Liability Drivers and Impediments to Individualized Medicine

Governance of Emerging Technologies Conference
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Innovating law, policy and ethics for science & technology

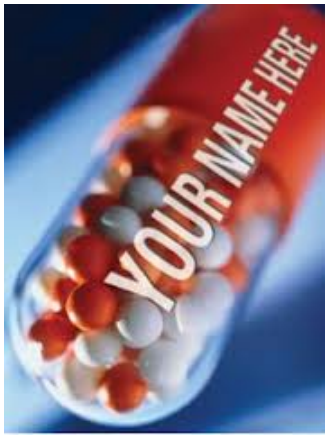
The Individualized Medicine Revolution

- "The power of the molecular approach to health and disease has steadily gained momentum over the past several decades and is now poised to catalyze a revolution in medicine"

Frances Collins,
NIH Director

Individualized Medicine Technologies

- Pharmacogenomics
- Biomarkers
- Whole Genome Sequencing
- Electronic Health Records
- Smart Medicine
- mHealth
- Nanomedicine



Liability Drivers for Individualized Medicine

1. Provider Unfamiliarity/Error Risk
2. Differential Uptake
3. Unrealistic Patient Expectations
4. Expert Disagreement/Uncertainty
5. Novel Legal Claims
6. Supply of Adverse Outcomes

New Medical Technology & Liability

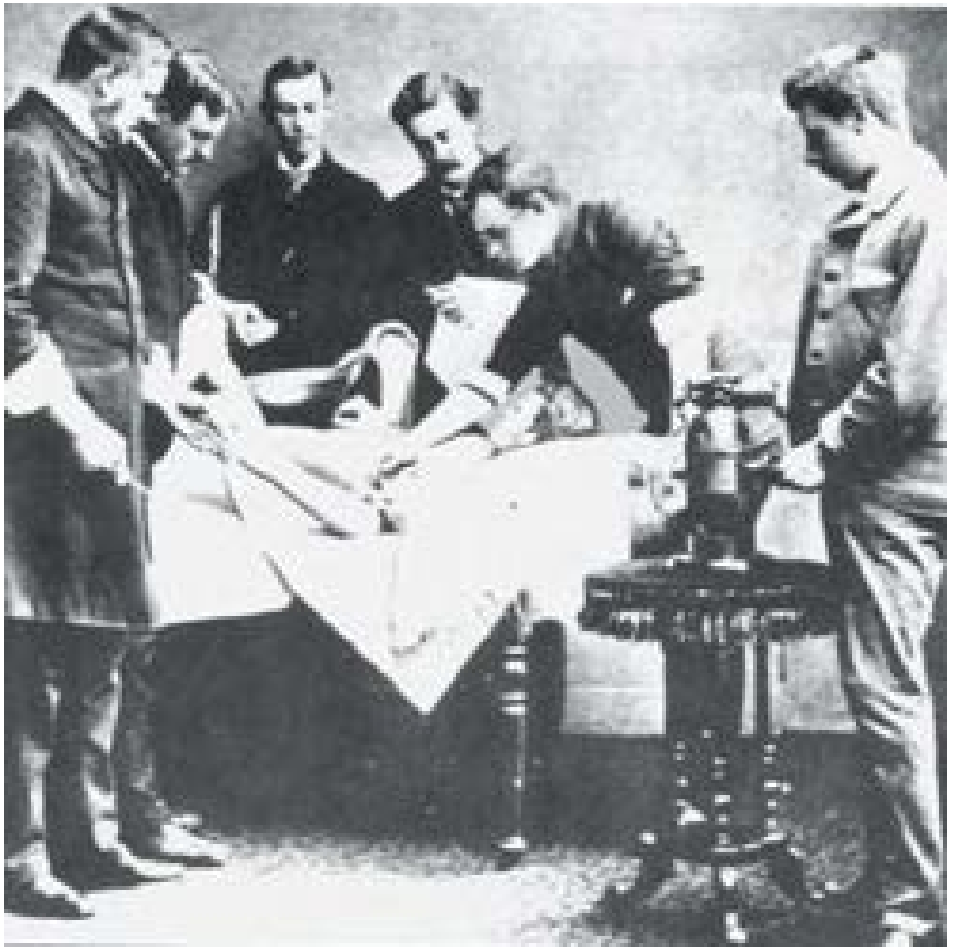
- "Although technology is generally seen as a boon to safety, no other factor historically has surpassed it as a stimulus for litigation. Gains in clinical competence redefine success upward and make delay actionable."

