Liability and Personalized Medicine: Manufacturers

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Key Drivers for Personalized Medicine

- Scientific Development and Validation
- Economics
- Regulatory Standards
- Reimbursement
- Intellectual Property/Data Access
- Professional Training
- Liability

Who's the Target? Loci of Liability Exposure

- 1. Pharmaceutical manufacturers
- 2. Genetic Test Providers
- 3. Third Party Payers
- 4. Physicians
- 5. Pharmacists



Manufacturers: Types of Liability

- [Manufacturing Defect]
- Failure to Warn
- Design Defect
- Failure to Test?
- PGx Defenses to Liability?

Manufacturers: Liability for Failure to Warn?

- Drug manufacturers may face liability for failure to warn of need for genetic testing prior to drug use
 - e.g., Cassidy v. SmithKline Beecham
 - Manufacturer of lyme disease vaccine (LYMErix) sued for failing to warn that 30% of population has genotype (HLA-DR4+) which places them at risk of developing "treatment-resistant Lyme Arthritis"
 - Plaintiffs argue that manufacturer should have recommended genetic test prior to vaccination

Manufacturer Liability: Standard of Proof

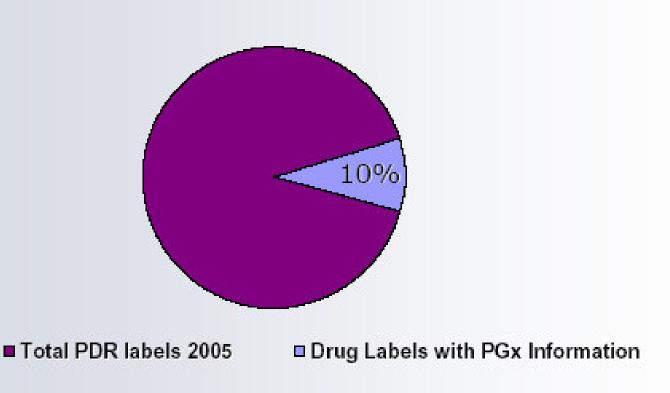


- Manufacturer, FDA and CDC all concluded that LYMErix was safe
- Company settled lawsuits and removed LYMErix from market
- Question: What level of scientific certainty in required to impose liability?

Duty to Warn: Learned Intermediary

- Has traditionally required drug manufacturer to warn only the physician
 - Physician responsible for communicating risk to individual patient because s/he assumed to be in best position to diagnose patient's condition
- Learned intermediary doctrine has been limited when manufacturer in better position to communicate directly to patient
 - e.g., vaccines
 - e.g, DTC advertisements

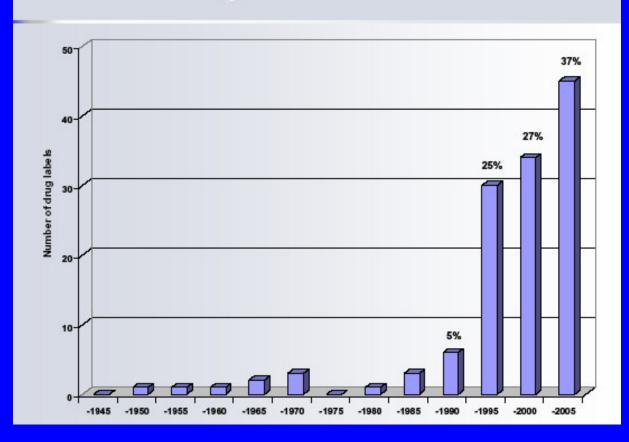
PGx Drug Labeling



~ 1200 labels screened (PDR, Drugs@FDA) 121 found to contain pharmacogenomic information

PGx Labeling by Year

Labels of Approved Drugs with Pharmacogenomic Information



Source: Felix Frueh, FDA

Failure to Warn: Segmented Populations

- If drug approved for only certain genotypes, manufacturer will have duty to label drug accordingly
 - Issue: Will manufacturer have any liability for widespread "off label" use of drug in non-approved genotypes?
 - e.g., Phen-Fen litigation
- If post-approval data suggests that drug may present risk to certain genotypes, manufacturer may be required to incorporate appropriate warnings on its label
 - Issue: When are data showing susceptible genotype adequately substantiated to require label change?

