



Overview of Clinical Care

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Machine Learning in Healthcare
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Example of diagnostic process
from Madhur Nayan,
NYU Urology



**Massachusetts
Institute of
Technology**

What makes healthcare different?

(summary of omitted end of lecture 1)

- Life or death decisions
 - Non-fungibility of patients
 - Need **robust** algorithms
 - Checks and balances built into ML deployment
 - (Also arises in other applications of AI such as autonomous driving)
 - Need **fair** and **accountable** algorithms
- Dearth of labeled data, dearth of available public data
- Many questions are about unsupervised learning
 - Discovering disease subtypes, or answering question such as “characterize the types of people that are highly likely to be readmitted to the hospital”?
- Many of the questions we want to answer are *causal*
 - Naïve use of supervised machine learning is insufficient

Outline

- Goals of Health Care (preventing:)
 - Mortality
 - Disability
 - Morbidity
- An extended example (from Madhur)
 - Bayesian diagnostic reasoning
- Cycles of care

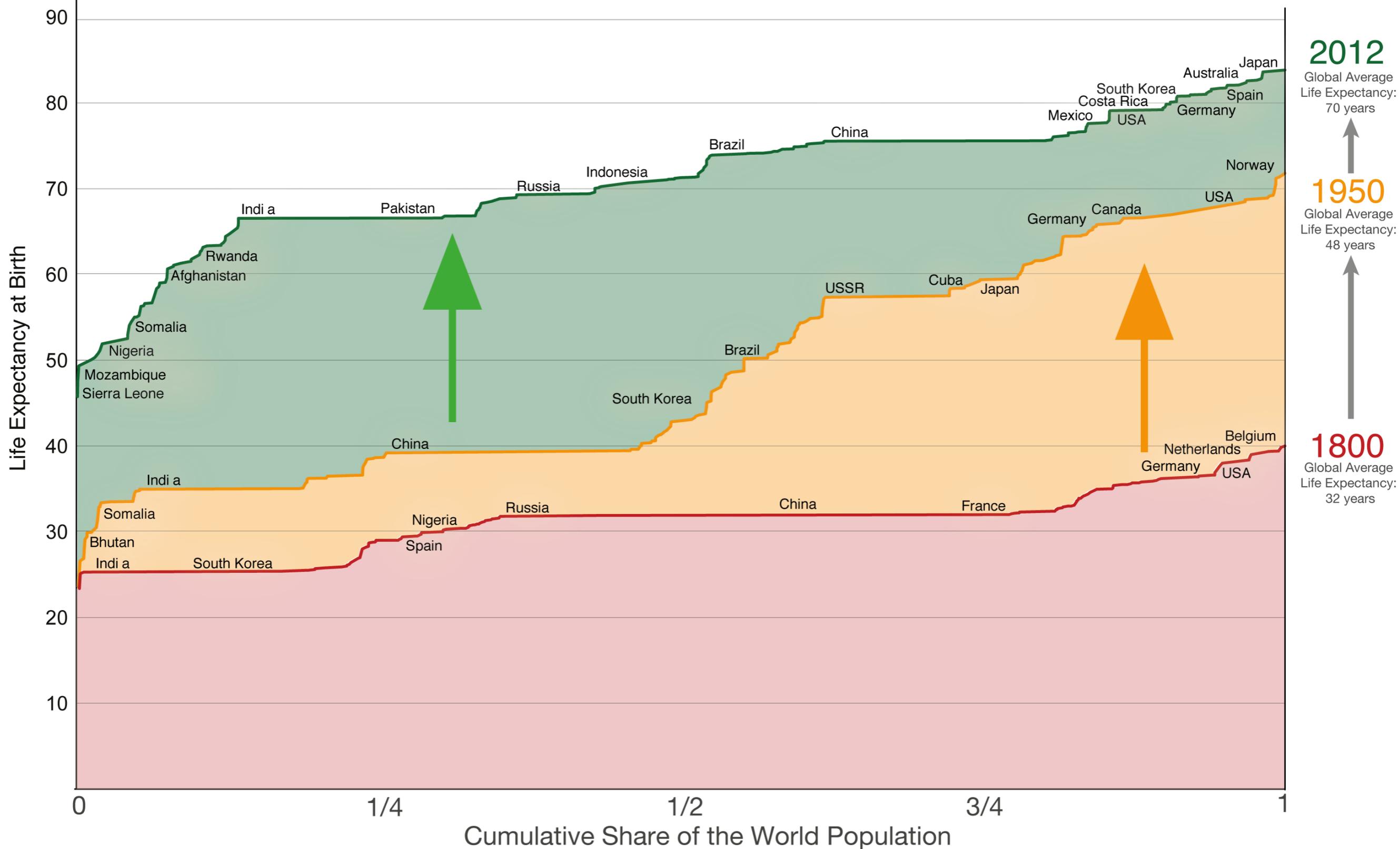
WHO Constitution defines “health”

“a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”

- Physical
- Mental
- Social
 - very hard to measure

Life Expectancy of the World Population in 1800, 1950 and 2012

Countries are ordered along the x-axis ascending by the life expectancy of the population. Data for almost all countries is shown in this chart, but not all data points are labelled with the country name.



