A Primer on Patents and Policy

With special attention to the impact of intellectual property on access to genetic testing

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Factors affecting access

Price

Hassle (perturbation in existing service)

Regulatory approval

Reimbursement and coverage

Capstone project model: development cycle from Lewin report

Student case examples

- Breast v colon cancer
  - BRCA versus HNPCC/FAP
- 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
- Severe Combined Immune Deficiency
  - Many genes, cases rare, specialized care, patenting variable, possibility of microarray test?
- Hearing loss
  - Many genes, some common & patented, others rare, some unpatented, effort to form pool, possibility of microarray test?

Who really did the work?

Subhashini Chandrasekharan, PhD
Ilse Wiechers, MD, MPP
Noah Perin, MPP + MBA
Sapna Kumar, JD
Jennifer Pohlhaus, PhD
Colin Crossman, JD (PhD cand computational bio)

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 cand(Philosophy)
Britt Rusert, PhD cand(English)
Stacy Lavin, PhD cand(English)
Marie Hicks, PhD cand(History)
Marjorie Gurganus, JD

Reminder: what is a patent?

- Novel, useful, “nonobvious” invention
- Disclosed in enough detail that others can make and use it
- Enforced through the courts of national jurisdiction
- Open (“patent”) sharing of invention in return for right to exclude others from making, using, or selling it (without permission) for a period (20 year default)

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
Coming: Perlegen, Illumina, 454 pyrosequencing, Solexa

Unpatented Patented-academic Patented-private
* = litigation

Justifications

Human (inherent or natural) right

Instrumental "right" (intended to foster innovation—add "fuel of interest to fire of genius" [Lincoln])

1. Tool to fairly distribute fruits of invention
2. Tool to induce investment in R&D
3. Tool to solve problem for inventions that require substantial post-discovery development (R&D free-rider problem)

Examples of patent function

Just Desserts

- PCR & recombinant DNA: inventing institution gets a stream of funding

Induced Investment

- BRCA: prospect of patents induces investment in Myriad
- Incyte and Human Genome Sciences do cDNA sequencing

Prevent Free Riders

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

Some numbers

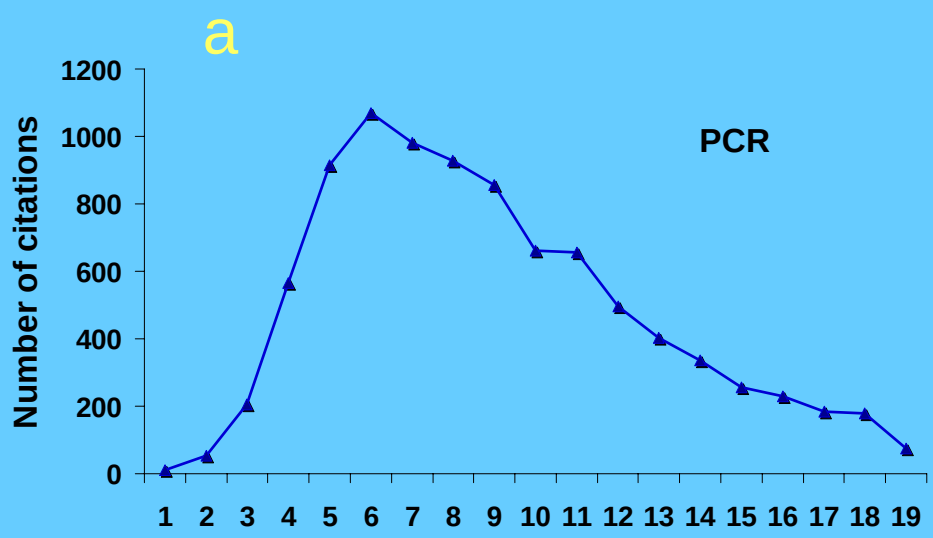
- ~44,000 *US* *DNA* patents
- ~16,000 world *sequence* patent families
- ~3,000 US human *genes* patented
- ~750 EuroPO *sequence* patents
- ~500 Japan *sequence* patents

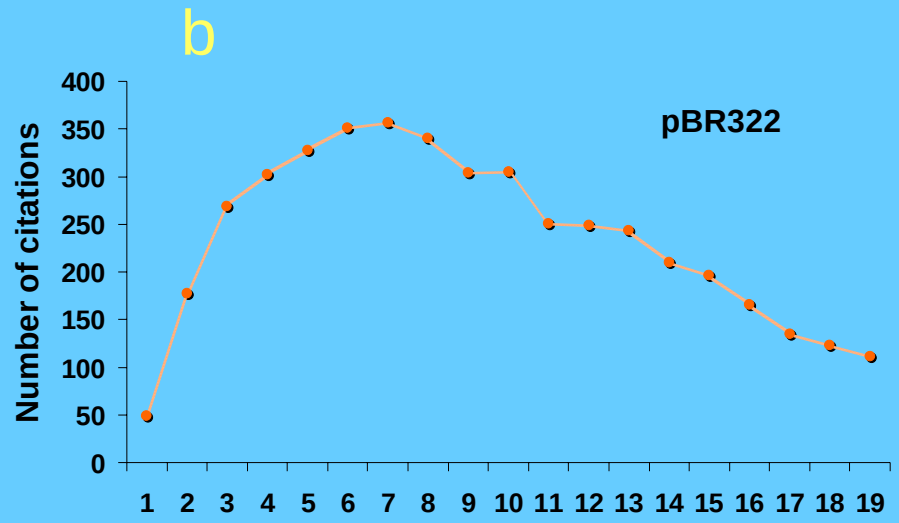
Sources: LeRoy Walters, DNA patent database (Mar 2007)
Jensen & Murray *Science 310 (15 Oct)* 2005 (match RefSeq from among ~4300 patents and ~4400 claimed gene sequences; removing multi-probe claims; Apr 2005 data)
Hopkins, et al., SPRU, Univ. Sussex (data through 2004)

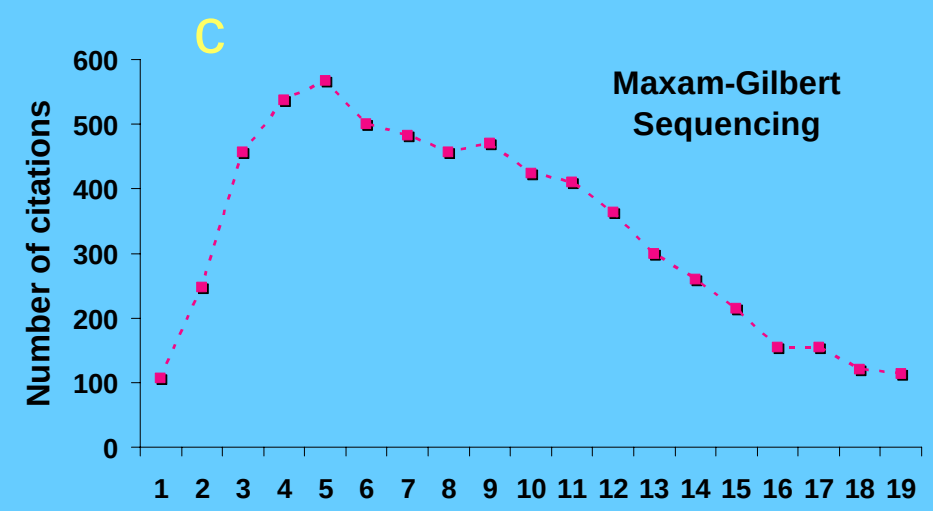
Patents & Research
good and bad

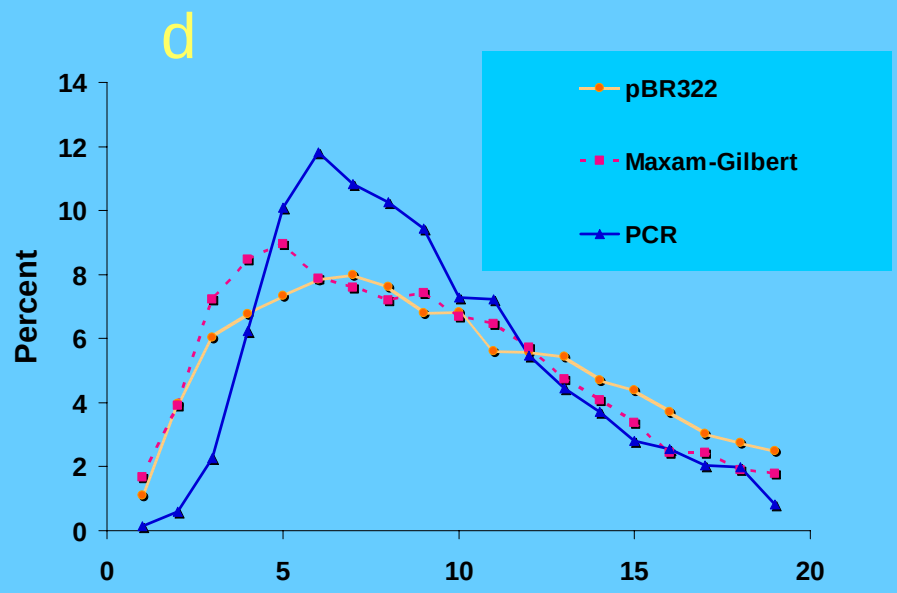
- Induce private R&D
- Create assets for startups
- Enable returns on post-discovery development (e.g., drugs)
- Generate income for universities

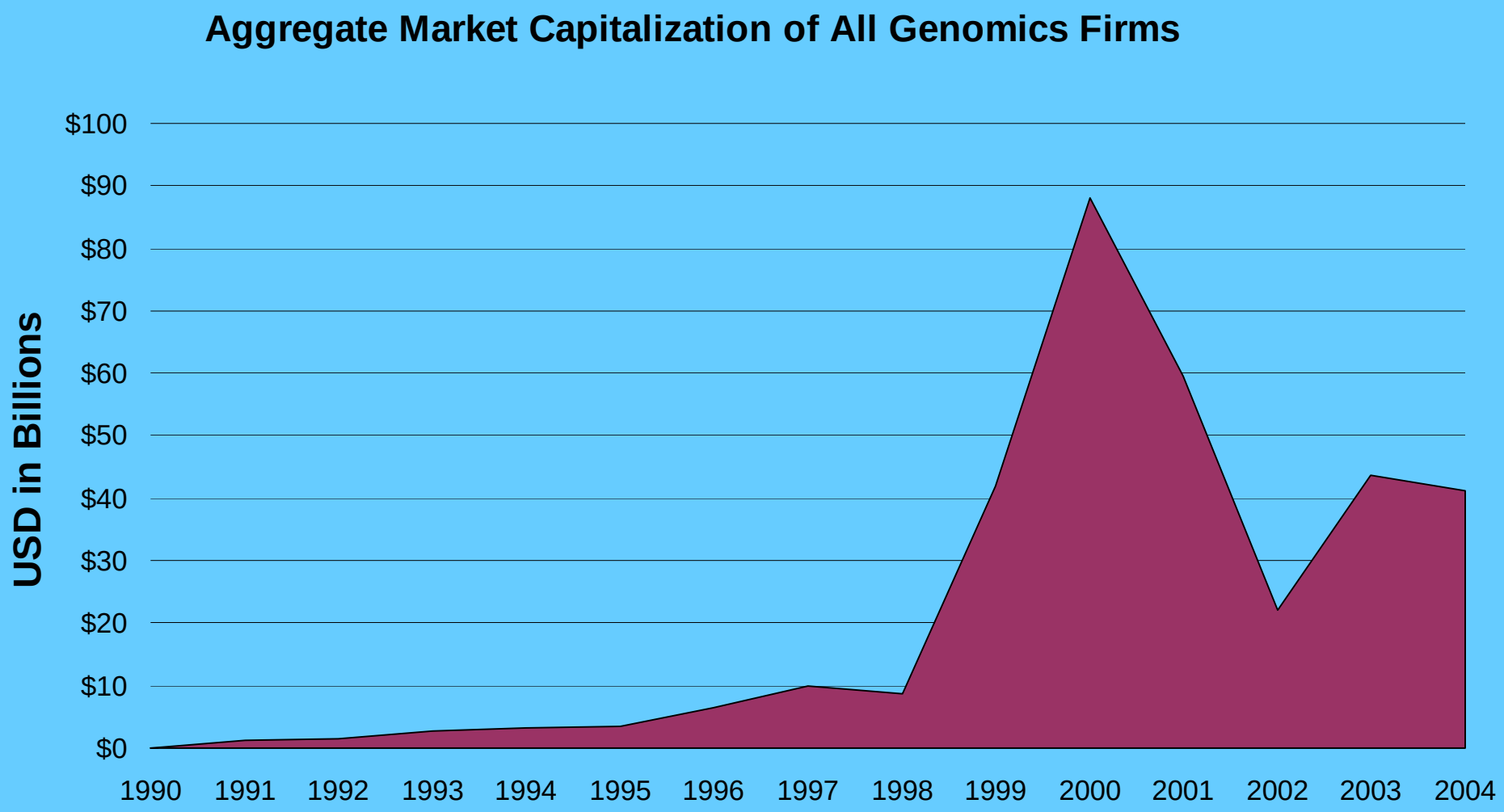
- Make research more expensive
- Require investment and bureaucracy for patenting
- Tax on innovation
- Gum up network benefits of cumulative innovation
- Cut out some uses


a
PCR
Number of citations
0
200
400
600
800
1000
1200
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19

