

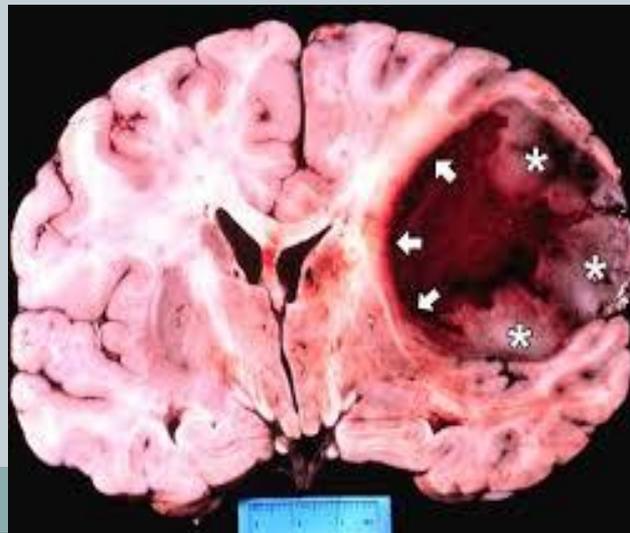
First and Third World Countries/ Technology Transference/ Glioblastomas/ Some Suggestions for Improvement



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JOE SAM ROBINSON M.D.

Introduction

- Attention in regards to Glioblastoma in the West is devoted to improving the poor outcome. There has been a major effort to find a breakthrough in treating this disease. However, the slight advances that occurred have been largely confined to few developed countries.
- The rest of developing world apparently has no access to such technology rising the question of how can this be reversed.



Limitations of presented data

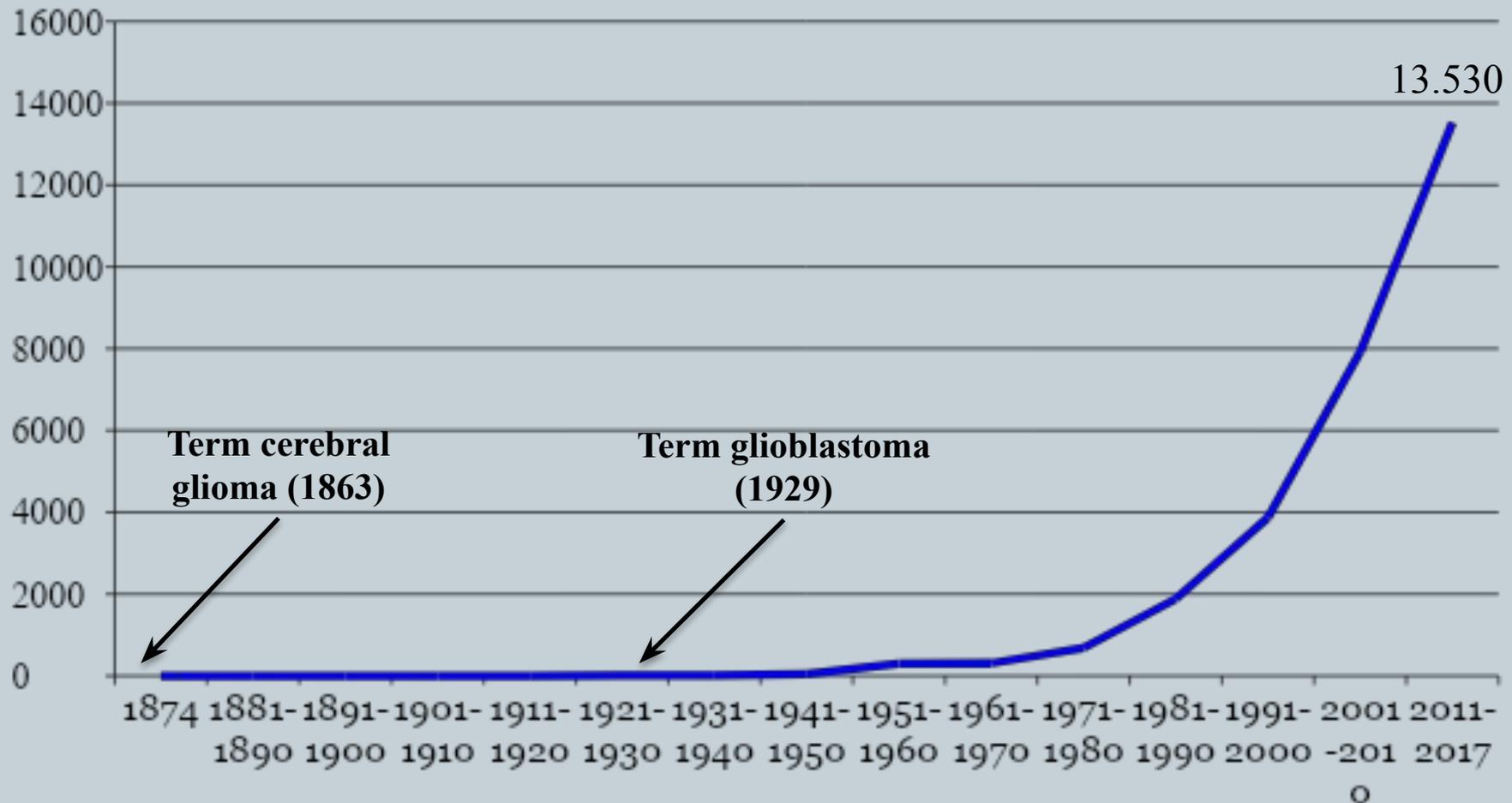
- Fluctuations in currency rates
- Insufficiency or inaccuracy of the available international data
- Errors in population numbers
- Errors in international statistical data
- Methodological difficulties and data summation



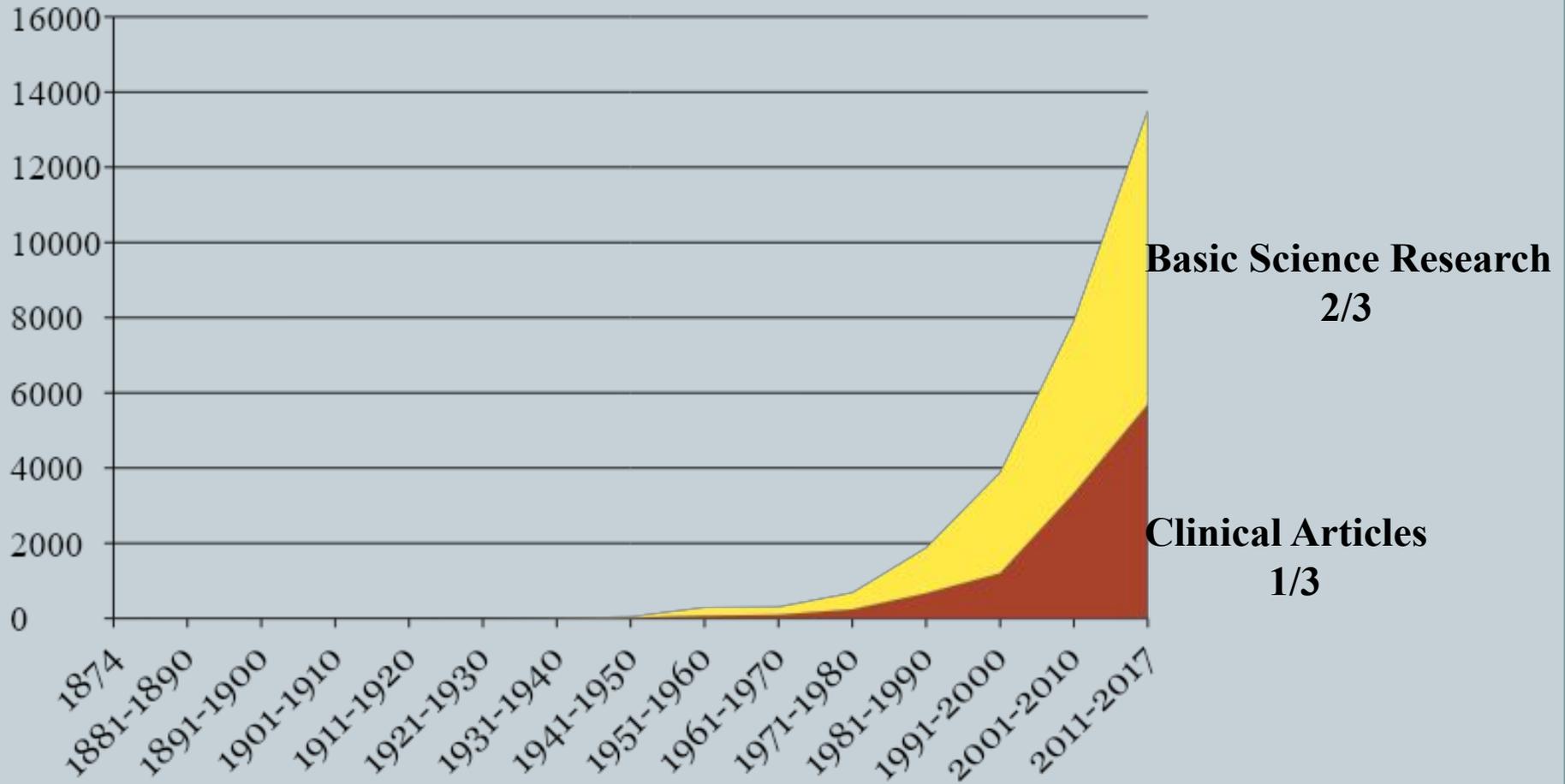
The view from Mt. Olympus



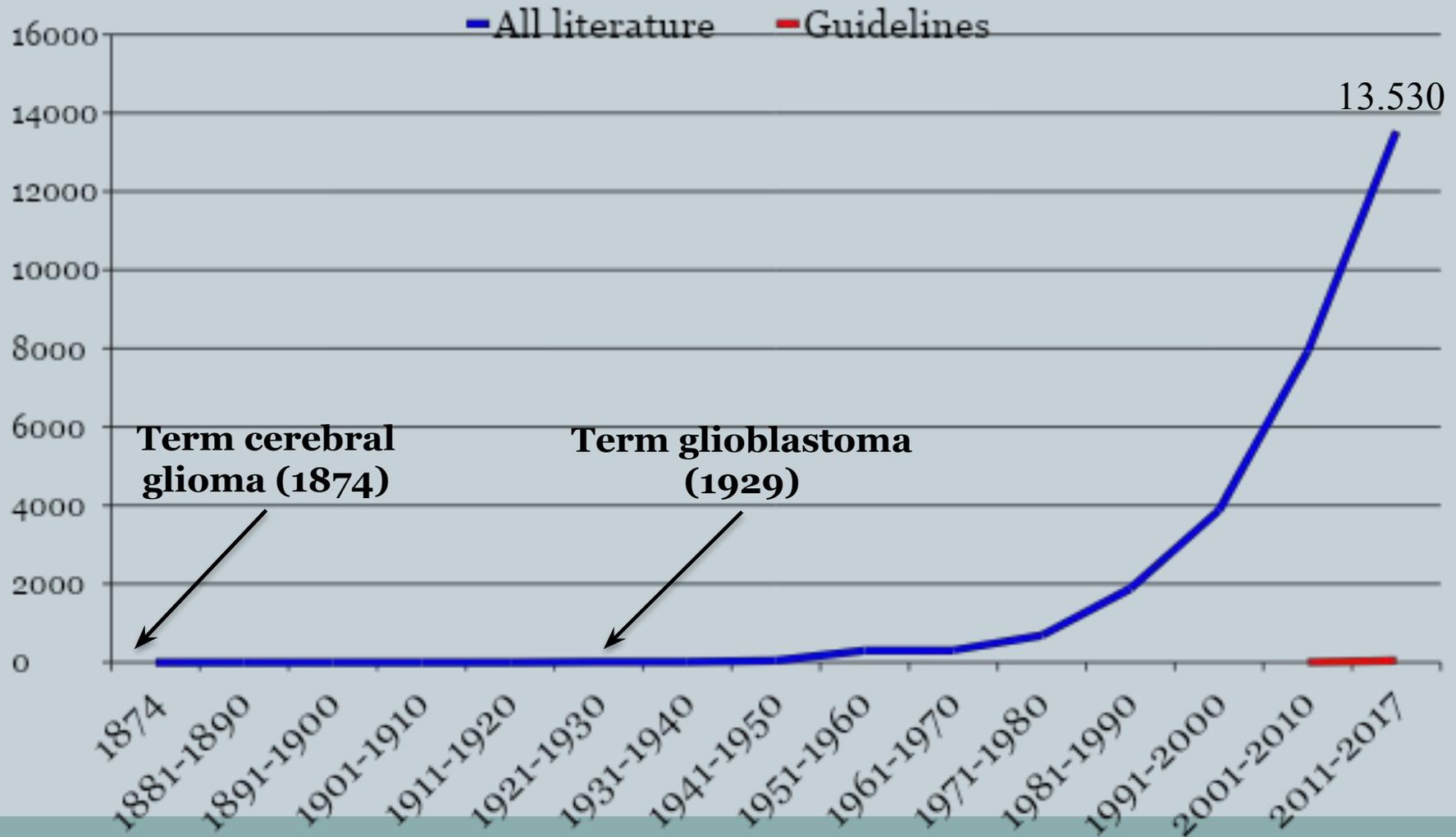
Cited articles related to cerebral gliomas or glioblastomas – 28.577