Data source: The data on life expectancy by country and population by country are taken from Gapminder.org.

The interactive data visualisation is available at OurWorldinData.org. There you find the raw data and more visualisations on this topic.

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Longevity at birth

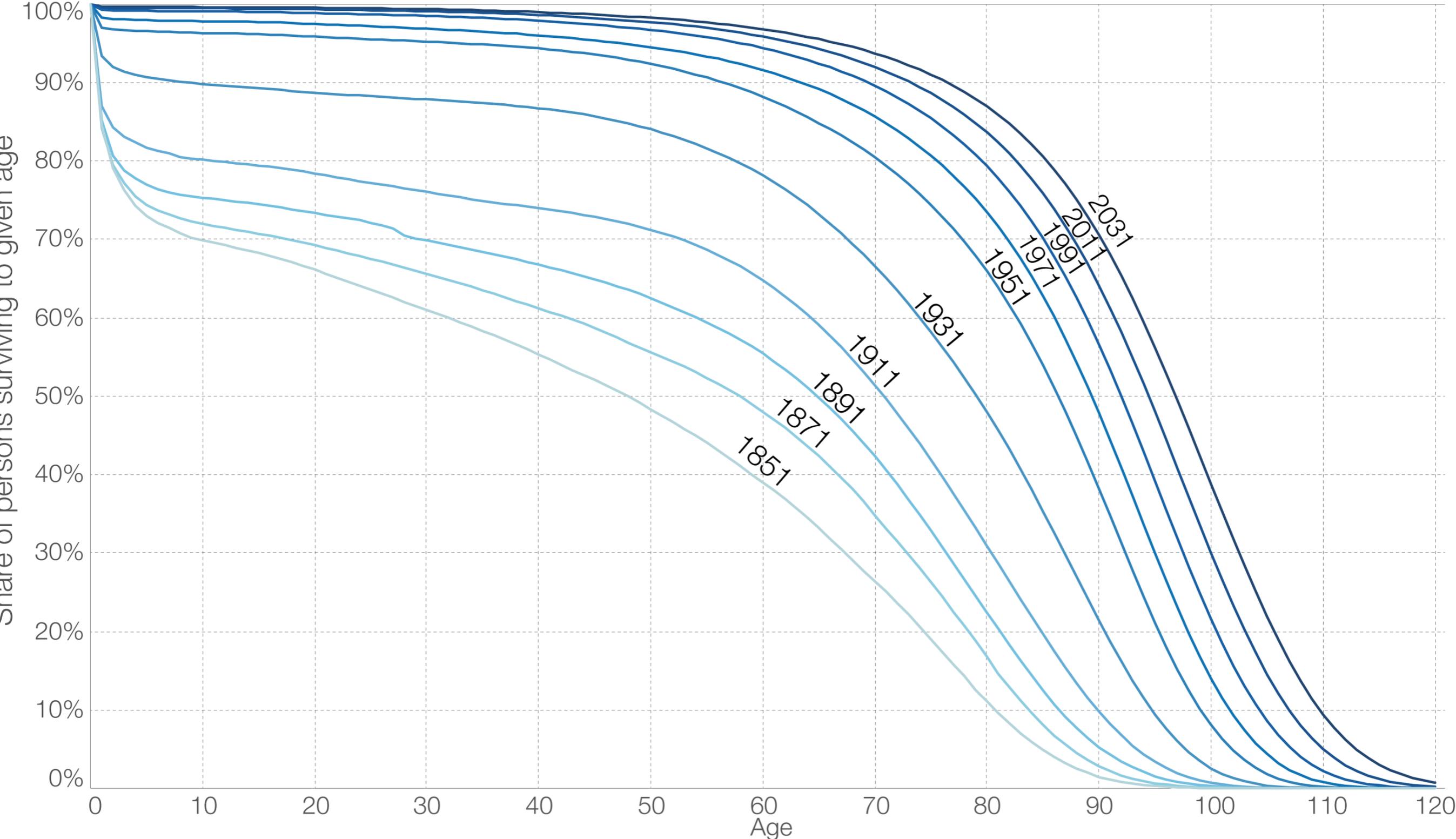
(CIA World Fact Book, 2001, 2022)

<i>Country</i>	<i>Male</i>		<i>Female</i>	
	<i>2022</i>	<i>2001</i>	<i>2022</i>	<i>2001</i>
Rwanda	63.9	38.4	67.9	39.7
South Africa	64.0	47.6	66.7	48.6
Kenya	68.0	46.6	71.4	48.4
Cambodia	68.8	54.6	72.6	59.1
Russia	66.9	62.1	78.3	72.8
Brazil	72.5	59.0	79.5	67.7
Turkey	73.8	68.9	78.7	73.7
Albania	76.8	69.0	82.3	74.9
Israel	81.5	76.7	85.3	80.8
USA	78.4	74.4	82.8	80.1
France	79.5	75.0	85.8	83.0
Japan	81.9	77.6	87.9	84.2

