Personalized Medicine and the Diagnostics Business

Steve Gullans, PhD

Excel Venture Management
Boston, MA
Excel Invests in Life Science Technologies
Headlines Today
- Diagnostic Tests

- Genomics is driving rapid innovation
- Personalized Medicine is being reduced to practice

But...
- FDA regulatory timelines have grown longer
- Reimbursement is getting more challenging
- Patent landscape is in flux
- Venture funding is tight
Value of Diagnostics

- 60-70% of clinical decisions-making is based on laboratory data
- Tests represent only 2-5% of healthcare costs

Mark Boguski - “Cancer Data and the Fallacy of $1000 Genome” – Forbes June 2012
Genomics Driving Personalized Medicine

Cost per Genome

Moore’s Law

National Human Genome Research Institute
genome.gov/sequencingcosts
Relative Efficacy of Drugs


Len V. HuaPrimary Care Optometry News, 2011
### Pharmacogenomic information is required on labels of these medicines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Biomarker/Test</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herceptin (trastuzumab, Roche) Tykerb (lapatinib, GlaxoSmith-Kline)</td>
<td>HER-2/neu receptor</td>
<td>Breast cancer with overexpression of HER-2</td>
</tr>
<tr>
<td>Erbitux (cetuximab, Bristol-Myers Squibb) Gefitinib</td>
<td>EGFR expression</td>
<td>N/A</td>
</tr>
<tr>
<td>Gleevec (imatinib mesylate, Novartis) Dasatinib</td>
<td>N/A</td>
<td>Chronic myeloid leukemia with presence of BCR-ABL (Philadelphia chromosome)</td>
</tr>
</tbody>
</table>

### Pharmacogenomic information is recommended on labels of these medicines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Biomarker/Test</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plavix (clopidogrel, Bristol-Myers Squibb)</td>
<td>CYP2C9, VKORC1</td>
<td>Stroke, to minimize excessive bleeding</td>
</tr>
<tr>
<td>Lipitor (atorvastatin, Pfizer)</td>
<td>LDLR</td>
<td>Familial hypercholesterolemia, to establish goal of therapy</td>
</tr>
<tr>
<td>Tegretol (carbamazepine, Novartis)</td>
<td>HLA-B1502</td>
<td>Epilepsy and bipolar disorder, to minimize serious skin reaction</td>
</tr>
</tbody>
</table>

Note: These tables only provide examples of medications with PGX labels. For a more exhaustive list, visit the FDA’s website: [http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm](http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm).
Gene Biomarkers for Drug Therapy

- Oncology: 36
- Neuro-Psychiatric: 15
- Anti-infectives: 8
- Cardiovascular: 5
- Gastroenterology: 8
- Hematology: 9
- Dermatology/Dental: 4
- Other: 33
## Diagnostic/Pharma Deals in 2012

