University of Leeds, 7 July 2010

DNA Patents and Policy

The Neverending Story

Robert Cook-Deegan, MD
Institute for Genome Sciences & Policy
Duke University

Layers of the stories

- Hot science, rapidly changing: from hypothesis testing to data mining
- Technology shocks
- Shifting jurisprudence
- Differences in how patents work for different applications
- Very different business models

Key events

- 1980: Chakrabarty, Bayh-Dole
- 1982: Court of Appeals for Fed Circuit
- Chugai (erythropoietin)
- 1991: EST patent controversy
- 1997: UC v Lilly (insulin)
- 1998: Myriad suits, Celera formation
- 2009: Metabolite v Labcorp
- 2010: Prometheus, Bilski, BRCA

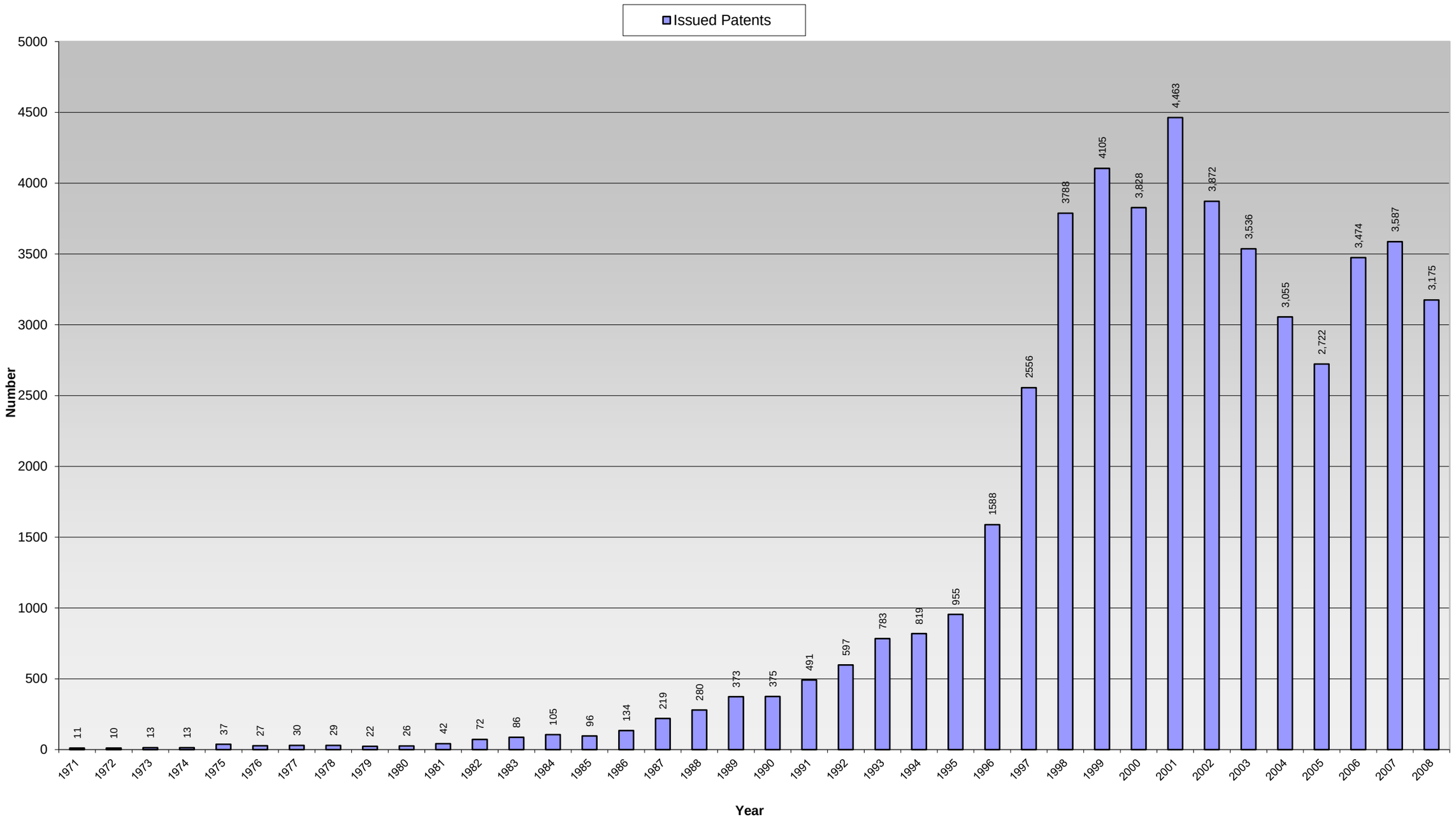
Next year at CAFC

- Must revisit Prometheus in light of an incoherent, unstable, and unpredictable Bilski ruling from Supreme Court
- Must decide BRCA case on appeal