Share of persons surviving to successive ages for persons born 1851 to 2031, England and Wales



according to mortality rates experienced or projected, (on a cohort basis)

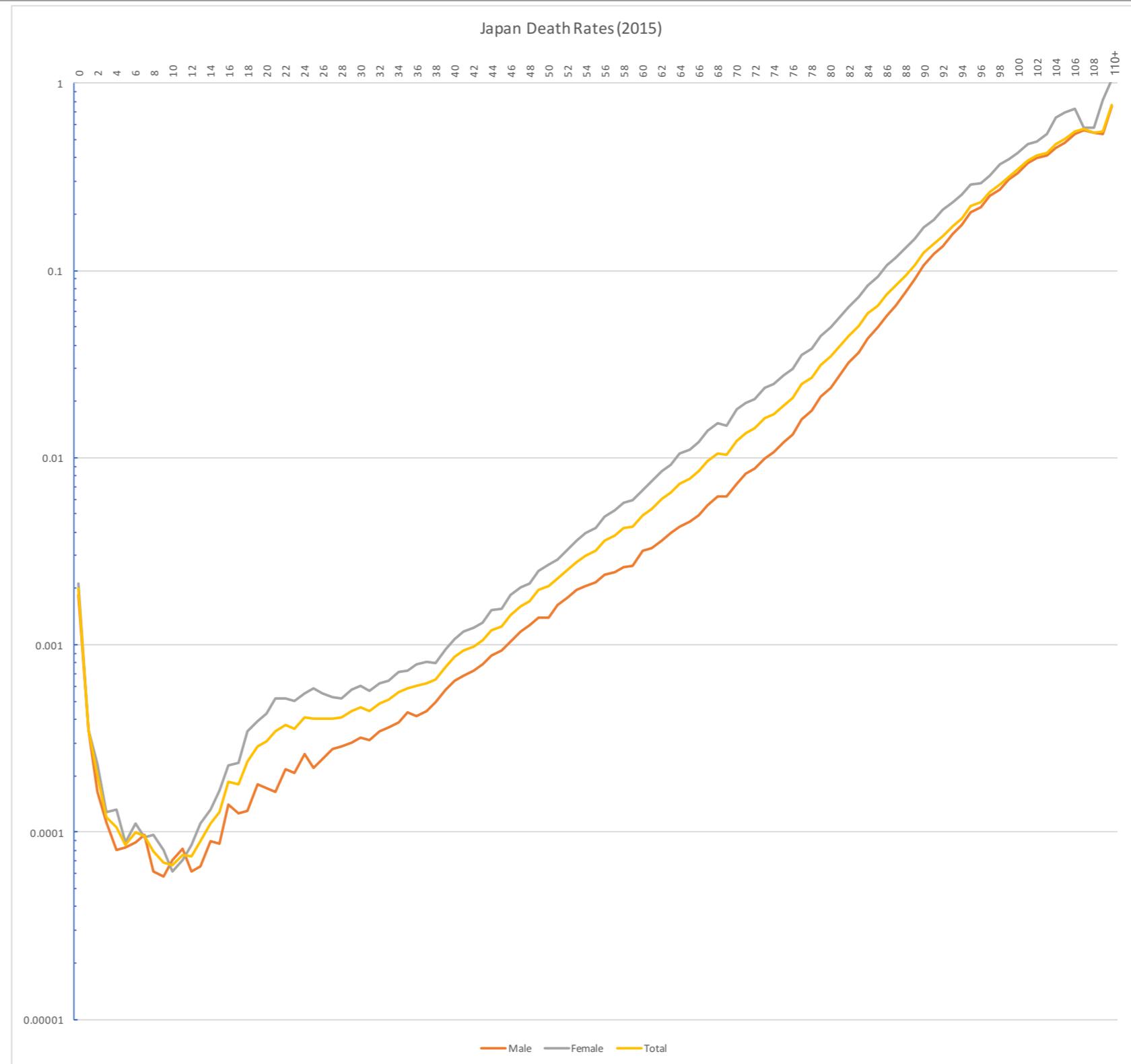


Data source: Office for National Statistics (ONS). Note: Life expectancy figures are not available for the UK before 1951; for long historic trends England and Wales data are used. The interactive data visualization is available at [OurWorldinData.org](https://ourworldindata.org). There you find the raw data and more visualizations on this topic. Licensed under [CC-BY-SA](https://creativecommons.org/licenses/by-sa/4.0/) by the author Max Roser.