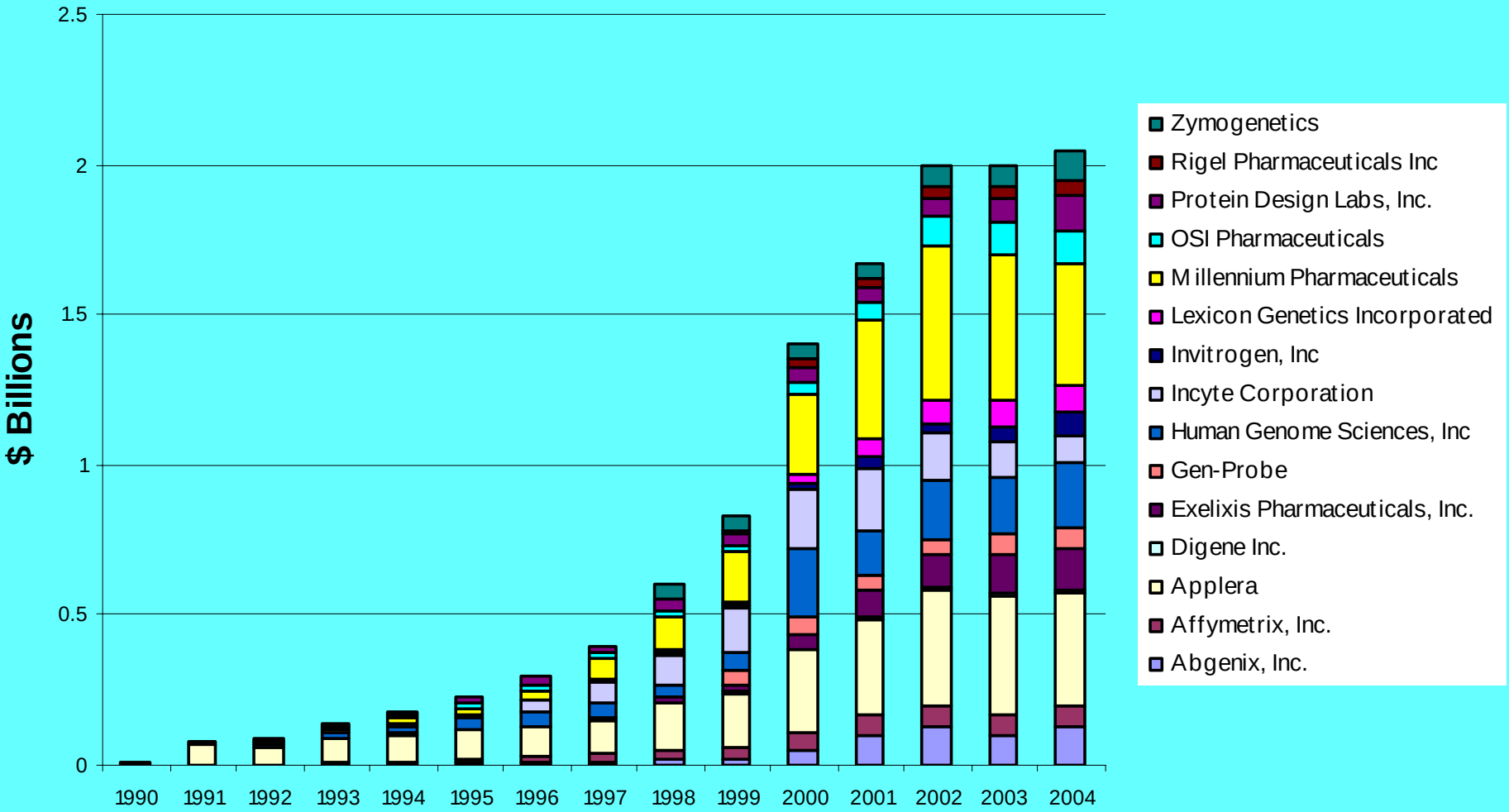

b
pBR322
Number of citations
0
50
100
150
200
250
300
350
400
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19


c
Maxam-Gilbert
Sequencing
Number of citations
0
100
200
300
400
500
600
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19


d
pBR322
Maxam-Gilbert
PCR
Percent
0
2
4
6
8
10
12
14
0 5 10 15 20

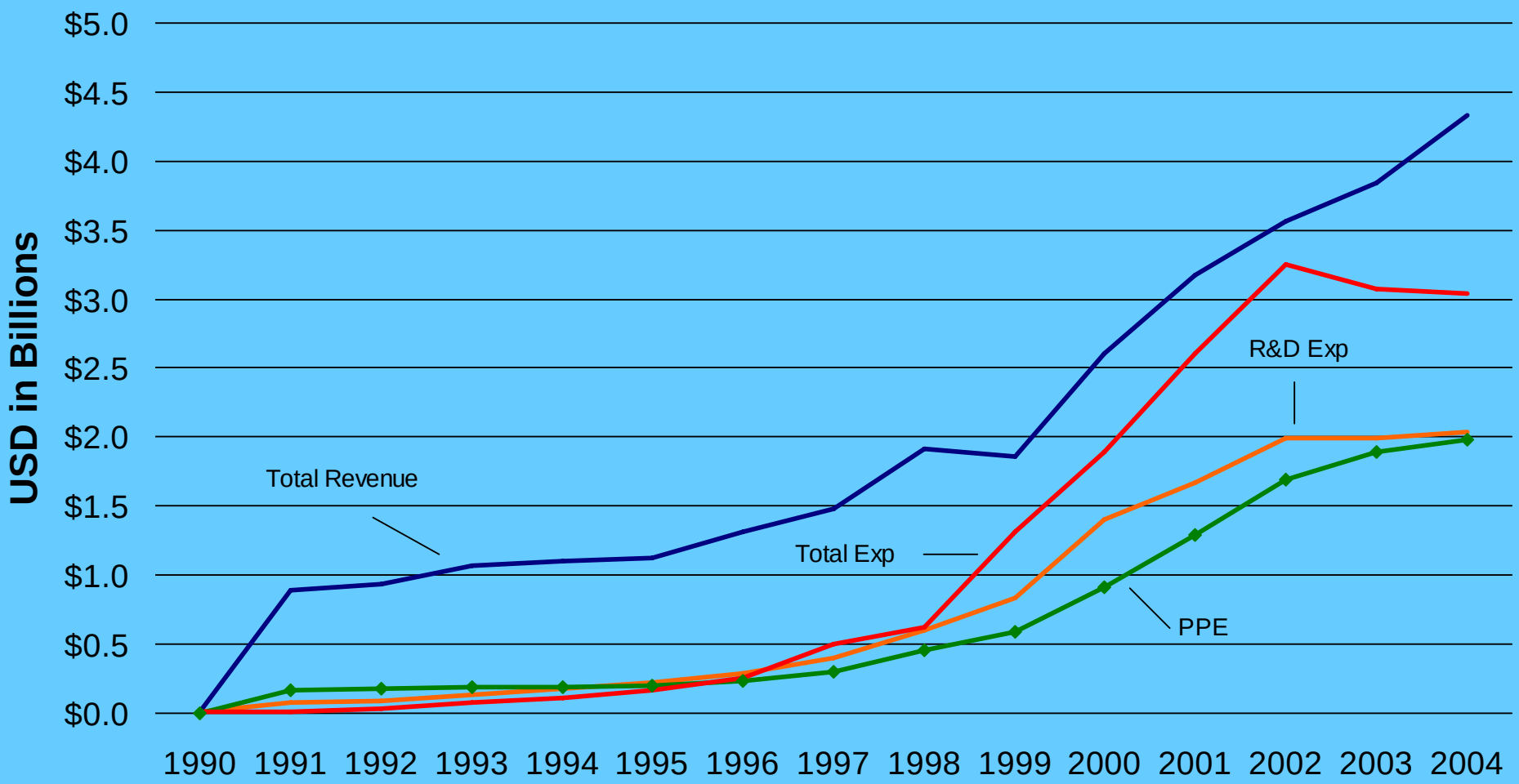

Aggregate Market Capitalization of All Genomics Firms
USD in Billions
$100
$90
$80
$70
$60
$50
$40
$30
$20
$10
$0
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004

Historical R&D of Top 15 Firms



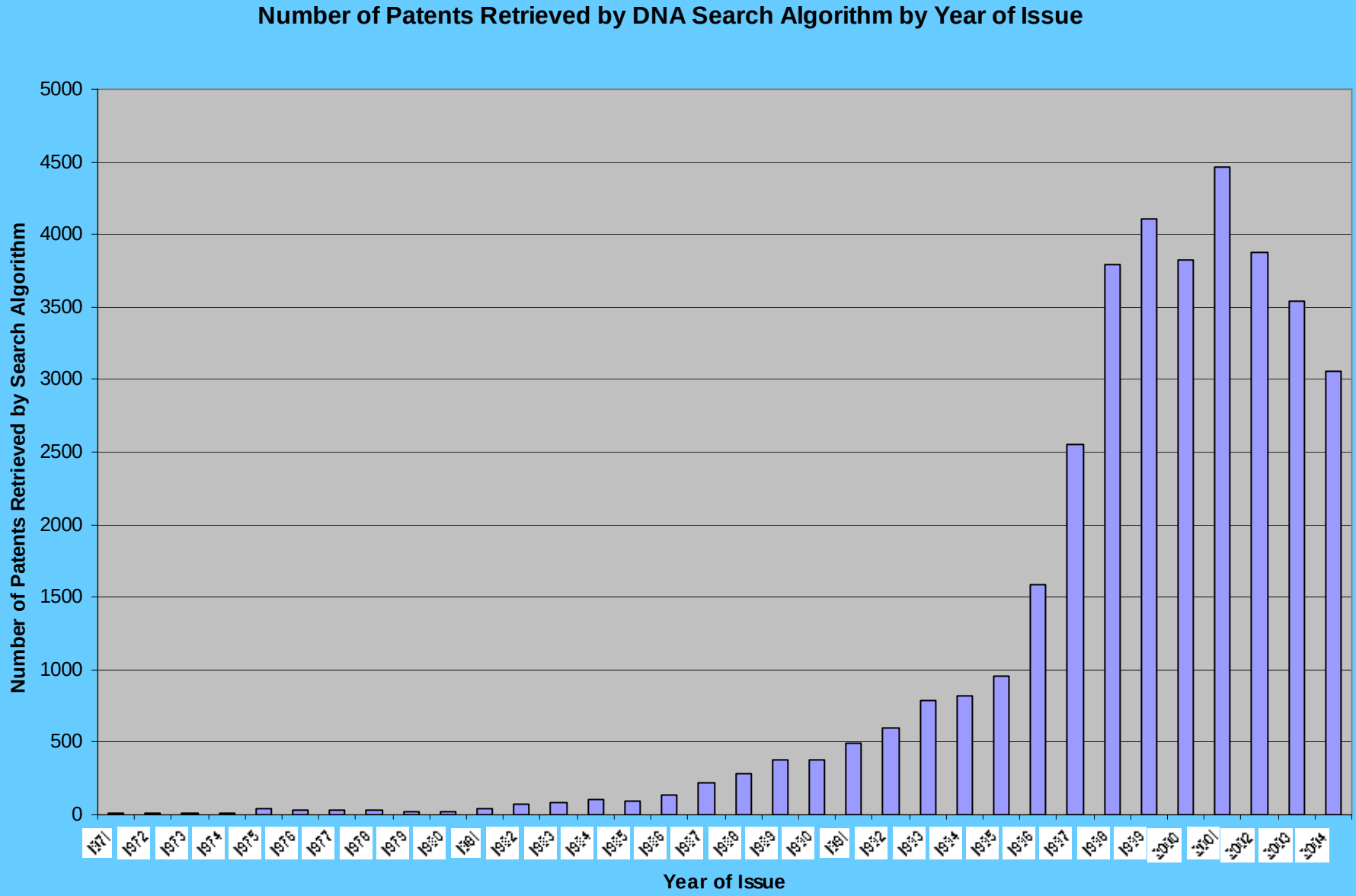
Source: Chandrasekharan, Perin, Wiechers & Cook-Deegan, 2006

Financial Trends of Top 15 Public Genomics Firms[a]