Sage, Medical Liability and Patient Safety

Old Technology
General Surgery, Pre-1920s

- Poor outcomes;
- Limited expectations;
- Very low rate of lawsuits.

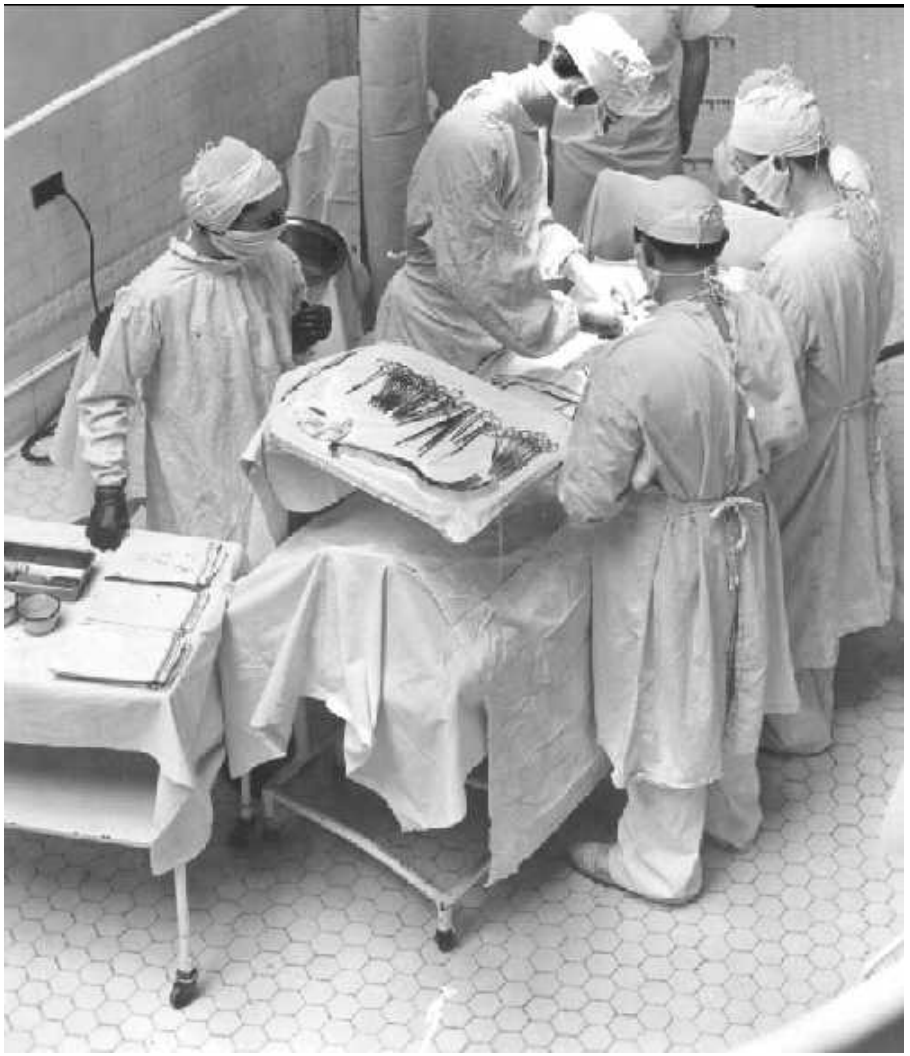
DeVille



New Technology
General Surgery, Post-1920s

After the 1920s, surgery was safer and more effective because of:

- Sulfa drugs
- Transfusions
- Aseptic practices
- Better instruments
- More intensive training

