Statistics, the Law, and the Future of Personalized Medicine

(What happened over spring break)

Mayo v. Prometheus

- Prometheus Laboratories, Inc. developed a diagnostic test for directing treatment of immune-mediated gastrointestinal disorders (e.g. Crohn's disease, colitis)
- Thiopurine drugs commonly used to treat these diseases; drugs are metabolized differently in different people
  - Too much leads to harmful side effects
  - Too little is ineffective
  - Only choice is to wait around and see what happens

PROMETHEUS®
Therapeutics & Diagnostics

For the person in every patient™

About Prometheus | News | Products & Services | Healthcare Professionals | Business Development | Careers

Carey, age 30, Teacher and avid volleyball player.

Diagnosed with mild-to-moderate Crohn's disease in 2003

Current Status: Clinical remission of symptoms.

PROMETHEUS *patients*
Patient information resource

ProNet
Prometheus Results Online
For Healthcare Professionals

We are committed to improving lives through the delivery of innovative diagnostic and therapeutic products that enable clinicians to provide optimal care for their patients.

Latest News

- **2/7/2012** Prometheus Signs Research & Collaboration Agreement with Leading Worldwide Pharmaceutical Company
- **2/3/2012** Prometheus Announces New Chief Commercial Officer
- **11/14/2011** Prometheus Announces New Chief Medical Officer

MyCeliacID™ **- the first do it yourself saliva-based genetic test dedicated to celiac disease**

Home | Contact Us | Site Map | Privacy Policy | Legal Notices | Recommend Prometheus

NestléHealthScience

Achieve optimal levels to increase the chance of response[1]

WHEN

3 to 4 weeks after initiating thiopurine therapy[1]

Inadequate or unexpected response

- Suspected lack of patient compliance

WHY

Reach therapeutic goal and increase likelihood of response

HOW

PROMETHEUS® **Thiopurine Metabolites**[b]

Metabolites monitoring identifies treatment failures who may be converted to responders[3,c]

6-TGN (pmol/8 x 10^8 erythrocytes)	**6-MMP** (pmol/8 x 10^8 erythrocytes)	**Interpretation**	**Patients n (%)** (n = 9187)
Undetectable	Undetectable	Noncompliance	263 (3%)
< 230	< 5700	Underdosed	4260 (46%)
< 230	> 5700	Preferential metabolism via TPMT pathway	534 (6%)
230-450	< 5700	Therapeutic goal	2444 (27%)
230-450	> 5700	Potential hepatotoxicity	552 (6%)
> 450	< 5700	Potential TPMT deficiency (potential myelotoxicity)	936 (10%)
> 1000	Undetectable	Potential TPMT absence (potential myelotoxicity)	58 (1%)
> 450	> 5700	Overdosed	140 (2%)

Mayo v. Prometheus

- Levels of blood metabolites 6-TG and 6-MMP are correlated with effectiveness of dose
- This was already published in Cuffari et al. 1996, *Gut*, in a study of 25 patients
- Prometheus patent 6,355,623 says
  - Level of 6-TG < 230 pmol per $8x10^8$ indicates a need to increase dose
  - Level of 6-TG > 400 pmol per $8x10^8$ indicates a need to decrease dose

Mayo v. Prometheus

- Measurements of 6-TG are done via standard blood tests (already standard treatment)
- Thiopurine drugs were already being used in this population of patients
- Primary contribution of the patent was identifying the cutoffs for suggesting treatment modification

Mayo v. Prometheus

- In 2004, Mayo marketed its own test that was the same as Prometheus's, but increased the upper bound to 450 pmol per $8x10^8$
- Prometheus sued Mayo for patent infringement
- At the time, sales of the test accounted for ~70% of Prometheus's revenue

Mayo v. Prometheus

- District Court found Mayo's test to be too similar to Prometheus's test because the upper bound of 450 was within the margin of error relative to 400
- However, Mayo won because District Court ruled that Prometheus patent was for a "law of nature" or "natural phenomenon", which is not patentable
- Prometheus appealed to Federal Circuit (has some specialty in patents), and Federal Circuit reversed
  - The patent involved a "transformation of the human body or of blood taken from the body" and so was patentable
  - Passed the so called "machine or transformation test"