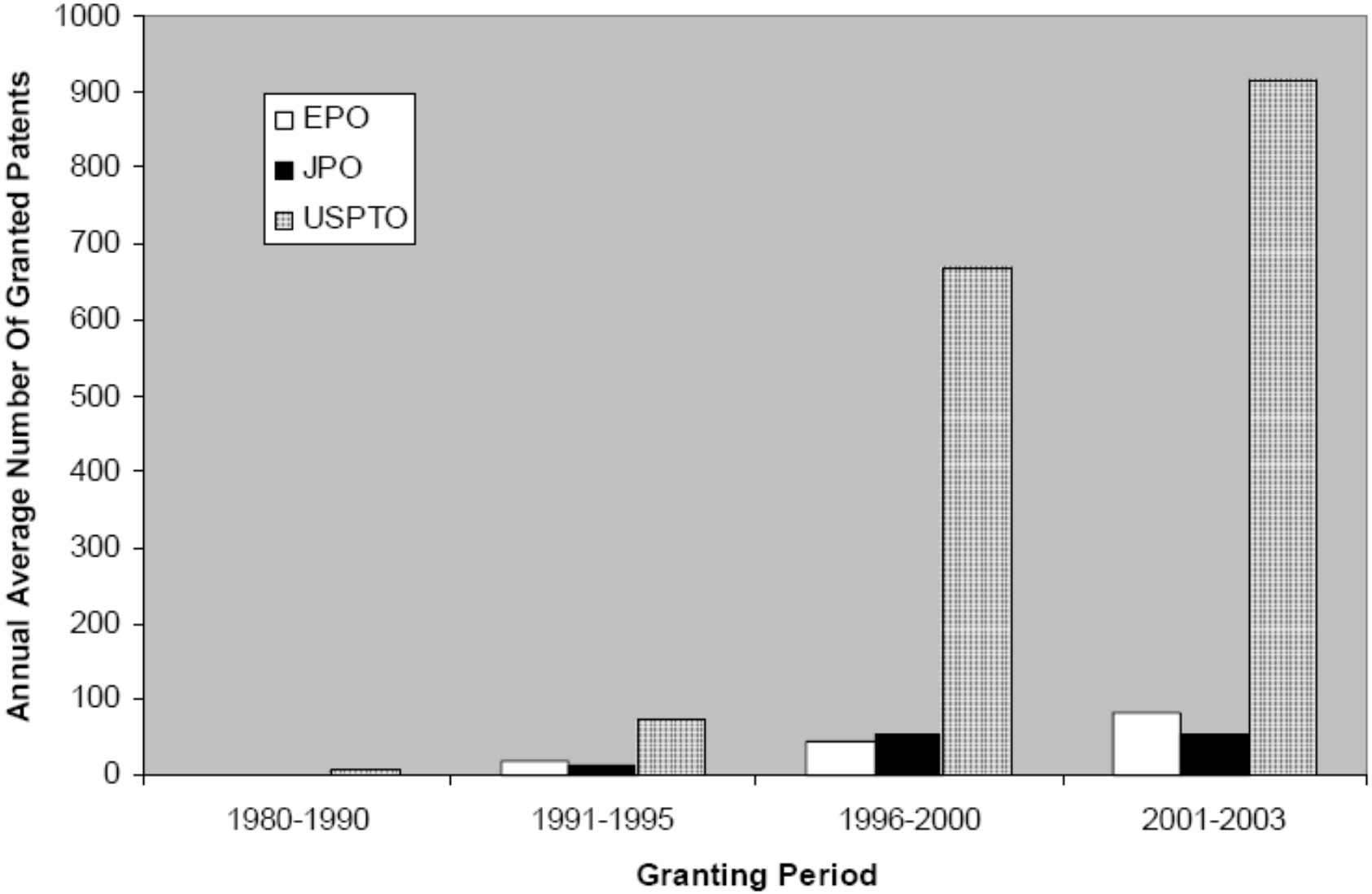


NOTES: Total Exp = total expenditures; R&D Exp = research and development expenditures; PPE = plant, property and equipment

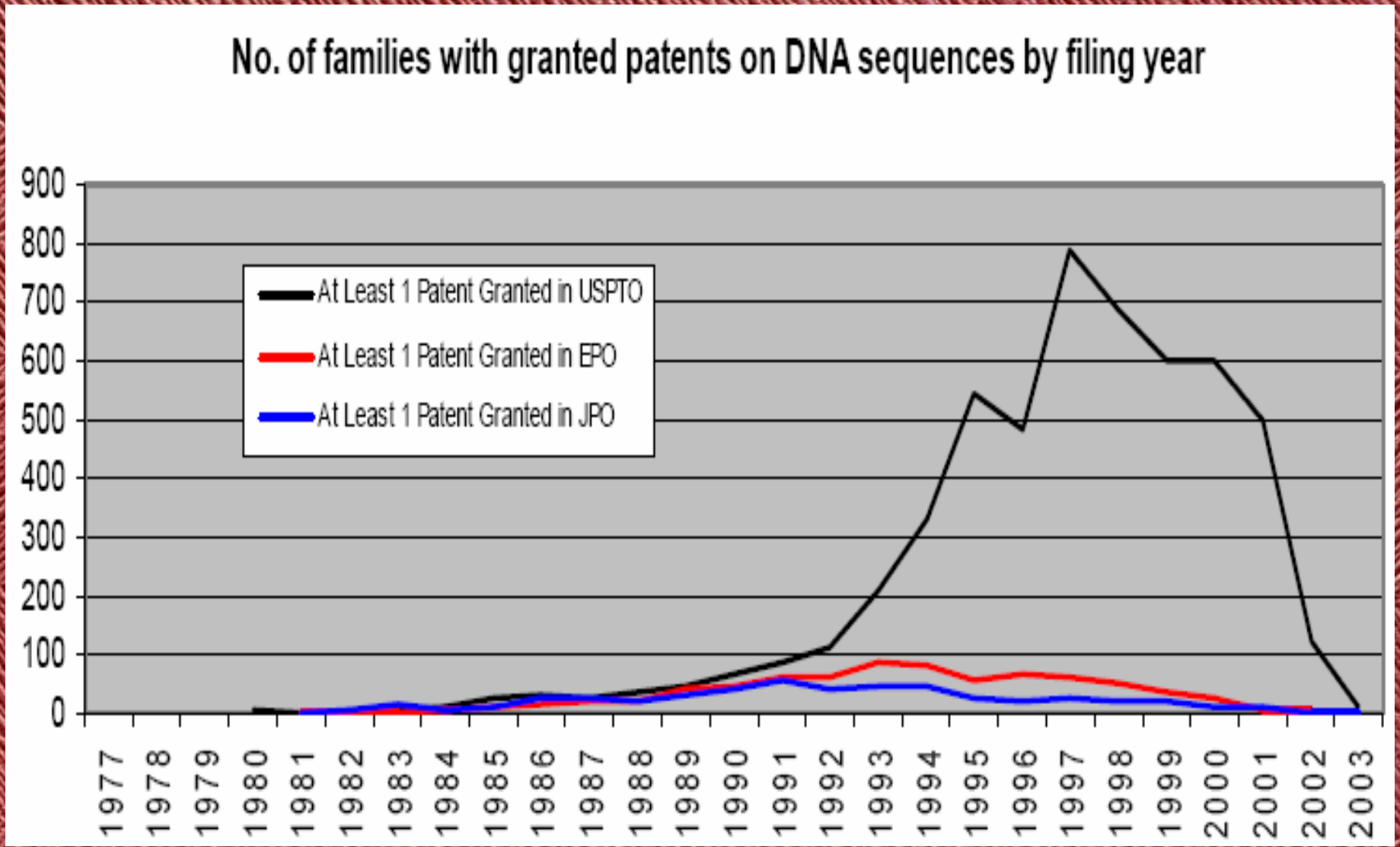
[a]Top 15 genomics firms by market capitalization are: Applera, Millennuim Pharmaceuticals, Invitrogen, OSI Pharmaceuticals, Gen-Probe, Affymetrix, Protein Design Labs, Human Genome Sciences, ZymoGenetics, Abgenix, Incyte, Digene, Exelixis Pharmaceuticals, Lexicon Genetics, Rigel Pharmaceuticals


Number of Patents Retrieved by DNA Search Algorithm by Year of Issue
Number of Patents Retrieved by Search Algorithm
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
Year of Issue

SPRU data on *Sequence* patents



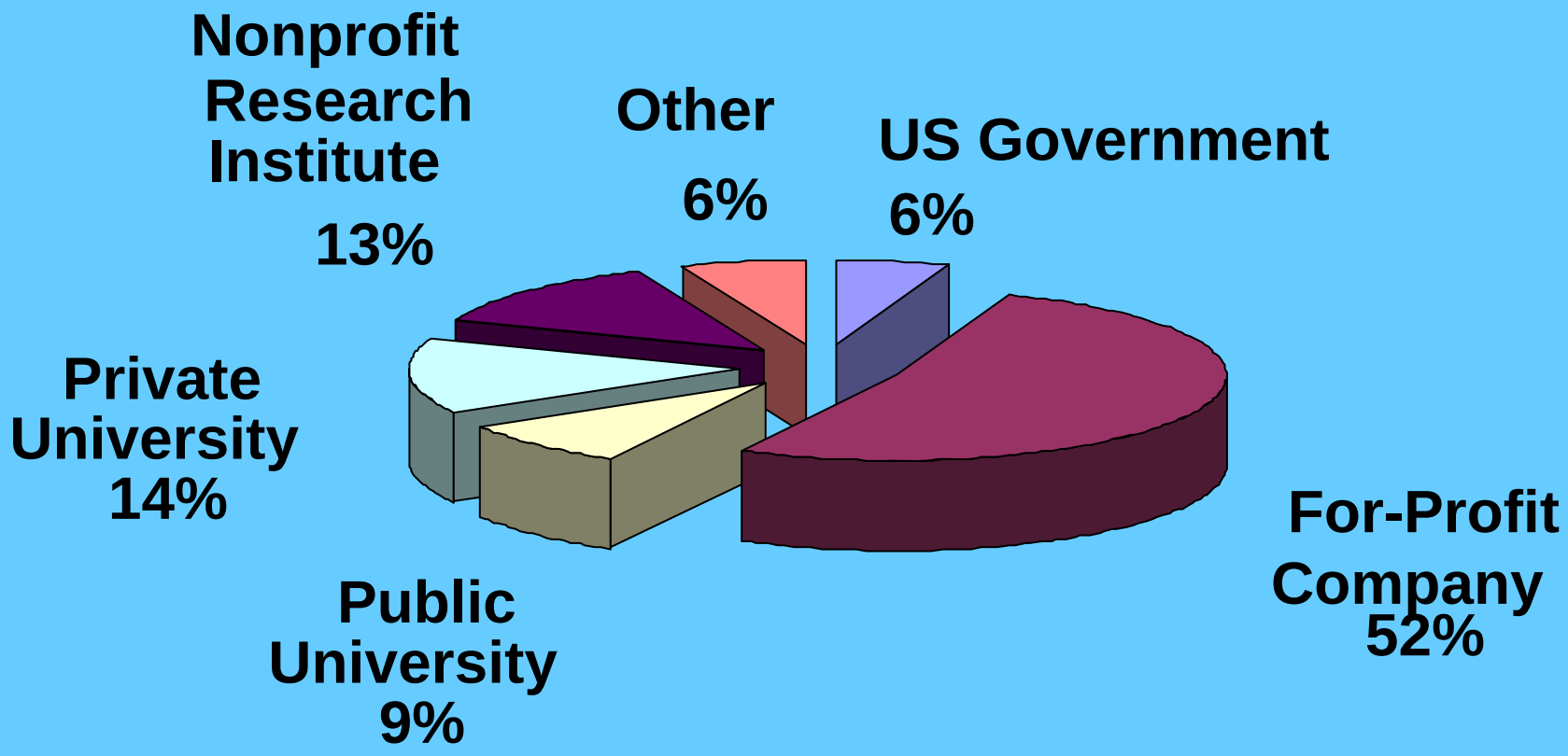
Source: Science Policy Research Unit, University of Sussex, p.
PATGEN Project final report http://www.sussex.ac.uk/spru/documents/patgen_finalreport.pdf