Distribution of Death Rates by Age

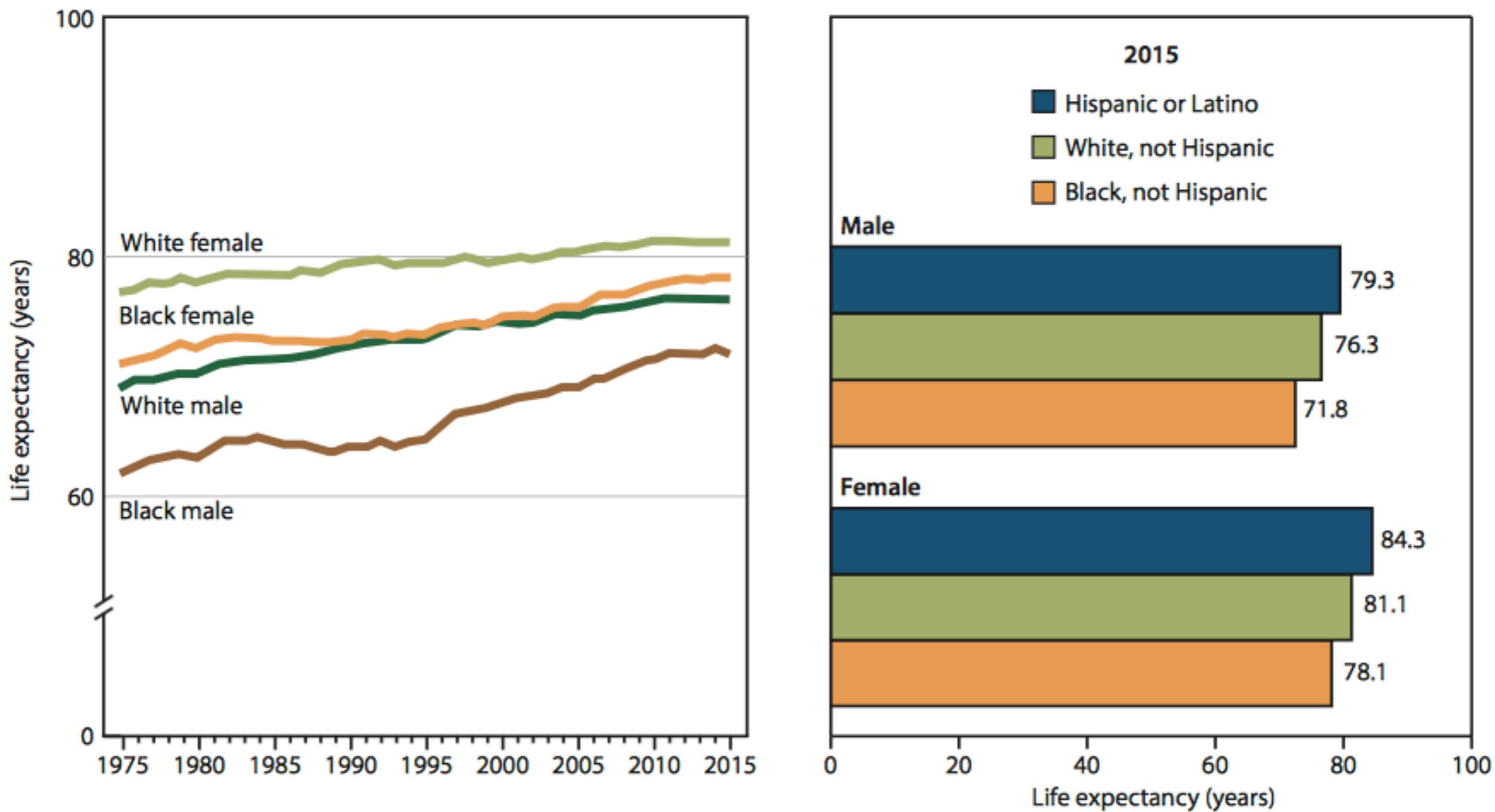
- Life table deaths by year (Japan, 2015)

http://www.ipss.go.jp/p-toukei/JMD/00/STATS/Mx_1x1.txt



Ethnic Disparities

Figure 6. Life expectancy at birth, by sex, race and Hispanic origin: United States, 1975–2015



Causes of death (USA, 2014)

Cause	Deaths/100K	%
Heart disease	192.7	23.4
Cancer	185.6	22.5
Chronic lower respiratory disease	46.1	5.6
Accidents	42.7	5.2
Stroke	41.7	5.1
Alzheimer's disease	29.3	3.6
Diabetes	24.0	2.9
Influenza and pneumonia	17.3	2.1
Kidney disease	15.1	1.8
Suicide	13.4	1.6
<i>OTHER</i>	<i>215.8</i>	<i>26.2</i>
TOTAL	823.7	100.0

Morbidity: Top 10 Chronic Conditions

Persons aged ≥ 65

Condition	Both	Male	Female
Arthritis	49.6	40.7	55.7
Hypertension	39.0	33.0	43.2
Hearing impairment	30.0	35.2	26.3
Heart disease	25.7	26.9	24.9
Orthostatic impairment	16.8	15.7	17.8
Cataracts	15.5	11.3	18.4
Chronic sinusitis	15.2	13.7	16.2
Visual impairment	10.1	12.0	8.8
Genitourinary	9.9	11.3	8.9
Diabetes	8.9	7.8	9.7

