Affordable Whole-Genome Sequence Analysis: What Will Change?

Robert Cook-Deegan, MD

Duke Institute for Genome Sciences & Policy

Preparing for a Consumer-Driven Genomic Age

James P. Evans, M.D., Ph.D., David C. Dale, M.D., and Cathy Fomous, Ph.D.

NEJM
18 Aug 2010

Advances in genomic technologies permit the simultaneous analysis of millions of variants across the genome and may soon allow for meaningful estimation of one's risks of developing cancer, diabetes, and other common diseases. These advances are converging with the movement toward consumer-driven health care and patient empowerment genomic information is now increasingly available outside traditional medical settings. Patients are no longer subordinate, passive recipients of physician-initiated genetic testing; rather, patients can instigate their own testing and often know more than their clinicians about particular genetic topics. Indeed, health care providers are increasingly bypassed for help in interpreting their results. In the future, a primary role of health care professionals may be to interpret patients' DTC genetic test results and advise them about appropriate follow-up.

How can we maximize the benefits of these new developments and minimize the harms? How can we encourage patients' involvement and autonomy yet

CORRESPONDENCE

Consumers have a right to affordable genetic testing

There is no good reason for people to have access to their personal genetic information only through medical experts, as Arthur Beaudet suggests (*Nature* **466**, 816–817; 2010). Such tests provide an incentive for consumers to learn about genetics information will harm them is speculative.

Because some genetic tests may have to compete with less expensive, direct-to-consumer products, people calling for a ban on such tests should declare any competing financial interests.

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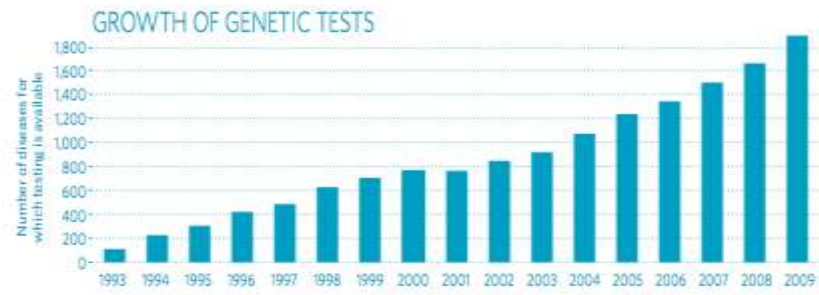
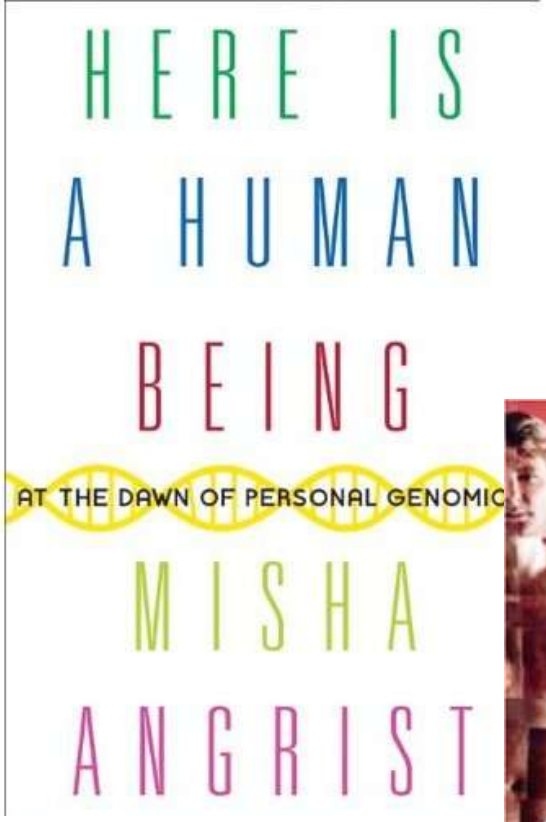
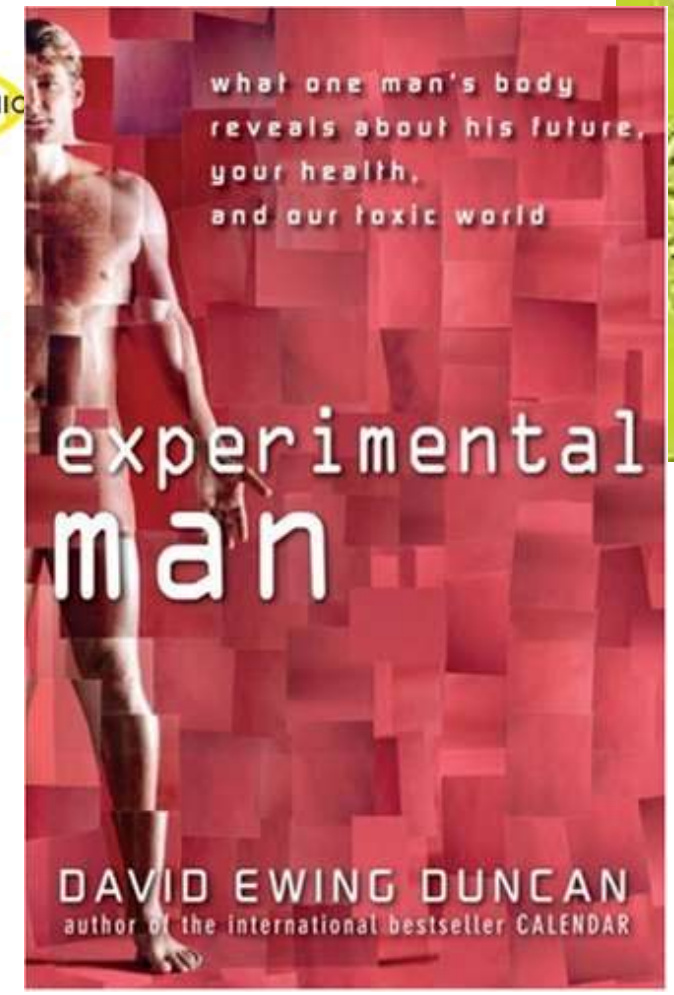
OPINION

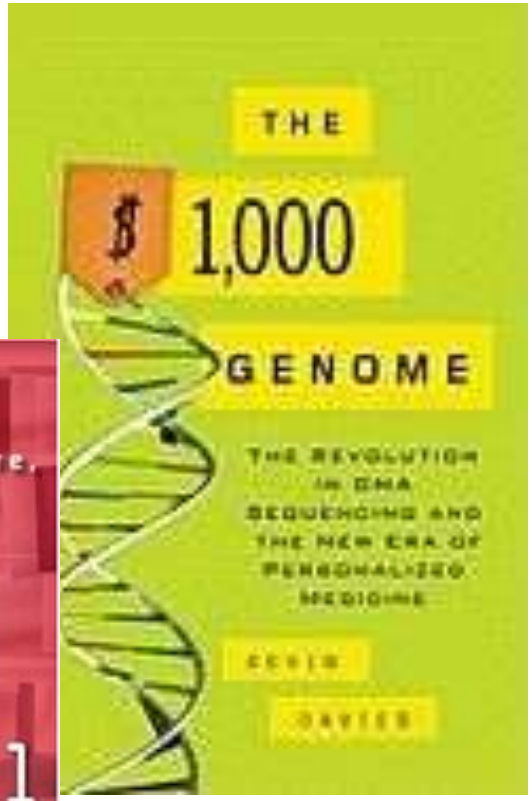
Which way for genetic-test regulation?