Mayo v. Prometheus

- Laws of nature or natural phenomena are not patentable, but *applications* of laws of nature *are* patentable
- Passing the "machine or transformation test" is necessary but not sufficient (*Bilski*)
- Supreme Court said that stating a law of nature and then saying "apply the law" is not patentable

Mayo v. Prometheus

- Court was sympathetic to Mayo's argument that Prometheus's correlations were wrong and that upholding the patent would impede progress
- US Government argued that a test like this was patentable, but should not be allowed because of lack of novelty
  - Court rejected this argument; would significantly raise the cost of challenging patents
- Implications for Myriad Genetics? (*Association for Molecular Pathology v. Myriad Genetics*)
  - Case sent back to Federal Circuit after *Mayo*

The Duke Saga

- A group at Duke University led by Joseph Nevins and Anil Potti developed a test that they claimed would predict an individual's response to chemotherapy
- If true, this is the holy grail of personalized medicine
- Test was based on a genomic signature
- Original test based on data from publicly available NCI 60 cancer cell lines
- Researchers at MD Anderson Cancer Center (Keith Baggerly, Kevin Coombes) tried to reproduce results; couldn't

The Duke Saga

- Nevins & Potti continued to published genomic signatures for other cancer/chemotherapy treatments
- Baggerly & Coombes obtained data from Potti lab and discovered numerous errors, omissions, potential fraud
  - Off-by-one error
  - Missclassification of responders/non-responders
  - Genes not on array
- Baggerly & Coombes published article in *Annals of Applied Statistics* listing the problems
- Meanwhile, randomized clinical trials being conducted where the *test was directing patient treatment*

The Duke Saga

- Potti eventually exposed as lying on his CV
- Clinical trials suspended
- Duke investigated but found no problems (did not use Baggerly & Coombes findings)
- ~30 prominent statisticians sent a letter to Harold Varmus (director of NCI) asking him to investigate
- Eventually, trials stopped
- Varmus requests IOM committee to investigate what happened and what can be done

The Duke Saga

- What happened?
- Duke Lab (Nevins & Potti) were woefully unprepared and ill-trained for the tremendous complexity of using genomic signatures
- Procedures not in place for monitoring use of such signatures when directing patient treatment
- Not clear whether IDE should be obtained from FDA to investigate genomic signatures

The IOM Report

REPORT BRIEF MARCH 2012

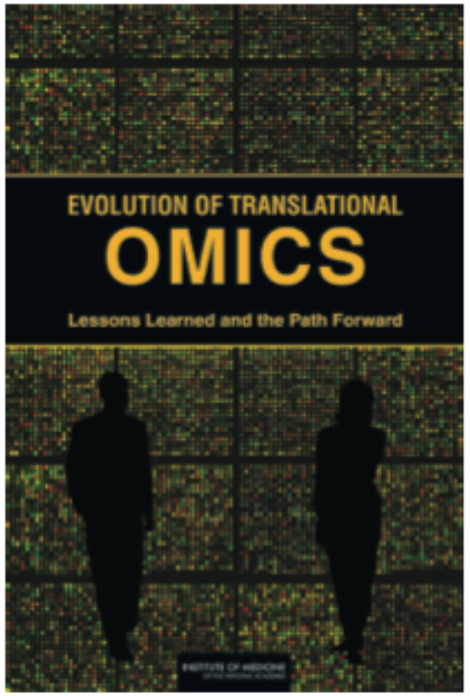
INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Advising the nation • Improving health

For more information visit www.iom.edu/translationalomics

Evolution of Translational Omics

Lessons Learned and the Path Forward



The IOM Report

- Omics-based tests should be confirmed with independent, blinded samples
- Data/metadata used to develop test should be made publicly available
- Computer code (statistical model) used should be publicly available
- Funders should provide support for making data/ code available
- FDA should develop guidelines for IDE requirements for omics-based tests

Adding it All Up

- Prometheus test represents a successful application of (non-genomic) personalized medicine ideas – not patentable
- Colossal failure of the Duke Lab shows how difficult it is to develop genomic signatures rigorously – Duke investigators stalled at each stage
- IOM Committee urges openness, transparency, and reproducibility in developing genomic signatures/tests

Adding it All Up

- What are the implications of *Mayo* for the future of personalized medicine?
- Will *Mayo* decision lead to more secrecy in developing personalized medical treatments?
- Will biotech companies avoid investment if patents cannot be obtained?
- Is there away for the field to move forward so that companies benefit from investing and science can progress rapidly?