Changing rules

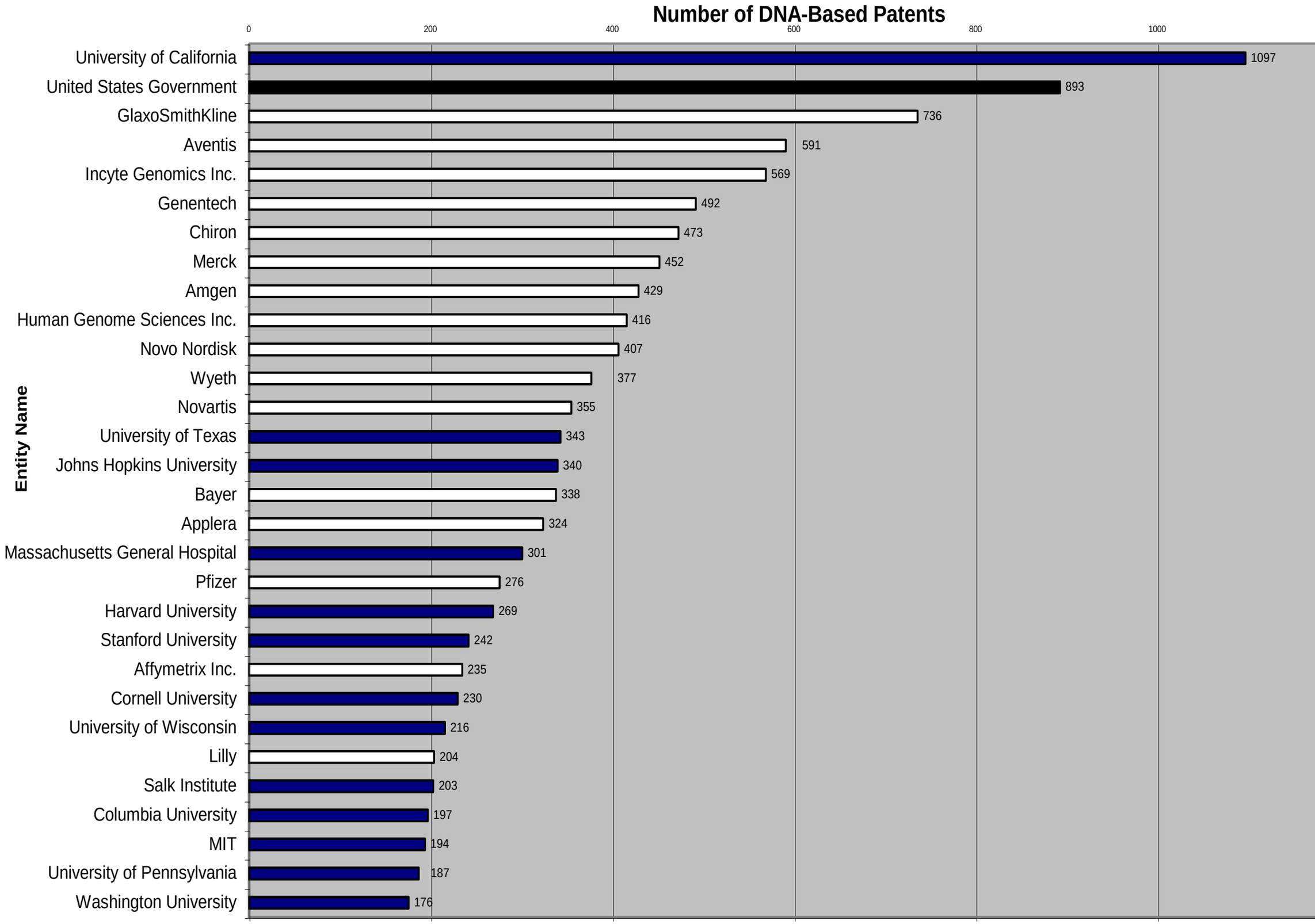
- Bilski and Prometheus: How viable and broad are “method” or “process” claims?
- KSR and In re Kubin: “obviousness” beginning to do some work again
- MercExchange: Injunctive relief less automatic (matter most for inventions that embody many patented elements)