Although largely unregulated, genetic tests are increasingly used to diagnose conditions, map ancestry or predict disease risk. In the first of two related pieces, **Arthur L. Beaudet** advocates the US Food and Drug Administration banning direct-to-consumer medical tests but leaving the analysis of clinical diagnostics to specialists. In the second, **Gail Javitt** argues that the agency should implement a regulatory framework for all health-related tests.









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Trends

- Precipitous drop in DNA sequencing unit costs
- Strong consumer movements in IT and health
- Internet access presumed

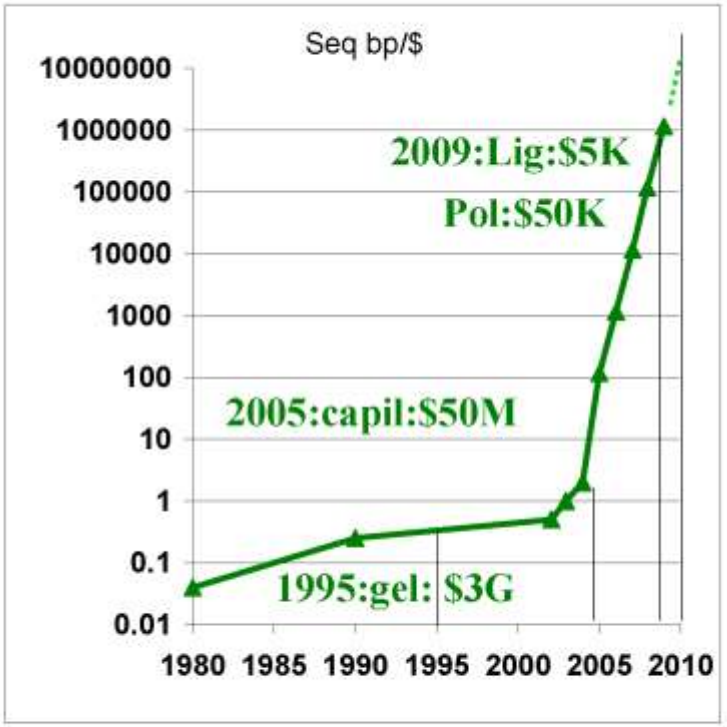
Factoids

- 2 genomes sequenced when “personal genomics” launched in November 2007
- Estimated 400+ three years later
- Projected exponential
- Application “creep” to gallop?

George Church's graph of DNA Sequencing Costs

4 logs in 4 years

(Moore's law)
1.5x/yr for electronics
vs
10x/yr for DNA Sequencing



Source: George Church, Harvard and MIT, Consumer Genetics, 9 June 2009, Boston's Hynes Convention Center

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Consequences of inexpensive sequencing costs

- Applications in science, then everything else
  - Medical testing, yes, but also…
  - Genealogy, relationship-finding, forensics, pet-marking, pathogen-detection, location detection
  - Many organisms we never knew existed
- New uses abound
- Network effects of ubiquity: your data are more valuable to me and mine to you

"reading the sequence itself turns out to be far less important than reading the sequence alongside other sequences"

Adrian Mackenzie, Institute for Cultural Studies
University of Lancaster "Bringing Sequences to Life"

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Full-Genome Sequence Analysis May Change …

- Many, perhaps most uses not yet envisioned
- Not a one-time "test," but information that once obtained is then re-interpreted throughout life
- Safety, efficacy, and accuracy, YES, but…
  - We will have to develop expertise and services to interpret genomic data for those using it
  - It won't be just medical, but also geneaological, ethnicity, relationship-mapping, and information about other organisms

Medical or Not?

- BRCA
- Huntington's
- 23andMe with BRCA variants
- deCODE Breast Cancer profile
- ApoE
- GWAS risk assessment
- Ancestry and genealogy
- Social Networking

Constants

- Complexity of genetic data
  - It was hard enough to explain Mendelian genetics
  - Now we have population substructure and layers of statistics and probabilities
- Potency of genetic risk predictions
  - Studies generally show mild, transient, anxious response to bad news, but reversion to baseline
  - But difficult conversations happen in practice
  - REVEAL study says little about safety

Regulatory framework

- Consumer goods: truth in advertising
- Drugs and devices: safety, efficacy and accuracy
- Huntington's model for genetic testing

Wild Card: Legacy of DNA Patents

- More than 50,000 DNA patents in US alone
- Some claims *are* infringed by research and diagnostic use
- *BRCA* case first to reach a judge's decision
- Evidence of harms and benefits equivocal
- Evidence of problems unequivocal
  - Not patenting per se, but business models & licensing: OECD guidelines of 2006
  - Point of collision: multi-allele Dx profiles

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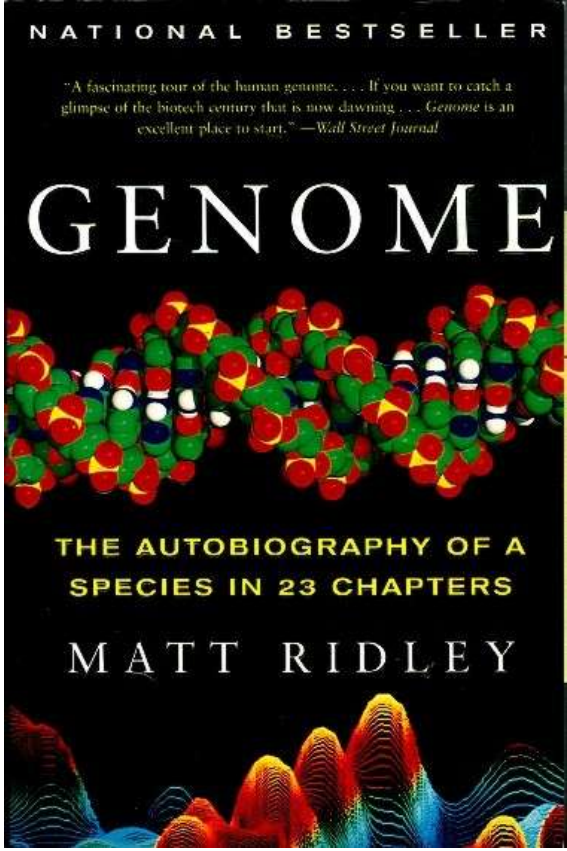
Focus has been on…

