Applications of Genomics to Toxic Torts

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Potential Uses of Toxicogenomics

Medical Applications:

- Personal physicians
- Public health officials
- Pharmaceutical development

Legal Applications:

- Toxic torts / Products liability
- Environmental regulation
- Occupational health and safety regulations

Genomic Data Relevant to Toxic Torts

- Gene expression data (biomarkers)

  - DNA microarray use to monitor expression of genes involved in response to toxic agent

  - Gene expression pattern to provide a signature profile of specific toxicant or mechanism

- Susceptibility genes

  - Genetic polymorphisms affect susceptibility to exposure, e.g., xenobiotic metabolism and detoxification, DNA repair, receptors, etc.

Applications of Genomic Data to Toxic Torts Scenarios

- Gene Expression Data

  General Causation
  Specific Causation
  Quantifying Exposure
  Absence of Causation
  Medical Monitoring
  Duty to Test

- Susceptibility Genes

  Specific Causation
  Duty to Warn
  Idiosyncratic Defense
  Assumption of Risk
  Alternative Causation
  Multiple Causation
  Damages
  Class Certification

Gene Expression: General and Specific Causation

General Causation (toxic agent has potential to cause plaintiff's health condition)

- cases are often dismissed because plaintiffs lack adequate evidence on specific agent-disease combination
- gene expression data showing agent causes response comparable to known toxic agent or disease in other tissue may overcome hurdle

Specific Causation (agent was the cause of the disease in the individual plaintiff)

Gene Expression: Quantifying Exposure

- Gene expression data could potentially provide quantitative dosimeter of plaintiff's exposure
- *In re TMI* litigation:

  - Plaintiffs lacked data quantifying exposure from TMI accident; instead relied on "biological indicators of radiation dose" (dicentric chromosomes)

  - Held: Dicentric chromosomes provide a valid and reliable quantitative dosimeter of exposure,but not stable for use until 15 years after exposure

  - Measurement of translocations using FISH would provide a "valid and reliable scientific methodology"

Gene Expression: Absence of Biomarkers

- Defendant can rely upon the absence of a characteristic genetic response to argue lack of exposure or causation
- *Wells v. Shell Oil Co.*

  - Worker alleged that he contracted acute myleogenous leukemia (AML) from benzene

  - Defendant successfully argued that benzene can only produce AML by breaks in chromosomes 5 & 7

Gene Expression: Medical Monitoring

- Some states now permit costs for medical monitoring of exposed plaintiffs in limited circumstances
- Such claims are often rejected because of lack of medically effective screening tests
  - E.g., W.V. jury rejects claim for periodic medical surveillance claim of smokers using new diagnostic lung test (spiral CT scan) (2001)
- Gene expression data may help plaintiffs overcome these obstacles

Gene Expression: Duty to Test

- *Sbrush v. Dow Chemical*

  - Worker at Dow facility died of leukemia

  - Widow brought suit claiming that Dow was negligent for <u>not</u> conducting cytogenetic tests of its workers

  - Dow had discontinued such testing in 1980 in response to widespread criticism

Gene Expression Data: Challenges and Limitations

- Distinguishing true toxicity from adaptive responses
- Standardization or comparability of data from different microarrays
- Validation of results from different species, tissues,developmental stages, and time courses
- Data management, analysis and presentation
- When is the approach ready for adoption?

Susceptibility Genes: Specific Causation

- Many courts require plaintiffs to prove that exposure results in relative risk > 2
- Plaintiff with genetic susceptibility may have higher relative risk than general population
- *In re Hanford Nuclear Reservation* litigation

- Court required plaintiffs to show doubling of risk

- Plaintiff's expert added 5-fold genetic susceptibility factor in calculating doubling dose

- Court rejected because: 1) no method to identify or quantify those at increased risk; 2) not everyone is genetically susceptible

Susceptibility Genes: Duty to Warn

- Does product manufacturer have duty to warn or recommend genetic testing for susceptible product users?
- *Cassidy v. SmithKline Beecham*

  - Class action alleges that LYMErix vaccine contains protein (OSPA) that produces autoimmune arthritis in individuals with HLA-DR4k genotype (30% of population)

  - Complaint alleges that drug manufacturer has duty to warn of susceptibility and advise consumers to obtain genetic test prior to vaccination

Susceptibility Genes: Idiosyncratic Response Defense

- Defendants can argue that they are not liable for product that only harms genetically hyper-susceptible individuals
- *Cavallo v. Star Enterprises*

  - Plaintiff alleges chronic health problems from vapors produced by underground oil plume

  - Plaintiff testifies that she is “highly susceptible” to these fume

  - Courts holds company only has duty to protect against harms “that would be suffered by a normal person”

Genetic Susceptibility: Assumption of Risk

- Approximately 30% of population carries susceptibility gene (glu-69) for chronic beryllium disease
- EPA has very strict emission standards for Be, but not zero
- Very low level of exposure may harm susceptible individuals
- Should residents near Be processing facilities be tested and, if susceptible, relocated?
- Should companies be required to pay for testing, relocation and/or medical monitoring?

Susceptibility Genes: Alternative Genetic Causation

- Defendants often allege that genetics is alternative cause of plaintiff's illness
- *Severson v. KTI Chemical*

  - Pregnant mother occupationally exposed to solvent (MEK) gave birth to a severely retarded child

  - Defendant chemical supplier argued that child suffered from Fragile X syndrome

  - Court ordered genetic testing of child

Susceptibility Genes: Multiple Causation

- Individuals with a variant of metabolic gene CYP2EI are more susceptible to solvents such as trichloroethylene (TCE)
- Enzyme is induced by ethanol, increasing risk
- Should drinking habits of plaintiffs who claim injury from TCE exposure be considered in assessing liability / damages?

Susceptibility Genes: Class Certification

- Certification of a class in a class action suit requires “predominance” of common issues within the class
- Genetic heterogeneity in susceptibility to defendant’s product could be used to argue against class certification
- *Mahoney v. R.J. Reynolds* (2001)

  - Certification of class of Iowa smokers denied in part because of differences within class in genetic susceptibility to tobacco smoke requires individualized proof of causation

Susceptibility Genes: Damages

- Defendants found to be sole cause of injury may seek reduction of damages if plaintiff has genetic disposition to same disease / condition
- Defendant may seek reduction of damages based upon diminished life expectancy from any genetic predisposition

  - HIV precedent
  - Fishing expeditions?
  - Should Ds routinely request tests from Ps?
  - Statistical reductionism?

Utility of Genetic Data for Toxic Torts

- Doctrinal templates already exist for many applications of genetic biomarkers in tort law
- Biomarkers could be useful to plaintiffs and defendants in appropriate case

  - Similar to forensic DNA: potential to inculpate the guilty and exonerate the innocent

Policy and Normative Issues

- Strong incentives for early (premature?) use
- Need to validate biomarker data (for relevance & reliability)
  - High stakes
  - Many one-time players
- Substantive policies of tort law
  - Compensation
  - Deterrence
  - Appropriate thresholds (judicial gatekeeper)
- Jury comprehension issues (can lay decision-makers competently evaluate genomic data?)
- Privacy / Discrimination