U.S. Nat'l Ctr Health Stat, *Vital and Health Statistics*, 1985 (1982 data)

Quality of life

Value of a total life depends on

- Length (assume now is N)
- Quality (q) over time
- Discounts (g) for future and past
 - depends very much on what the value is to be used for
 - what is an appropriate discount factor?

$$V_N = \int_{t=0}^T q(t)g(t - N)dt$$

Activities of Daily Living

Basic

- Bathing and Showering
- Personal hygiene and grooming
 - brushing/combing/styling hair
- Dressing
- Toilet hygiene
- Functional mobility (“transferring”)
 - walk, get in and out of bed
 - get into and out of a chair
- Self-feeding (not including cooking or chewing and swallowing)

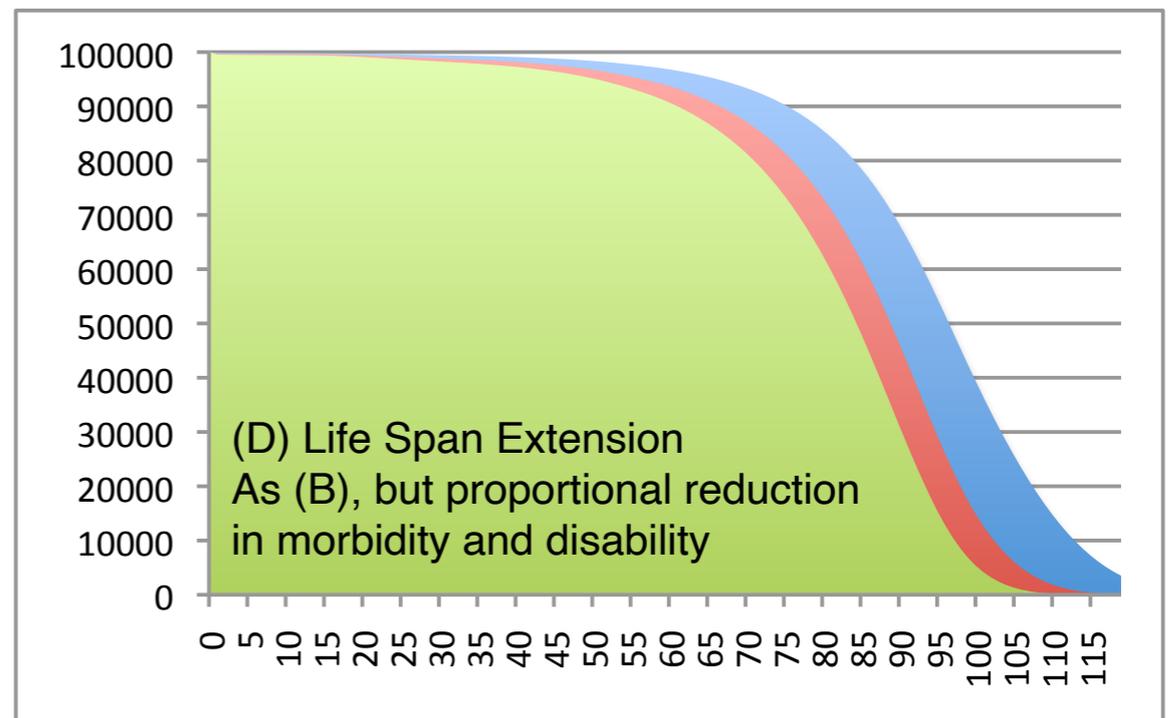
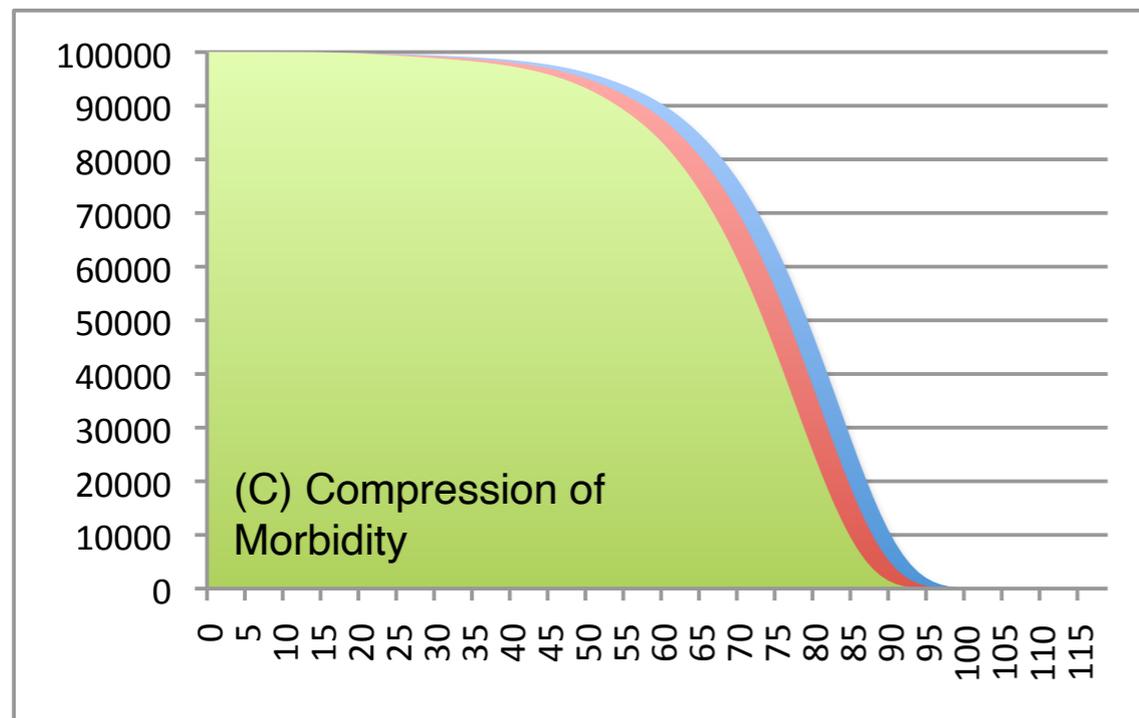
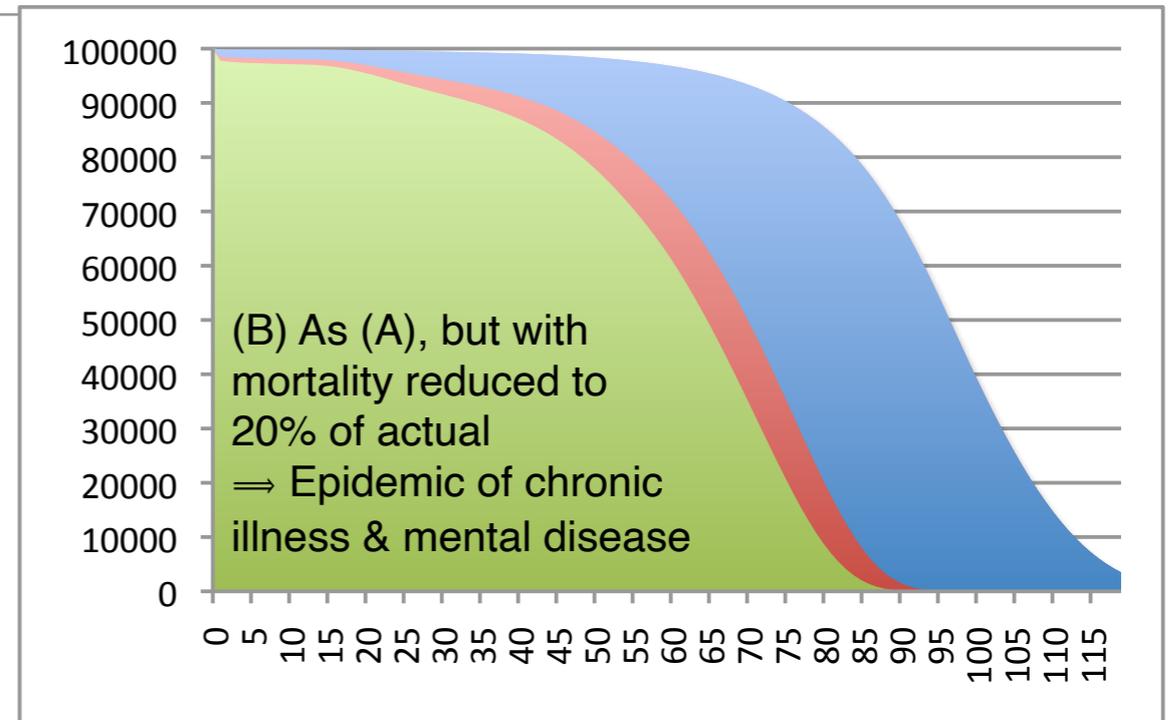
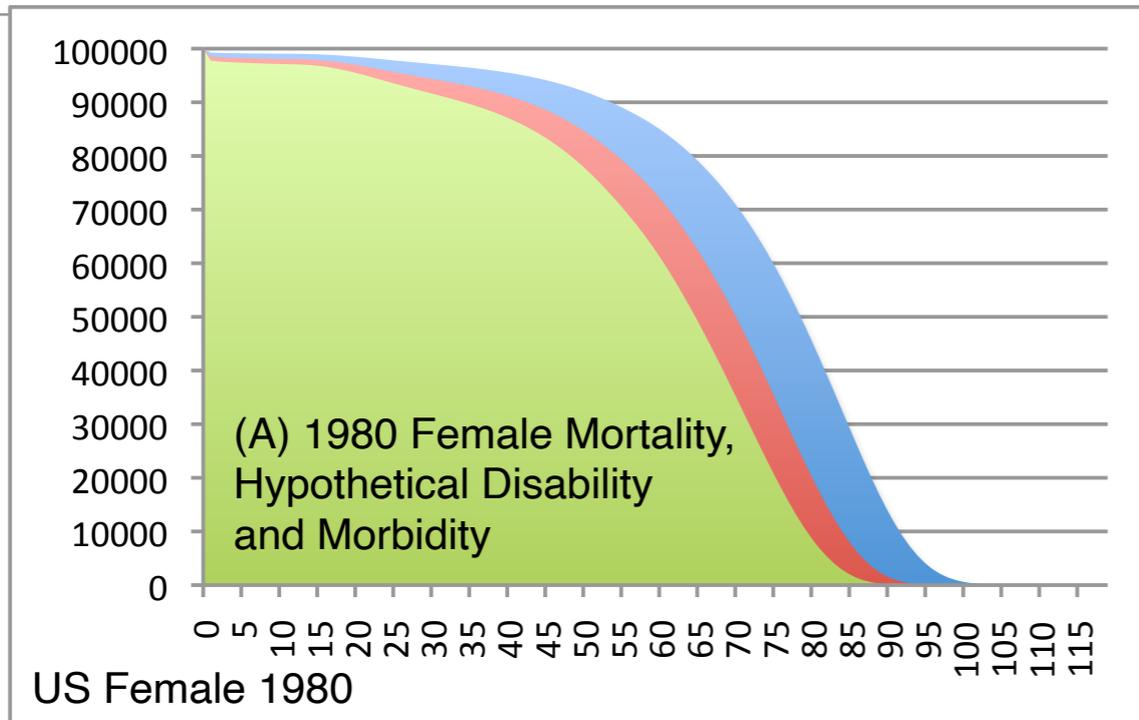
Instrumental