- "Danger" of potent information
- Need for expertise when interpreting complex information: health professional intermediary (Calif and NY states; German law)
- Informed consent for uses: prespecification or "blanket" consent?
- Privacy and confidentiality
- Patentability of DNA *per se*

Problems of regulating based on "genetic test" model

- Will forever be expensive, no matter how inexpensive sequencing and informatics get
- Barriers to entry high
- Innovation slow
- Most problems are about interpretation of information, not the "device" or its accuracy
- "Don't get between me and my genome"

"I am adamant to the point of fanaticism that it is my decision. My genome is my property and not the state's... It is for me. There is a terrible, paternalistic tendency to think that "we" must have one policy on this matter, and that government must lay down rules about how much of your own genetic code you may see and whom you may show it to."



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Focus should be on…

- How to interpret data that attain value only by pooling, linkage to other data, and observation over long periods
- How can I know whom to trust?
- Will my service give me my data back?
- Who else will they give it to? How will they use it?
- Will they stay in business? If they don't?
- How patents are used, not just whether they exist

The slides that follow are detail/data/graphics slides in case questions come up, not part of the presentation

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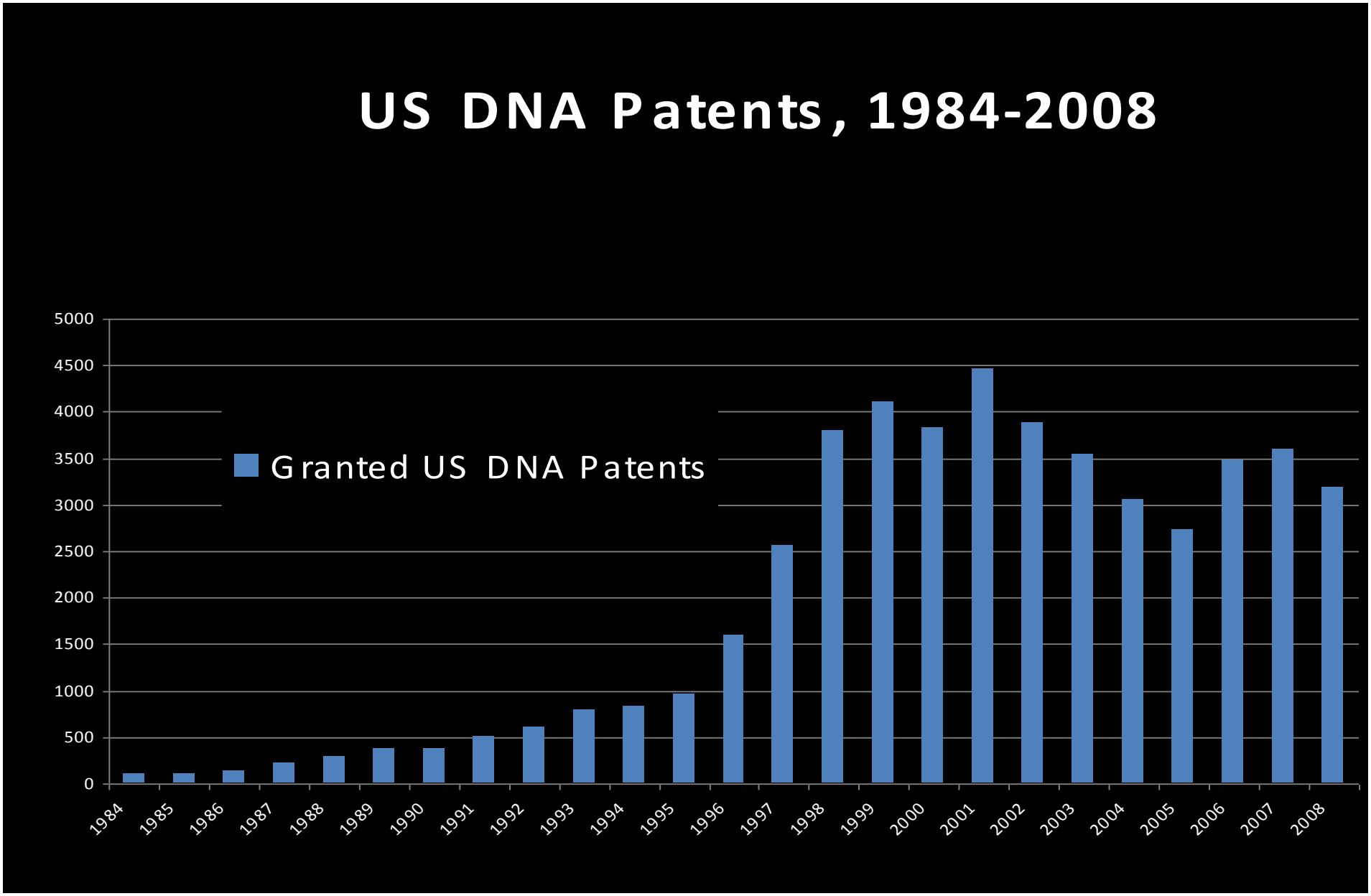
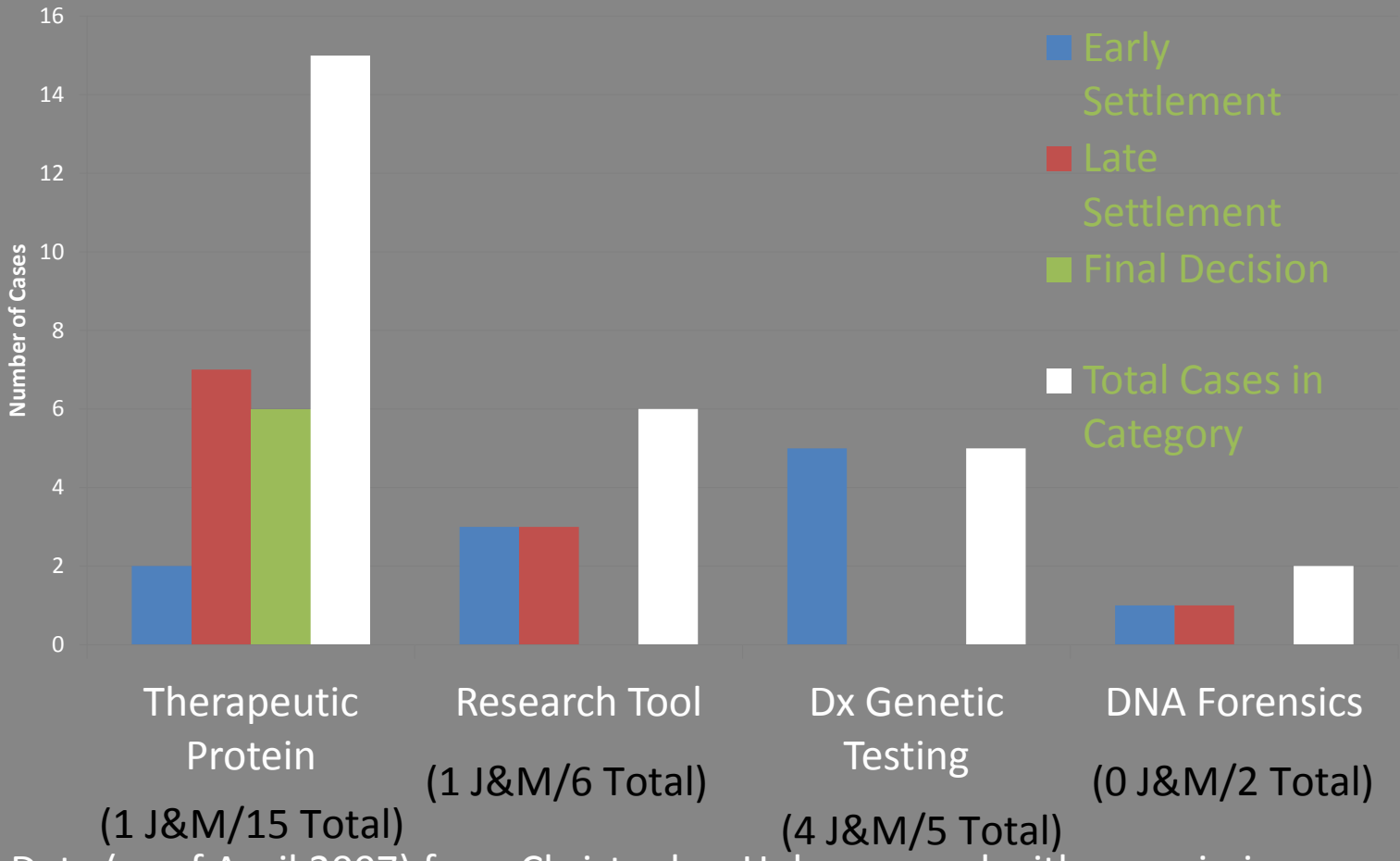
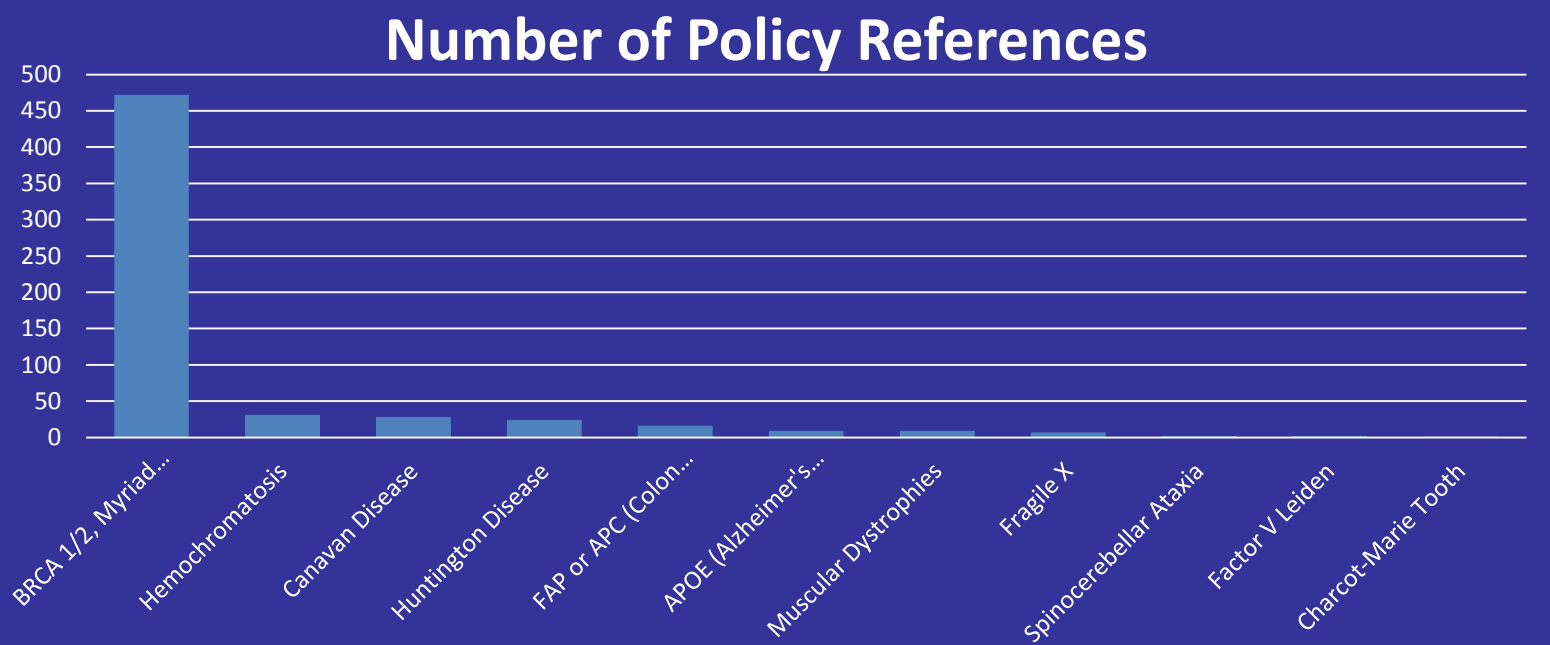