<table>
<thead>
<tr>
<th>Diagnostics Partner</th>
<th>Pharmaceutical Partner</th>
<th>Disease Area</th>
<th>Deal Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foundation Medicine</td>
<td>Novartis (NVS)</td>
<td>Cancer-Multiple</td>
<td>12-Jun</td>
</tr>
<tr>
<td>PrimeraDx</td>
<td>Eli Lilly (LLY)</td>
<td>Cancer-Multiple</td>
<td>12-Jun</td>
</tr>
<tr>
<td>Genomic Health (GHDX)</td>
<td>OncoMed Pharmaceuticals</td>
<td>Cancer-Undisclosed</td>
<td>12-May</td>
</tr>
<tr>
<td>Dako</td>
<td>Genentech</td>
<td>Cancer-Breast</td>
<td>12-May</td>
</tr>
<tr>
<td>Roche/Ventana (RHHBF.PK)</td>
<td>Millennium/Takeda (TKPHF.PK)</td>
<td>Cancer-lymphoma</td>
<td>12-Apr</td>
</tr>
<tr>
<td>Roche/Ventana</td>
<td>Seattle Genetics (SGEN) and Millennium</td>
<td>Cancer-lymphoma</td>
<td>12-Apr</td>
</tr>
<tr>
<td>HTG Molecular Diagnostics</td>
<td>Sanofi (SNY)</td>
<td>Cancer-Undisclosed</td>
<td>12-Mar</td>
</tr>
<tr>
<td>Meso Scale Discovery</td>
<td>Bristol-Myers Squibb (BMY)</td>
<td>Neurology-Alzheimers</td>
<td>12-Mar</td>
</tr>
<tr>
<td>Abbott Molecular (ABT)</td>
<td>Merck &amp; Co (MRK)</td>
<td>Cancer-Undisclosed</td>
<td>12-Mar</td>
</tr>
<tr>
<td>Myriad Genetics (MYGN)</td>
<td>Cephalon (CEPH)</td>
<td>Cancer-ovarian and breast</td>
<td>12-Mar</td>
</tr>
<tr>
<td>Biodesix Inc.</td>
<td>Kadmon Corporation</td>
<td>Cancer-Lung</td>
<td>12-Feb</td>
</tr>
<tr>
<td>Dako</td>
<td>Amgen (AMGN)</td>
<td>Cancer-Undisclosed</td>
<td>12-Feb</td>
</tr>
<tr>
<td>Siemens AG (SI)</td>
<td>GSK/ViiV (GSK)</td>
<td>Infection-HIV</td>
<td>12-Feb</td>
</tr>
<tr>
<td>Siemens AG</td>
<td>Tocagen</td>
<td>Cancer-Brain</td>
<td>12-Feb</td>
</tr>
<tr>
<td>Foundation Medicine</td>
<td>Sanofi</td>
<td>Cancer-Multiple</td>
<td>12-Jan</td>
</tr>
<tr>
<td>Roche/Ventana</td>
<td>Aeterna Zentaris Inc.</td>
<td>Cancer-Multiple</td>
<td>12-Jan</td>
</tr>
<tr>
<td>Xenon</td>
<td>Genetech</td>
<td>Pain</td>
<td>12-Jan</td>
</tr>
<tr>
<td>Roche/Ventana</td>
<td>Bayer (BAYZF.PK)</td>
<td>Cancer-Undisclosed</td>
<td>12-Jan</td>
</tr>
<tr>
<td>Roche/Ventana</td>
<td>Pfizer (PFE)</td>
<td>Cancer-Lung</td>
<td>12-Jan</td>
</tr>
<tr>
<td>Roche/Ventana</td>
<td>Syndax</td>
<td>Cancer-lung</td>
<td>12-Jan</td>
</tr>
</tbody>
</table>
Roche’s Personalized Medicine Push

60% of drug pipeline includes companion diagnostic

September 5, 2012
Status of Personalized Medicine

This diagram portrays the stage of readiness of the important players for implementation of personalized medicine, according to the Personalized Medicine Coalition.
Noninvasive Prenatal Testing (NIPT)

- The largest clinical use of genomic tests today is prenatal diagnosis
- Maternal plasma sequencing of fetal aneuploidy became clinically available in the U.S. in Oct 2011
- Aneuploidy testing of 20,000 cases in U.S. already
- Insurance can cover the cost
Oncology Is Growing Rapidly
From Discovery to Patient

In Vitro Diagnostics (IVD)

Discover a Biomarker → Develop a Test → Clinically Validate → Regulatory Approval → Clinical Acceptance
From Discovery to Patient

In Vitro Diagnostics (IVD)

Must be
- Clinically actionable information
- >90% sensitivity; >95% specificity
- Published
- Patent filed - Intellectual Property (IP)
BRACAnalysis®
A genetic test for Hereditary Breast and Ovarian cancer.

Specimen Collection and Transportation Kit
Keep at room temperature

- Breast Cancer by age 50: 33% - 50%
- Breast Cancer by age 70: 56% - 87%
- Ovarian Cancer by age 70: 27% - 44%

BRCA mutation carriers vs. General population
DO NOT PATENT MY GENES
VS.

ACLÜ
AMERICAN CIVIL LIBERTIES UNION

VS.