DNA Patents in USA



Source: LeRoy Walters and Mara Snyder, Georgetown Univ, March 2009

Preliminary Data about the 30 Entities Holding the Largest Numbers of DNA-Based Patents (as of 03-20-07)



Source: LeRoy Walters & Randeep Singh, DNA Patent Database, Georgetown University

(In)Famous Patents

- BRCA1 and BRCA2
- Canavan's disease
- Athena Diagnostics exclusives (Alz, brain, kidney, endocrine)
- Cre-Lox and oncomouse

- Erythropoietin, insulin, growth hormone, clotting factors, immune modulators
- Cohen-Boyer recombinant DNA; Axel-Wigler-Silverstein
- Illumina, fluorescent sequencing, cell-sorting, pyrosequencing

Seminal Technologies

Southern blot
pBR322 cloning vector
BLAST
Cohen-Boyer rDNA method and plasmids
Axel-Wigler-Silverstein cotransformation*
Cloning of insulin and growth hormone genes*
Sanger-Coulson sequencing
Maxam-Gilbert sequencing
RFLP genetic linkage mapping (abandoned)
Polymerase Chain Reaction*
Automated fluorescent 4-color DNA sequencing instruments*
DNA microarrays*
BioPERL
Sequence assembly methods and analysis

In progress: Illumina, 454 pyrosequencing, Solexa,Pacific BioSciences, Oxford Nanopore, other new sequencing methods

Unpatented Patented-academic Patented-private

* = litigation

Examples of patent function

- Just Desserts

  PCR; recombinant DNA; Axel: inventing institution gets a stream of funding
- Induced Investment

  BRCA: prospect of patents induces investment in Myriad

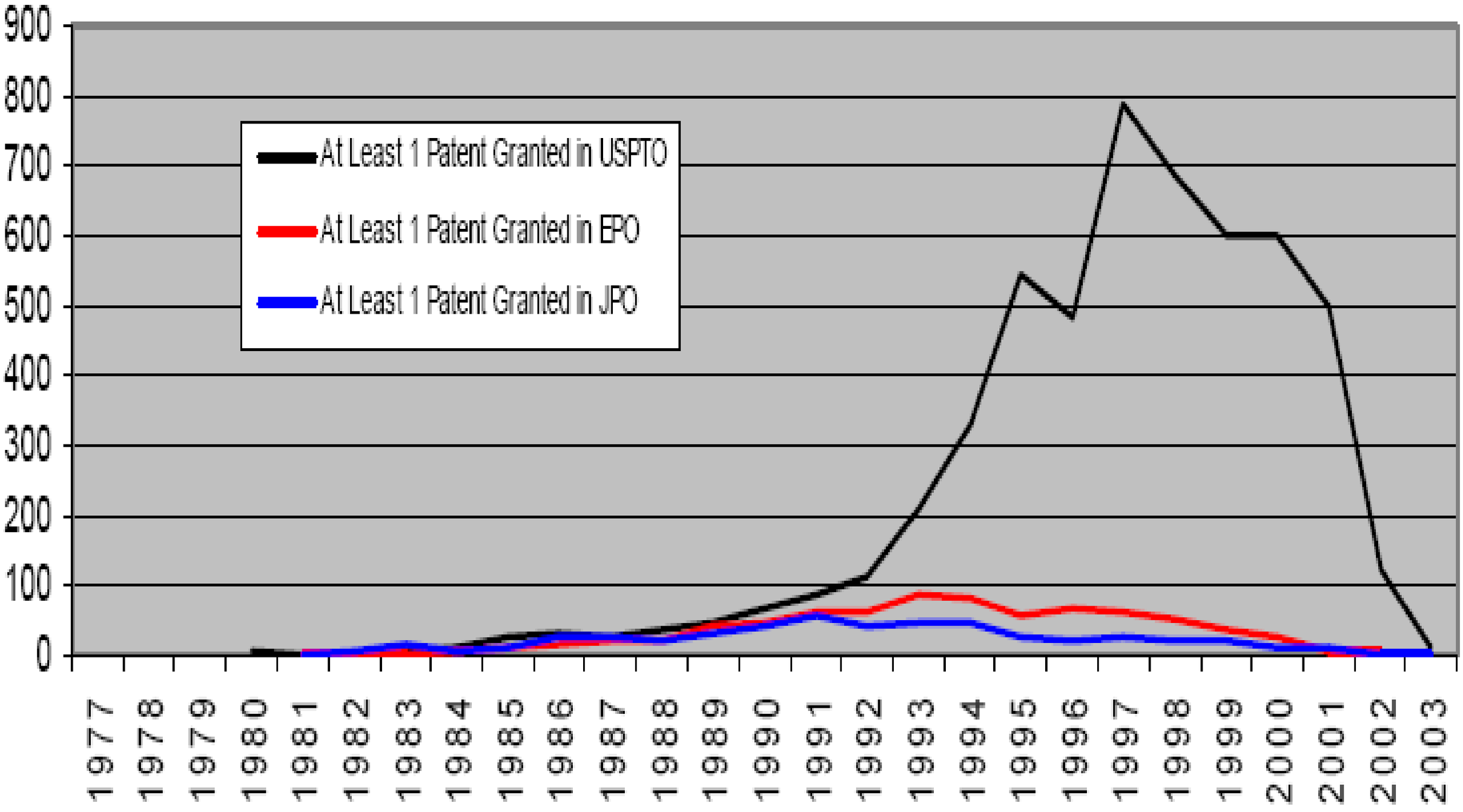
  Incyte and Human Genome Sciences: cash for cDNA sequencing