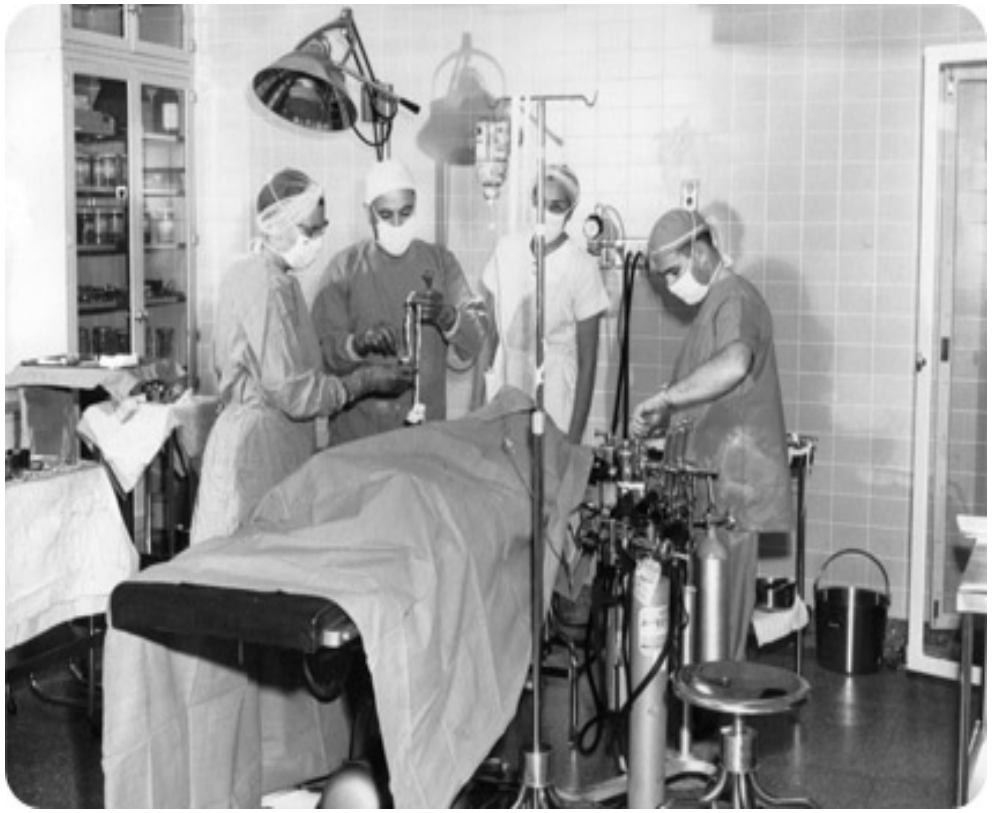


DeVille

New Technology
General Surgery, 1940-1950s

- “[S]urgeons were able to boast noteworthy and more numerous successes,” and
- Suits against surgeons overtook orthopedics suits as the most common source of medical malpractice suits.

DeVille



New Medical Technologies Increase Liability Risks

"Dramatic and genuine medical advances are invariably followed by heightened, and frequently excessive professional and lay expectations.... [I]mproved procedures more often than not require greater learning, skill, and care.... Consequently, technological advancement carries with it greater opportunity for error or accident."