MYRIAD
UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

ASSOCIATION FOR MOLECULAR PATHOLOGY,
ET AL.,

Plaintiffs,

-against-

UNITED STATES PATENT AND TRADEMARK
OFFICE, ET AL.,

Defendants.

----------------------------------

APPEARANCES:

Attorneys for Plaintiffs

AMERICAN CIVIL LIBERTIES UNION FOUNDATION
125 Broad Street - 18th Floor
New York, NY 10004
By: Christopher A. Hansen, Esq.
    Aden Fine, Esq.
    Lenora M. Lapidus, Esq.
Judge Invalidates Human Gene Patent
March 29, 2010

AMERICAN CIVIL LIBERTIES UNION FOUNDATION
125 Broad Street - 18th Floor
New York, NY 10004
By: Christopher A. Hansen, Esq.
    Aden Fine, Esq.
    Lenora M. Lapidus, Esq.
SUPREME COURT OF THE UNITED STATES

Syllabus

BILSKI ET AL. v. KAPPOS, UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND DIRECTOR, PATENT AND TRADEMARK OFFICE

CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR FEDERAL CIRCUIT

No. 08–964—Argued November 9, 2009—Decided June 28, 2010

Petitioners’ patent application seeks protection for a claimed invention that explains how commodities buyers and sellers in the energy market can protect, or hedge, against the risk of price changes. The key claims are claim 1, which describes a series of steps instructing how to hedge risk, and claim 4, which places the claim 1 concept into a simple mathematical formula. The remaining claims explain how claims 1 and 4 can be applied to allow energy suppliers and consumers to minimize the risks resulting from fluctuations in market demand. The patent examiner rejected the application on the grounds that the invention is not implemented on a specific apparatus, merely

DENIED
Classen Immunotherapies – Immunization schedule

August 11, 2011
MAYO CLINIC

VS.

PROMETHEUS®
Therapeutics & Diagnostics
SUPREME COURT OF THE UNITED STATES

Syllabus

MAYO COLLABORATIVE SERVICES, DBA MAYO MEDICAL LABORATORIES, ET AL. v. PROMETHEUS LABORATORIES, INC.

CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Argued December 7, 2011

This case involves the patentability of a law of nature, natural phenomenon, or product of nature. The Syllabus indicates that the subject matter under §101 of the AIA, 35 U. S. C. §101, “an application of a law of nature or process may [deserve] patent protection if the application transforms an unpatentable subject matter into something new and patent eligible.” Gottschalk v. Benson, 409 U. S. 63, 71–72. The question presented is whether a claim that states the law of nature while adding the words “apply it” to the claims is patent eligible under §101. See, e.g., Gottschalk v. Benson.
SUPREME COURT OF THE UNITED STATES

Syllabus

MAYO COLLABORATIVE STUDIES TRUST v. PROMETHEUS LABORATORIES INC.

CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Argued November 7, 2012

The Patent Act defines a patentable subject matter under §101 of the U.S. Code as a “process, machine, manufacture, or composition of matter.” An invention that adds a non-obvious step of following a natural phenomenon or law of nature by a correlation or relationship of such a law, a patent cannot be granted unless it is “part of a useful or patentable combination.” See e.g., Gottschalk v. Benson, 409 U.S. 63, 71-72. It must limit its reach to a particular, inventive application of the law.

DENIED
Mayo vs. Prometheus

SUPREME COURT OF THE UNITED STATES

MAYO v.

MEREDITH COOPER

NATURAL PROCESS + KNOWN ELEMENTS

is

NOT PATENTABLE

March 20, 2012
Court Reaffirms Right of Myriad Genetics to Patent Genes

August 16, 2012
DNA patent upheld
process patent not

August 16, 2012

A 2-1 panel of the U.S. Federal Circuit Court of Appeals in Washington, D.C.

Upheld right to patent "isolated" genes known as BRCA1 and BRCA2...