  Illumina startup
- Enable private R&D for engineering and development

  Applied Biosystems, Solexa, Illumina, 454, etc.
- Prevent free riders, prevent obliteration by “Big Guys”

  Erytyropoietin, growth hormone—expensive safety & efficacy trials: patents enable clinical testing and rise of Amgen/Genentech to “baby pharma”

No. of families with granted patents on DNA sequences by filing year



Source: Science Policy Research Unit, University of Sussex, p. 14
PATGEN Project final report http://www.sussex.ac.uk/spru/documents/patgen_finalreport.pdf

Dx v Rx

- Rx: DNA as the therapeutic agent or a way to make such an agent
- Dx: Purpose of test is to glean information about sequences in a person’s cells

Method claims

US Patent 5,753,441 (BRCA1)

1. A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises comparing germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1 cDNA, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from wild-type indicates an alteration in the BRCA1 gene in said subject.

US Patent 5,508,167 (ApoE, Alzheimer’s)

1. A method of detecting if a subject is at increased risk of developing late onset Alzheimer's disease (AD) comprising directly or indirectly: detecting the presence or absence of an apolipoprotein E type 4 isoform (ApoE4) in the subject; and observing whether or not the subject is at increased risk of developing late onset AD by observing if the presence of ApoE4 is or is not detected, wherein the presence of ApoE4 indicates said subject is at increased risk of developing late onset AD.

Sequence/molecule claims

US Patent 5,747,282 (BRCA1, breast CA)

1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.

2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1.

5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.

US Patent 5,679,635 (ASPA, Canavan)

1. An isolated nucleic acid molecule comprising: (a) a nucleic acid sequence encoding a human aspartoacylase polypeptide; (b) a nucleic acid sequence fully complementary to nucleic acid sequence (a); or (c) a nucleic acid sequence at least 16 nucleotides in length capable of hybridizing specifically with one of said nucleic acid molecules (a) or (b).