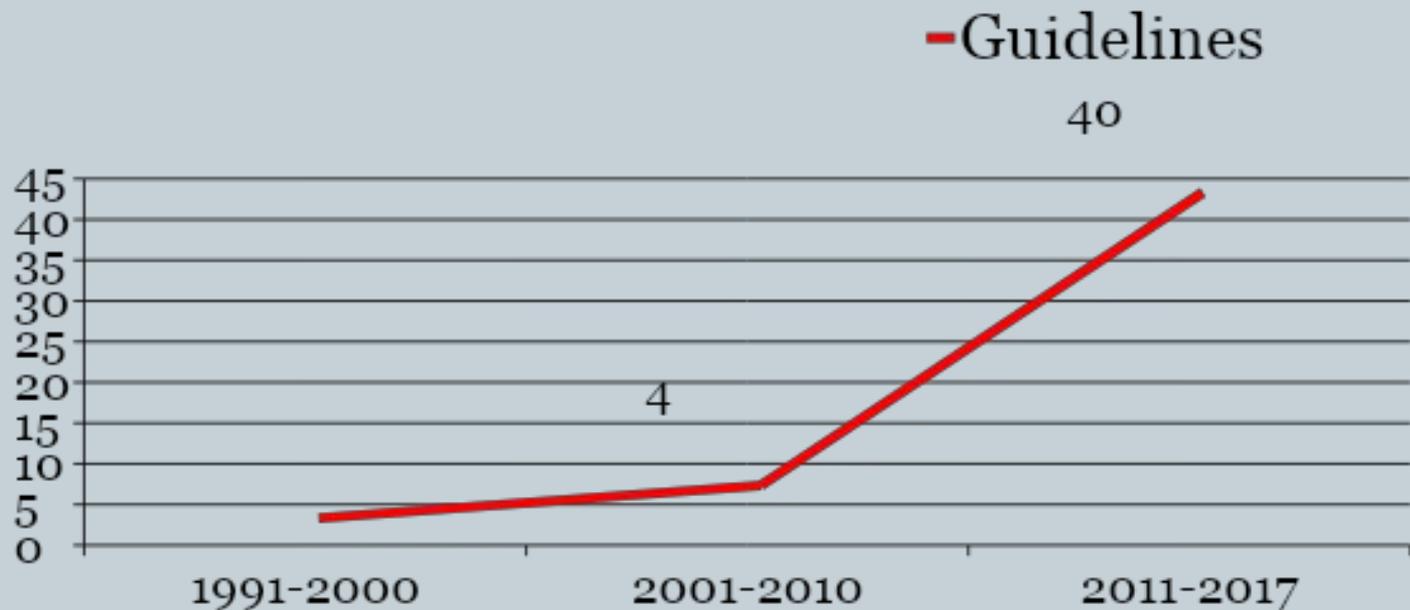
Cited articles by type of research



Articles related to cerebral gliomas or glioblastomas – 28.577



Articles related to clinical guidelines for treatment of gliomas or glioblastomas – 40



Most published guidelines for GBM are from US or Western Europe

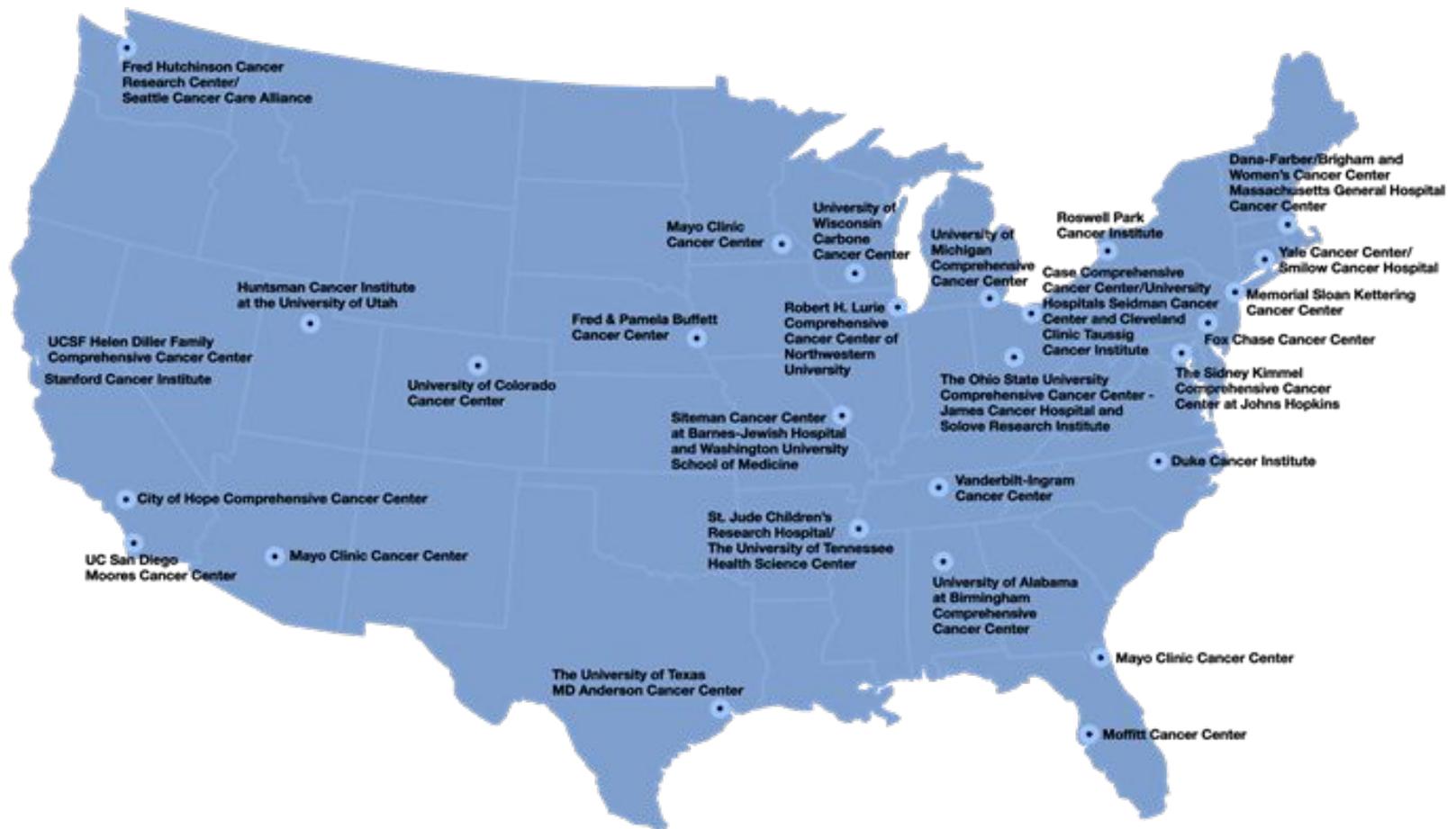
	USA	UK	Switzerland	Germany	Netherlands	Spain	Belgium
2006	1						
2007		1	1				
2008		1					
2009							
2010		1				1	
2011	1						
2012	5	1					1
2013	2						
2014	9		1	1	1		
2015	7	1	1				
2016	3			1	1		
2017	1						



National Comprehensive Cancer Network

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National Comprehensive Cancer Network (NCCN) is an alliance of 27 cancer centers in the United States, most of which are designated by the National Cancer Institute as comprehensive cancer centers.



GBM Guidelines – Adjuvant Treatment (Age <70)

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NCCN Guidelines Version 1.2016 Anaplastic Gliomas^a/Glioblastoma

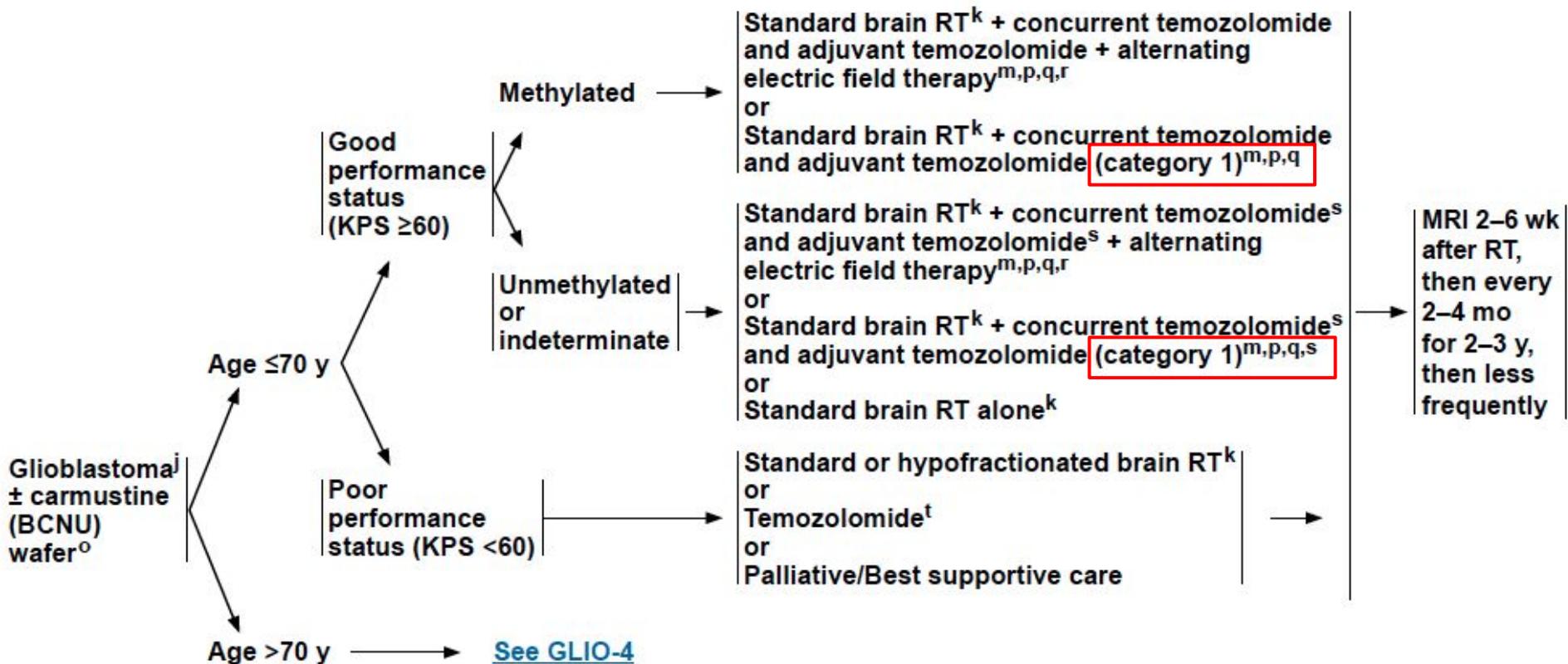
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**GLIOBLASTOMA
PATHOLOGY^d**