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

Patent assignees

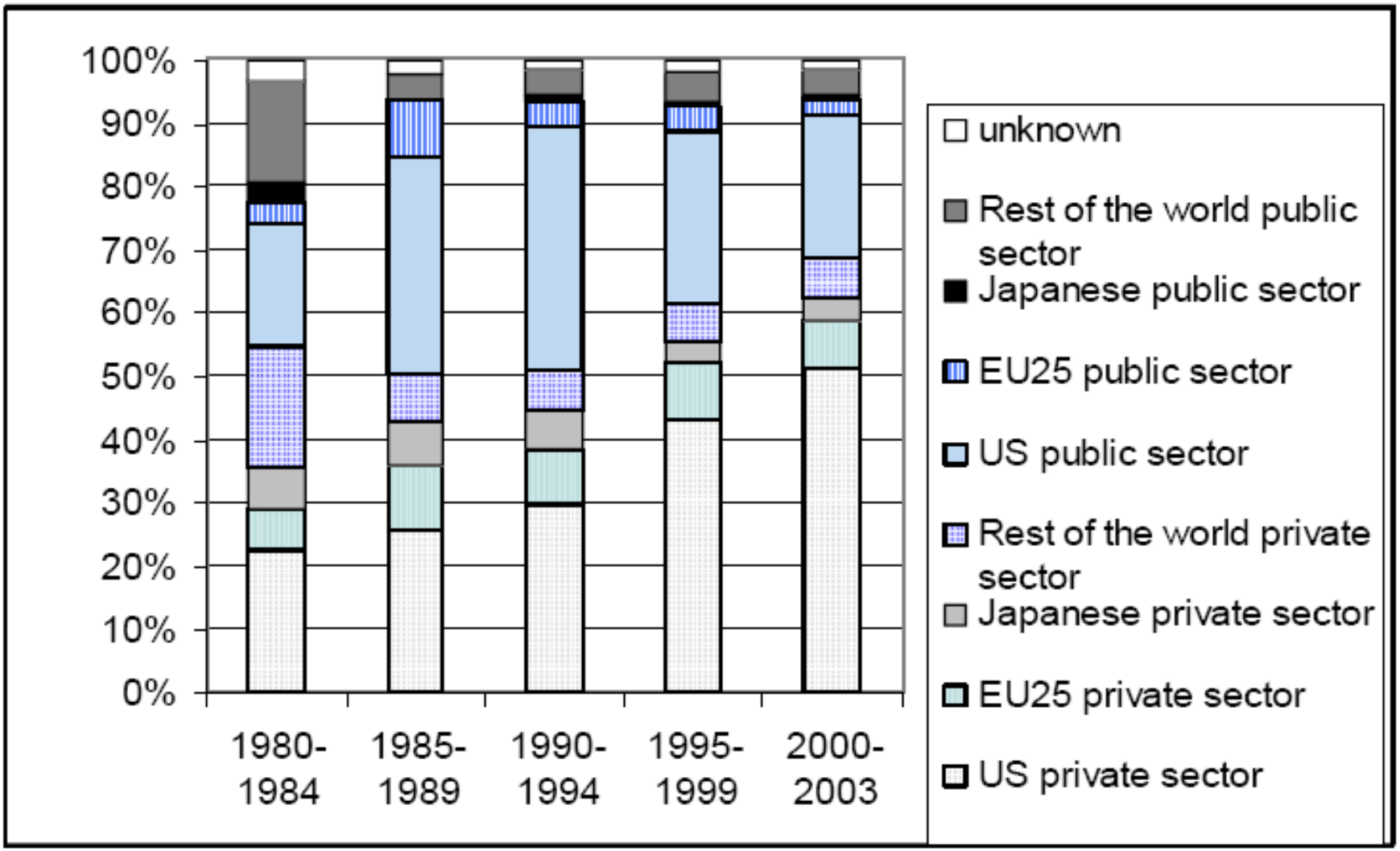
US DNA Patents *1980-1993*



Source: Stephen McCormack and Robert Cook-Deegan DNA Patent Database

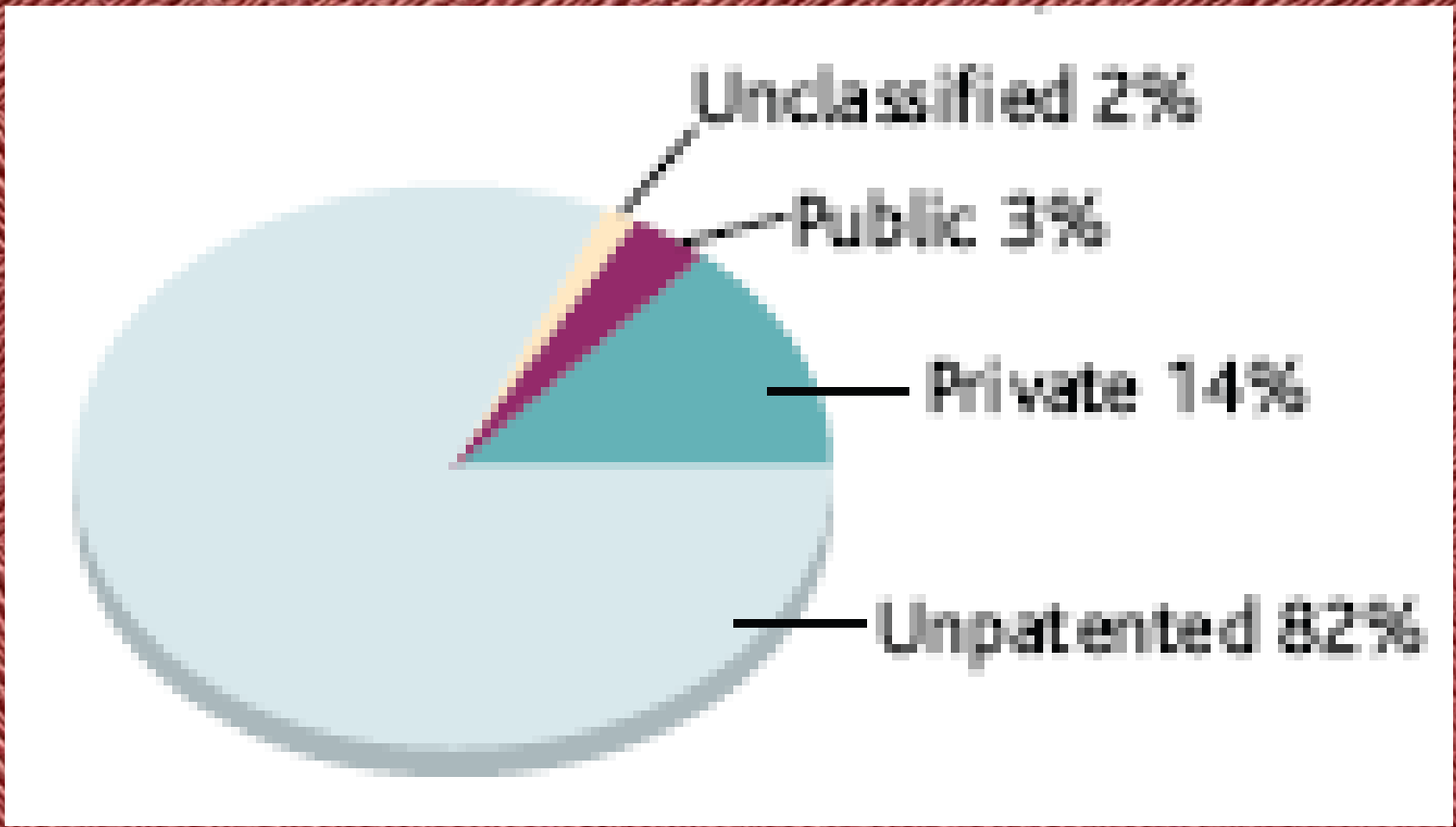
Sequence Patents: SPRU group data

Figure 8. Assignee share of granted patents by year at the USPTO



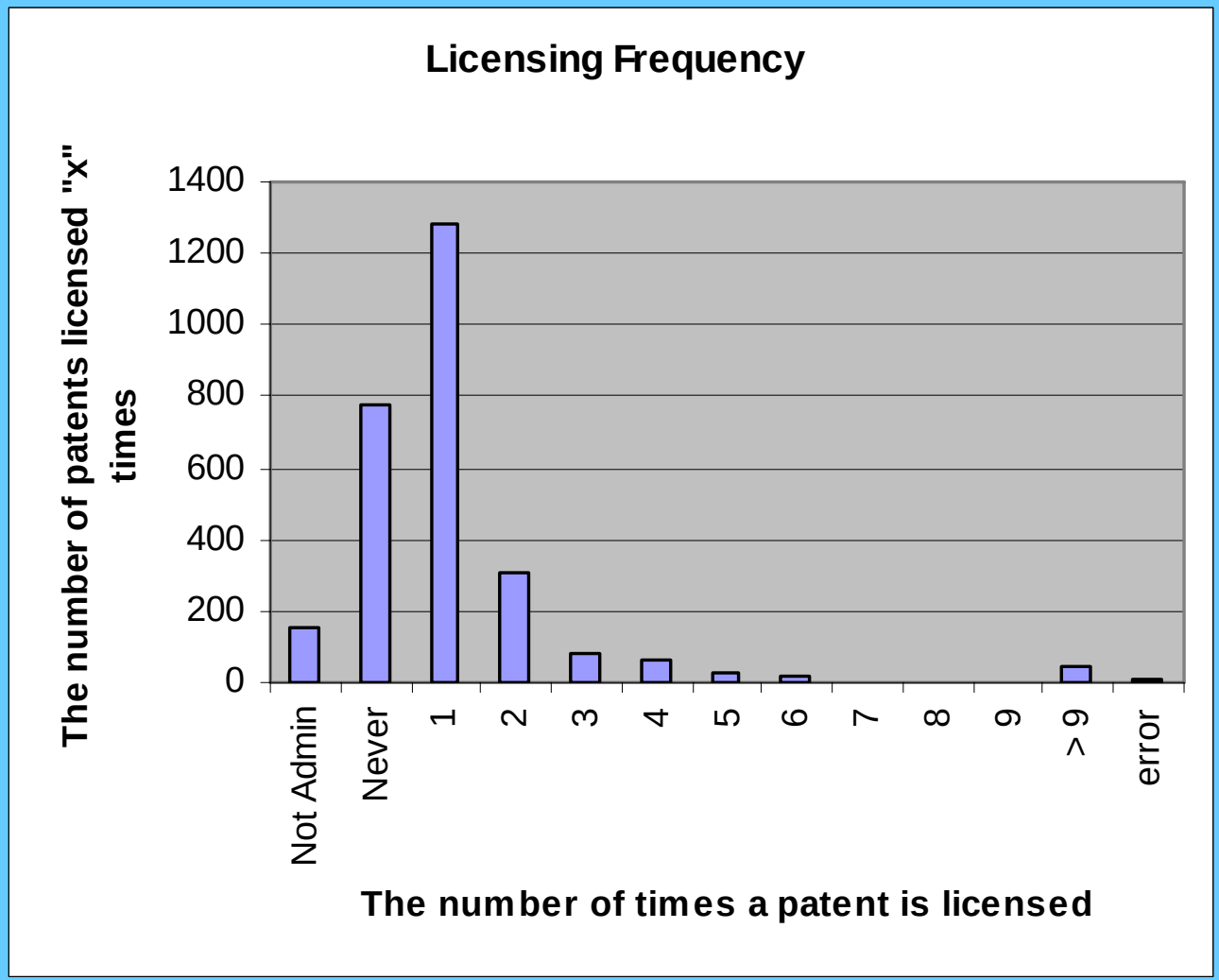
Source: Science Policy Research Unit, University of Sussex, p.
PATGEN Project final report http://www.sussex.ac.uk/spru/documents/patgen_finalreport.pdf

Jensen & Murray, US *Gene* patents



Human gene patent ownership
Jensen & Murray *Science 310 (14 Oct) 2005*

About 70% have, at one time, been licensed
1- 2% were licensed >9 times



Licensing Status	# of patents
Not Admin	151
Never	773
1	1287
2	303
3	78
4	62
5	24
6	14
7	4
8	3
9	3
> 9	45
error	13

Policy tools: general

- Patent reform by statute
  - Current House and Senate bills
  - Becerra-Weldon bill
  - Rivers bills of 108th Congress
- Examination practices in patent offices (USPTO v other)
- Research exemption (see Belgium, France)
- Compulsory licensing (see Belgium, India)

Current patent reform

From “first to invent” to “first inventor to file”

Opposition process after patent publication

-BRCA opposition in Europe

-Cohen-Boyer (because openly prosecuted, in effect had opposition during examination)

Policy tools:
Freedom to operate in research

- Push-back from Scientists
  - PCR
  - Oncomouse
  - Cre-lox
  - NIH & National Academies re USPTO examination guidelines on DNA patents
- Norm-setting in science
  - Bermuda rules for sequence release (1996)
  - SNP Consortium
  - “Public domain” strategies in software and some genomics
  - NIH research tool guidelines (1999)
  - NIH “Best Practices” for genomic inventions (2004)
  - OECD Licensing Guidelines (2006)
  - University statement (2007)
  - Increasing reliance on data-openness plans in grants and contracts (e.g., Wellcome Trust, NIH)

Empirical data on diagnostics

- Cho-Merz-Leonard data survey of lab directors
  - Many labs gave up patented tests such as ApoE for Alz or BRCA
  - No direct evidence about *access*
- BRCA case
  - US story mainly about patents
    - but even in US, only ~30% patent premium
  - Canada, Australia, etc., patents but no monopoly (state testing servcies)
  - Euro oppostion=>narrow scope
- Canavan's case
  - Secrecy + betrayal + overpricing + licensing restrictions = controversy (out of court settlement)

Policy tools: Diagnostics

- Coverage and reimbursement
  - Demand for data on clinical utility?
  - Cost-value assessment?
- FDA regulation?
  - Single-analyte tests (e.g., “gene tests”)
  - Multiplex texts (e.g., expression profiles)
- National or provincial health systems
  - (monopsony meets monopoly: BRCA in UK, Canada, Australia)

Foreseeable trends in genetic tests

Multiple genes

Multiple alleles for those genes

Expression profile for those alleles

If true, then

Myriad and Athena (Mendelian testing) models will not dominate

Multiplex technologies will be more important

- Need to aggregate gene-based IP to enable testing of many sequences
- Other IP also relevant: detection instruments, interpretive software, "IP clusters"