Problems with claim 5

- It claims over 1.6 million 15-mer molecules
- Those molecules are found in about 80 percent of “gene” sequences contributed to GenBank the year before the patent application was filed
- Hits 300,000 sequences in chromosome 1, probably many millions in human genome and ? in other genomes

Cho et al. *J Molec Dx* 2003

Condition	Gene(2)	No. labs that stopped testing
Alzheimer's	APOE	9
Breast & ovarian CA	BRCA1/2	9
Muscular dystrophy	dystrophin	5
Hemochromatosis	HFE	4
Spinocerebellar ataxia	SCA genes	4
Canavan disease	ASPA	4

68% of patents from academic institutions, 59% from federally funded research

Case studies

- Breast v colon cancer
  - BRCA 1&2 versus HNPCC/FAP, BRCA through Myriad; colon through Myriad and other testing services
- Tay-Sachs v Canavan's
  - Patent + restrictive license v liberal licensing/no licensing of gene patent
- Cystic Fibrosis
  - Broad nonexclusive licensing/patents
- Hemochromatosis
  - Patented by startup, sold, nonexclusive licensing, but with nongenetic screening test that constrains price
- Spinocerebellar ataxias
  - Many genes, cases rare, specialized care, patenting variable, mainly through Athena
- Hearing loss
  - Many genes, some common & patented, others rare, some unpatented, effort to form pool, possibility of microarray test?
- Alzheimer's disease
  - Three autosomal dominant early-onset, ApoE susceptibility testing for late onset, mainly through Athena

SACGHS Case Studies

Patenting and Licensing for Ten Conditions with Mendelian Inheritance

Medical condition (Test providers)	Gene(s) associated	Patent/licensing status
Inherited risk of breast and ovarian cancer (Myriad dominant in US)	*BRCA1, BRCA2*	Patents held by universities, NIH, and Myriad Genetics. Exclusively licensed to Myriad.
Inherited risk of colorectal cancer (Myriad and others)	*APC, MYH* (FAP and attenuated FAP) *MLH1, MSH2, MSH6* (Lynch Syndrome)	University patents nonexclusively licensed
Tay-Sachs disease (Various providers)	*HEXA* (enzyme function usually tested)	*HEXA* gene patent owned by NIH; not licensed
Canavan disease (Various providers)	*ASPA*	Miami Children's Hospital Research Institute owns patent; initial restrictive licensing; confidential settlement
Cystic Fibrosis (Various providers)	*CFTR*	University patents nonexclusively licensed
Alzheimer's disease (Athena Diagnostics dominant in US)	Early Onset: *APP, PSEN1, PSEN2* Late onset: *APOE*	*PSEN2* university patent exclusively licensed to Athena; *PSEN1* and *APOE* university method patents, exclusively licensed to Athena
Spinocerebellar ataxia (Athena Diagnostics dominant in US)	30+ autosomal dominant genes (also recessive and X-linked, but not studied)	*SCA1, 2, 3, 6, 7 & 8* exclusively licensed to Athena; mostly university owned; *SCA-10* university patent, nonexclusively licensed to Athena; Athena owns patent for Aprataxin Others unpatented
Hemochromatosis (Various providers using Bio-Rad tests)	*HFE* (most common)	Patents owned initially by Mercator Genetics; Current owner BioRad Ltd Initial exclusive licensing; now nonexclusively licensed
Hearing loss (Athena Diagnostics main provider, but several others; sublicense to Pediatrix)	100+ genes; many mutations Connexin 26, 30, *MTRNR1*, *MTTS1*, *SLC26A4* commonly tested	Just 2 of most commonly tested 5 genes have patents owned by non-profits, exclusively licensed to Athena. Most other patents university owned
Long-QT Syndrome (PGxHealth and GeneDx)	11+ genes	University patents on several mutations and genes exclusively licensed to PGxHealth; other genes and mutations to GeneDx. Both firms testing 10+ genes

Table 1: Summary of findings from eight case studies prepared for a task force of the Secretary's Advisory Committee on Genetics, Health, and Society, U.S. Department of Health and Human Services. [URL when established].

Dx scenarios

- Patent, no license (no conflict): Tay-Sachs
- Patent, nonexclusive licenses (no major conflict): CF, Huntington's, colorectal CA
- Patent, exclusive licenses
  - Transient controversies: HFE, Long-QT, Canavan
  - Sole provider: BRCA, SCA, Alzheimer's

Blocking patents in genetic Dx

- Huys et al., 16 of 22 most commonly tested conditions have one or more blocking claims
- SACGHS case studies, exclusive licensing in 7 of 10 clinical conditions
- In no case was exclusive licensee first to market