- Cleaning and maintaining the house
- Managing money
- Moving within the community
- Preparing meals
- Shopping for groceries and necessities
- Taking prescribed medications
- Using the telephone or other form of communication

Goals of “Occupational Therapy”

- Care of others (including selecting and supervising caregivers)
- Care of pets
- Child rearing
- Communication management
- Community mobility
- Financial management
- Health management and maintenance
- Home establishment and maintenance
- Meal preparation and cleanup
- Religious observances
- Safety procedures and emergency responses
- Shopping

Mortality, Disability, Morbidity



Societal quality of life

- Aggregation of individual qualities
 - + Equity (distributions)
- Is more better? (Population control)
- Is less better?
- How much to spend?

A Patient's Perspective

(from Madhur)

- I woke up this morning and my urine was red. I got scared, I've never seen that before.
- I went to the ER with my wife.
 - *What are the goals of the patient?*
 - *What are the expectations of the patient?*
- I took a number and waited for it to be called. I then saw the nurse and told them what had happened. The nurse took my information and told me to wait until I was called.
 - *What is the purpose of triage?*
 - *What information is used to triage patients?*

Triage note

- Jim Jones
- DOB: 10/18/1957
- Address: 8035 King Street, Boston, MA
- History of presenting illness: Gross hematuria x1 episode this AM.
- Exam:
 - Appears anxious
 - Vitals: HR 85, BP 130/90, temperature 37.8, RR 20
- Time of arrival to ER: 13:14

A Patient's Perspective

- I woke up this morning and my urine was red. I got scared, I've never seen that before.
- I went to the ER with my wife. The nurse took my information and told me to wait until I was called.
- **About an hour later, I got called in to see the doctor.**

A Provider's Perspective

- After clicking “Submit” for the orders in the last patient’s chart, the next chart in the triaged order is “picked up” by the ER physician.
 - *What are the goals of the provider?*
 - *Do the goals of the ER differ than other clinical settings?*
 - *What are the expectations of the provider?*
 - *What are potential tasks that the physician may perform in their interaction (beginning to end) with the patient?*

Tasks of a Physician

- Prevention
 - Smoking cessation strategies to decrease risk of bladder cancer
- Diagnosis
 - Cause of blood in the urine (gross hematuria)
- Treatment
 - Antibiotics of urinary tract infection
- Prognosis
 - Expected course after treatment
- Documentation
- And more!!

A Provider's Perspective

- After placing orders in the last patient's chart and signing the encounter, the next chart in the triaged order is “picked up” by the ER physician.
- The physician assesses the triage note and begins the **diagnostic process**