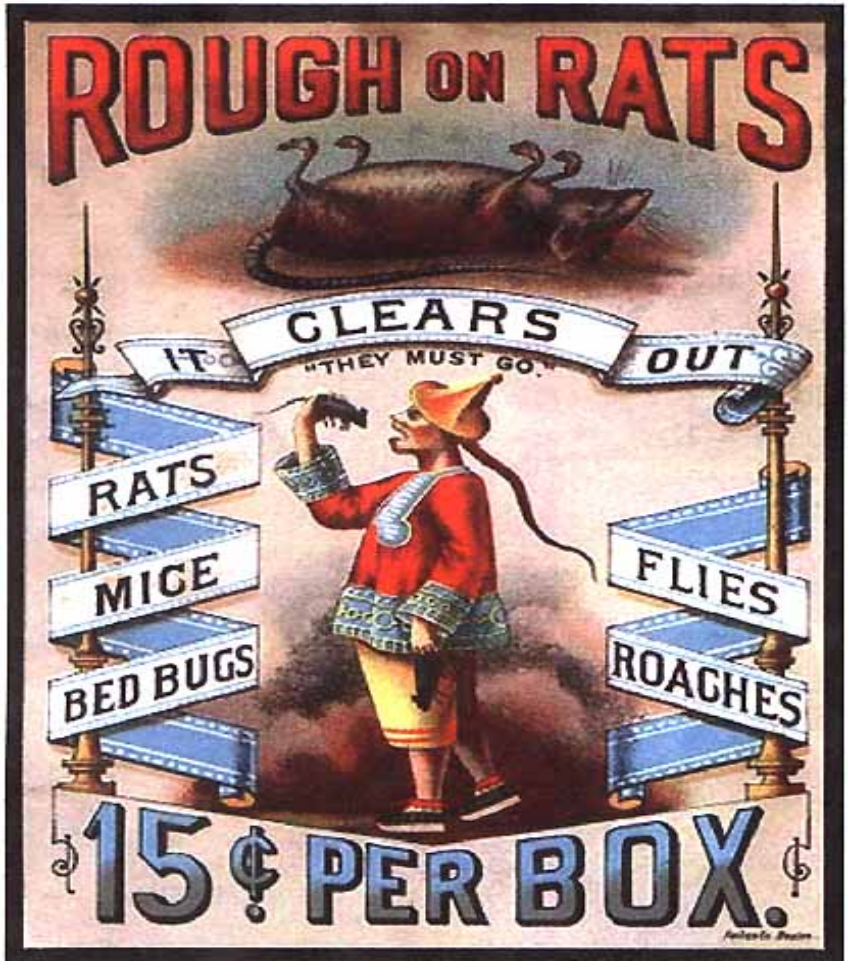
DeVille, Historical Origins of Medical Malpractice Litigation

Expert Disagreement/ Uncertainty

- Significant disagreement/ uncertainty about which genetic tests are clinically appropriate:
  - Warfarin
  - Plavix
  - CYP2A9/
  - Breast cancer recurrence/gene expression assays

Supply of Adverse Outcomes

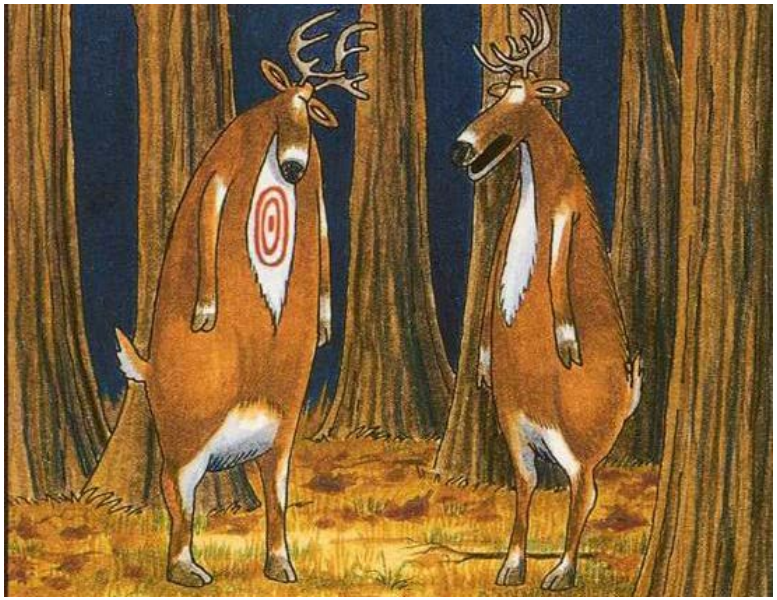
- ADRs are the fifth leading cause of death in the US.
  Lazarou, et al, JAMA, 1998
- “Poisons and medicines are often the same substance given with different intents.” Peter Latham



Potentially Culpable Defendants

- Pharmaceutical manufacturers
- Device/test manufacturers
- Testing labs
- Physicians
- Retailers
- Pharmacists