Denied patenting of methods of "comparing" or "analyzing" DNA sequences
Evolving Patent Landscape

- Bilski - Algorithm for hedging energy markets
  - June 28, 2010 (Supreme Court)
- Classen - Immunization schedule
  - Aug 31, 2011 (Federal Court Appeals)
- Prometheus - Drug dosing
  - March 20, 2012 (Supreme Court)
- Myriad - BRCA gene tests
  - August 16, 2012 (Federal Court Appeals)
What is patentable?

- Must be brought into physical world
- The physical element must be novel
- Cannot be a simple calculation, comparison, or mental process
So...

- Isolated genes and groups of genes are patentable

- Defining how to use them to diagnose diseases is potentially challenging

- Hire a clever lawyer

- Stay tuned...
From Discovery to Patient

In Vitro Diagnostic (IVD)

Options
- Pursue internally
- License to company
- Form a startup company
Innovator as Entrepreneur

“I call my invention ‘The Wheel’ but so far I’ve been unable to attract any venture capital.”

Forbes, Nov 2004
Bridging the Gap - Translational Development

What Academia Offers
- Early-stage IP
- Incomplete Technology Validation
- Unclear Market Potential

What Market Wants
- Validated IP
- Ready to Commer- cialize
- Clear Market Potential

Higher Risk, Unproven

Translation from Lab to Market = Translational Development

Lower Risk, Proven

Courtesy Daniel Behr
Most IP in Academia is Unproven

<table>
<thead>
<tr>
<th>% of IP Assets</th>
<th>Type of IP Asset</th>
<th>Path to Commercialization</th>
</tr>
</thead>
<tbody>
<tr>
<td>~10%</td>
<td>“Obvious low hanging fruit”</td>
<td>Easy to commercialize</td>
</tr>
<tr>
<td>~60%</td>
<td>“Promising, if only....”</td>
<td>Proof of concept needed</td>
</tr>
<tr>
<td>~30%</td>
<td>“Dogs”</td>
<td>No commercial value</td>
</tr>
</tbody>
</table>
What Investors Are Looking For

- **Product**
  - Diagnostic
  - Therapeutic
  - Device
  - Software
- **Service**
- **Service/Product Combo**
- **Strong IP position**
  - Clinical validation
  - Animal data, unmet need
  - Easy path to adoption
  - Sales, rapid adoption
- **Customers / revenue**
- **Slow but lower risk**

*Number 1 Question: Who cares and will pay for it?*

*Will it save someone money? How much?*
FDA Medical Device Approval Process

Including Diagnostic Tests and Instruments

- **R&D Concept and Design**: months- yrs
- **Pre-Clinical Product Development**: 12-36 mos
- **Clinical Trials**: 510(k) 0-9 mos, PMA 9-36 mos
- **FDA Review**: 510(k) 3-5 mos, PMA 12-24 mos
- **Available to Patients**: 0-24 mos
- **Reimbursement**: 0-24 mos

Adapted from Alfred E. Mann Foundation Biomedical Engineering
In Vitro Diagnostic (IVD) Devices

- An instrument, apparatus, implement, machine, contrivance, implant, *in vitro reagent*, or similar or related article, including any component, part, or accessory, which is ...

  - Intended for use in the *diagnosis of disease* or other condition, or in the *cure, mitigation, treatment, or prevention of disease*...
Multiple Regulatory Paths

- **Class I – Low risk**
  - Generally exempt from FDA pre-market review

- **Class II – Intermediate risk**
  - 510(k) submission, substantially equivalent to existing device

- **Class II – Highest risk**
  - PMA submission, novel device
FDA requires a diagnostic to be

- Safe
- Reliable
- Effective
  - Have clinical utility
  - Low false positive / false negative rates
Average Time to Decision: 510(k)s* (Receipt Cohorts as of March 11, 2012)

Fiscal Year (Receipt Cohort)

Days

- Total
- FDA
- Submitter

*SE and NSE decisions only; times may not add to total due to rounding

**Cohorts still open; FY 2011 cohort is only 85% closed and average times will increase

http://www.fda.gov/NewsEvents/Testimony/ucm300576.htm
Percent of 510(k)s With Additional Information (AI) Request on 1st FDA Review Cycle

Fiscal Year (Receipt Cohort)