Distinctive features of Dx

- Genes would have been discovered and tests developed without patents
- Low barriers to entry
- Enforcement by “notification” or “cease and desist” letters, not litigation
- University and reference labs usu. first to market
- *Very* broad method claims, but based on chromosomal location or other structural features (or medical condition)
- Some invalid claims based on sequence
- Patent on one common gene or mutation can leverage testing for an entire condition, including mutations never yet discovered
- Patent-protected testing generates proprietary databases for clinical interpretation that do not expire
- Many claims would be easy to work around if drafted in a way that is not invalid

Academic institutions

- >2/3 of patents are held by academic research institutions (Huys et al.)
- ~3/4 of patents held by academic institutions (Athena Dx exclusive licenses)
- Many laboratories that withdrew genetic tests are at universities (Penn, BU, Baylor, UCLA, Mayo, Harvard)
- Pervasive infringement in research: system depends on ignoring patents in research

Why Is Judge Sweet's BRCA ruling so different from CAFC decisions?

- Plaintiffs are not competitor companies but either clinicians, scientists, or patients (all potential users or customers)
- Came to 'gene patents' via diagnosis: not DNA engineered to produce something else, but useful only to degree that test captures the *information* found in samples

Judge Sweet's perspective

- Conflated "embodiment of information" with "therefore unpatentable"
- But the information is of a particular kind: valuable to the degree it reproduces information in cells, samples, or people
- Skolnick did not invent BRCA in the way cDNA constructs enabled EPO production, but discovered where to look in the genome for mutations, and identified some common mutations
- Judge Sweet is right that in this context "isolated" is doing no work
- DNA need not be inherently unpatentable, but this kind of claim might be
- DNA "things" that still could be patentable: regulatory sequences, vectors, inhibitory sequences, mutations with known effects…

Same gene, different Dx

- APOE4: Alzheimer’s, cardiovascular, macular degeneration
- Hearing impairment genes
- HFE and childhood leukemia
- PALB2
  - Discovered by Stratton, et al. for Fanconi’s anemia, childhood cancers, and breast-ovarian cancer
  - Vogelstein et al., for familial pancreatic cancer mutations

Whole genome scans

- 23andMe tests for 3 common BRCA mutations
- Navigenics reports an ApoE4 risk ratio
- Full-genome scans or sequencing would infringe many patents based on gene-by-gene sequence and method patents
- OncotypeDx breast cancer profile excludes BRCA
- >16,000 patents with claims that mention a DNA sequence in 2004 (Hopkins et al. 2006)

Why does it matter that some claims are invalid?

- Can’t have a pool with invalid patents
- Uncertainty about enforcement
- Costly litigation to define the boundaries
- Investors can’t depend on
- Follow-on invention investment confronts an additional layer of uncertainty

Policy options

- Let it work out
- Exemption from infringement liability for research use
- Exemption for diagnostic use (Belgium, SACGHS)
- Compulsory licensing for Dx when access is problematic (Belgium, France, Switzerland, US march-in under Bayh-Dole)
- No gene patents at all (Becerra-Weldon, ACLU suit)
- Patent pools (Goldstein and others)
- Licensing practices (esp. university)

Is the problem patents, or crummy business models?

- Myriad, PGxHealth, Athena Diagnostics depend on sole-source Mendelian testing
- Other firms are developing multiple-allele testing, microarray, or full-genome methods

Cleaning up the mess

- Infringement analysis takes new case law into account
- Re-examination of patents with vulnerable claims
- Emboldened users
- Litigation and case law

So where are we?

- Many patents on genes and methods
- Many claims broad and infringed by research
- Some claims probably invalid
- Wildly incoherent and unstable jurisprudence
- No case law until current ACLU suit

Where are we headed?

- Multi-allele testing and full-genome sequence analysis will infringe some claims
- Some such claims may not be held valid
- But some will be, and all are presumed valid until challenged

References

- Cho et al. *J Molec Diag 5: 3-8, 2003.*
- Huys et al. *Nature Biotechnology* 27: 903-909, 2009.
- Goldstein & Markowicz, ch 4 in *Clinical Trials in Psychopharmacology*, 2nd Ed., 2010, pp. 62-85.
- Cook-Deegan et al. *Nature* 458: 405-406, 2009.
- Secretary's Advisory Committee on Genetics, Health and Society, forthcoming.
- Hopkins et al. The Patenting of Human DNA, Univ Sussex (for Euro Commission), Nov 2006.