Physicians at Highest Risk



"Bummer of a birthmark, Hal"

- Most practicing physicians have little or no genetics training
- Disparities in practice/ uptake of genetics
- Limited infrastructure, practice guidelines, prescribing systems for incorporating genetics
- Doctrinal changes in standard of care

Adapted from Robert Milligan

Slow Adoption of PGx by Physicians

The Pharmacogenomics Journal (2002) 2, 20–24
© 2002 Nature Publishing Group All rights reserved 1470-269X/02 $25.00
www.nature.com/tpj

EELS (Ethical, Economic, Legal & Social) ARTICLE

Pharmacogenomic-guided drug development: regulatory perspective

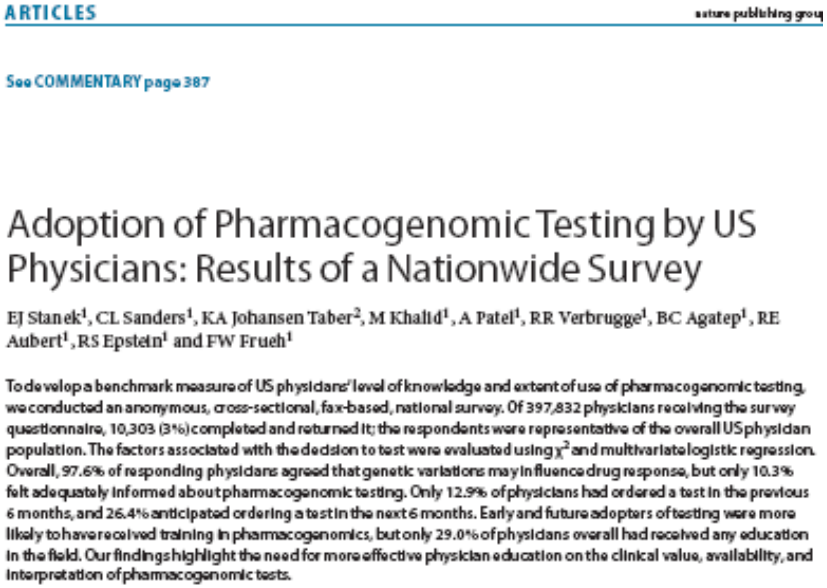
LJ Lesko[1] and J Woodcock[2]

[1]Office of Clinical Pharmacology and Biopharmaceutics, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD, USA; [2]Office of the Center Director, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD, USA

- **"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 …"**

AMA/Medco Survey of 10,303 Doctors

- 97.6% agreed that genetic variations may influence drug response
- 10.3% felt adequately informed about pharmacogenomic testing
- 12.9% of physicians had ordered a test in the previous 6 months, and 26.4% anticipated ordering a test in the next 6 months
- 29.0% of physicians overall had received any education in the field