**MGMTⁿ PROMOTOR
STATUS**

ADJUVANT TREATMENT

FOLLOW-UP



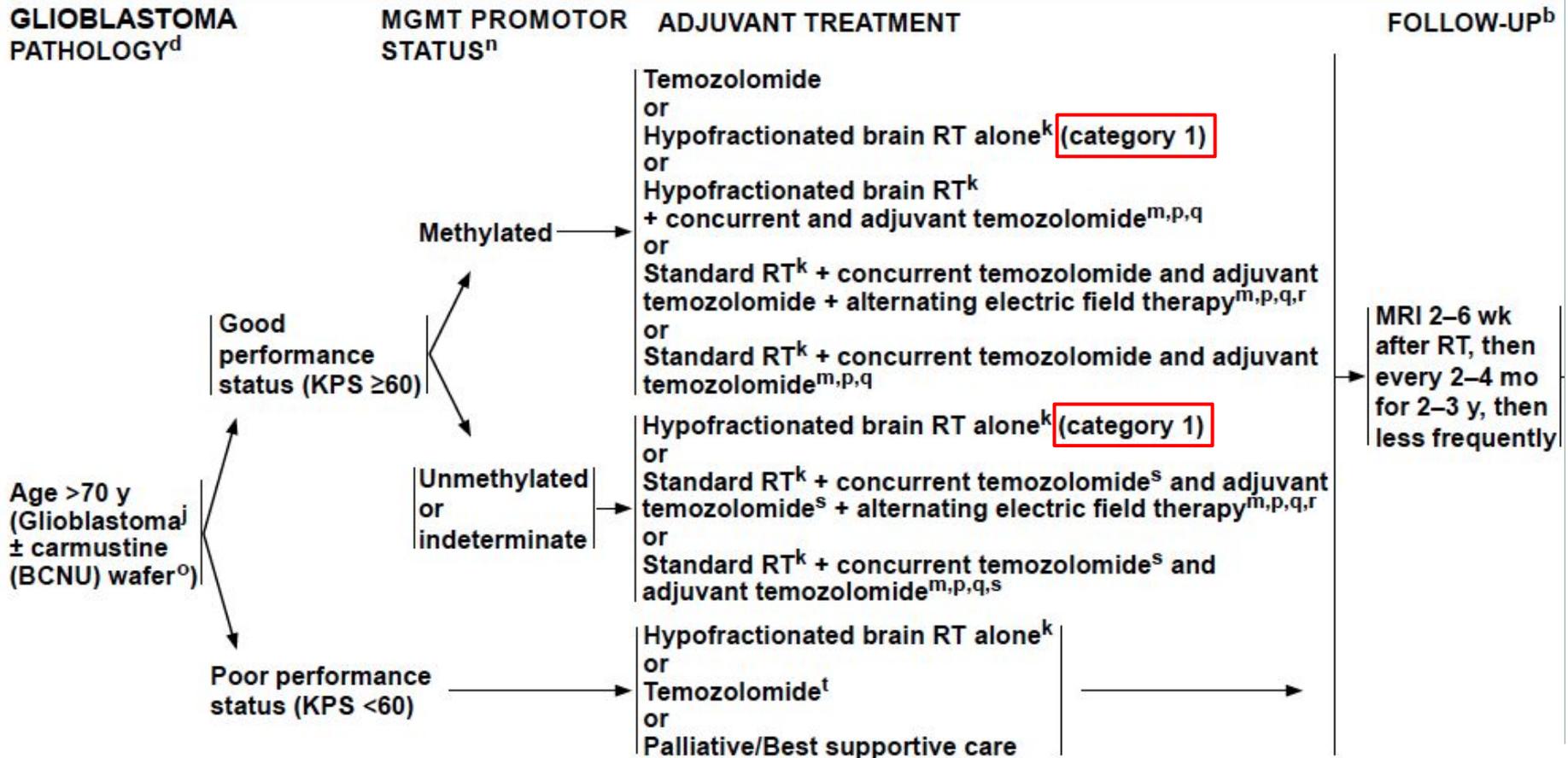
GBM Guidelines – Adjuvant Treatment (Age >70)

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NCCN Guidelines Version 1.2016 Anaplastic Gliomas^a/Glioblastoma

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Summary of published clinical guidelines

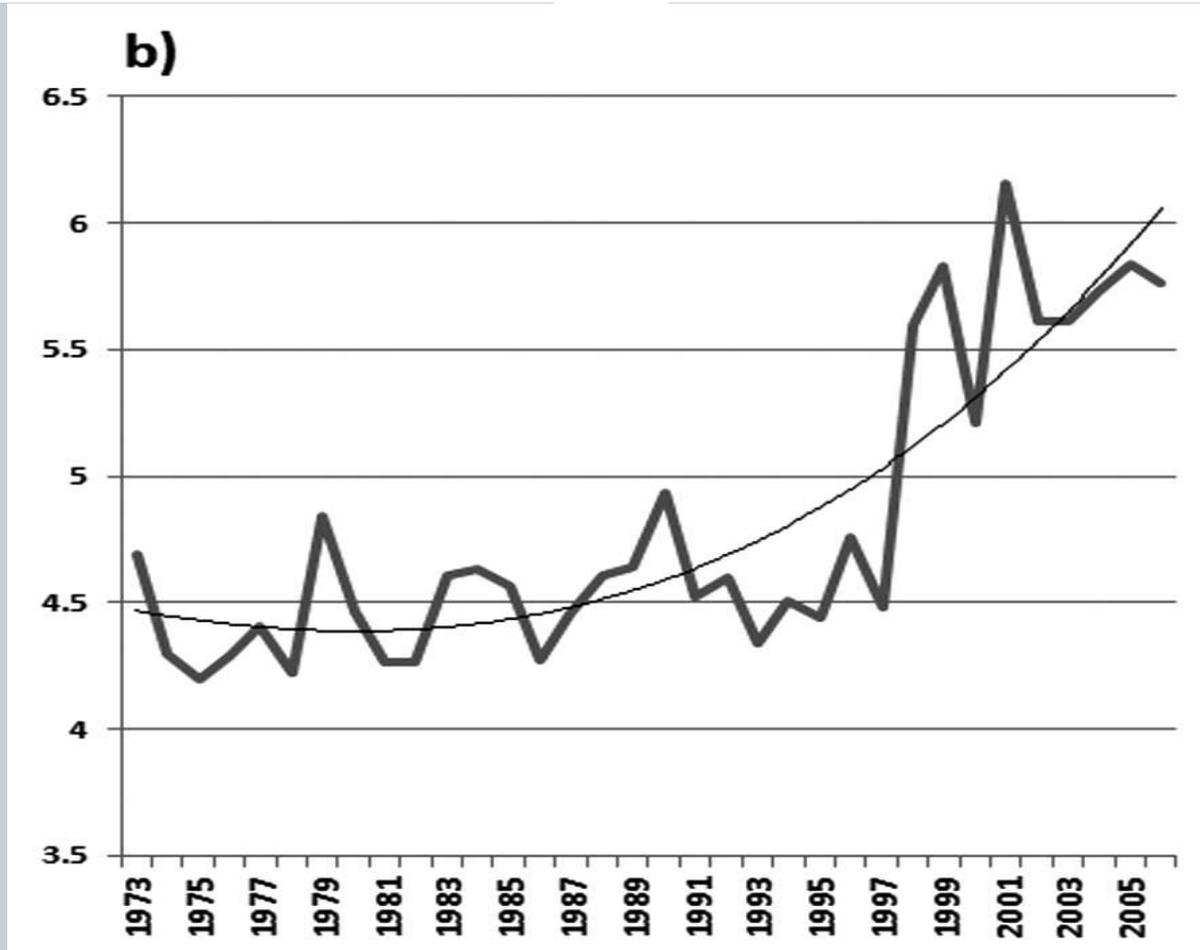
Generally addressed issues

- Who to treat?
- Role of surgery
- Role of chemotherapy
- Role of radiation
- Management of recurrence

Guideline limitations

- Applicable only to developed countries (Western world)
- Only 3 out of 40 guidelines support any of the recommendations with partial Grade I evidence
- No Grade I evidence before 2014
- There is no any reference to cost
- Often incompletely address treatment algorithm

Benefit of clinical guidelines: Survivability in GBM



Kaplan-Meier plot, 21,783 GBM patient yearly median survival development over time

Outcome (GBM)

Median survival **without** treatment is 3 months¹

Median survival **with** maximal treatment is 14.6 months²

Treatment adds 11,6 months or about 1 year of life

1. Schapira, Anthony H.V. (2007). *Neurology and clinical neuroscience*. Philadelphia: Mosby Elsevier. p. 1336. ISBN 9780323070539.

2. *World Cancer Report 2014*. World Health Organization. 2014. pp. Chapter 5.16. ISBN 9283204298.

... a little digression

Standard of Care vs Clinical Guidelines

● Standard of Care

- In certain industries and professions, the standard of care is determined by the standard that would be exercised by the reasonably prudent manufacturer of a product, or the reasonably prudent professional in that line of work
- Derived from English Tort Law it was first brought about in *Vaughn vs Menlove* (1837)

● Clinical Guidelines

- A **medical guidelines** (also called a **clinical guideline**, **clinical protocol** or **clinical practice guideline**) is a document with the aim of guiding decisions and criteria regarding diagnosis, management, and treatment in specific areas of healthcare. Such documents have been in use for thousands of years during the entire history of medicine. However, in contrast to previous approaches, which were often based on tradition or authority, modern medical guidelines are based on an examination of current evidence within the paradigm of evidence-based medicine



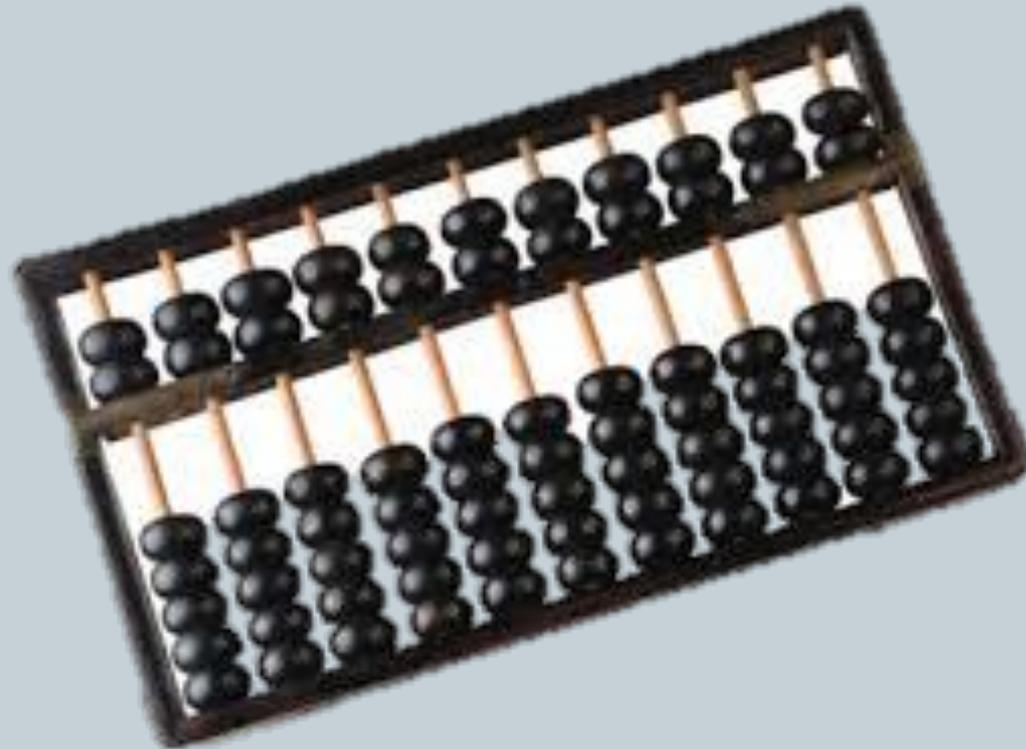
Standards of care/ Clinical Guidelines around the world :



Standards of Care/Clinical Guidelines for GBM from the WHO

- No WHO standard of care for GBM
- Generally the following match US standards of care
 - European Union
 - Japan
 - Singapore
 - Australia
 - Canada
 - New Zealand
 - South Korea

And now a little math...



- The question we ask: How many people in the world are actually getting the standard of care?



How Many People are Actually Receiving the “Standard of Care”/Clinical Guidelines

- Even in developed places there are limitations to access
- US 13,000 new GBM cases
- US population 320,000,000
- Number of people over 40 is about 130,000,000
- Incidence per older person in the US is 1/10,000
- More or less the world population is about 7.5 billion
- World population over 40 is about 2.8 billion
- Thus if the incidence is 1/10,000 - **280,000 people** in the world that will be yearly affected by GBM

- How many people are receiving standards of care world wide at the present?
- Estimated yearly incidence of GBM worldwide is 280,000
- $280,000 - 13,000(\text{US}) - 41,000 (\text{EU}) = 226,000$
- About 5% of the remainder of world's population is getting appropriate treatment, which is 11,500
- $226,000 - 11,500 = 214,500$

- Why not worldwide access to standard of care/
clinical guidelines/ treatment of Glioblastomas?