Uncertain trends: litigation strategies

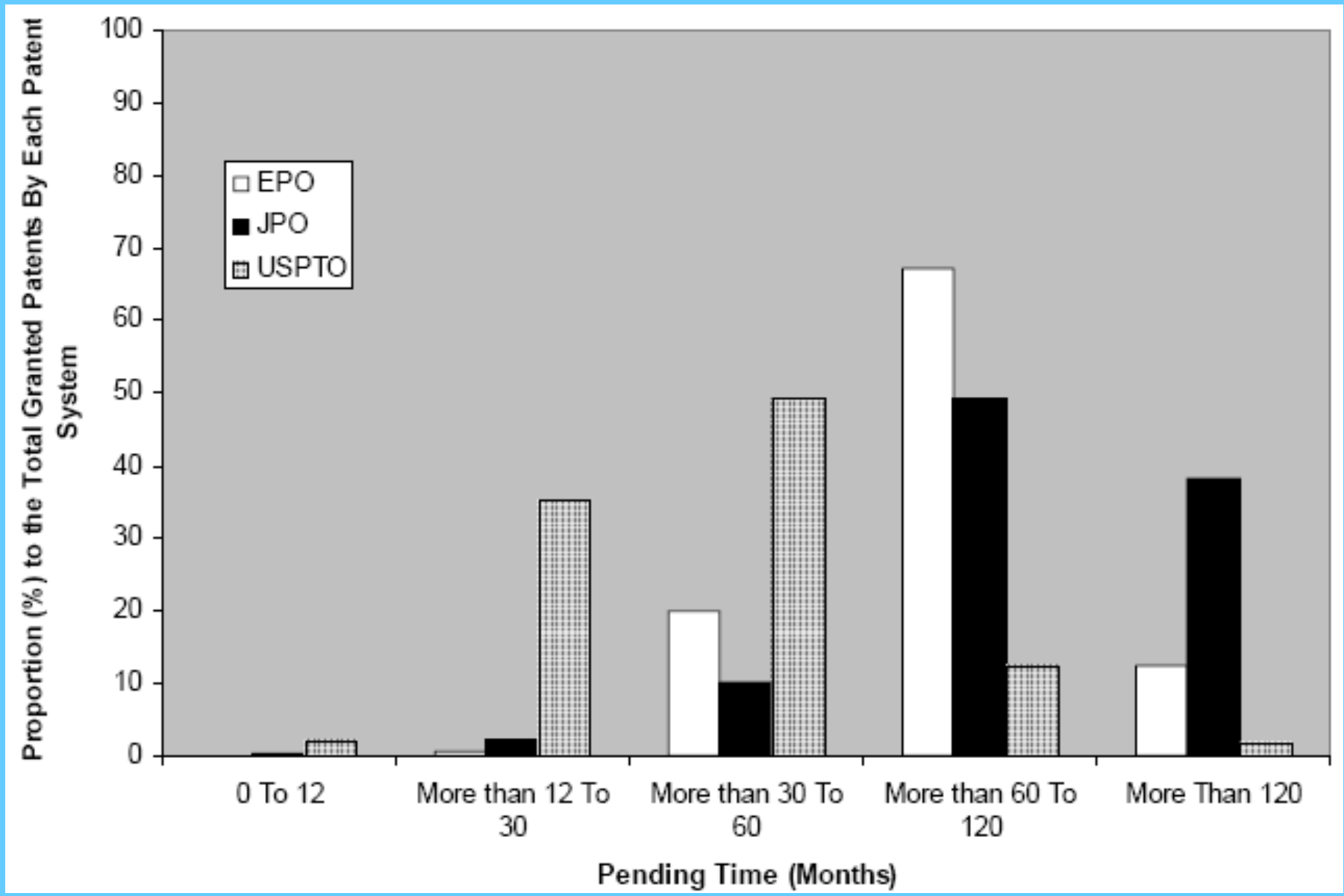
- ApoE and Bayh-Dole: if universities pushed back against Athena
- BRCA and UPenn: "research service" under NCI contract
- Supreme Court inviting challenge case?
  - "Would have been discovered anyway, and soon" criterion from 1980s
- BRCA in Canada and UK: factors beyond patents
- US only jurisdiction with many sequence patents

A few reminders

- Gene patents may not be the most important patents (methods, instruments)
- Patents will often not be the most important element in the story
- When patents do matter, they mainly matter in distribution of rewards
- The policy landscape is shifting and somewhat unstable
- The US is remarkably different from Europe and Japan