ARTICLES

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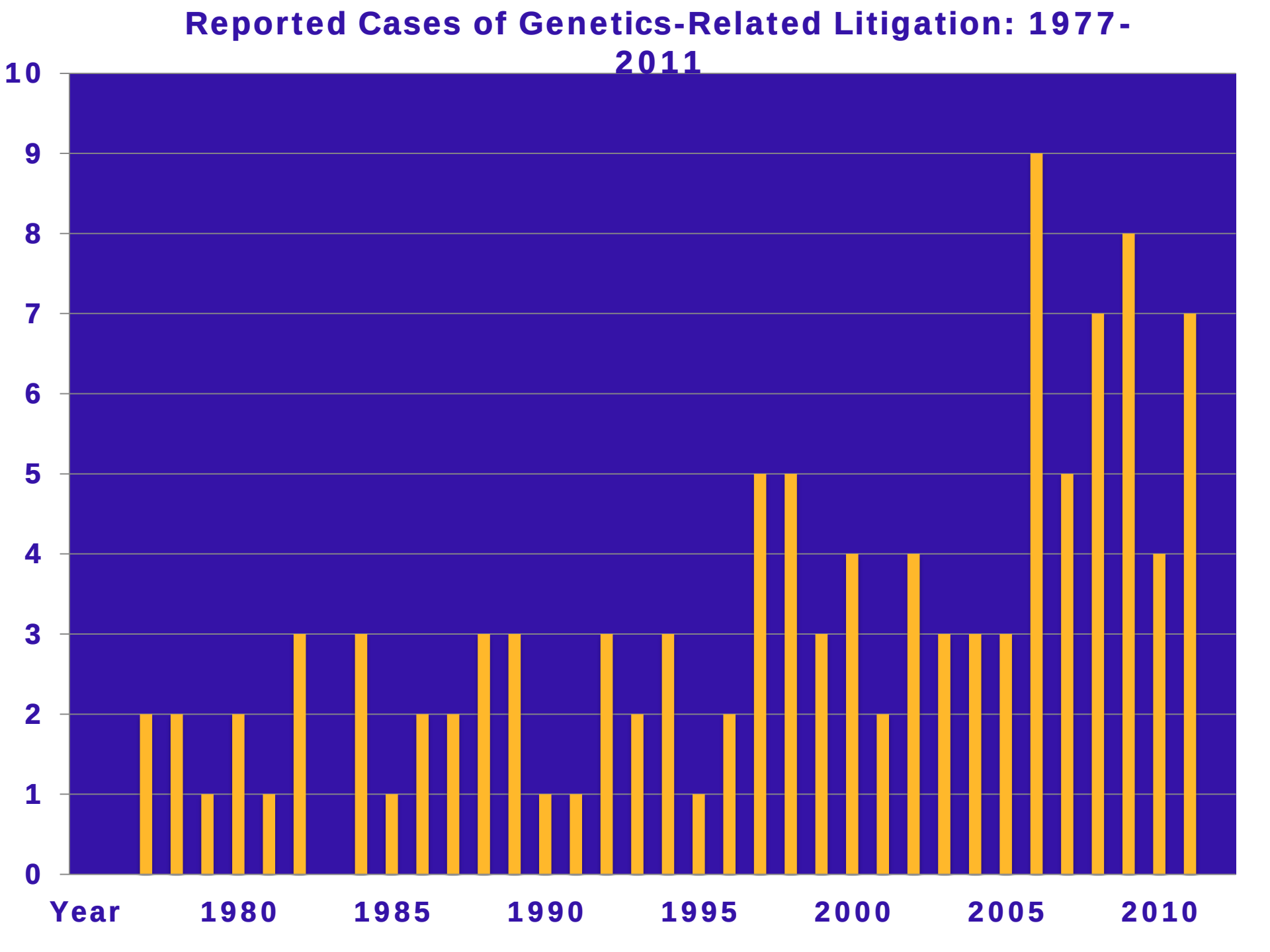
See COMMENTARY page 387

Adoption of Pharmacogenomic Testing by US Physicians: Results of a Nationwide Survey

EJ Stanek[1], CL Sanders[1], KA Johansen Taber[2], M Khalid[1], A Patel[1], RR Verbrugge[1], BC Agatep[1], RE Aubert[1], RS Epstein[1] and FW Frueh[1]

To develop a benchmark measure of US physicians' level of knowledge and extent of use of pharmacogenomic testing, we conducted an anonymous, cross-sectional, fax-based, national survey. Of 397,832 physicians receiving the survey questionnaire, 10,303 (3%) completed and returned it; the respondents were representative of the overall US physician population. The factors associated with the decision to test were evaluated using χ^2 and multivariate logistic regression. Overall, 97.6% of responding physicians agreed that genetic variations may influence drug response, but only 10.3% felt adequately informed about pharmacogenomic testing. Only 12.9% of physicians had ordered a test in the previous 6 months, and 26.4% anticipated ordering a test in the next 6 months. Early and future adopters of testing were more likely to have received training in pharmacogenomics, but only 29.0% of physicians overall had received any education in the field. Our findings highlight the need for more effective physician education on the clinical value, availability, and interpretation of pharmacogenomic tests.