I. Worldwide Supply Difficulties...



Mal-Supply of Physician Work-force



Supply: Neurosurgeons Around the World

27

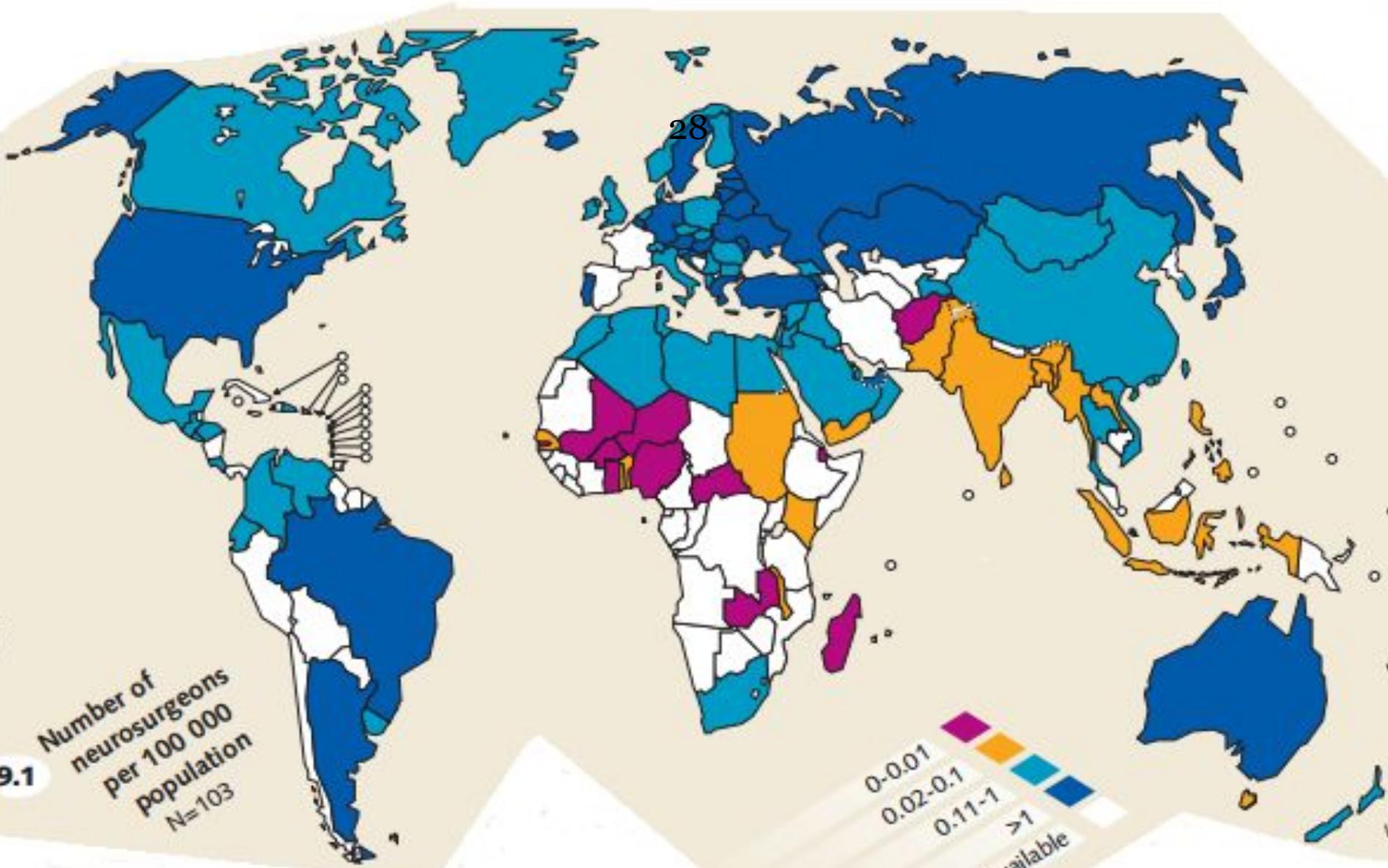
- A total of 33 193 neurosurgeons are reported to be available in 103 countries in 2004.
- The median number of neurosurgeons per 100 000 population is:
 - 0.01 in Africa
 - 0.76 in the Americas
 - 0.03 in South-East Asia
 - 0.37 in the Eastern Mediterranean
 - 1.02 in Europe

0000

28

9.1

Number of neurosurgeons per 100 000 population
N=103



Neuropathologists around the world

- American Association of Neuropathologists has 800 members from around the world
- Number of neuropathologists in UK: 98

Tertiary Care: China



China: Tertiary Hospital Care Imbalanced

	Name of Hospital	Total Score	Research Score	Total Score
1	Beijing Union hospital	80.00	10.95	90.95
2	Sichuan Huaxi hospital	69.42	20.00	89.42
3	PLA General hospital	58.16	14.52	72.68
4	Ruijin Shanghai Jiaotong Univ.	42.92	11.90	54.83
5	Xijing 4 th Military Medical Univ.	33.99	12.99	46.98
6	Zhongshan, Fudan Univ.	32.83	13.66	46.48
7	Huashan, Fudan Univ.	34.70	10.23	44.93
8	First hospital, Peking Univ.	32.43	9.10	41.53
9	People's Hospital, Peking Univ.	29.25	8.88	38.13
10	Tongji hospital,	26.43	11.13	37.56
11	First Hospital, Zhongshan Univ.	25.15	12.26	37.41
12	Peking Univ. 3 rd Hospital,	18.42	9.29	27.72
13	Union hospital, Tongji Med. College	15.61	10.85	26.45
14	First hospital, Zhejiang Univ.	13.13	13.09	26.22
15	Changhai, 2 nd Military Med. Univ.	14.35	11.25	25.60
16	First hospital, China Med. Univ.	15.05	10.17	25.21
17	Fuwai Heart-Vascular Disease Hospital	12.75	12.43	25.16
18	Xiangya 2 nd hospital. Zhongnan Univ.	13.53	9.06	22.59
19	Renji hospital, Jiaotong Univ.	12.82	9.64	22.46
20	Southern Hospital, Southern Medical Univ.	12.98	9.32	22.29

Table 6. Top 20 hospitals in China (2011)

Absence of radiographic diagnostic facilities



Table 123 (page 1 of 2). Number of magnetic resonance imaging (MRI) units and computed tomography (CT) scanners: Selected countries, selected years 1990–2009

Updated data when available, Excel, PDF, and more data years: <http://www.cdc.gov/nchs/hus/contents2011.htm#123>.

[Data are based on reporting by Organisation for Economic Co-operation and Development (OECD) countries]

Country	1990	1995	2000	2007	2008	2009	1990	1995	2000	2007	2008	2009
	Number of MRI units per million population						Number of CT scanners per million population					
Australia ¹	0.6	2.9	†3.5	5.1	5.6	5.9	13.8	††20.5	††26.1	††38.7
Austria	11.0	17.7	18.0	18.4	26.1	30.0	29.6	29.3
Canada ²	0.7	1.4	2.5	6.7	...	8.0	7.2	8.0	...	12.7	...	13.9
Czech Republic ³	...	1.0	1.7	4.4	5.0	5.7	...	6.7	9.6	12.9	13.3	14.1
Denmark	5.4	15.4	11.4	18.5	21.5	23.7
Estonia	5.2	8.2	7.5	11.2	14.9	14.9
Finland	1.8	4.3	9.9	15.3	16.2	16.9	9.8	11.8	13.5	16.5	...	20.4
France	1.7	5.5	6.1	6.5	7.0	10.4	10.9	11.1
Greece	17.9	19.6	21.7	29.0	30.6	33.8
Hungary ⁴	0.1	1.0	1.8	2.8	2.8	2.8	1.9	4.6	5.7	7.3	7.1	7.2
Iceland	3.9	7.5	10.7	19.3	18.8	21.9	11.8	18.7	21.3	32.1	31.3	34.5
Ireland	8.5	9.0	†11.9	4.3	14.3	14.5	15.3
Israel ⁵	...	0.9	1.4	2.0	2.1	1.9	...	1.6	5.7	8.5	8.8	9.4
Italy ⁶	7.8	18.5	20.1	21.6	21.1	30.1	30.9	31.7
Japan ⁷	6.1	43.1	...	55.2	97.3	...
Luxembourg	2.6	2.5	2.3	10.4	12.4	14.2	5.2	26.9	25.2	27.1	26.9	26.3
Mexico	1.5	1.7	1.9	4.0	4.2	4.3
Netherlands ⁸	0.9	3.9	...	7.6	10.4	11.0	7.3	7.8	10.3	11.3
New Zealand	8.8	9.6	9.7	3.5	...	8.8	12.3	12.4	14.6
Poland	2.7	2.9	3.7	4.4	9.7	10.9	12.4
Portugal ⁹	8.9	26.0
Republic of Korea	...	3.9	5.4	16.0	17.6	19.0	...	15.5	28.4	37.1	36.8	37.1
Slovak Republic ¹⁰	1.1	5.7	6.1	6.1	13.7	13.7	13.3
Slovenia	3.5	4.5	4.5	10.9	12.4	11.9
Switzerland	††31.4	††32.0	††32.8
Turkey	5.4	†7.2	8.9	1.6	7.7	†10.6	11.6
United Kingdom ¹¹	††5.6	...	††5.6	††5.3	...	††7.4	...
United States ¹²	...	12.3	...	25.9	34.3

COST



II. Cost issues*

- a. US costs
- b. European Community costs
- c. Developing world

*Supply costs are not included in this section

II.a. US Cost data

- Currently in the U.S., the cost of temozolomide (Temodar, Temodal) treatment is over \$10,000 per month. If you add in Gliadel Wafers, it adds another \$10,000 to your initial resection surgery. And treatment with Avastin + CPT-11 can be over \$50,000 per year.

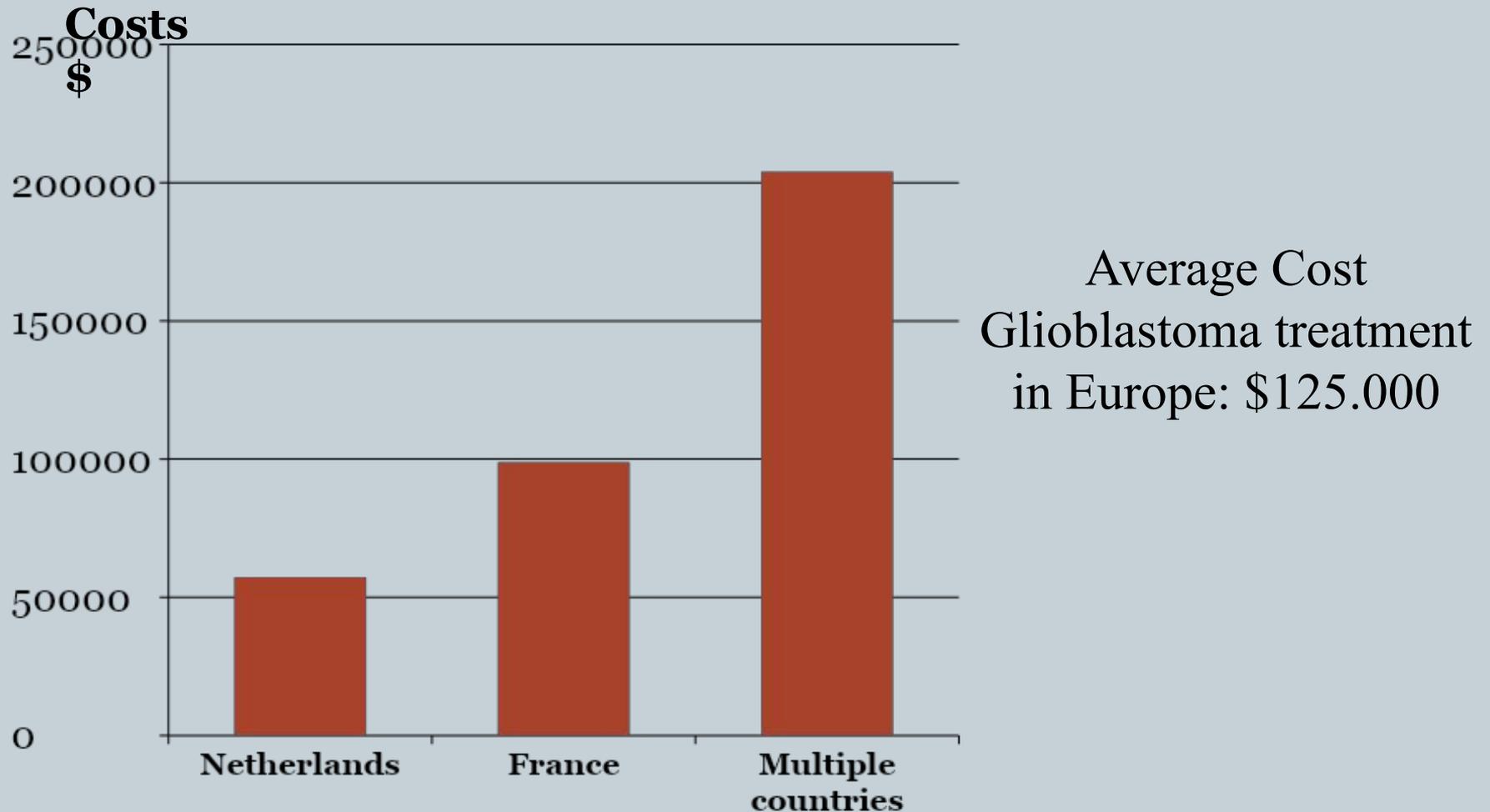
Cost data in the USA :

- Dx
 - MRI/CT-Scan
 - \$1200
 - Biopsy
- Neuropathology
- Craniotomy
 - \$50,000-\$70,000
- Radiation
 - \$7,000-\$20,000

II.a. US Cost data, cont.