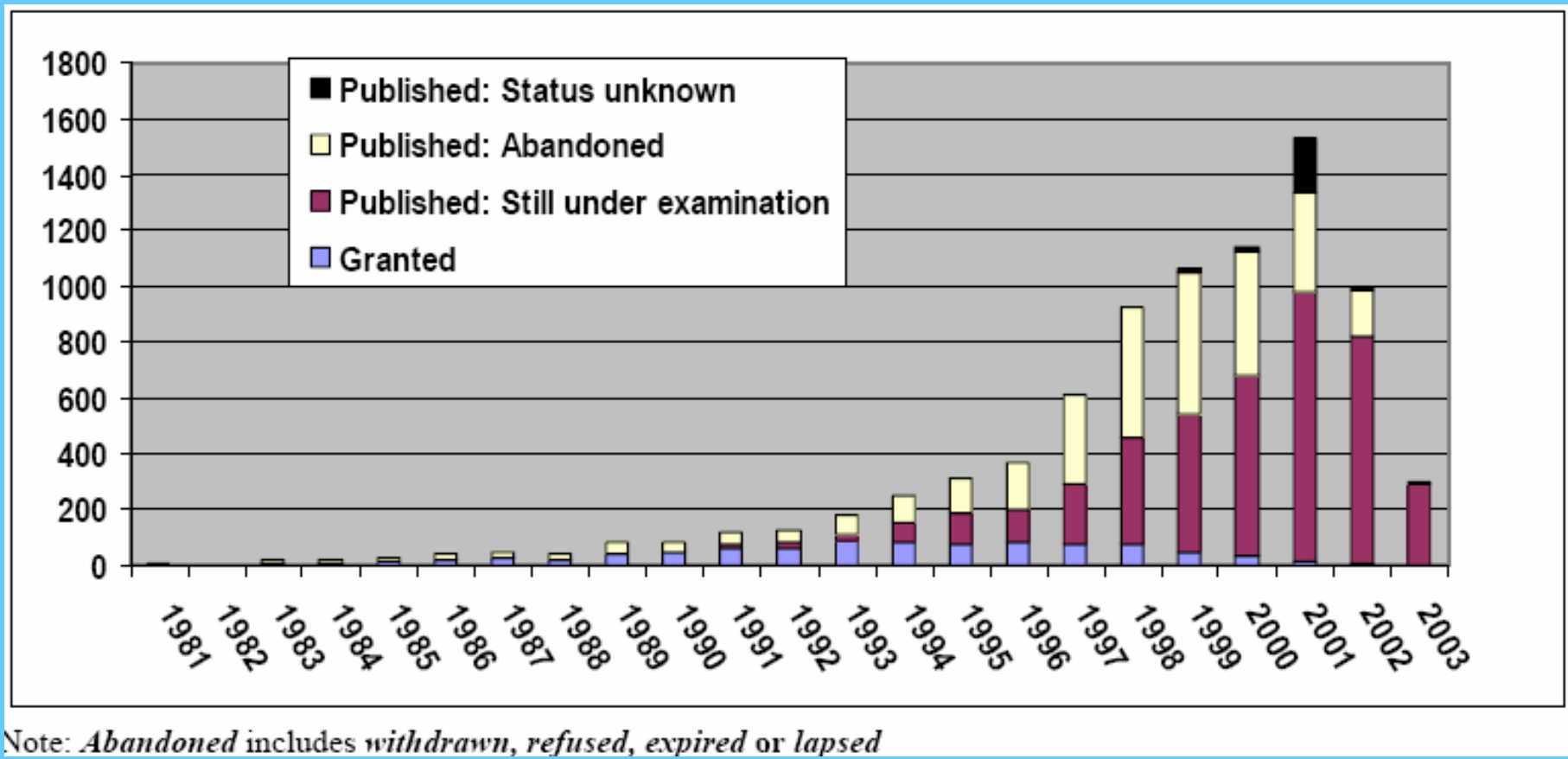
End of presentation slides

- A few slides follow, in case questions arise



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

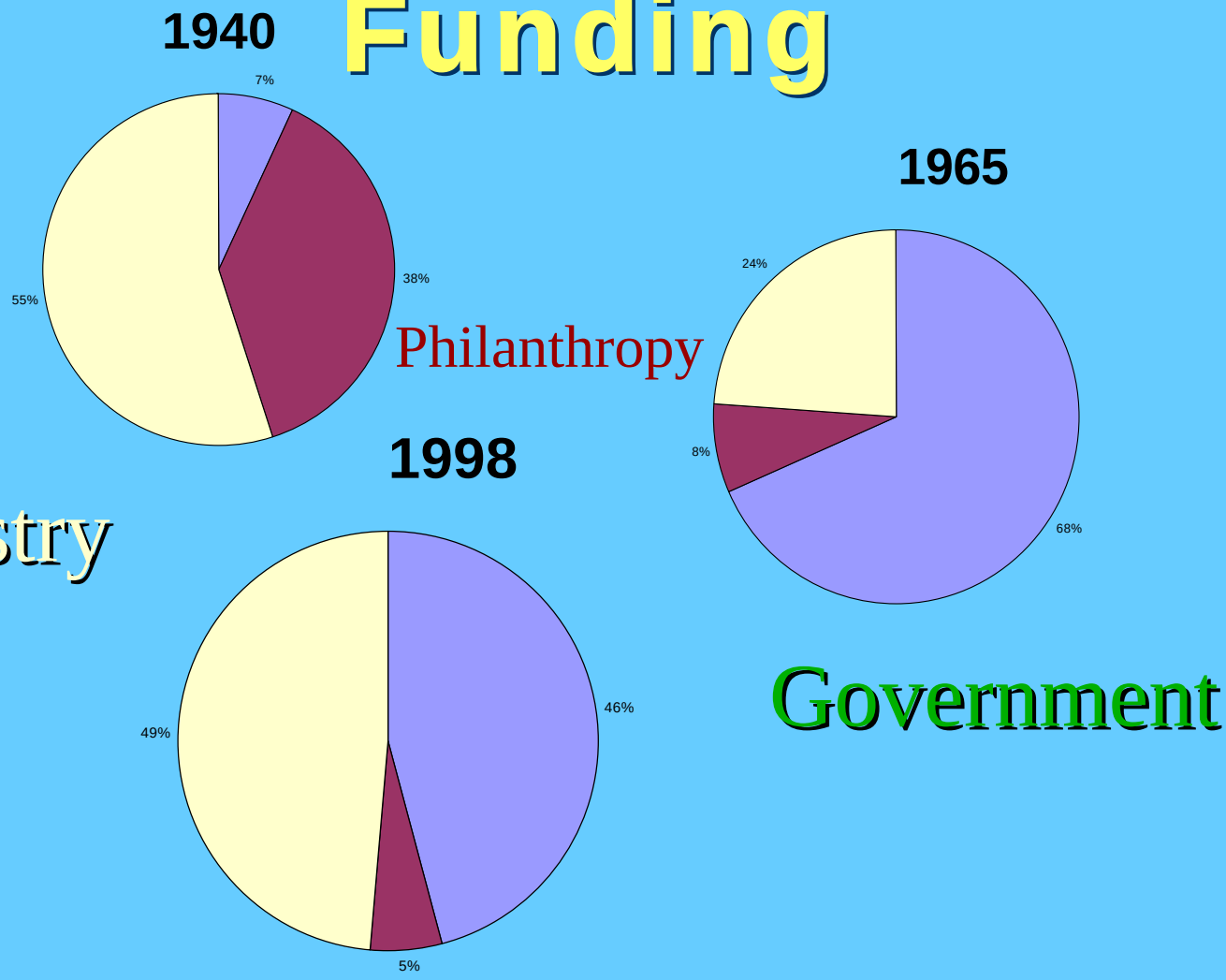
SPRU data on fate of sequence patents



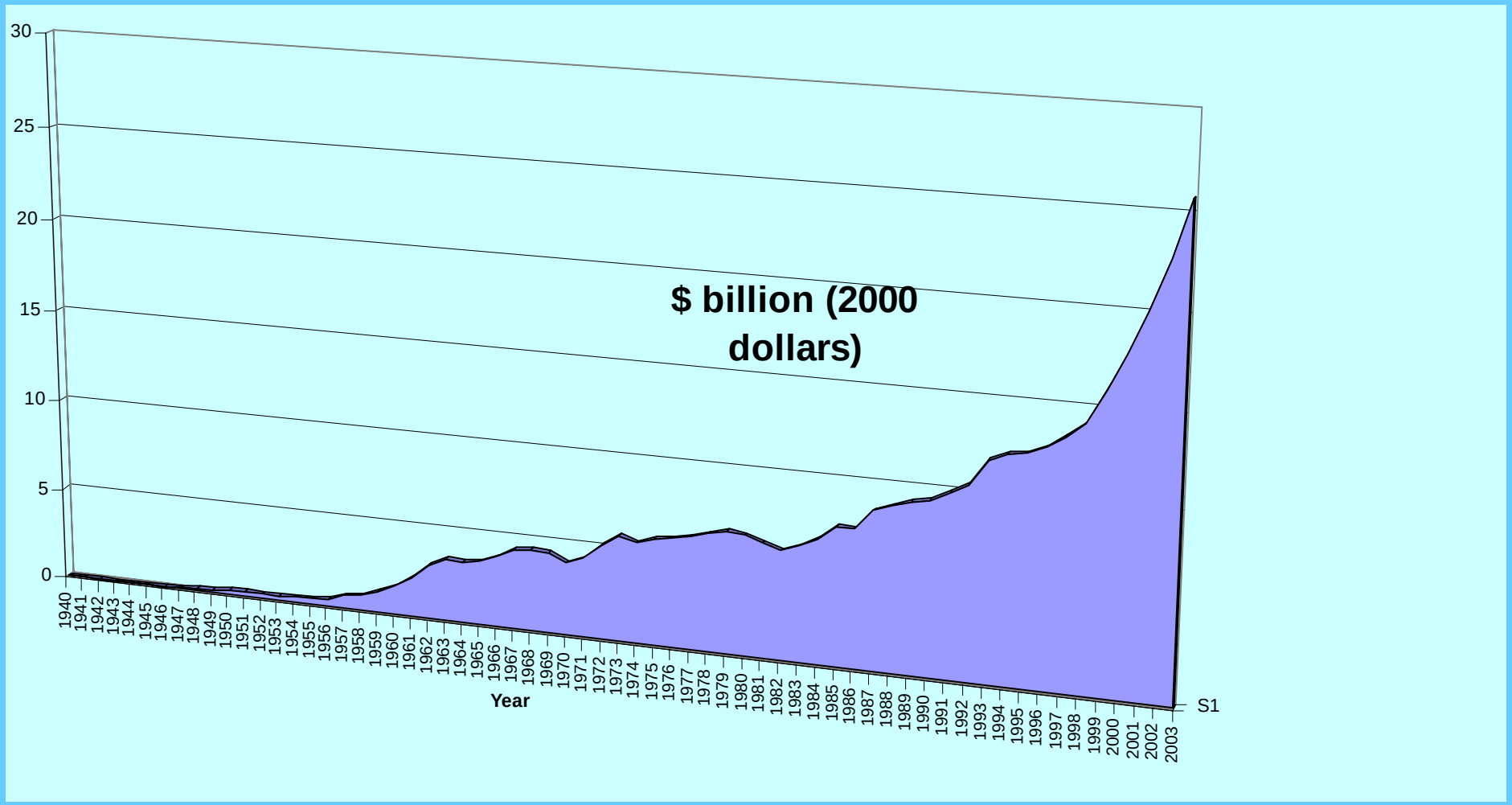
Note: *Abandoned* includes *withdrawn, refused, expired* or *lapsed*

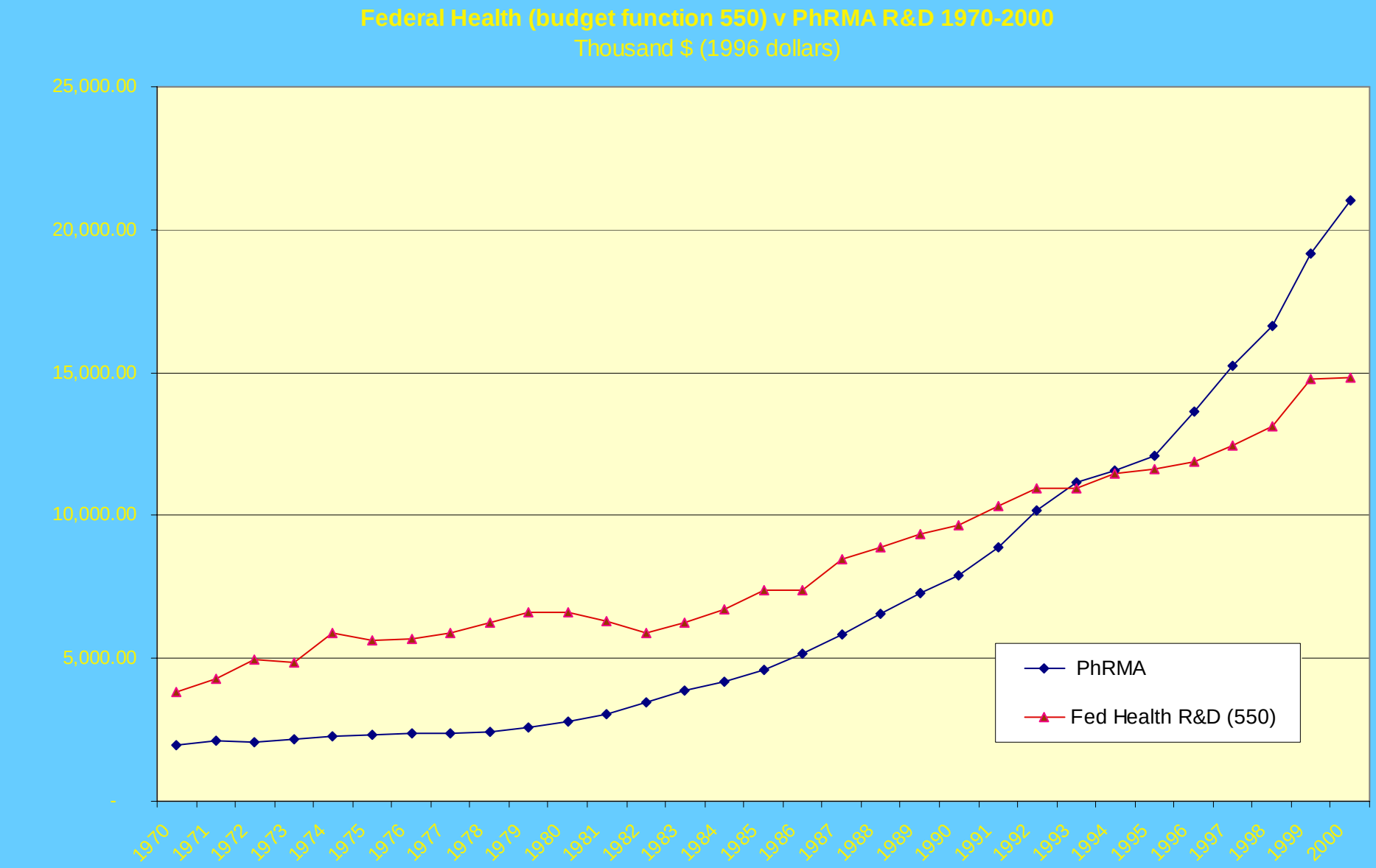
Source: Science Policy Research Unit, University of Sussex, p.
PATGEN Project final report http://www.sussex.ac.uk/spru/documents/patgen_finalreport.pdf

Health Research Funding



NIH Appropriations 1940-2003




Federal Health (budget function 550) v PhRMA R&D 1970-2000
Thousand $ (1996 dollars)
25,000.00
20,000.00
15,000.00
10,000.00
5,000.00
-
1970
1971
1972
1973
1974
1975
1976
1977
1978
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1988
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1994
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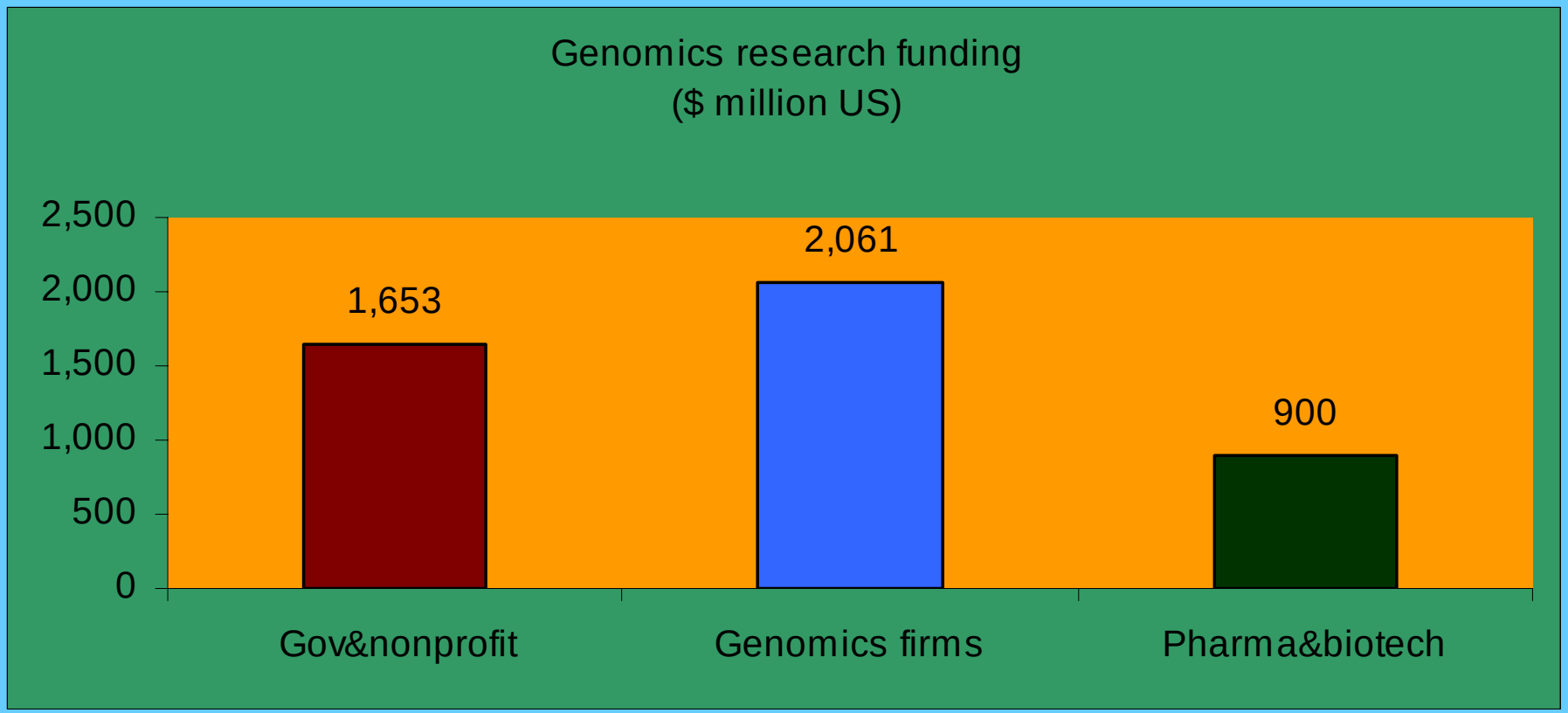
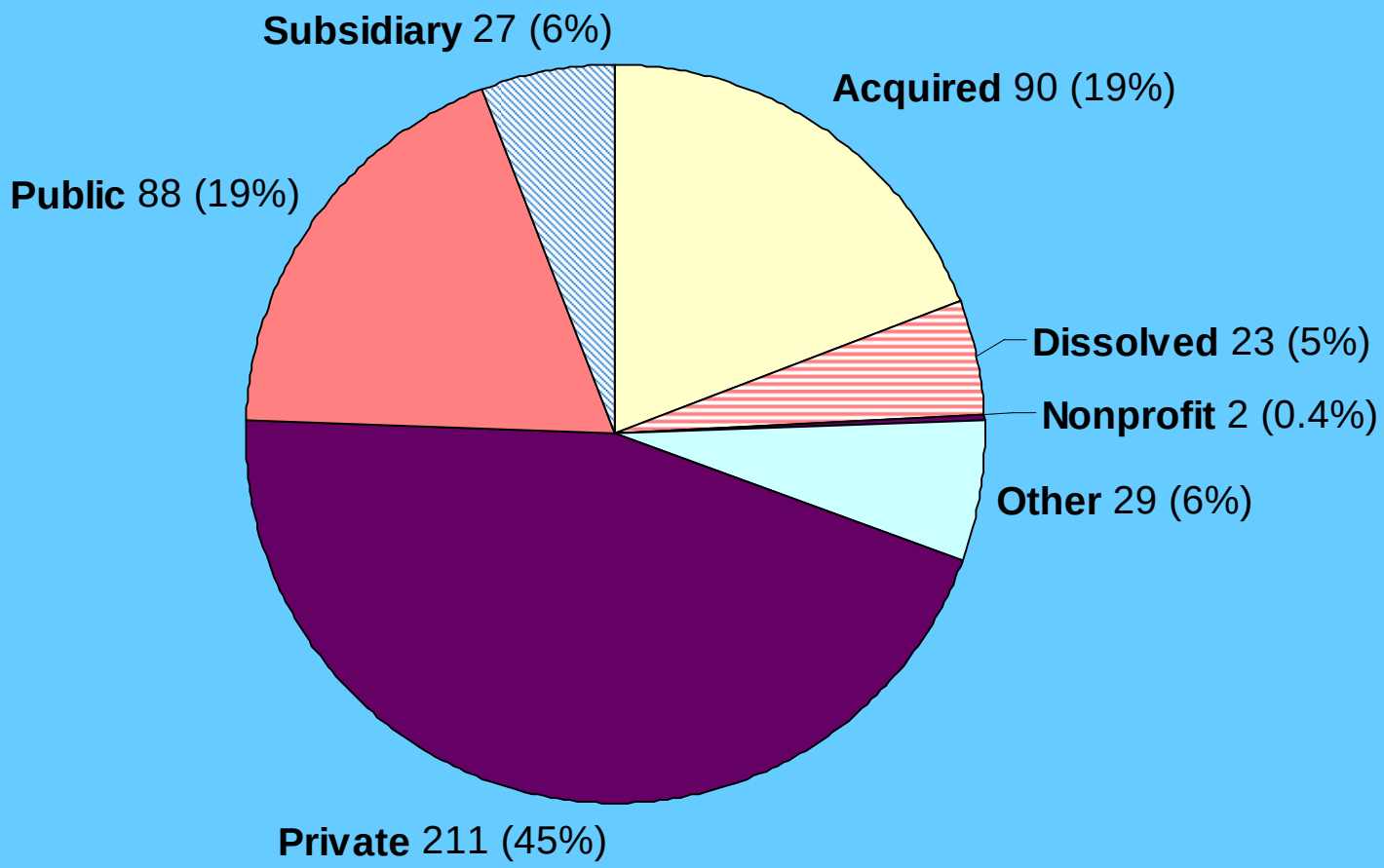
1996
1997
1998
1999
2000
PhRMA
Fed Health R&D (550)