Clinical Pharmacology & Therapeutics 91(3): 450-458 (March 2012)

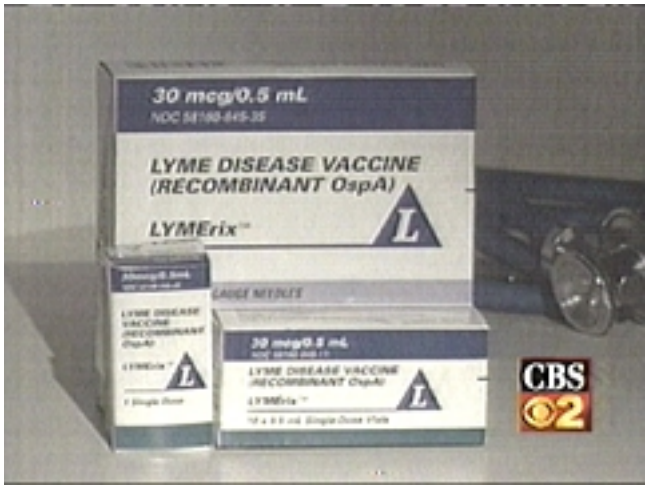

Reported Cases of Genetics-Related Litigation: 1977-2011
10
9
8
7
6
5
4
3
2
1
0
Year
1980
1985
1990
1995
2000
2005
2010

Genetic Testing/Medical Malpractice: Causes of Action

- Wrongful conception
- Wrongful birth
- Wrongful life
- Informed consent
- Lost chance
- Delayed diagnosis
- Negligence
- Negligent infliction of emotional distress
- Negligent preconception counseling
- Negligent misrepresentation
- Duty to third parties
- Breach of confidentiality

Personalized Medicine: The First Case - Lymerix

- Manufacturer of lyme disease vaccine sued for failing to warn that 30% of population had gene variant that allegedly placed them at risk of developing treatment-resistant arthritis
- Plaintiffs argued that manufacturer should have recommended genetic test prior to vaccination
- Manufacturer denied factual basis of claims; settled cases; vaccine eventually removed from market



Scholz v. Kaiser Found. Hospital,
Cal. Sup. Ct. (Almeda County, filed Jan. 30, 2012)

- Irma Scholz, an American of Asian descent, was prescribed carbamazepine to treat myelitis
- She developed Stevens-Johnson Syndrome, a life threatening, painful and disfiguring skin condition
- Scholz has sued her doctor and the hospital for not recommending a genetic test before prescribing carbamazepine

Carbamazepine Label: FDA Black Box Warning

WARNING

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH CARBAMAZEPINE. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH CARBATROL. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH CARBATROL UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE WARNINGS AND PRECAUTIONS/LABORATORY TESTS).

Other Early Personalized Medicine Cases

- *Rimbert v. Eli Lilly*, D.N.M. 2009
  - Family claimed that Prozac caused man to shoot and kill his wife and himself; claimed man had a slow metabolizer variant CYP2D6; court excluded testimony because man never tested
- Ohio, 2002 case (22 No. 4 Verdicts, Settlements, and Tactics 155)
  - Woman tested positive for BRCA mutation and underwent prophylactic mastectomy and totally hysterectomy; settled for $2 million when later revealed that she did not actually have the mutation

Future Accelerators

- More validated genetic tests
  - e.g., randomized control trials
- More FDA-approved PGx labels
- Growing disparities in medical practice
- Increasing familiarity/precedents by plaintiff's bar
- Direct to consumer genetic testing
- Whole genome sequencing