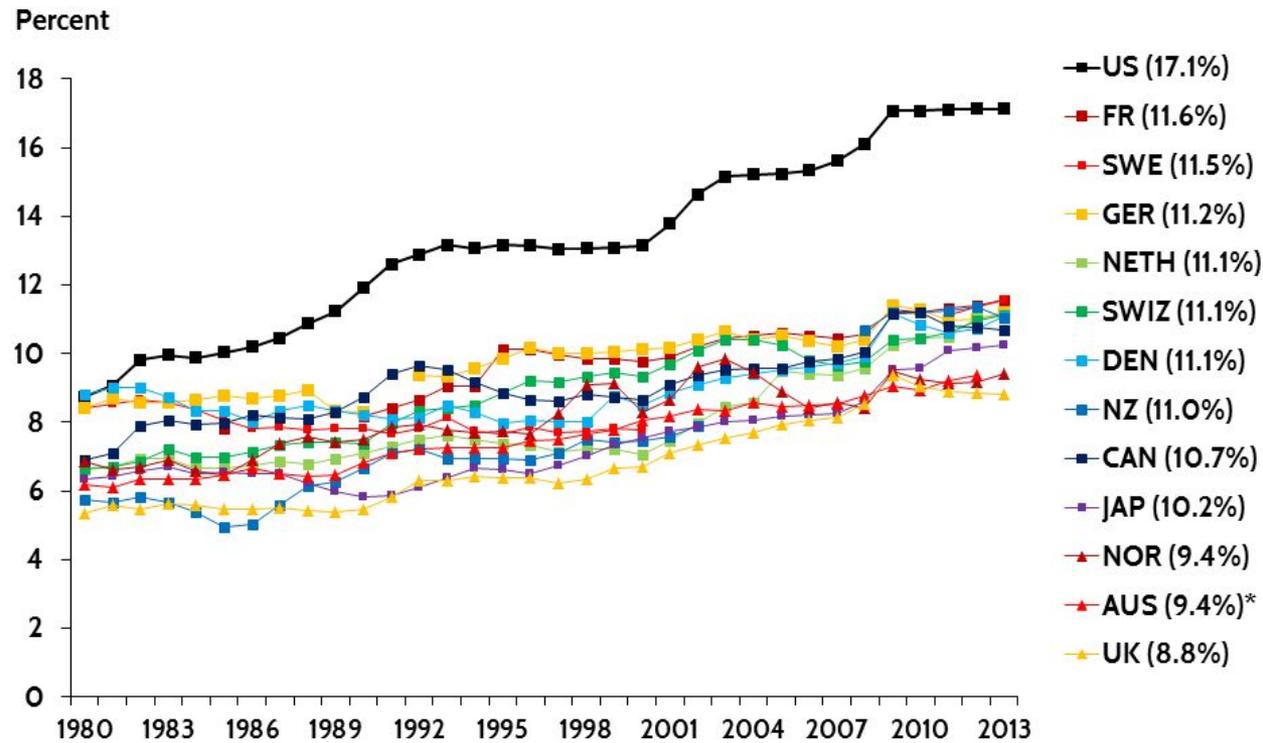
- Chemotherapy with the drug temozolomide is the current standard of treatment for GBM
 - \$51/5 capsules (6 times treatment)
- Hospice
 - \$150/day
- Meds
 - Seizure meds
 - Steroids
- Follow up scans
- Hospice Care
- Pain Management

II.b. Average Glioblastoma Treatment Costs in Europe



II.b. Amount of GNP Spent on Healthcare

Exhibit 1. Health Care Spending as a Percentage of GDP, 1980–2013



* 2012.

Notes: GDP refers to gross domestic product. Dutch and Swiss data are for current spending only, and exclude spending on capital formation of health care providers.

Source: OECD Health Data 2015.

II.b. EU Cost data

- Thus we estimate the cost of GBM treatment in the United States would be \$250,000
- Estimated cost of GBM treatment in EU is \$125.000

II.c. Developing world cost data

USA

1. Neurosurgery consultation - \$378
 2. Labs - \$400
 3. Imaging (MRI) – 6 x \$600
 4. Hospital costs - \$8.813
 5. Surgery costs - \$25.204
 6. BCNU costs - \$10.000
 7. Genetic study - \$550
 8. Immunohistology - \$416
 9. Radiation costs - \$11.520
 10. TMZ (initial) - \$12.136
 11. TMZ (maintenance) - \$2.041/month
 12. Electric field therapy - \$21.000/month
 13. Other medications - \$300/month
 14. Hospice - \$4.500/month
- Total: \$73.017 + \$23.341/month + Hospice**

INDIA

1. Neurosurgery Consultation - \$11
 2. Labs - \$119
 3. Imaging (MRI) – 6 x \$400
 4. Hospital costs - \$467
 5. Surgery costs - \$3.500
 6. BCNU costs - \$4.285
 7. Genetic study - \$243
 8. Immunohistology - \$124
 9. Radiation costs - \$6.898
 10. TMZ (initial) - \$1.410
 11. TMZ (maintenance) - \$365/month
 12. Electric field therapy - NA
 13. Other medications – \$180/month
 14. Hospice – NA
- Total: \$19.457 + \$545/month + Hospice**