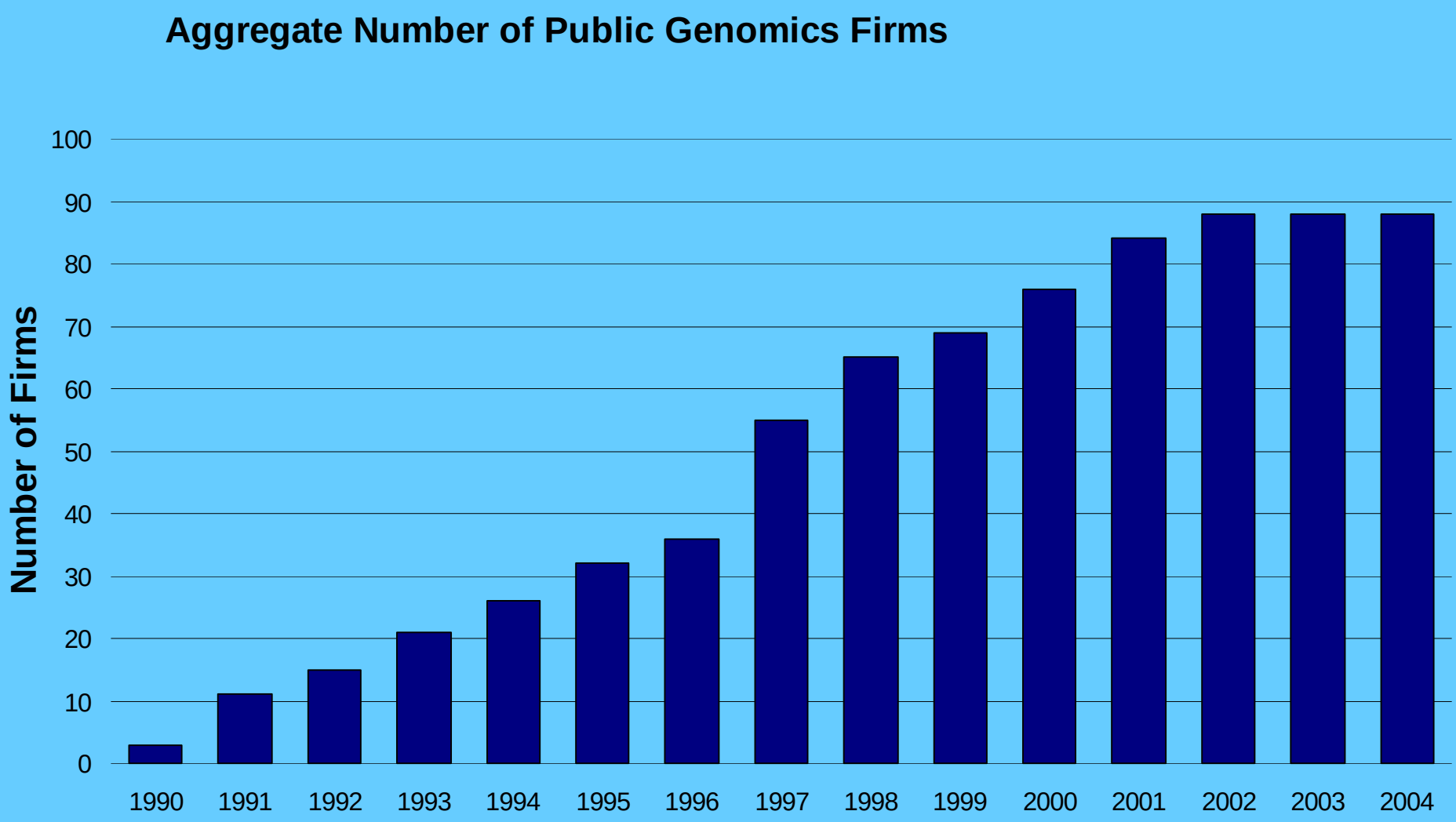
Genomics Funding: private>public (Year 2000)



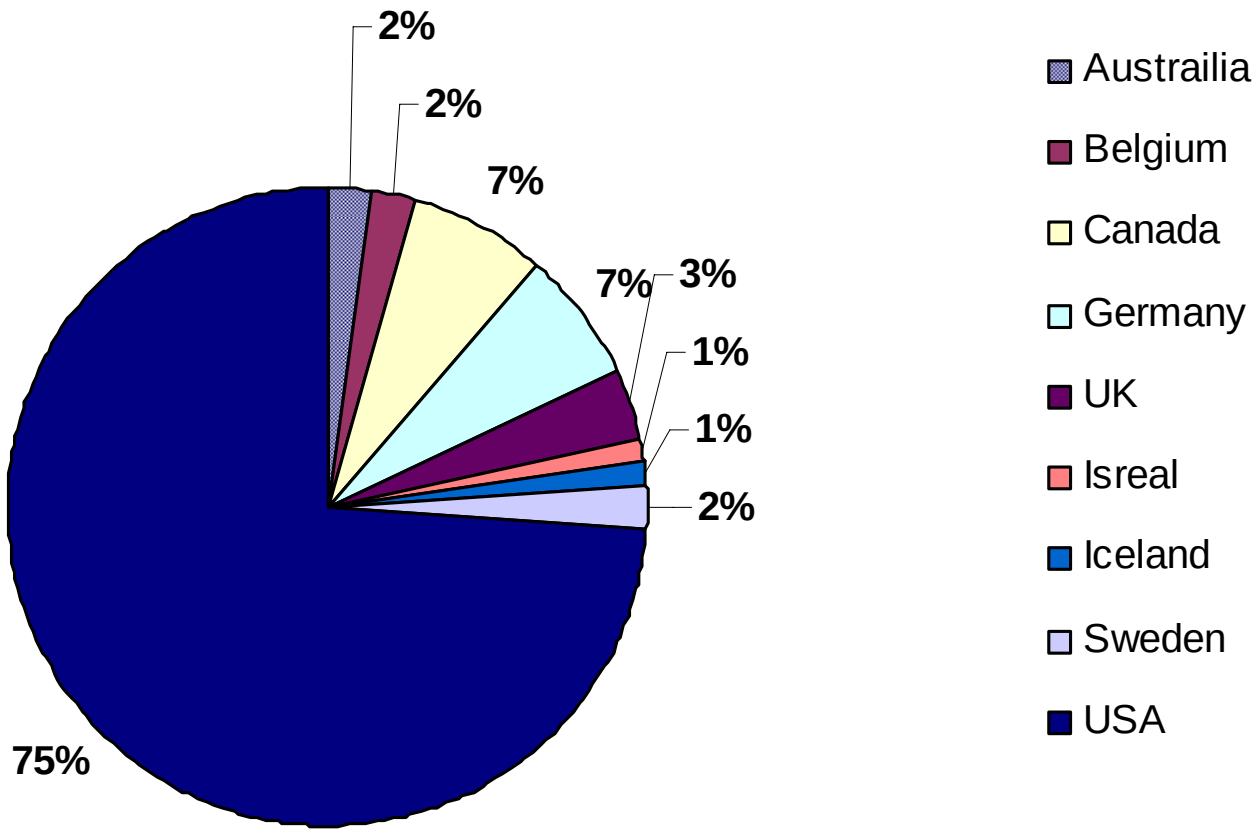
Source: World Survey of Funding for Genomics Research
Stanford in Washington Program (Amber Johnson, Carmie Chan, Robert Cook-Deegan)
http://www.stanford.edu/class/siw198q/websites/genomics/

Firm by Type in 2004

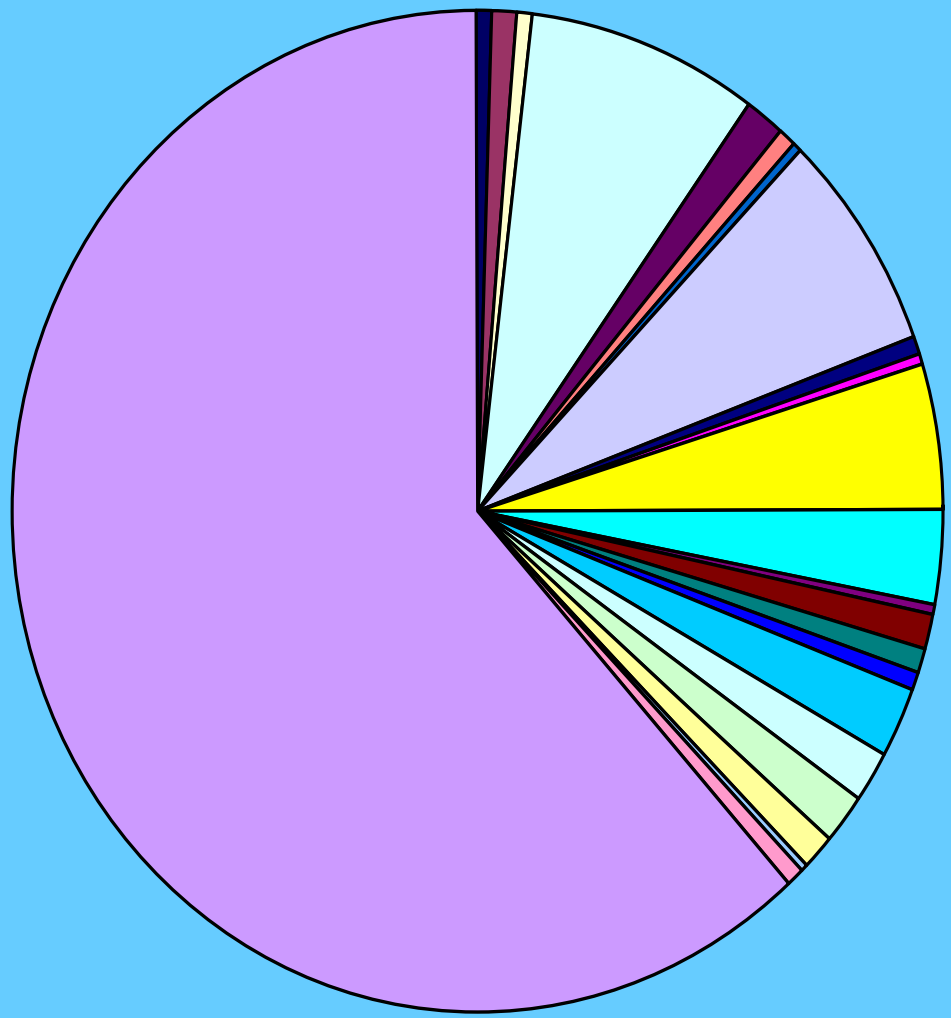



Aggregate Number of Public Genomics Firms
Number of Firms
100
90
80
70
60
50
40
30
20
10
0
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004

88 Public Firms by Country



211 Private Firms by Country



- Austria
- Austrailia
- Belgium
- Canada
- Sw itzerland
- Chile
- China
- Germany
- Denmark
- Spain
- France
- UK
- Hungary
- Ireland
- India
- Iceland
- Japan
- Korea (Demo)
- Korea (Republic)
- Neatherlands
- Singapore
- Taiw an