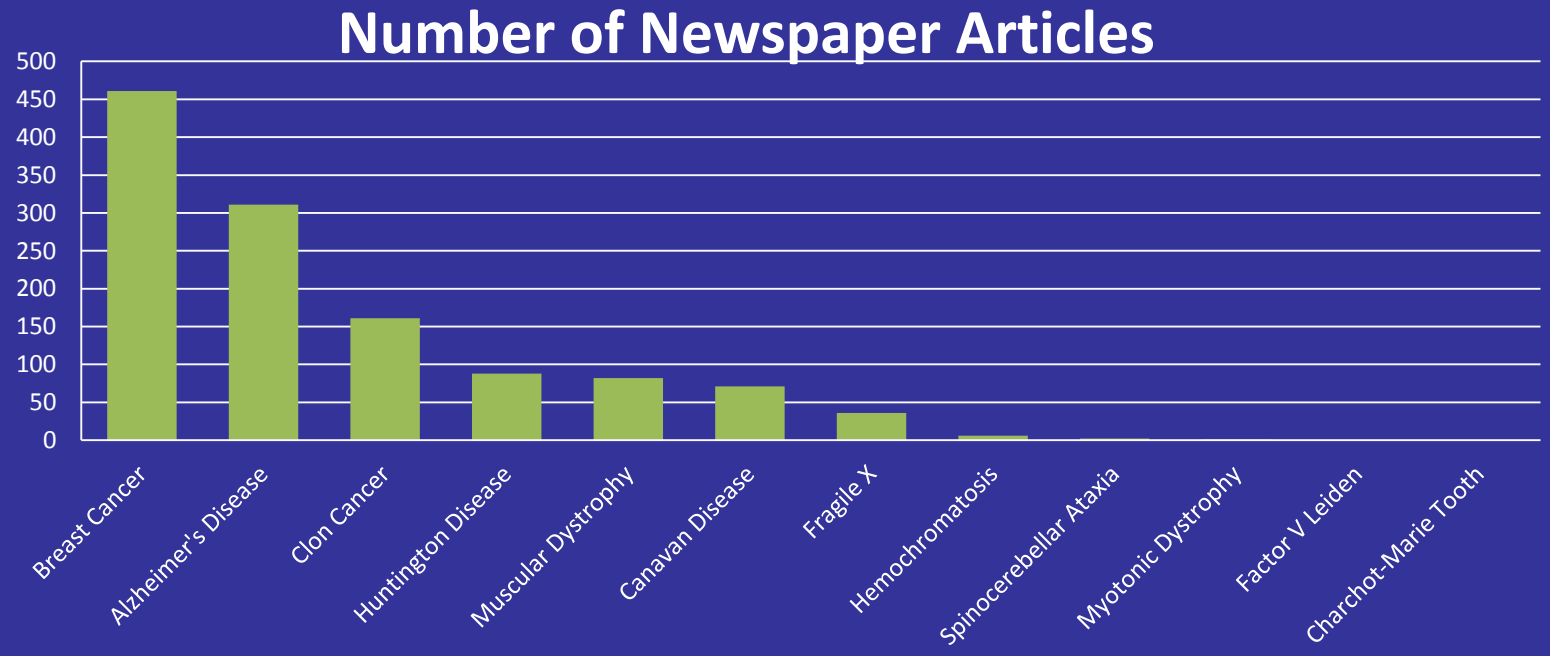
The DNA Patent Database (LeRoy Walters and Mara Snyder, Georgetown University) through Dec 2008).

Instances and Outcomes of Human Gene Patent Litigation



Data (as of April 2007) from Christopher Holman, used with permission. Does not include the suit against Myriad Genetics or the Canavan lawsuit.





Data from Caulfield *et al*., used with permission. Number of times a gene, condition, or controversy was cited in policy reports or English-language newspaper articles.

Sample 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).**

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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.

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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% note federally funded research

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].

Genetics in Medicine, Special Supplement, April 2010

References

Caulfield et al. *Nature Biotechnology* 24: 1091-4, 2006

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, and case studies published as supplement in April 2010 *Genetics in Medicine*

Holman, *Science* 322: 198-9 (10 October), 2008

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Who really did the work?

Michael McGeary, PhD
Subhashini Chandrasekharan, PhD
Ilse Wiechers, MD, MPP
Noah Perin, MPP + MBA
Sapna Kumar, JD
Jennifer Pohlhaus, PhD
Colin Crossman, JD

Alessandra Colaianni (U)
Joe Fore (U)
Whitney Laemmli (U)
Anupama Kotha (U)
Nancy Wang (U)
Suparna Salil (U)
Daidree Tofano (U)
Phebe Ko, BA
Molly Nicholson, BA
Cindy Wang, MPP
Matt DeCamp, MD/PhD (Philosophy)
Britt Rusert, PhD cand. (English)
Stacy Lavin, PhD cand. (English)
Marie Hicks, PhD cand. (History)
Marjorie Gurganus, JD