Design Defects: Restatement of Torts

- Recent Restatement (Third) of Torts:
 Products Liability has a new standard for design defect claims for pharmaceuticals:
 - A design defect claim can only be brought if the drug's risk-benefit ratio is unreasonable "for any class of patients"
 - This will be very favorable to manufacturers in era of PGx/biomarkers

Manufacturers: Liability for Failure to Test?

- Some courts have recently recognized a separate common law cause of action for negligent "failure to test"
 - Although precise requirements still developing, claims seek liability for a product manufacturer's failure to undertake appropriate safety testing of its product
 - Claim often feeds into punitive damages claims
- Question: When does a pharmaceutical manufacturer incur a common law duty to study pharmacogenomic response to its drug?

Concerns about Segmentation: A Liability Risk?

- "Our general philosophy is not to initiate a drugdevelopment programme that would limit the group of patients a drug could treat."
 - Drug company executive,quoted in Nature; 425: 760-62 (October 23, 2003)



Source: Robert Milligan

Manufacturers: Retrospective Liability?

- Fears that biomarkers of unknown or ambiguous significance today will be interpreted retrospectively as marker of toxicity that should have been considered
- State of art defense?
 - "reasonably scientifically knowable at the time of manufacture"
- Emphasis in current litigation on corporate malfeasance
 - Punitive damages

Pharmacogenomic Research: Unacceptable Risk?

- May be unethical and potential source of liability to conduct PGx study that includes individuals with a genetic biomarker that might indicate enhanced susceptibility to drug toxicity
 - What level of certainty and suspicion is needed to make such a study unethical/illegal?
 - Is it ever possible to verify a "suspected" genetic susceptibility?
 - When there is some evidence that there may be a genetic susceptibility to a drug within the population, is it ever possible to do a clinical study without stratifying and limiting the study population by genotype?
 - Role of informed consent?

PGx Defense in Pharmaceutical Litigation

- PGx data could provide a defense in product liability case where only some patients have susceptibility gene
- E.g., thimerosal/vaccine/autism cases
 - "The plaintiffs have conceded that they cannot prove, in Jordan's case, that his autism was caused by thimerosal. This is because Jordan does not meet the genetic profile for children who, according to the plaintiffs, are at an increased risk for developing autism caused by thimerosal in pediatric vaccines."
 - Easter v. Aventis Pasteur, 358 F.Supp. 574 (E.D. TX. 2005)
- PGx could be sword as well as shield if patient does have susceptibility gene

Liability and Personalized Medicine: Physicians

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Tort Liability: Theory

In theory, the elements of a common law negligence claim are

- Duty owed to the claimant and a
- Breach of that duty
- That <u>causes</u>
- Damages

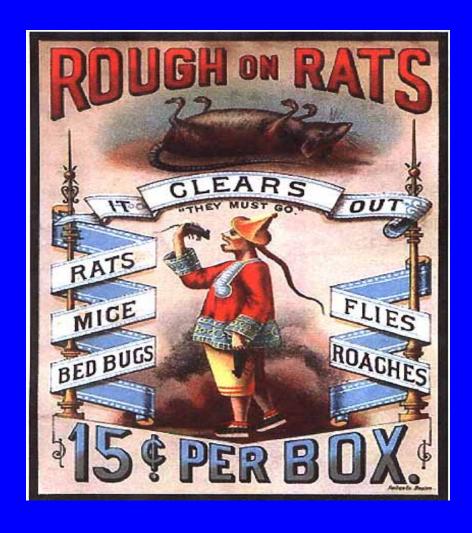
Liability: Practice

In practice, the elements of a <u>lucrative</u> negligence claim are:

- A perceived adverse outcome
- Significant damages
- Solvent or insured defendant(s)
- A good story
- A weak defense

A Supply of Adverse Outcomes

 "Poisons and medicines are often the same substance given with different intents." Peter Latham, 1789-1875.