EXHIBIT 6
Top 5 Firm Taxonomies by Firm Type

Public Firms

Taxonomy	Percent[a]	Representative Firms
DRUGDEV	55%	Millennium, Incyte
INSTRMT	25%	Gen-Probe, Affymetrix
SUPPLYR	23%	Invitrogen, Affymetrix
DNATEST	22%	Gen-Probe, Digene
GENEXPR	15%	Exelixis, Diversa

Private Firms

Taxonomy	Percent[a]	Representative Firms
DRUGDEV	33%	AGY Therapeutics, Xenon
INFRMTX	29%	Genomatix, DNAStar
GENEXPR	21%	Ipsogen, Ambion
DNATEST	15%	Gentris, HandyLab
GENEFNL	14%	Agilix, Xantos

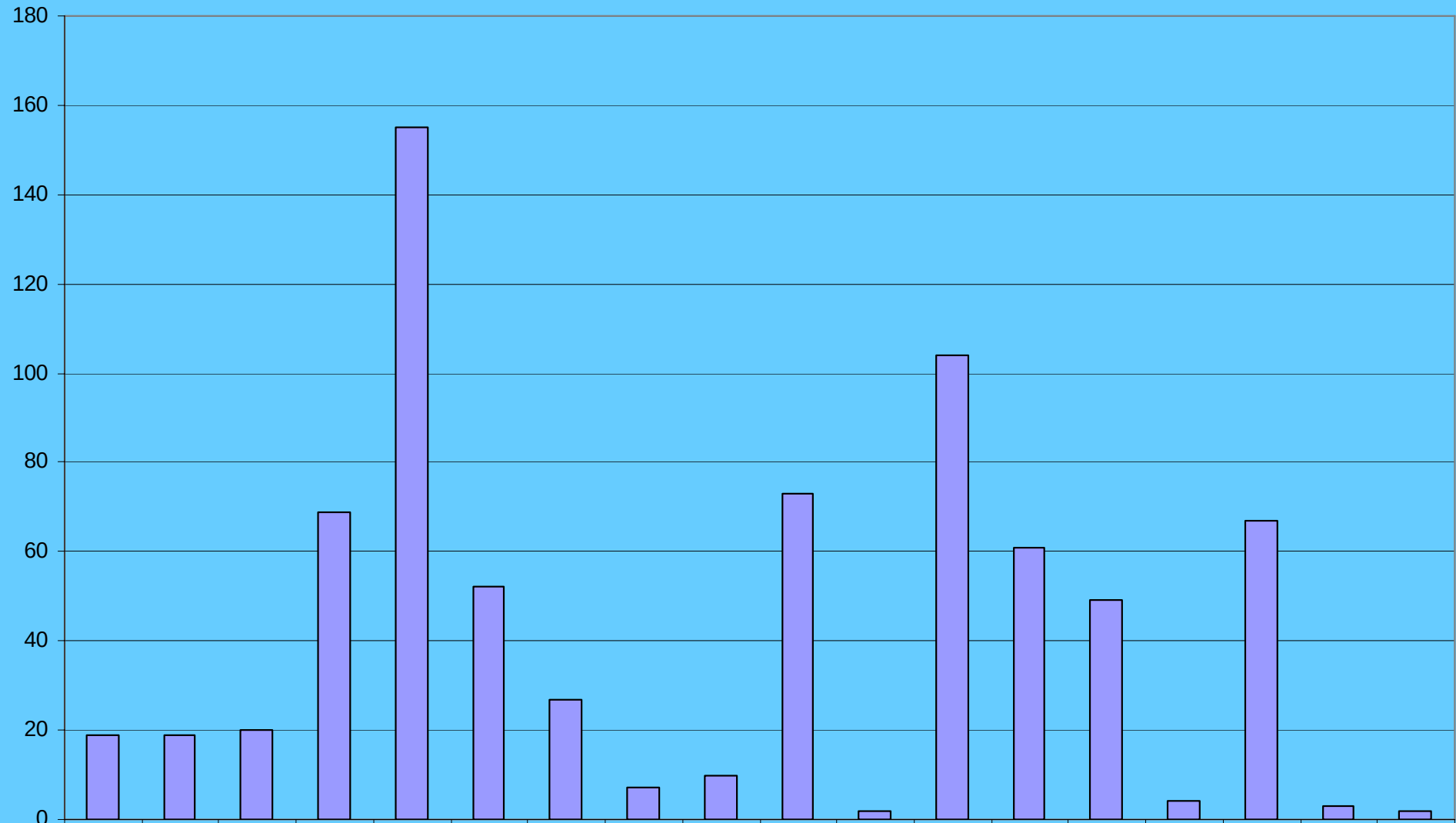
SOURCE: Authors' analysis of study data

NOTES: Firms can be classified by multiple taxonomies based upon business function.

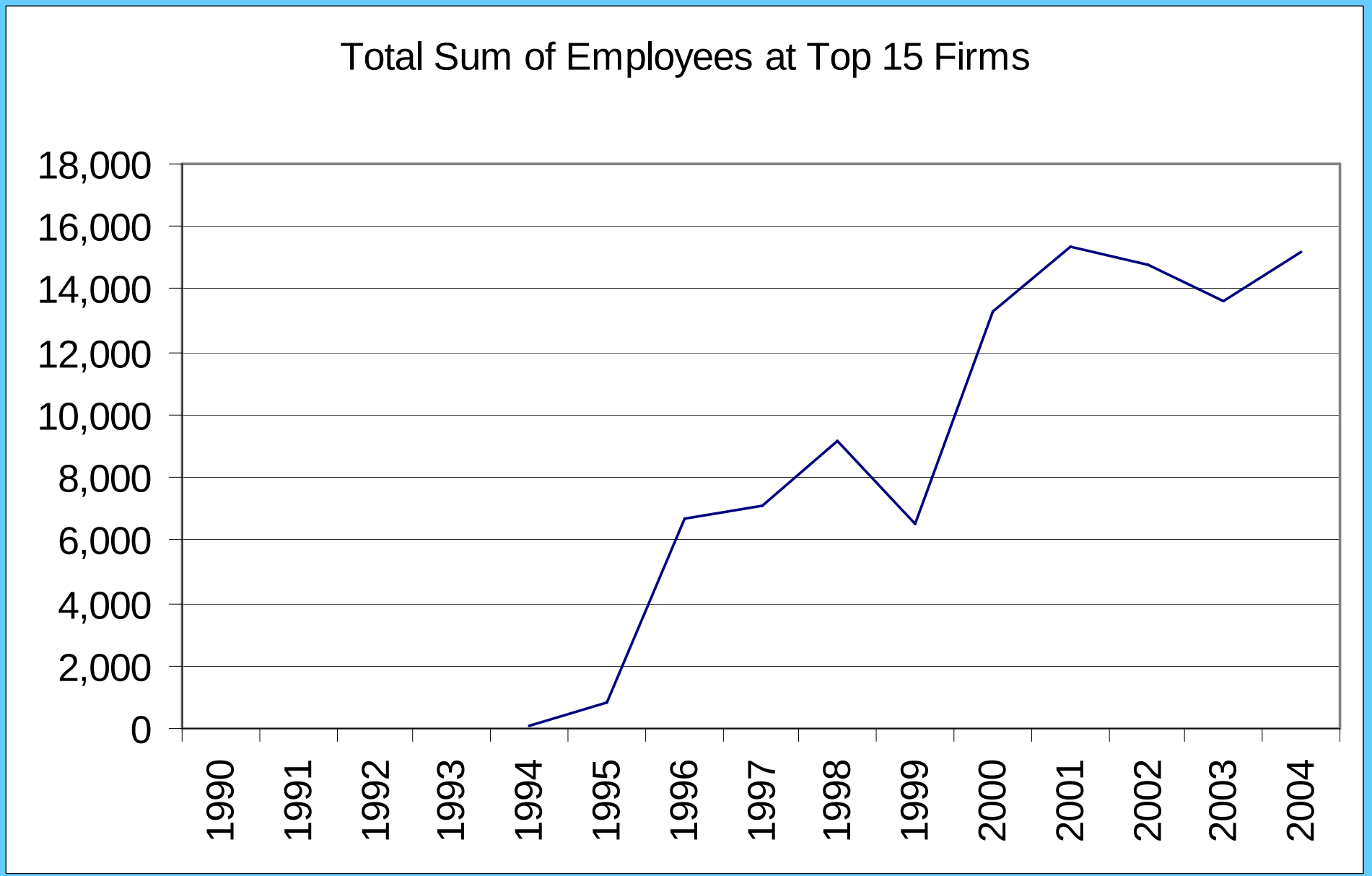
[a] Percent of firms conducting research or business under a given taxonomy classification.

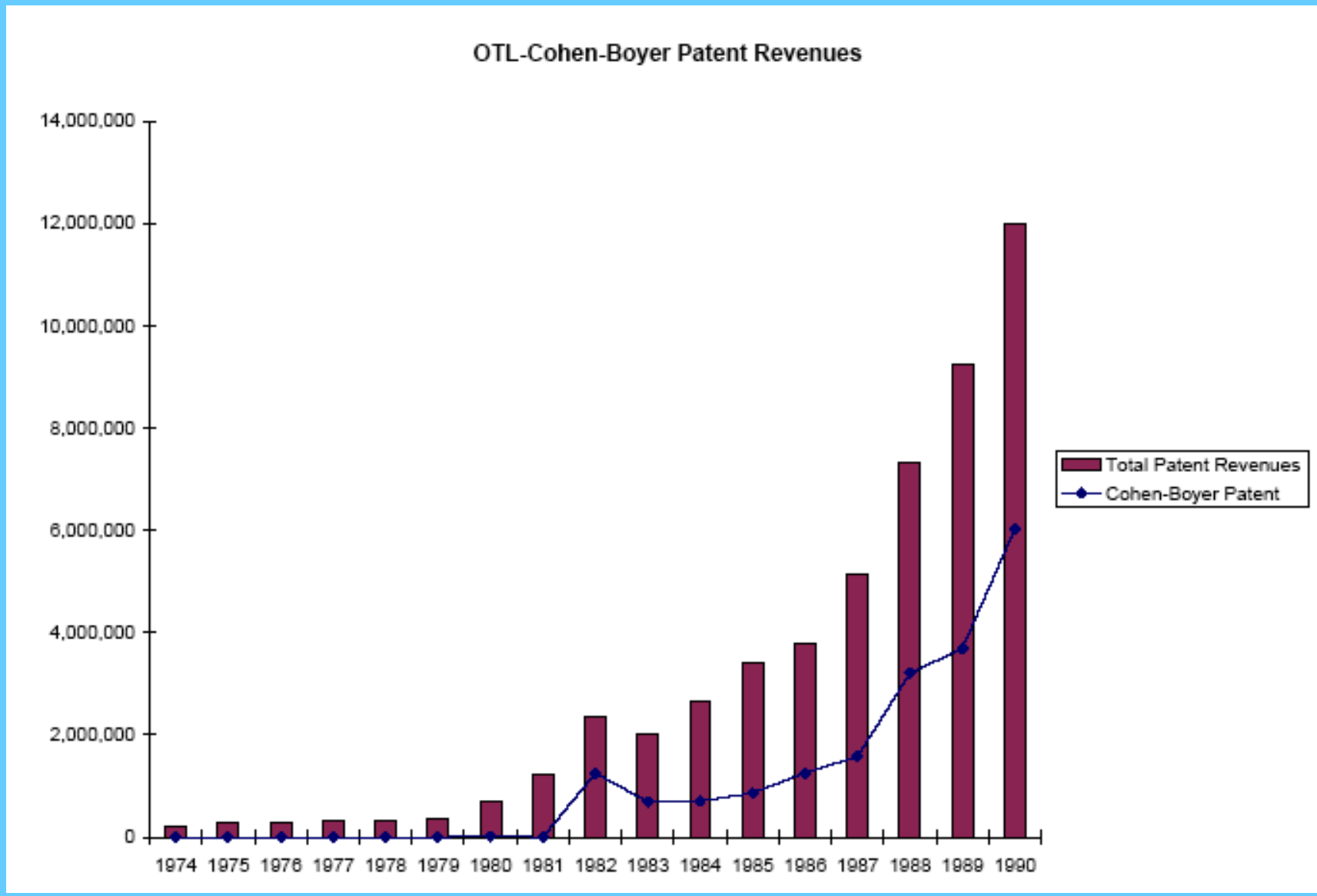
Source: Perin, Wiechers & Cook-Deegan, 2006

All Firms in Database by Taxonomy



	AGRIVET	DATABSE	DNASEQN	DNATEST	DRUGDEV	GENEFNL	GENEMAP	GENEPOP	GENETFR	GENEXPR	IDNTFCN	INFRMTX	INSTRMT	PHRMGEN	STANDRD	SUPPLYR	TRSTFND	SYNBIOL
# Firms	19	19	20	69	155	52	27	7	10	73	2	104	61	49	4	67	3	2


Total Sum of Employees at Top 15 Firms
18,000
16,000
14,000
12,000
10,000
8,000
6,000
4,000
2,000
0
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004



Source: Tim Lenoir, “Biochemistry at Stanford: A Case History in the Formation of an Entrepreneurial Culture,” April 2002.

Health R&D as Percent National Health Expenditures