How much would it cost to treat this population

**For typical patient with an average length
of survival net calculated cost will be:**

● **US** – 220,000 X \$250,000 = \$55 billion

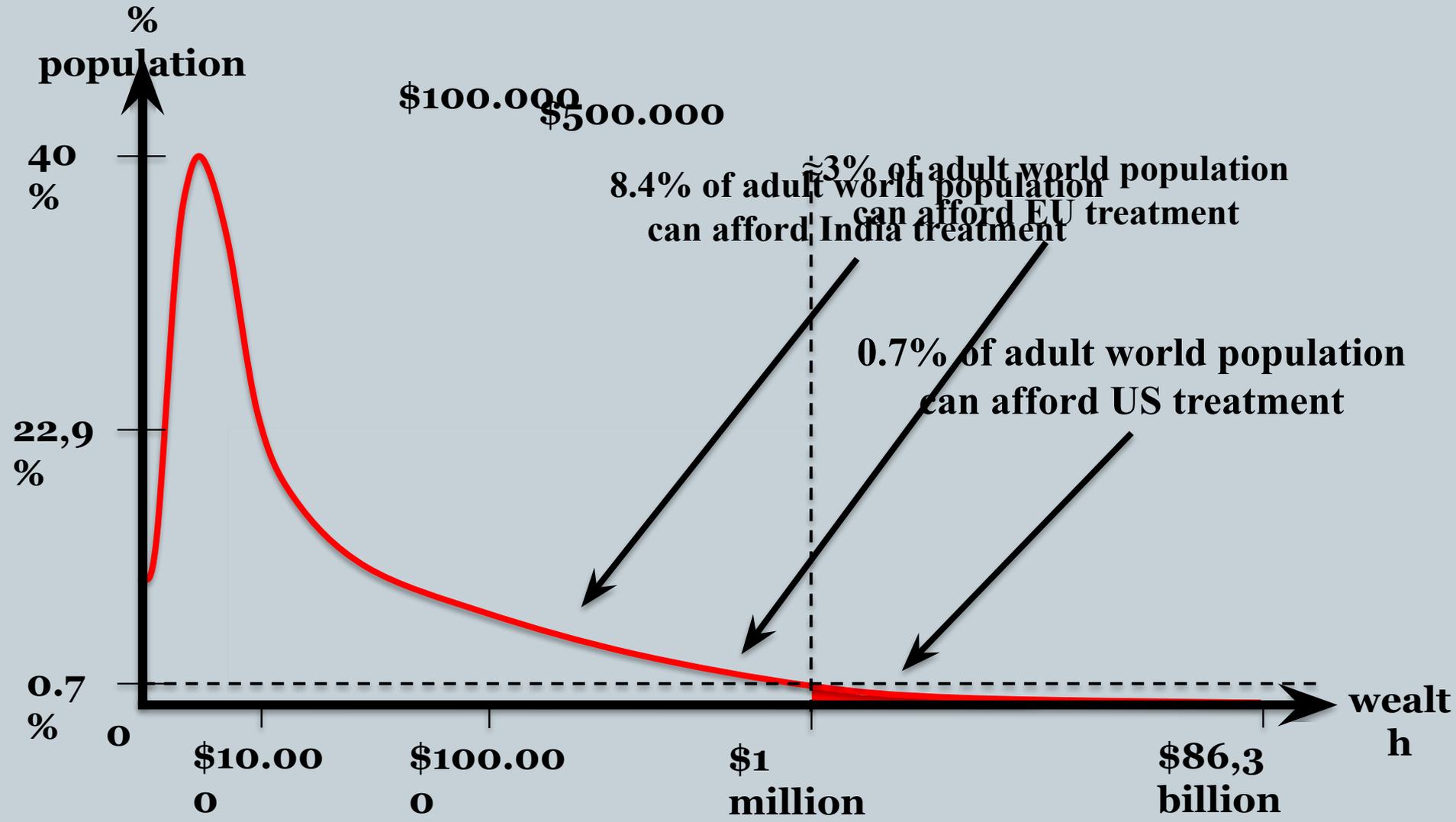
VS

● **EU** – 220,000 x \$125,000 = \$27.5 billion

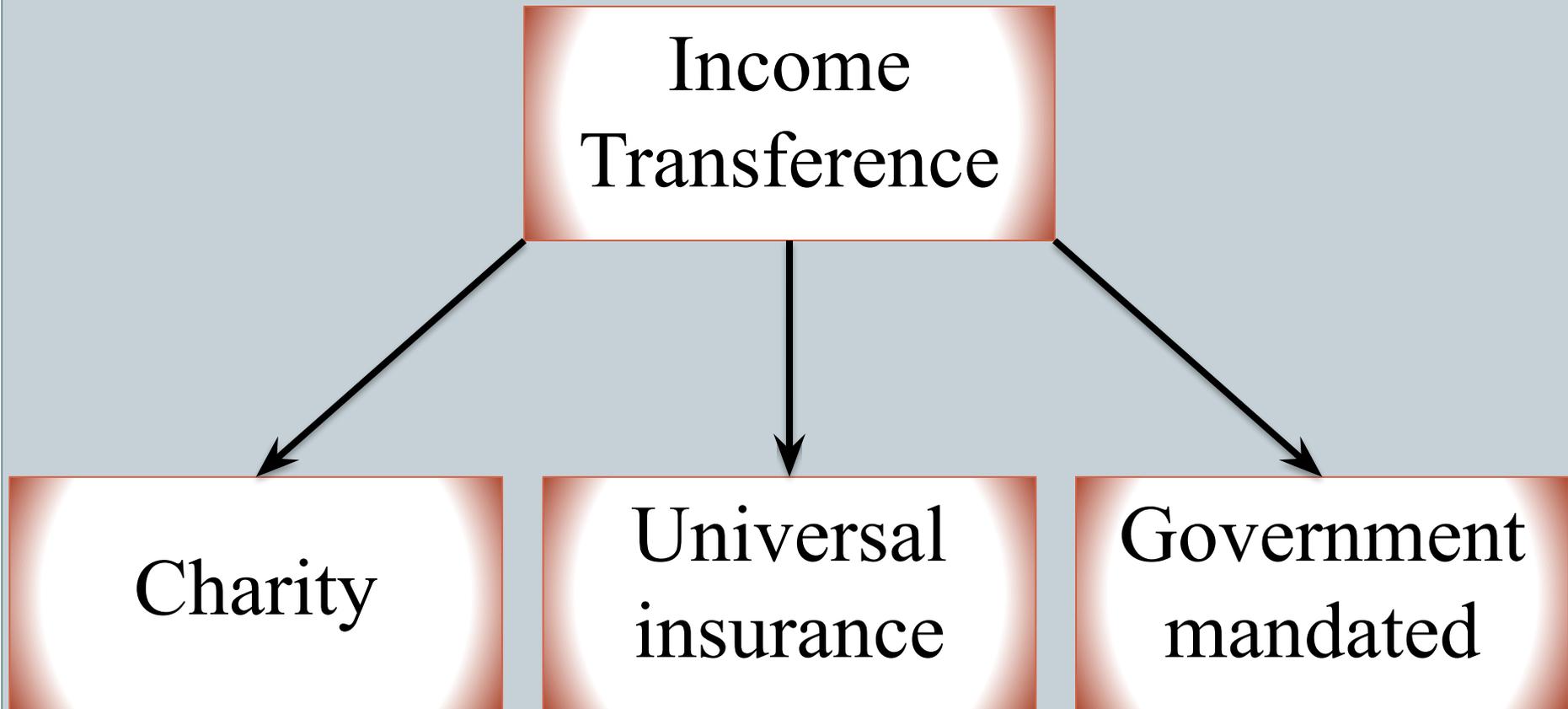
VS

● **India** - 220,000 x \$27.414 = \$6 billion

% of people who can independently pay for reduced costs of GBM



So income transference is necessary

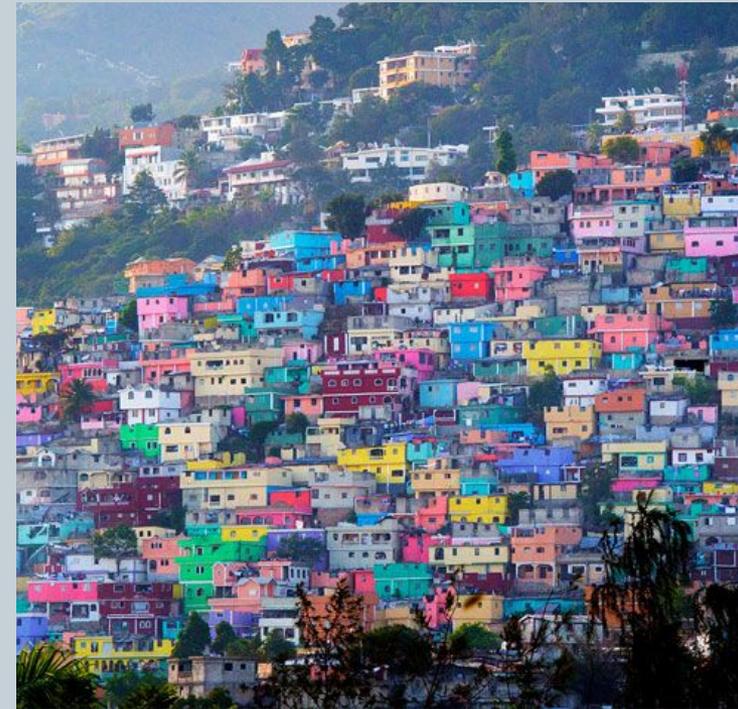


II. Universal insurance

- Health expenditure per capita in US is \$9.000/year
- For a family of four will be \$36.000/year
- Thus, developing countries cannot afford it.

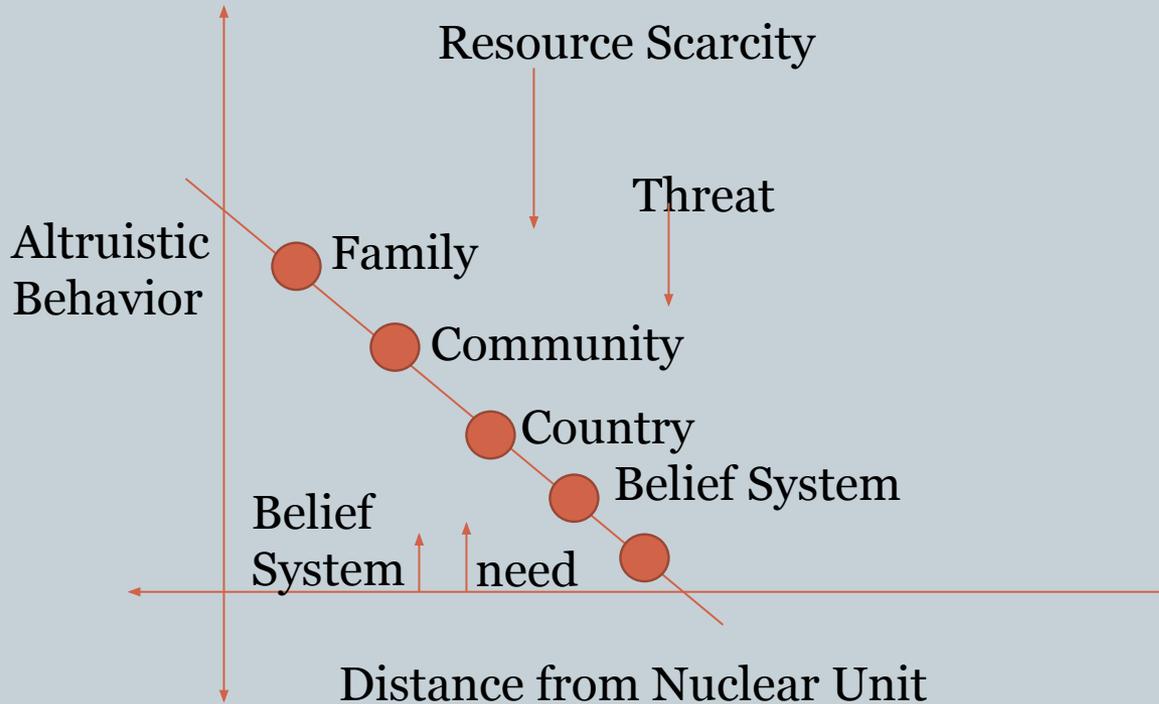
Haiti

- Population: 10.711.000^(World bank)
- GDP: 8.765 billion^(World bank)
- GNI per capita: \$810^(World bank)
- Population older than 40: 2.5 million (23%)^(Wikipedia)
- Calculated number of GBM per year: 250
- Treatment cost: \$62.5 million
- Even if we treat GBM 10 times cheaper, it will still be impossible in Haiti.



Capital of Haiti
Port-au-Prince

Altruistic coefficient graph



Other Ideas, Other Solutions for Both Supply and Cost (a collaborative arrangement between the developed and developing world)



The developed world's efforts



The developed world's efforts

- I. Better resource allocation
- II. Direct Cash transference
- III. Transference of Technology (Mercer University)
- IV. Profit Motive
 - a. Used Equipment
 - b. Develop overseas production facilities
- V. Patent Law
- VI. Accept overseas patients
 - a. Run facilities around the clock
- VII. Technology research around the world
- VIII. Telemedicine

I. Better resource allocation with development of appropriate methodological system



II. Direct Cash transference



Total Value - \$256 trillion (Credit Suisse)

GWP – \$77.9 trillion (CIA World Factbook)

Health expenditure – \$6.5 trillion (WHO)

II. Direct Cash transference

- **US** – \$55 billion (0.8% of WHE)
- **EU** – \$27.5 billion (0.4% of WHE)
- **India** – \$6 billion (0.09% of WHE)

- A relatively trivial amount considering the world's GNP of \$77.9 trillion and the amount the world spends on healthcare approximately \$6.5 trillion

III. Transference of Technology



III. Transference of Technology, cont.

- Mercer university in Vietnam: Manufacturing prosthetic limbs for landmines victims in Vietnam
- \$200 in Vietnam vs \$10,000 in US



IV. Profit motive





IV.a. Used Equipment



IV.a. Used Medical Equipment

- Mexico imports medical equipment, instruments, disposable and dental products totaled US \$10.58 billion in 2015.
- This represented about 80 % of the medical equipment and instrument market and approximately 40 % of the disposable products and dental materials.
- Information on import regulations for pre-owned medical devices was available for 106 markets.¹
- Of 106 markets, 85 markets appear to permit the unrestricted importation of used or refurbished medical equipment on the same terms as new.
- In 2005 India lifted its restrictions, and Niger and Slovak Republic submitted reports in 2005 and 2007 respectively for the first time and indicated that there are no restrictions. Sixteen markets impose restrictions. Five generally prohibit the importation of pre-owned devices.

V. Members of the International Patent System



VI. MD Anderson Cancer Center



Establish Institutions in Developing Countries to Deal with Tertiary Neurosurgical Problems



VI.a. Advanced Medical Technology in Full Time Use Expensive Technology around the Clock



Blue and Gold Crews

VII. Technology research around the world

Top 20 countries for scientific output are first world countries with the USA publishes twice as much as the 2 countries after it in the list

(Japan, Germany)

The top 20 countries for scientific output

66

Top 20 countries by the number of scientific publications (1999-2009)



Rising stars:

-  Bulgaria
-  Pakistan
-  Iran
-  Tanzania
-  Saudi Arabia
-  Serbia
-  Ghana

 Countries with the highest % increase in citations in 2011

* Numbers indicate the number of papers in millions (M)

- However, in regards to Glioblastoma inquiries there needs to be higher grade clinical research studies with better demarcation of clinical expenditures.



VIII. Telemedicine



What Can Developing Countries do?



What Can Developing Countries do?

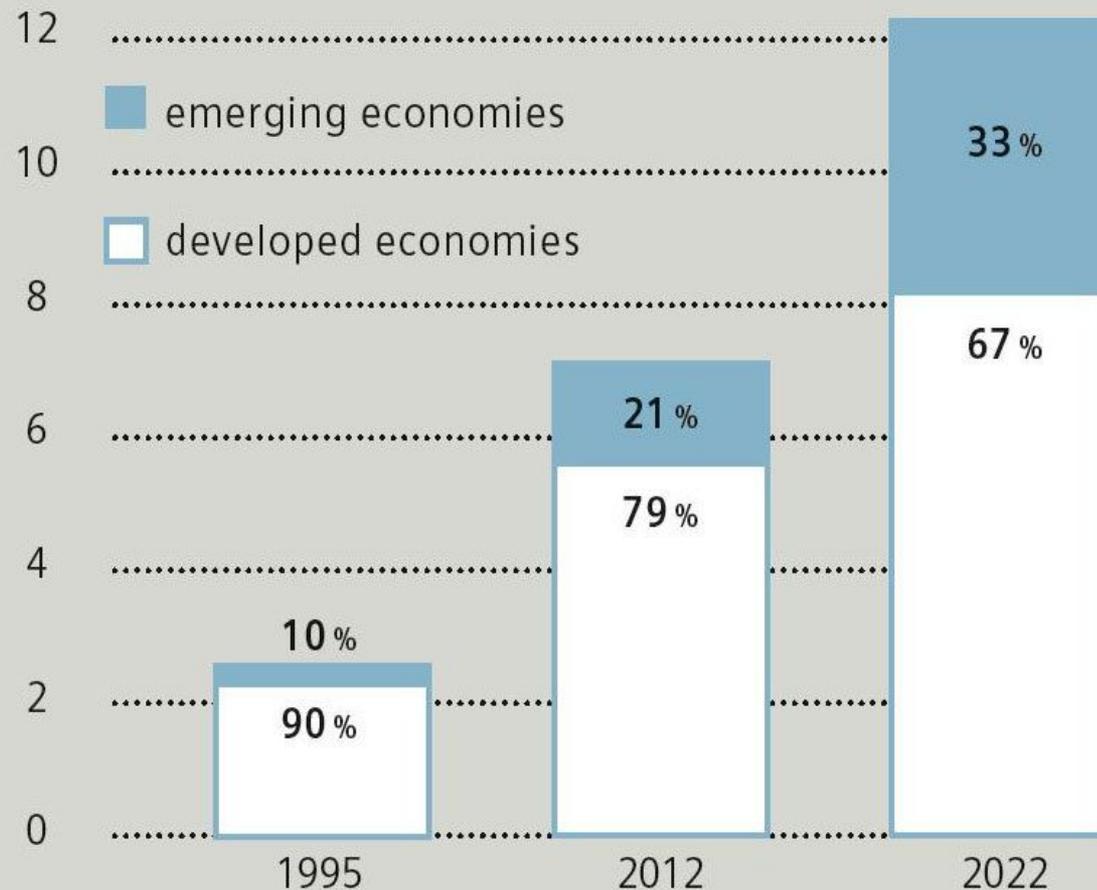
- I. Become more prosperous
- II. Develop cheaper technology exportable to the 1st world
- III. Become innovators
- IV. Discover outrider operative variables
 - a. Discover unusual GBM presentations
 - b. Human genome variability
 - c. Discover possible environmental causable agents of GBM
 - d. T cell & variability of the immune system
 - e. Differing successful treatment modalities

What Can Developing Countries do? (continued)