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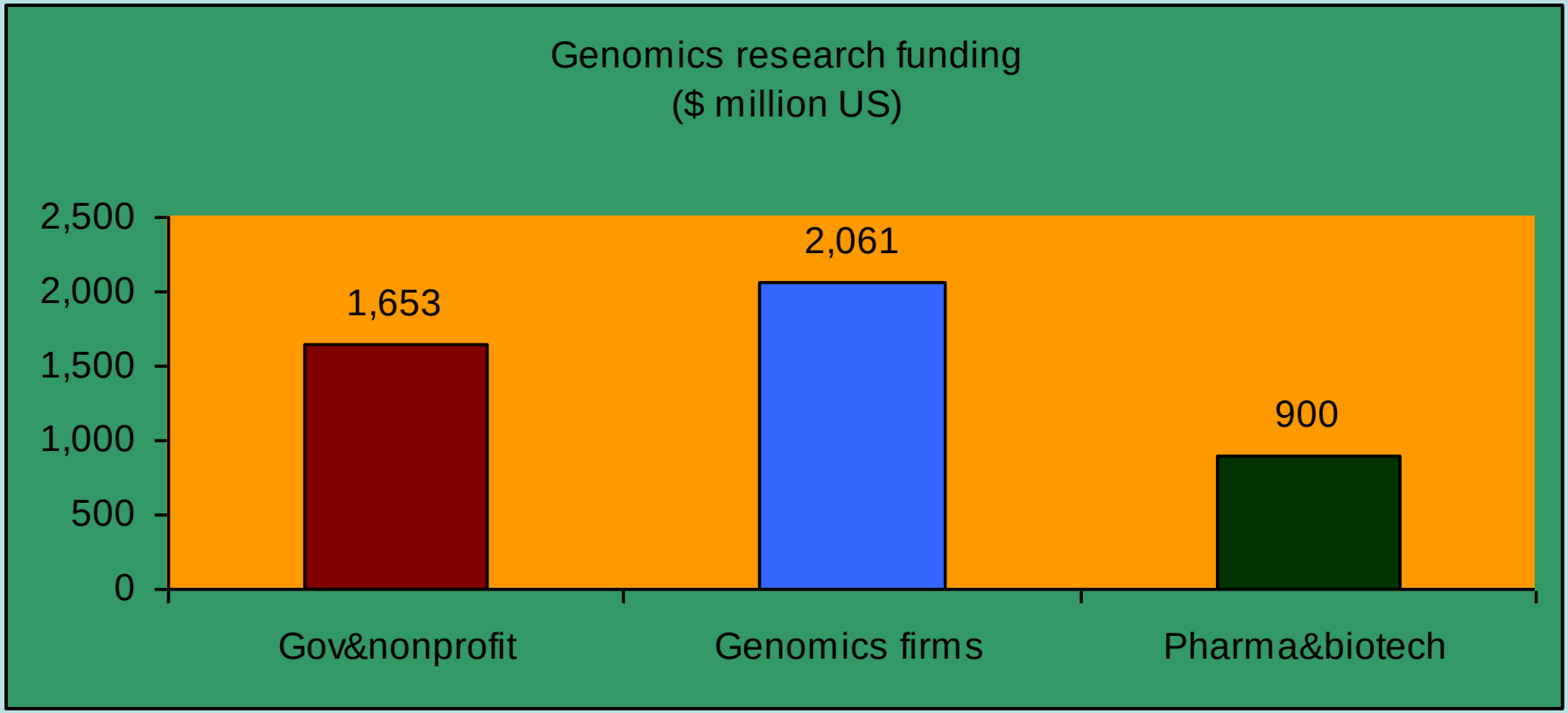
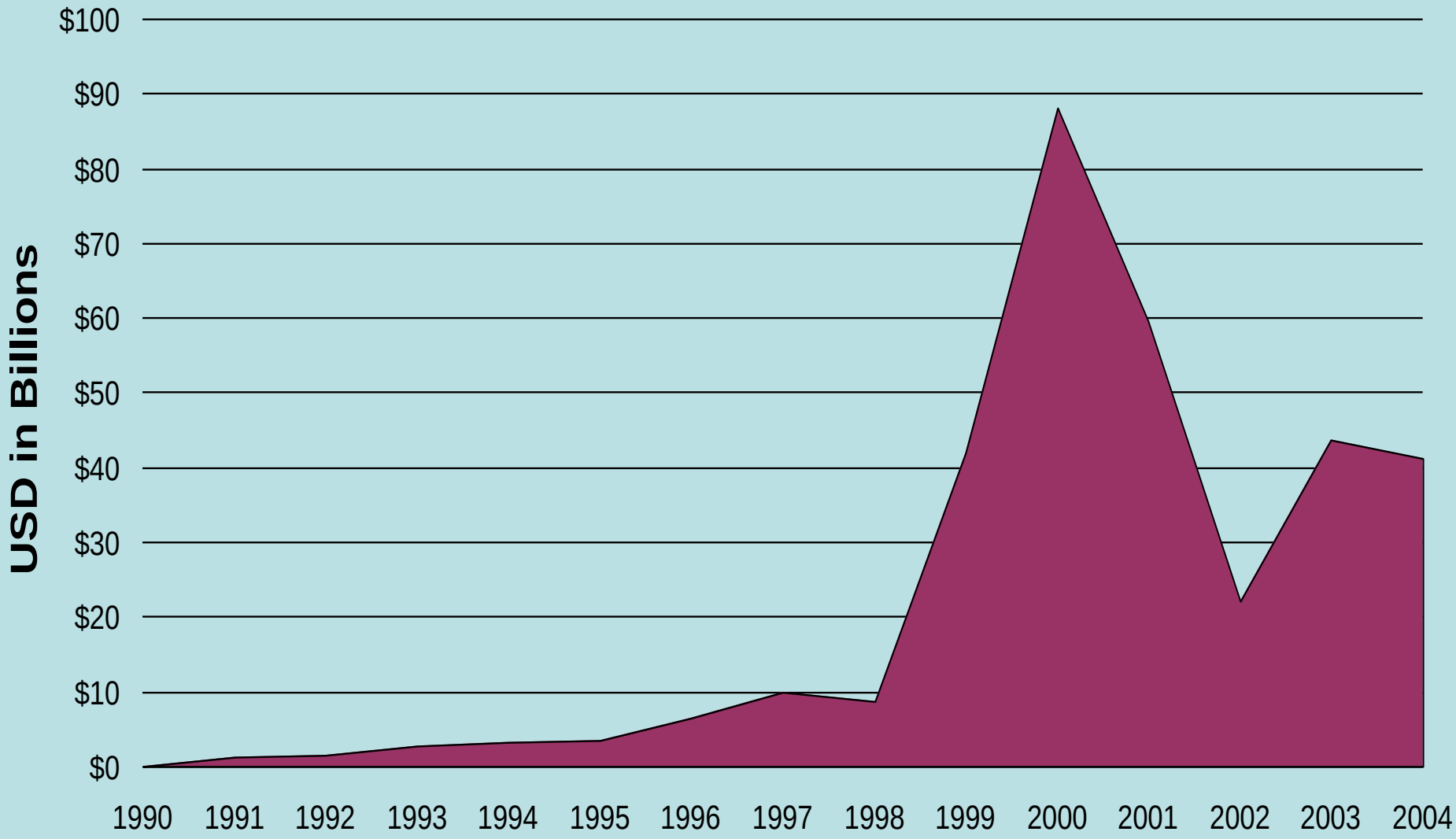
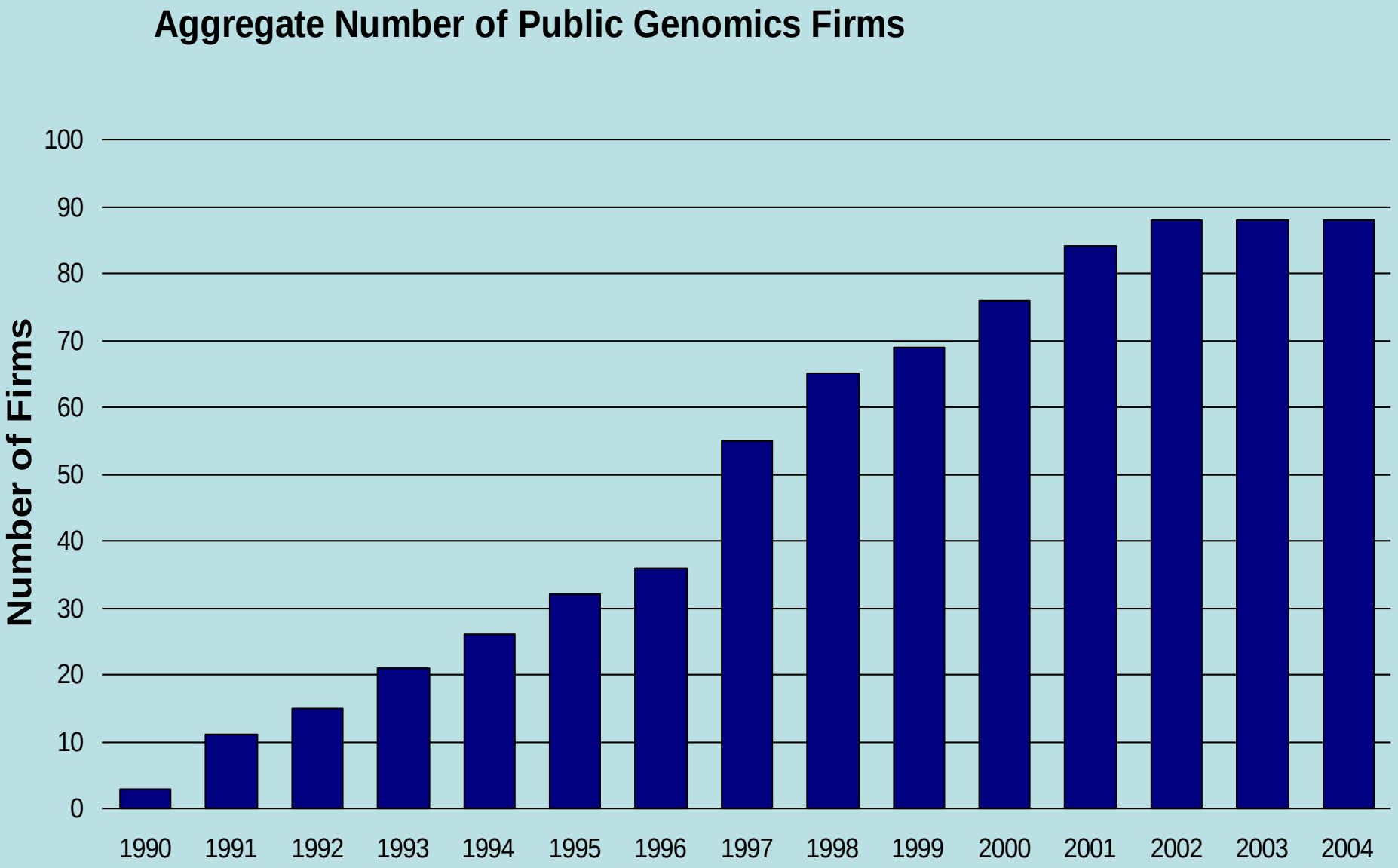
Genomics Funding: private>public (Year 2000)