Percent With AI Request

- 2000: 37%
- 2001: 38%
- 2002: 36%
- 2003: 40%
- 2004: 44%
- 2005: 50%
- 2006: 56%
- 2007: 61%
- 2008: 65%
- 2009: 72%
- 2010: 77%
- 2011: 75%

http://www.fda.gov/NewsEvents/Testimony/ucm300576.htm
Average Time to Decision on PMAs

**As of January 30, 2012 there are 4 applications without a decision; the average time to decision will increase as the cohort closes.**
Alternative Path #1
- CLIA Lab Service Model

- **R&D Concept and Design**
  - months- yrs

- **Pre-Clinical Product Development**
  - 12-36 mos

- **Establish CLIA Lab**
  - 3-12 mos

- **Reimbursement**
  - 0-24 mos

- **FDA Trial & FDA Review**
  - 3-60 mos

**Available to Patients**

**IVD Kit For Patients**

Adapted from Alfred E. Mann Foundation Biomedical Engineering
CLIA Model

- Requires significant infrastructure
- Providing service is a challenge
- Typically not suitable stat tests
CLIA Requirements

CMS Oversight – Biennial Survey/Inspection

- Personnel
- Proficiency Testing
- Quality Control
- Patient Test Management
- Facility Administration
- Quality Assessment
Alternative Path #2
- Europe / CE Mark

- **R&D Concept and Design**
  - months- yrs

- **Pre-Clinical Product Development**
  - 12-36 mos

- **EU CE Mark**
  - 3-12 mos

- **EU Reimbursement**
  - 0-60 mos

- **Available To EU Patients**

- **FDA Trial & FDA Review**
  - 3-60 mos

- **Available To US Patients**

Adapted from Alfred E. Mann Foundation Biomedical Engineering
Emerging Trends

- Consumer genomics
23andMe store

23andMe is the best place to take a personalized journey through your DNA.

23andMe offers access to the following, at one price with NO subscriptions:

- Over 200 online health & traits reports
- The largest genealogical DNA database in the world
- Updates on new genetic discoveries that are personalized for your DNA by our experts

$299  add to cart

Ships in 1-2 business days. Expect results 2-3 weeks after we receive your sample.

In your cart
Emerging Trends

- Consumer genomics
- Crowd-sourcing discovery
Want to Join?

PatientsLikeMe is only open to current members as we upgrade the website. Want us to email you when the doors reopen? Learn more.

Share your health profile

Knome Services
Emerging Trends

- Consumer genomics
- Crowd-sourcing discovery
- Asia
Global IVD Markets

- Europe: 34%
- USA: 43%
- Asia: 15%
- ROW: 11%

Natarajan Sriram
Noninvasive Prenatal Testing (NIPT) - Genomic-based aneuploidy test

- 20,000 cases in U.S.
- 50,000 cases in China
Emerging Trends

- Consumer genomics
- Crowd-sourcing discovery
- Asia
- Changes at FDA
Case Study
- From lab to patients

ClevelandHeartLab®
Know your risk.
History of Cleveland HeartLab

- 2003 - NEJM Paper; MPO is a biomarker
Major Adverse Cardiac Events (MACE) Predicted by MPO

Risk of MACE at 30 days

Elevated MPO levels predict increased cumulative incidence of death or non-fatal MI

Initial baseline MPO level predicts risk for myocardial infarction at presentation

Adjusted hazard ratio 3.07 [1.21-4.26]
Rapidly Growing Awareness

The NEW ENGLAND JOURNAL OF MEDICINE

Prognostic Value of Myeloperoxidase in Patients with Chest Pain

Maria-Louise Bennet, MD, Marc S. Penn, MD, Ph.D, Frederick Van Lenten, Ph.D, Vijay Nambri, M.D., Mehdi H. Shafiee, D.O., Ronnier J. Aviles, M.D., Madhura Goonmast, M.P.H., Michael L. Popay, B.S., Ellen S. McEwen, M.S.N., Eric J. Topol, M.D., Steven L. Nissen, M.D., and Stanley L. Hazen, M.D., Ph.D.