- V. Participate in Clinical Trials
- VI. Western trained physicians from developing countries serving as a conduit for tertiary technology
- VII. Better statistics

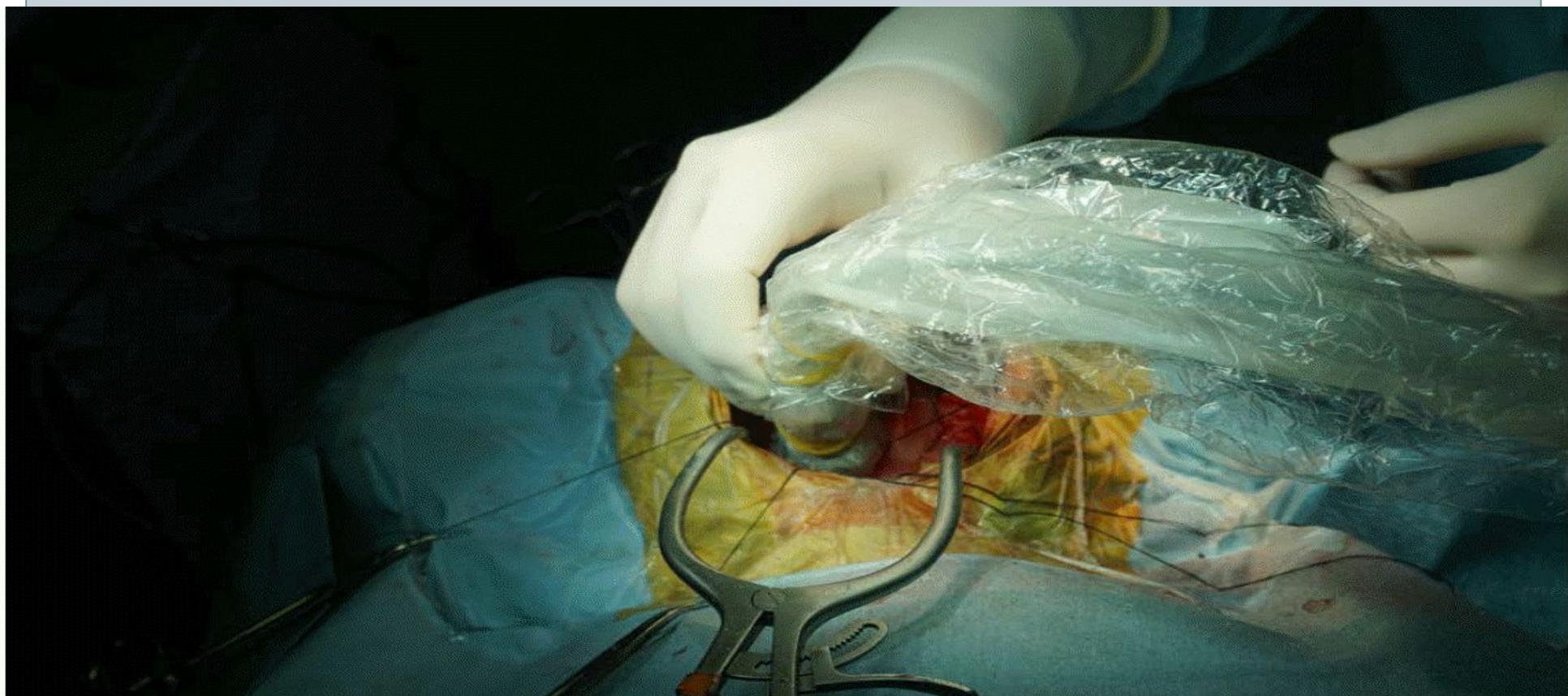
I. Become more prosperous

Global health expenditure (in trillion US\$) ⁵⁾

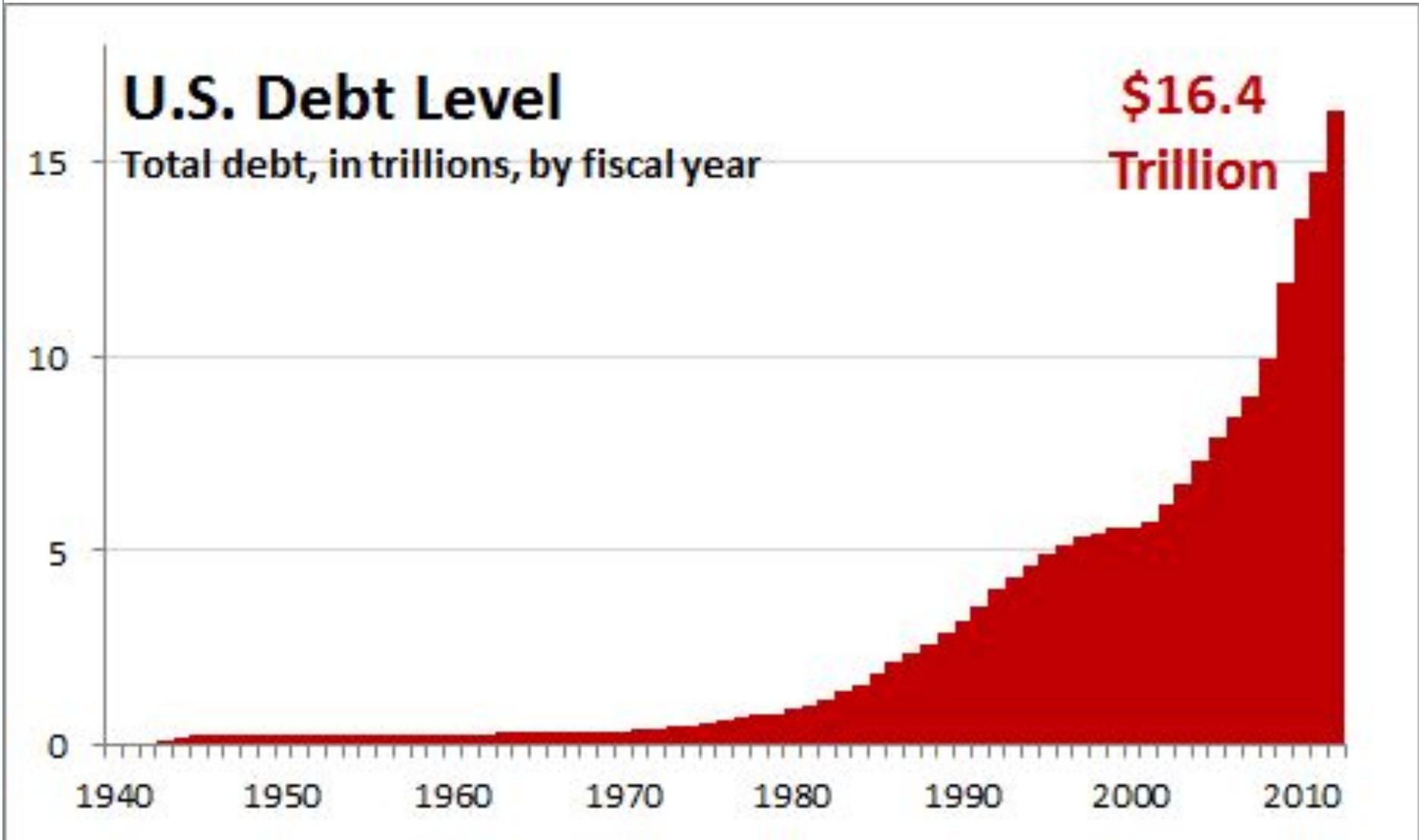


II. Burr hole with ultrasound

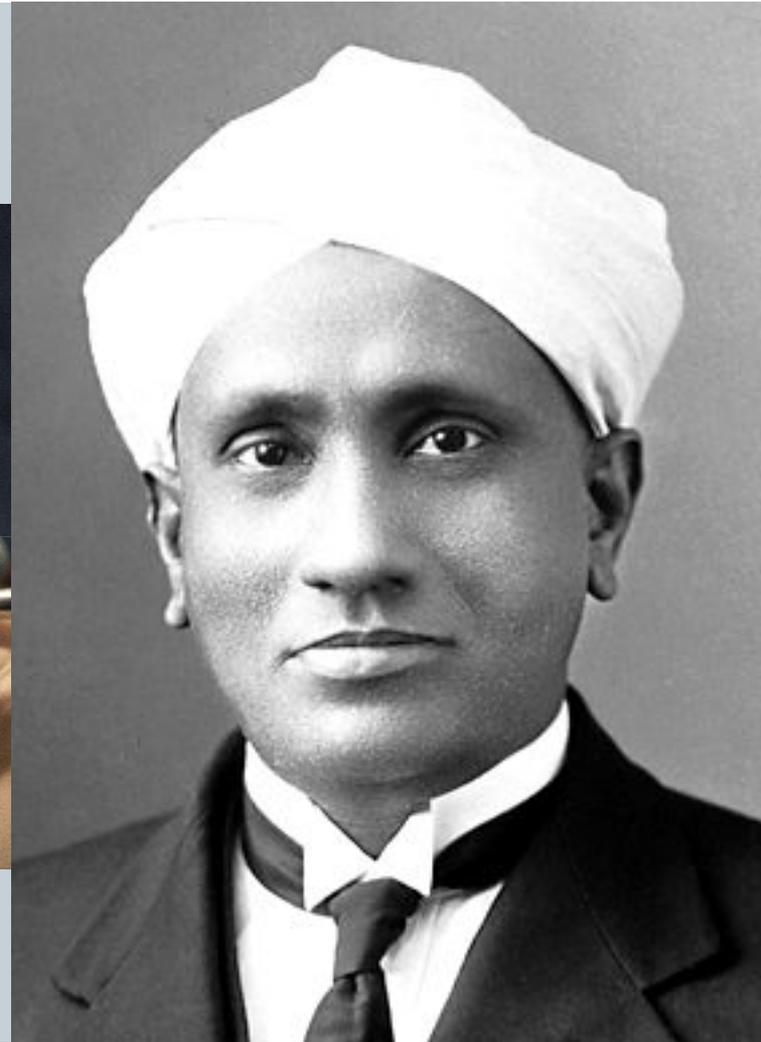
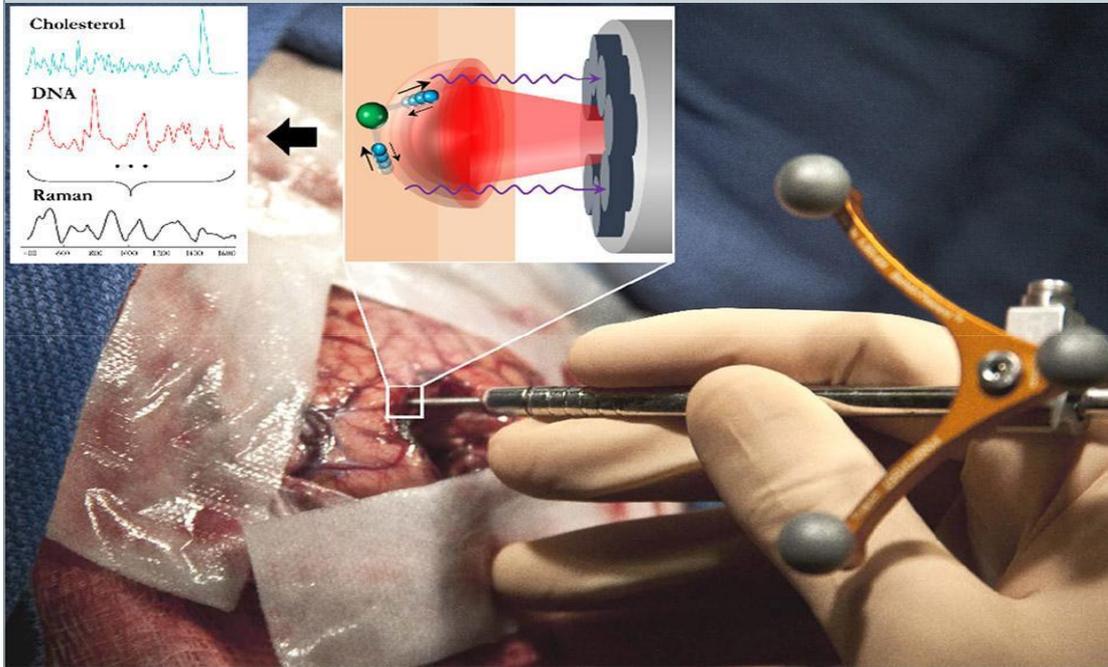
- They can experiment with less expensive options and see if they work, which could not be done in the US
- Ultrasound (\$200) vs CT-Scan (\$1200)