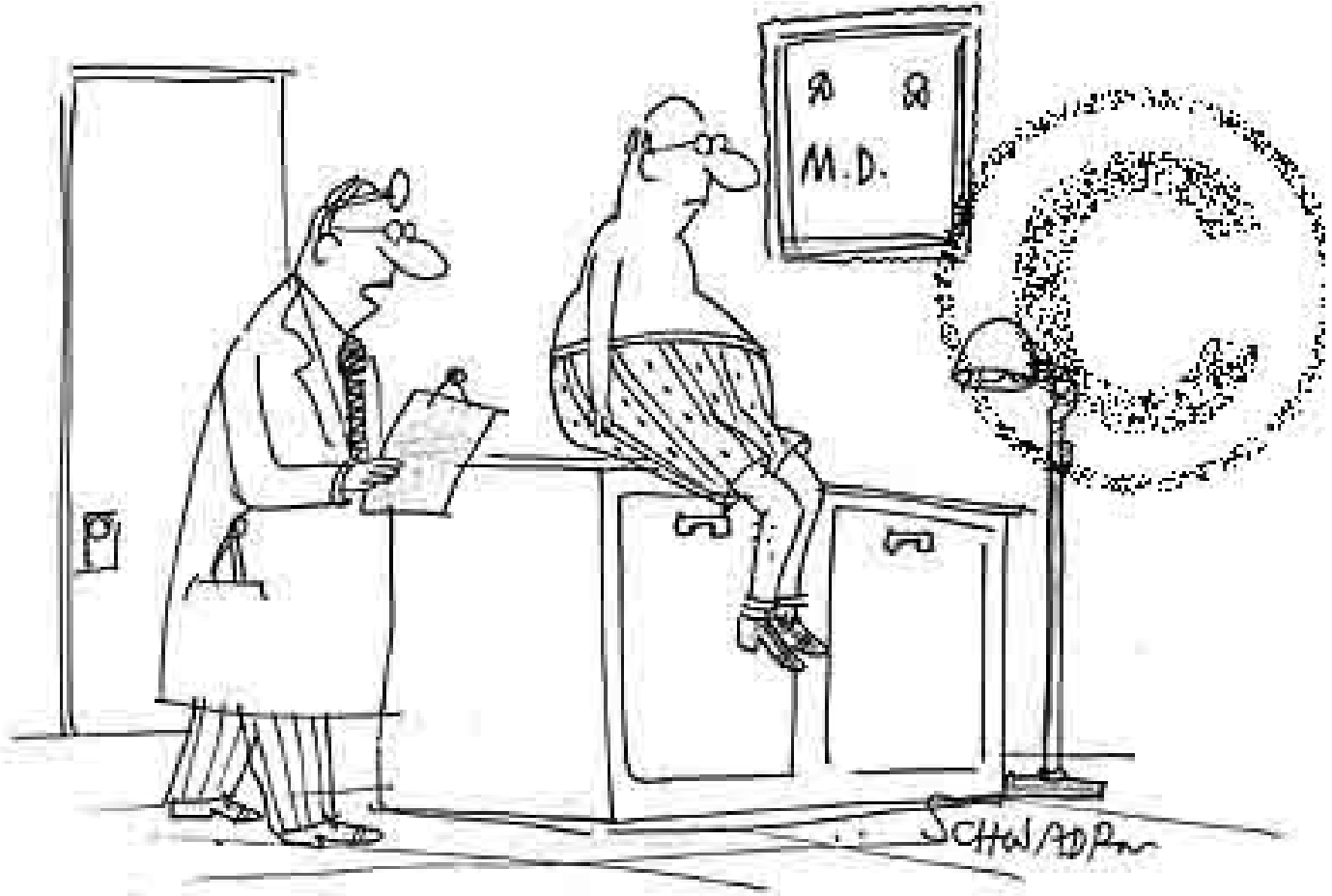
Future Impacts of PGx Liability

- Positive:
  - May drive faster adoption of safer technologies
  - Compensation for injured victims
- Negative:
  - May drive premature or inappropriate use of genetic tests
  - Defensive medicine

Liability as a Governance Tool

- Pros:
  - Deterrence against undue risk
  - Compensation of injured victims
  - Identify and remedy medical errors
  - Automatically; no enactment lag
- Cons:
  - Ex poste rather than ex ante
  - Inconsistent and sporadic results
  - Participation limited to parties
  - Potential for over-deterrence
  - Some judgment-proof defendants

The Future of Genetic Testing?



Acknowledgment

- Funding for this work was provided by NHGRI ELSI Grant #R01HG006145-01A1