A Supply of Adverse Outcomes

- In the most widely cited report on the incidence of ADRs, the authors estimate that in 1994, 2,216,000 hospitalized patients had serious ADRs and 106,000 patients had fatal ADRs.*
- Based on those figures, ADRs are between the fourth and sixth most common causes of death in the United States.

^{*}Lazarou, J, et al

Terminology

"Adverse Drug Reaction" refers to a reaction from an inherent property of a drug, and ADRs typically have been viewed as "unpreventable."

"Adverse Drug Events" include preventable events, such as human error and patient noncompliance.

Significant Damages

- General damages
 - Pain and suffering, etc.
 - Caps on non-economic damages?
- Economic/special damages
 - Medical bills, lost wages, etc.
 - The total annual cost associated with ADEs in the United States has been estimated at \$76 billion.
 - Brazell, C,

Solvent or Insured Defendant(s)

Physicians

Pharmaceutical companies

Payors

A Good Story

- In the absence of a pharmacogenomic test, drug selection and dosage is a trial and error process.
- From the physician perspective, both errors and trials are to be avoided.
 "Empirical selection and dosing...."
- "Errors" may result in administration of the wrong drug, the wrong dose, or both.

Trial and Error: The Wrong Drug

"The vast majority of drugs - more than 90 per cent - only work in 30 or 50 per cent of the people I wouldn't say that most drugs don't work. I would say that most drugs work in 30 to 50 per cent of people."

Alan Roses

Trial and Error: The Wrong Drug

 "One of the most striking features of modern medicines is how often they fail to work. Even when they do work, they are often associated with serious adverse reactions."

Goldstein, DB

Trial and Error: The Wrong Dose

 Since no drug is safe and effective in all patients, the dosage of a drug "is always a compromise between 'not too high' and 'not too low" for an individual patient.

Urs Myer

Pharmacogenomics as an Alternative to Trial and Error

- Historically, adverse drug <u>reactions</u> were the result of inherent properties of the drug.
 - They are unforeseeable and unavoidable.
 - Therefore, they are not compensable.
- Adverse drug <u>events</u> are the result of some error (patient or physician).
 - Therefore they are compensable.

An Alternative to Trial and Error

- With the advent of pharmacogenomic testing, adverse drug events due to drug selection or drug dosage will become more:
 - Foreseeable
 - Preventable
 - Compensable

Weak Defenses?

 The science does not support the use of pharmacogenomic testing.

"They have a test for that?"

"No one else is doing it."

The Science Doesn't Support Pharmacogenomic Testing

"We continue to be concerned that despite the widespread availability of simple PG tests to determine a patient's genotype with regard to CYP 450 enzymes, there has been little use of this information to tailor drug dosing..."

Lesko, L and Woodcock, J

"They have a test for that?"

- Physician education.
 - Few physicians have had "even one hour of pharmacogenomic instruction...."
 - K. Phillips, JAMA
- Unless tests results are binary, interpretation of results will require special expertise.

No One Else is Doing It

Arizona's "one expert per issue" rule:

- Plaintiff retains one expert who testifies that PGx testing was required by the standard of care.
- Defendant retains one expert who says it was not required.
- The jury decides which of the two is correct.
- Even if PGx testing is not routinely done

No One Else is Doing It

- In some jurisdictions, for some types of cases, the plaintiff may not be required to produce expert testimony.
- "[A] patient's right to know all material facts pertaining to proposed treatment cannot be dependent upon the self-imposed standards of the medical profession."

Festa v. Greenberg, PA

Are Physicians the Best Targets?

Other potential defendants have better defenses

Payors

Manufacturers

Payors' Defenses

ERISA preemption limits recovery against employer-sponsored plans:

"The result ERISA compels us to reach means that the Corcorans have no remedy, state or federal, for what may have been a very serious mistake."

Corcoran v United Healthcare, 965 F. 2d at 1321 at (5th Cir. 1992)

Manufacturers' Defenses

 The "Learned Intermediary Doctrine," i.e., "it's the doctor's fault."

 Defense to design defect claims: No recovery against the manufacturer if the product is safe for "any class of patients."*

*Restatement (3d) of Torts

The Best Target?