US National Debt

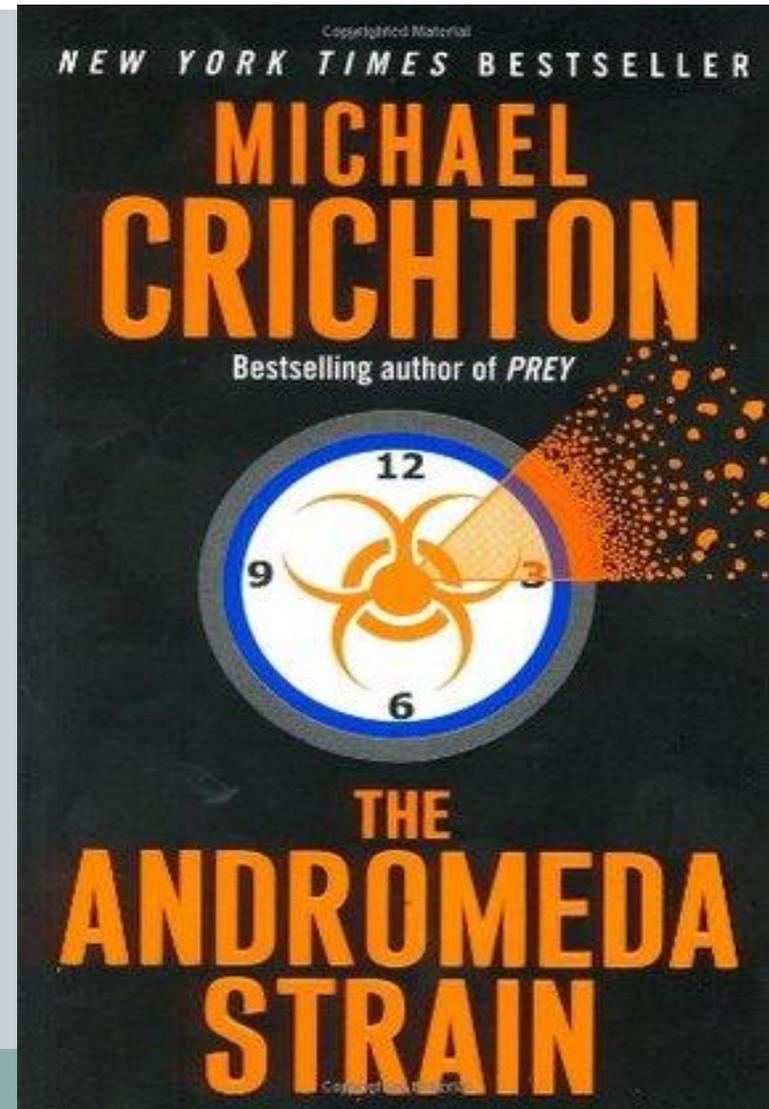


III. Become Innovators-Raman technique



IV.a. Discover Unusual GBM Presentations And Treatment Patterns (find outlier operative variable)

- Maybe certain DNA protects against GBM/Glioma
- Maybe everybody has infections, can an infection lead to a GBM cure?



IV.b. The human genome variability



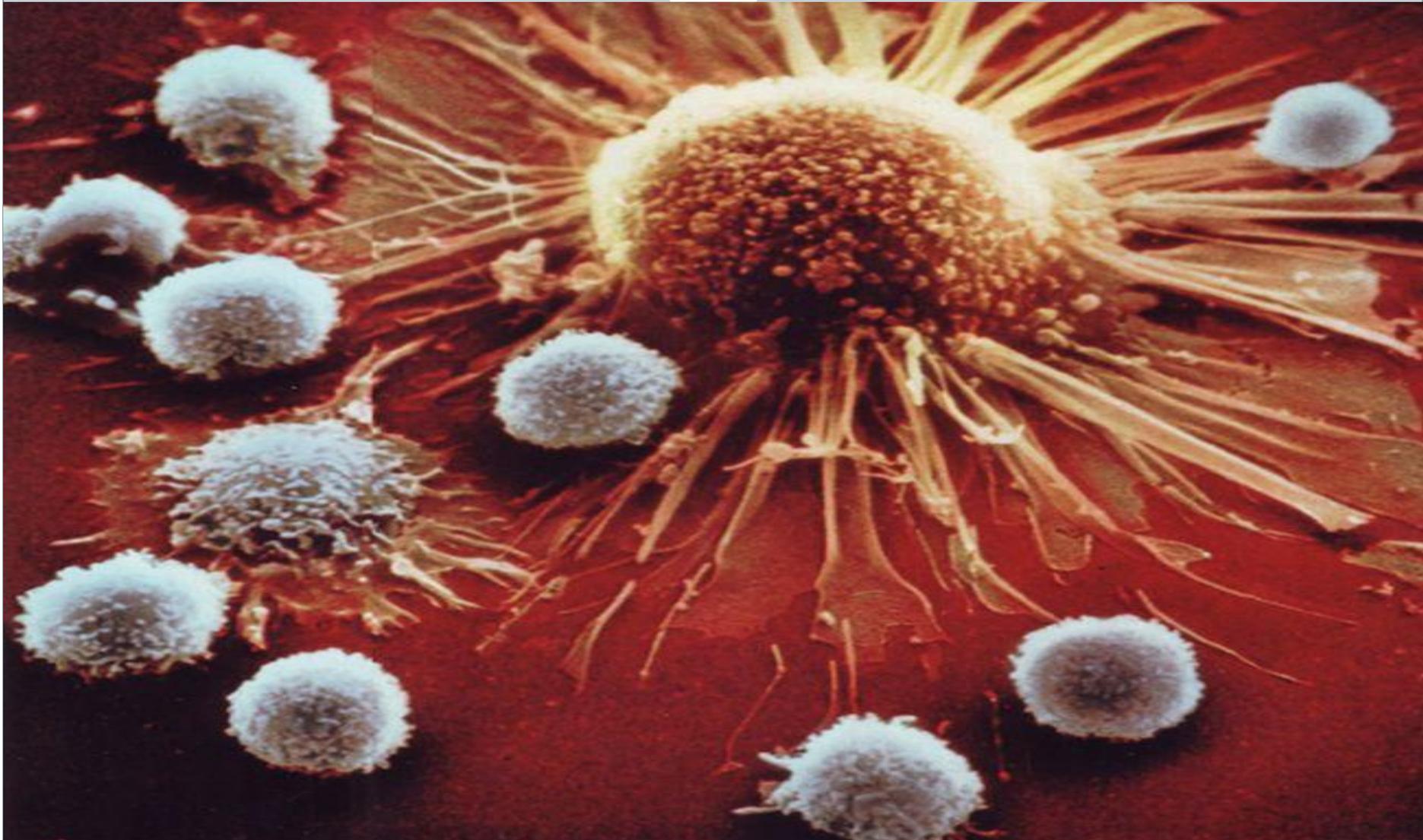
IV.b. African tribe (Massai warriors)



IV.c. Pollution and cancer



IV.d. T-cell & variability of the immune system



V. Participate in Clinical Trails - Avoid the mistakes made in The Tuskegee Studies of untreated syphilis

- The study was conducted between 1932 and 1972. The study initially involved 600 african american men – 399 with syphilis, 201 who did not have the disease. The study was conducted without the benefit of patients' informed consent.



The Constant Gardener

- Unethical clinical trials in Africa for financial gain



VI. Such physicians could pioneer technology and improve care arrangements for their home countries

- 14% of the approximately 20,000 new residents and interns in the US are not US citizens



- Those physicians in western countries that come from developing countries could have the responsibility to their countries of origin to facilitate treatment of GBM

VII. Better Statistics/Incidence is poorly established world wide...

● Canada

- “Currently, the Canadian medical system does not track statistics on primary brain tumors. Complete and accurate data is needed to facilitate the research that will lead to a better understanding of this disease and improved diagnosis and treatment.”

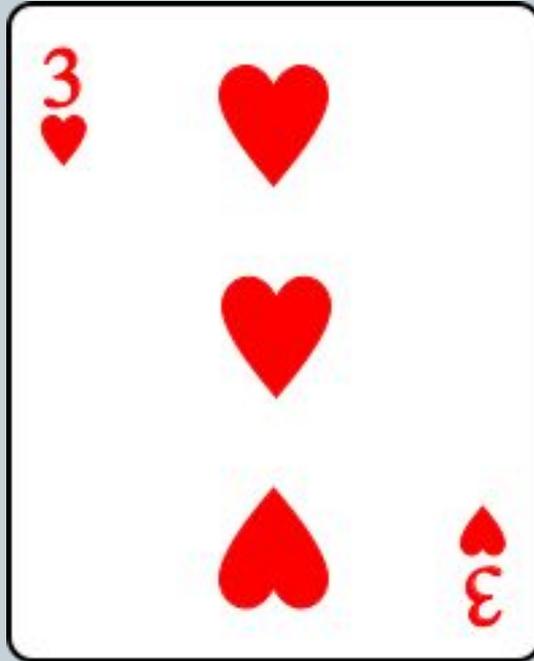
● Korea

- Despite its importance, there are no accurate statistics on primary CNS tumors in Korea.

● Sudan

- The reason there are few statistics on glioma incidence by country is because it is so expensive to diagnose
- We believe world statistics are greatly understated do to lack of available diagnostic medicine
- Furthermore, the world’s population is younger than the typical age of diagnosis for Glioma/GBM, causing under-reported numbers.

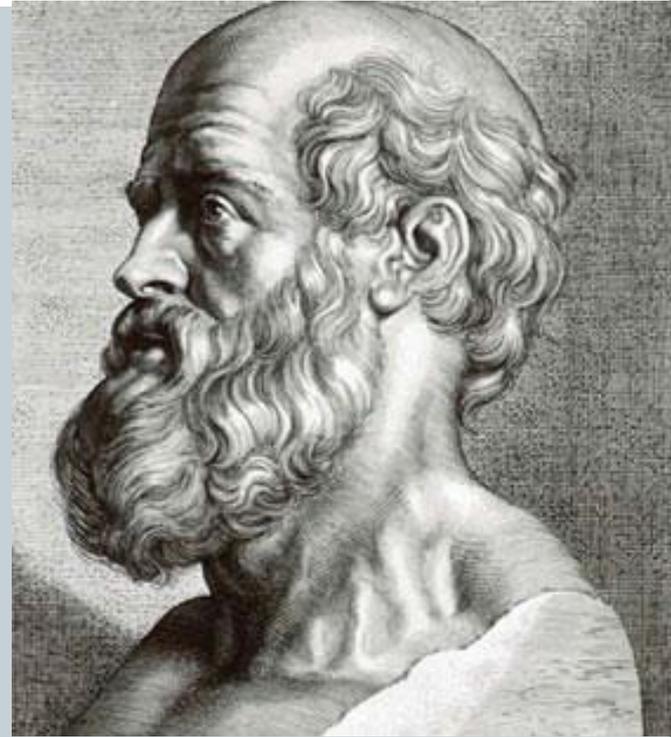
A third solution



Physician
Responsibility

Various Physician oaths

- The Oath of Hippocrates of Kos, 5th century BC
- Declaration of Geneva of the World Medical Association
- An Oath that “Bears the Name of Hippocrates”
- American Medical Association Code of Ethics (post-1980)



Responsibilities in the Hippocratic Oath

- I swear to fulfill, to the best of my ability and judgment, this covenant:...
- I will respect the hard-won scientific gains of those physicians in whose steps I walk, and gladly share such knowledge as is mine with those who are to follow.
- I will apply, for the benefit of the sick, all measures which are required, avoiding those twin traps of overtreatment and therapeutic nihilism.
- I will remember that there is art to medicine as well as science, and that warmth, sympathy, and understanding may outweigh the surgeon's knife or the chemist's drug.
- I will not be ashamed to say "I know not," nor will I fail to call in my colleagues when the skills of another are needed for a patient's recovery.
- I will respect the privacy of my patients, for their problems are not disclosed to me that the world may know. Most especially must I tread with care in matters of life and death. Above all, I must not play at God.
- I will remember that I do not treat a fever chart, a cancerous growth, but a sick human being, whose illness may affect the person's family and economic stability. My responsibility includes these related problems, if I am to care adequately for the sick.
- I will prevent disease whenever I can but I will always look for a path to a cure for all diseases.
- I will remember that I remain a member of society, with special obligations to all my fellow human beings, those sound of mind and body as well as the infirm.
- If I do not violate this oath, may I enjoy life and art, respected while I live and remembered with affection thereafter. May I always act so as to preserve the finest traditions of my calling and may I long experience the joy of healing those who seek my help.

Suggested additions to the oath

1. The responsibility of health care expenses sharing
2. Responsibility of spread of new medical technology



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- Headquarters: Geneva, Switzerland
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THANK YOU