Association Between Myeloperoxidase Levels and Risk of Coronary Artery Disease

Renliang Zhang, MD, PhD
Marie-Louise Bennet, MD
Xiaoming Fu, MS
Ronnier J. Aviles, MD
Gregory L. Pearce, MS
Marc S. Penn, MD, PhD
Eric J. Topol, MD
Dennis L. Sprecher, MD
Stanley L. Hazen, MD, PhD

Context Myeloperoxidase (MPO), a leukocyte enzyme that promotes oxidation of lipoproteins in atheroma, has been proposed as a possible mediator of atherosclerosis.

Objective To determine the association between MPO levels and prevalence of coronary artery disease (CAD).

Design, Setting, and Patients Case-control study conducted from July to September 2000 in a US tertiary care referral center, including 158 patients with established CAD (cases) and 175 patients without angiographically significant CAD (controls).

Main Outcome Measures Association of MPO levels per milligram of neutrophil protein (leukocyte-MPO) and MPO levels per milliliter of blood (blood-MPO) with CAD risk.

Results Leukocyte- and blood-MPO levels were both significantly greater in patients with CAD than in controls (p < 0.01). In logistic models adjusting for age...
History of Cleveland HeartLab

- 2003 - NEJM Paper; MPO is a biomarker
- 2004 - Spun-out of the Cleveland Clinic
History of Cleveland HeartLab

- 2003 - NEJM Paper; MPO is a biomarker
- 2004 - Spun-out of the Cleveland Clinic
- 2005 - Sub-licensed MPO test
History of Cleveland HeartLab

- 2003 - NEJM Paper; MPO is a biomarker
- 2004 - Spun-out of the Cleveland Clinic
- 2005 - Sub-licensed
- 2007 - US Patent Issued

---

(12) United States Patent
Hazen et al.

(54) MYELOPEROXIDASE, A RISK INDICATOR FOR CARDIOVASCULAR DISEASE

(75) Inventors: Stanley Hazen, Pepper Pike, OH (US); Renliang Zhang, Cleveland, OH (US)

(73) Assignee: The Cleveland Clinic Foundation, Cleveland, OH (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 574 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: 10/039,751

(22) Filed: Jan. 2, 2002

Prior Publication Data


Related U.S. Application Data

(60) Provisional application No. 60/259,340, filed on Jan. 2, 2001, provisional application No. 60/283,432, filed on Apr. 12, 2001.

(51) Int. Cl.

---

US 7,223,552 B2


(45) Date of Patent: May 29, 2007


(Continued)

Primary Examiner—David A. Saunders
(74) Attorney, Agent, or Firm—Callie, Halter & Griswold
History of Cleveland HeartLab

- 2003 - NEJM Paper; MPO is a biomarker
- 2004 - Spun-out of the Cleveland Clinic
- 2005 - Sub-licensed MPO test
- 2007 - US Patent Issued
- 2008 - Difficulty raising money
History of Cleveland HeartLab

- 2003 - NEJM Paper; MPO is a biomarker
- 2004 - Spun-out of the Cleveland Clinic
- 2005 - Sub-licensed MPO test
- 2007 - US Patent Issued
- 2008 - Difficulty raising money
- 2009 - Cleveland HeartLab; New management, New business model, CLIA Lab
History of Cleveland HeartLab

- 2003 - NEJM Paper; MPO is a biomarker
- 2004 - Spun-out of the Cleveland Clinic
- 2005 - Sub-licensed MPO test
- 2007 - US Patent Issued
- 2008 - Difficulty raising money
- 2009 - Cleveland HeartLab; New management, New business model, CLIA Lab
- 2010 - Rapid revenue growth, market presence
History of Cleveland HeartLab

- 2003 - NEJM Paper; MPO is a biomarker
- 2004 - Spun-out of the Cleveland Clinic
- 2005 - Sub-licensed MPO test
- 2007 - US Patent Issued
- 2008 - Difficulty raising money
- 2009 - Cleveland HeartLab; New management, New business model, CLIA Lab
- 2010 - Rapid revenue growth, market
- 2011 - Successful VC financing