure (part of counseling or IC process)
  - Deductive disclosure from aggregate data
- 3. Ensuring voluntary participation
  - Measuring in place to limit use of coercive pressure
  - Participation of labor in development of testing materials/procedures
- 4. Potential impact on industrial hygiene
  - Will employees w/o the marker be less diligent in limiting exposure
  - Will employers in the Be industry move to mandatory screening
  - Potential shift in notions of personal accountability for poor health

### **Moving Forward**

- Continued research on markers of genetic susceptibility (eg, limitations of the –Glu 69 marker, ways to increase PPV, etc.)
- Participation of labor and other interested stakeholders in development of testing programs
- Building of empirical knowledge base regarding worker interests and concerns (role for ELSI researchers and scholars)
- Pilot testing (via a research protocol); development of educational materials, counseling protocols, and confidentiality protections
- Reassessment of impact on worker interests and adherence to safety protocols
- Pilot testing in non-research contexts

# Relocating Moral Responsibilities for Health Outcomes: CBD, part II

Randall White has been offered a job at a DOE weapons facility in New Mexico. Mr. White is excited about the new position, but after reading a local newspaper article on the harmful effects of beryllium, he's a little concerned about the new job, which will involve some beryllium processing. At a recent doctor's visit, Mr. White discusses these concerns with his physician, who suggests that he consider several genetic tests that could be done to help assess his likelihood of developing beryllium-associated disease.

After giving much thought to whether he should be tested, White decides to have the tests, which reveal that he is at increased risk of developing beryllium sensitization and chronic beryllium disease. Despite this knowledge, White decides to "let the chips fall where they may" and accepts the new position. He subsequently develops chronic beryllium disease within a year of assuming his new position.

## Allegations that an Individual Has Made a Genetically Irresponsible Choice

- 1. Failing to act on information about one's genetic risks
  - Dismissing one's genetic risks as irrelevant or insubstantial
- 2. Failing to obtain information about one's genetic risks
  - Forgoing a genetic test that would shed light on an important aspect of one's actions
- 3. Failing to reveal one's genetic risks to others
  - Special variant of the above form of irresponsibility (e.g. failing to tell a spouse about a known genetic risk)

#### Problems in Assigning Responsibility for Poor Health

#### Excusing conditions:

- The choice may not have been fully voluntary (e.g. Mr. White's employment options may be severely limited).
- The choice may not have been fully informed (e.g. Mr. White may not understand the information provided by his physician).

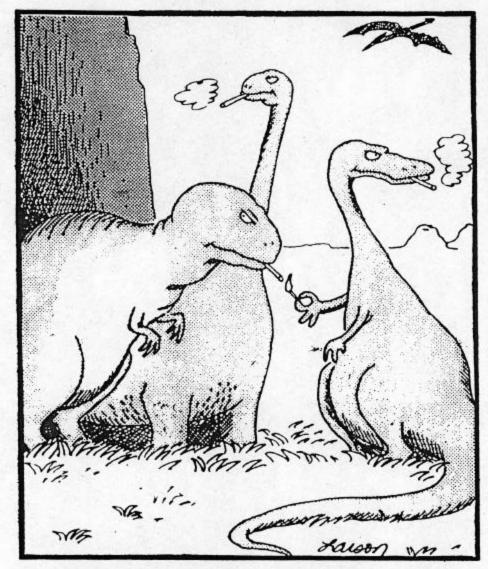
#### Justifying conditions:

 The choice may be reasonable in light of the circumstances (e.g. Mr. White may believe personal or family interests justify the increased risk of poor health).

## Defending an Allegation of Genetic Irresponsibility

Defending a judgment of genetic irresponsibility will require knowledge of many contextual features of the action, as well as some insight into how the actor weighed these consideration before choosing to act.

Point: Since we rarely have such detailed information, we should be cautious in making assertions of genetic irresponsibility, realizing that they often may be defeasible by various excusing conditions or act-justifying considerations.



The real reason dinosaurs became extinct.

Academic scholarship and creative popular writings

Transcendence of traditional policy debates

Constructive Catalysts

Identification with a charismatic spokesperson or seminal event Stimulation of public interest and sustained political debate

Genome Policy

Institute

Public worries about genetics
Calls for regulatory reform

Actual misuse of an emergent technology

Mobilization of political lobbyists

Scrutiny by investigative journalists

Congressional hearings

Catastrophic Concerns

Incremental Reforms

Federal advisory committee

Congressional task force

Expert review panels and policy recommendations

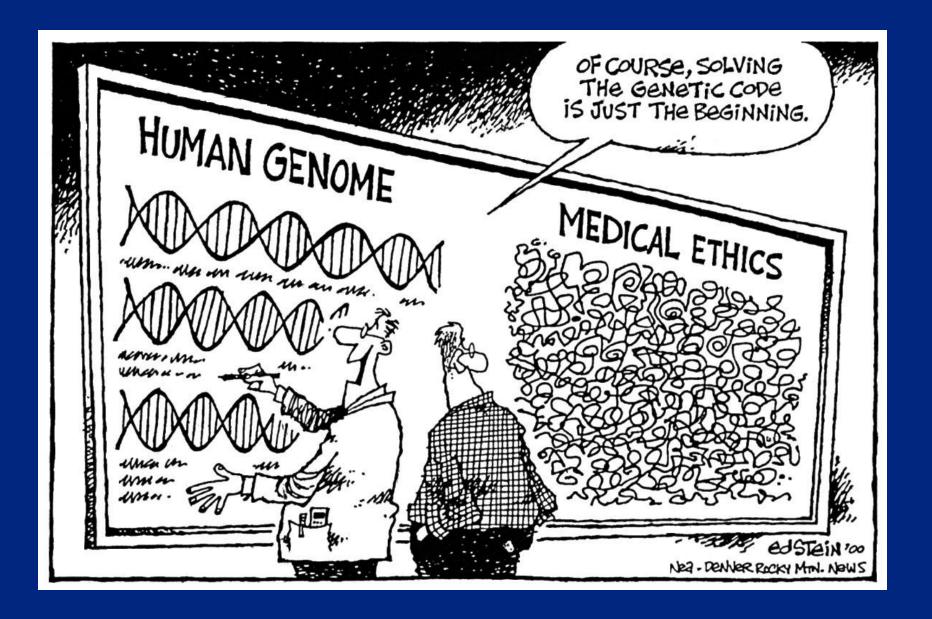
Alliances between interested stakeholders

Self-imposed regulation and institutional policies

Traditional political lobbying

#### "Conclusions"

- The application of genetic technologies to environmental protection will introduce a number of ethical challenges for researchers and policy makers:
  - Presentation of scientific findings to the public,
  - How we define the scope of future research with biological materials,
  - Potential discriminatory threats (of a more subtle nature), and
  - How we think about causal influences on, and assignments of individual and/or corporate responsibility regarding, health outcomes.
- How best to develop appropriate policy responses to these ethical challenges remains unclear
  - Role of ELSI-type initiatives (in an area with such diverse stakeholders)
  - Possible corrective to the increasingly narrow vision of the aims and methods of bioethics



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