Source: World Survey of Funding for Genomics Research
Stanford in Washington Program (Amber Johnson, Carmie Chan, Robert Cook-Deegan)
http://www.stanford.edu/class/siw198q/websites/genomics/

Aggregate Market Capitalization of All Genomics Firms




Aggregate Number of Public Genomics Firms
Number of Firms
100
90
80
70
60
50
40
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1990
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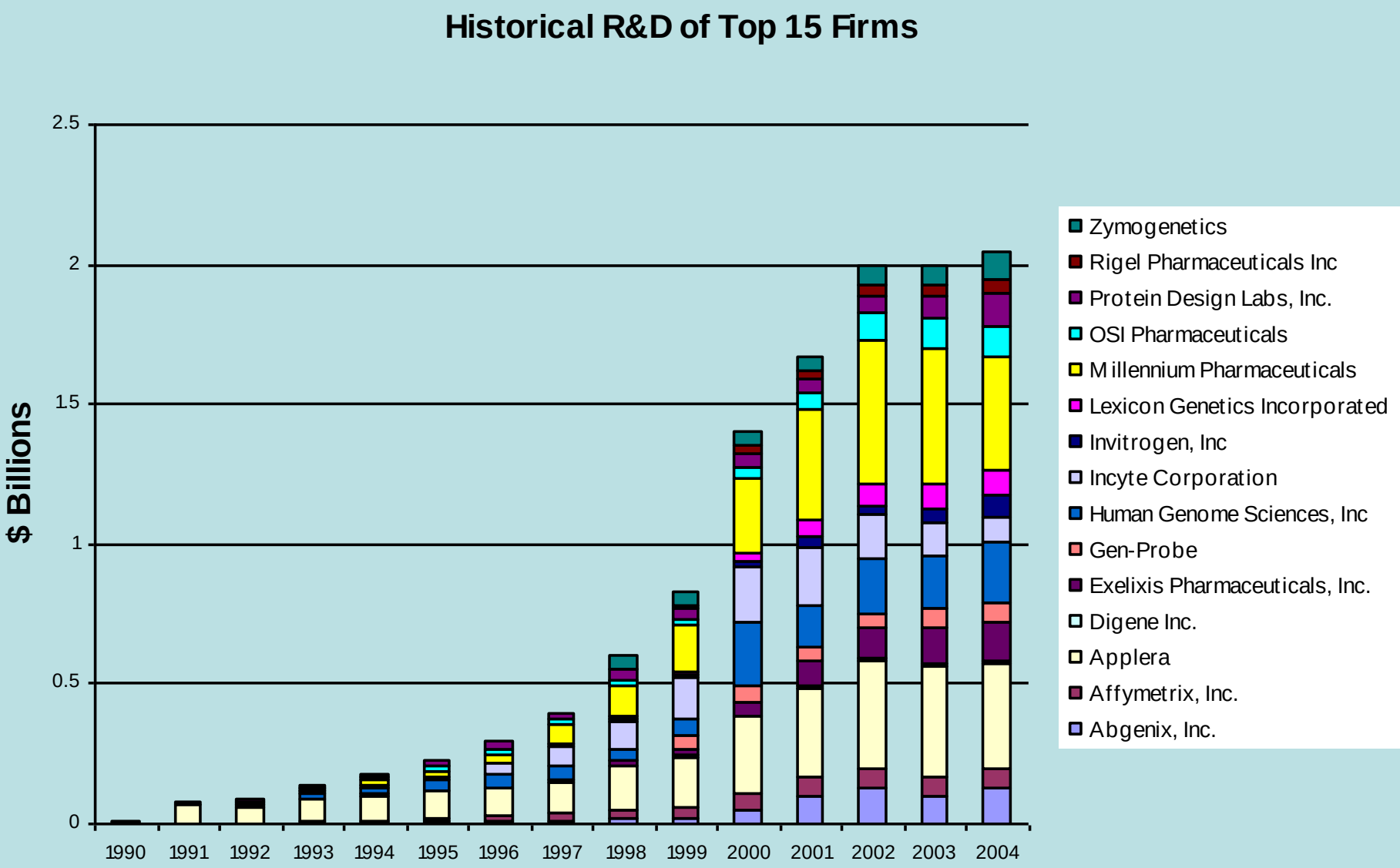

Source: Chandrasekharan, Perin, Wiechers & Cook-Deegan, 2008

Discovery of “Breast Cancer Genes”

- Genetic linkage 1990
- Mutations in BRCA1 and BRCA2 1994-5
- Myriad Genetics testing

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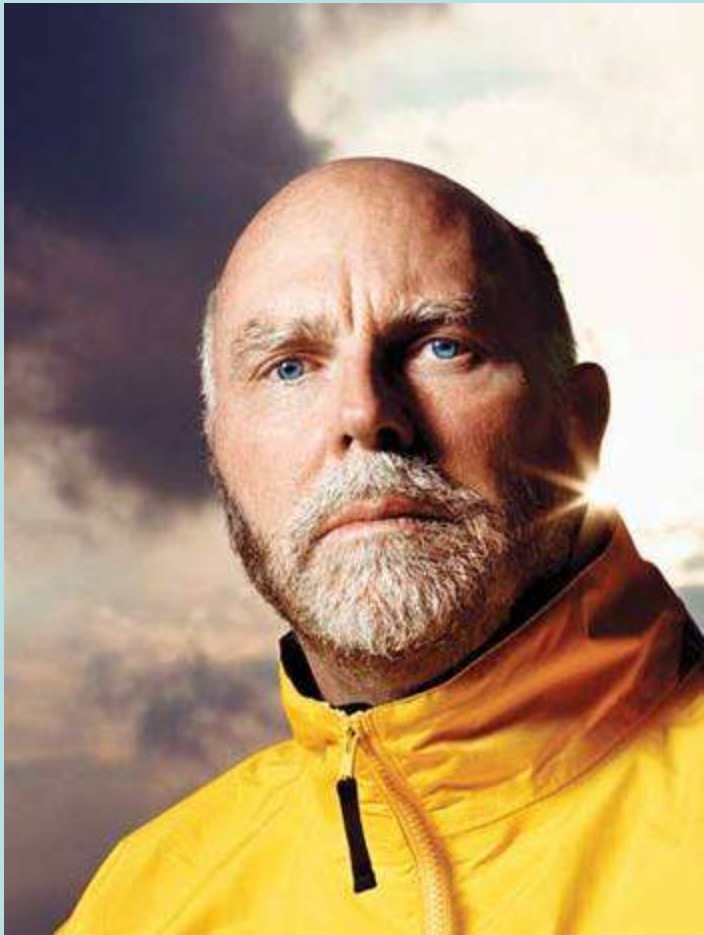
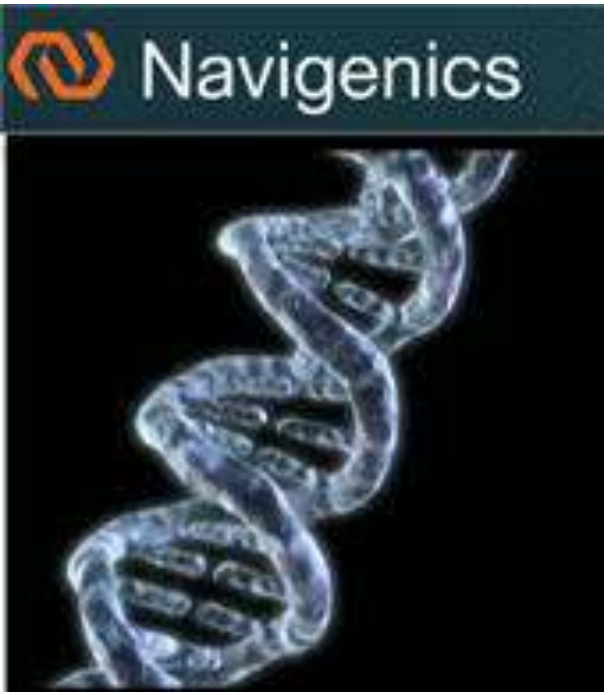
Genome of DNA Discoverer Is Deciphered
by Nicholas Wade, NYTimes June 1

6 Billion Bits of Data About Me, Me, Me!
by Amy Harmon, NYTimes June 3

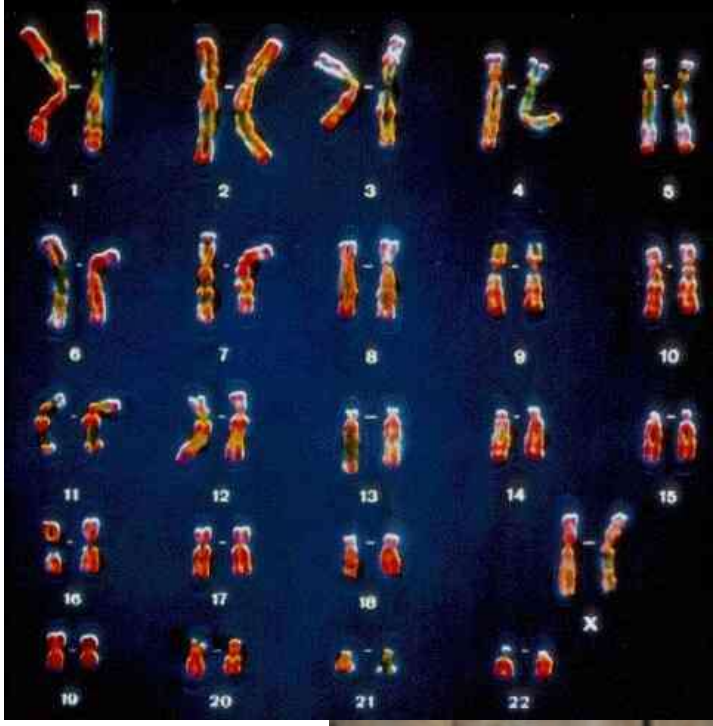


The Diploid Genome Sequence of an Individual Human
***PLOS Biology* October 2007**



David Agus &
Dietrich
Stephan

(Kleiner,
Perkins;
John Doerr)
Nov 6, 2007



Affymetrix technology

23andMe

Illumina technology
10 conditions + ancestry

Linda Avey & Anne Wojcicki
(Google, Sergey Brin)
Nov 19, 2007

deCODE ME

Kari Stefansson
Iceland
Nov 16, 2007

"For only $985 we scan over one million variants in your genome "
17 diseases + ancestry

8 of "PGP-10"

Knome

George Church

Nov 29, 2007

"Pricing for our services will start at $350,000, including whole-genome sequencing and a comprehensive analysis from a team of leading geneticists, clinicians and bioinformaticians."