Diagnostic process

- How does it work?
 - Varies by specialty
 - Varies by individual

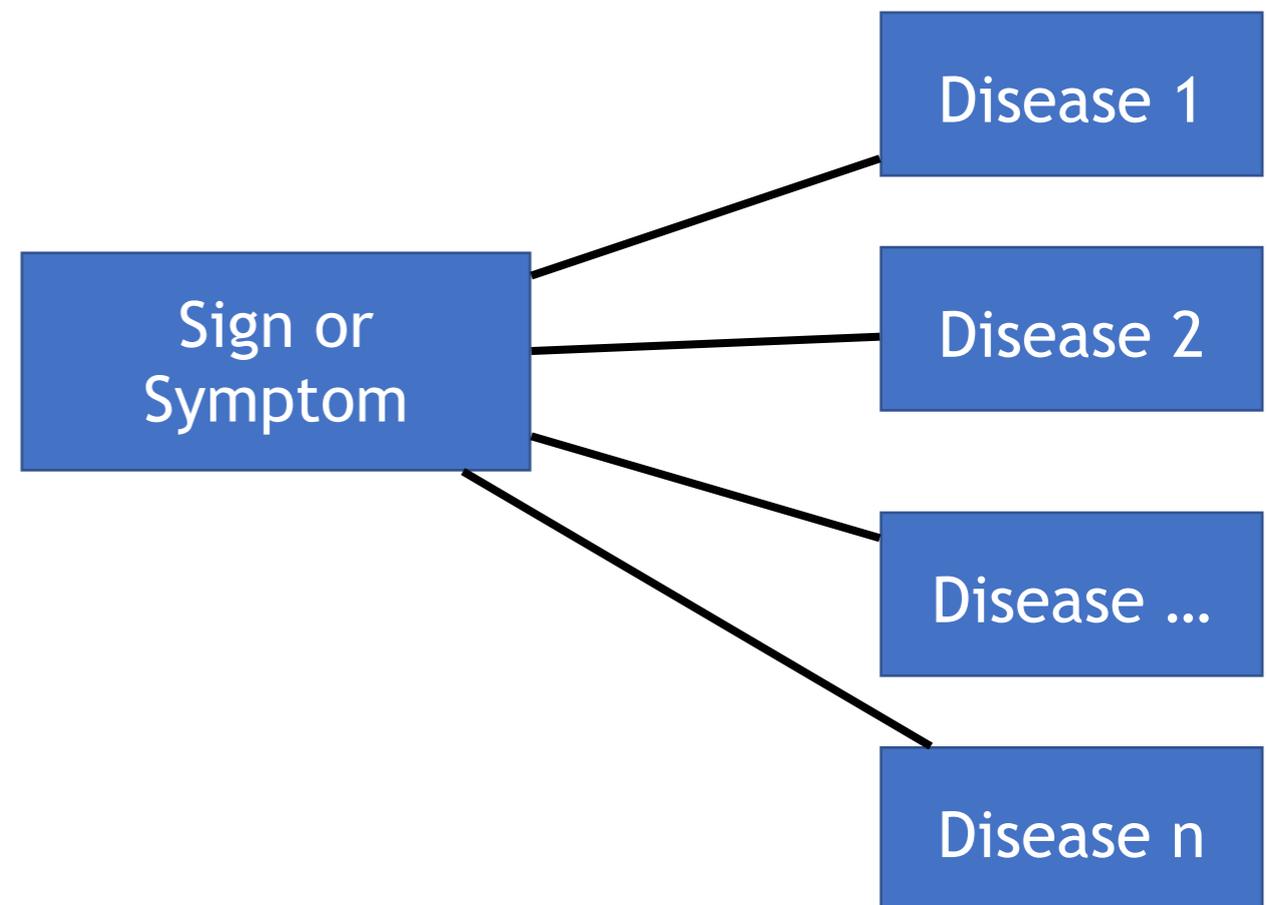
Diagnostic process

- Madhur's approach (in two steps):
 - Access knowledge **database** on the different possible diagnoses, i.e., **differential diagnosis** related to that **sign** or **symptom**
 - Obtain **data** to narrow differential diagnoses, repeatedly, until enough data is gathered to make a diagnosis

Knowledge Database

- +/- prior experience
- Medical school (4 years)
- Residency (5 + 3 years)
- +/- Fellowship (2 years)
- Attending (until I retire)
- Build & **update** the knowledge database
- **“The key to becoming a medical specialist, in any discipline, is experience.”**

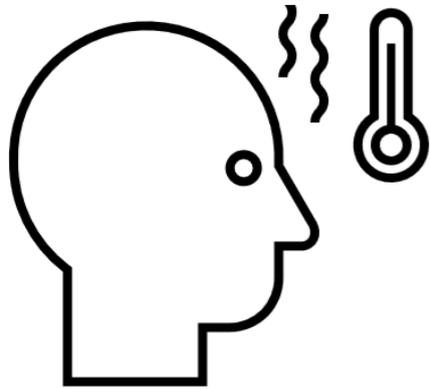
Differential Diagnosis



Types of data in healthcare

- History
 - Symptoms and their details, past medical/surgical history, medications, allergies, family history, etc.
- Physical exam
 - Height, weight, BMI, vital signs (temperature, blood pressure, heart rate, etc), tenderness, erythema (redness), etc.
- Labs
 - Complete blood count, serum electrolytes, urine culture, blood culture, etc.
- Imaging
 - Chest x-ray, CT scan, bone scan, MRI, ultrasound, etc.
- Pathology
 - Biopsy, surgical pathology
- Genetics
 - Germline testing, etc.

Diagnostic Process in Action



A **65M** is referred to you for **gross hematuria**

Patient presents with a **sign** OR **symptom**

1. Access knowledge **database** on the different possible diagnoses i.e. **differential diagnoses** related to that **sign** or **symptom**

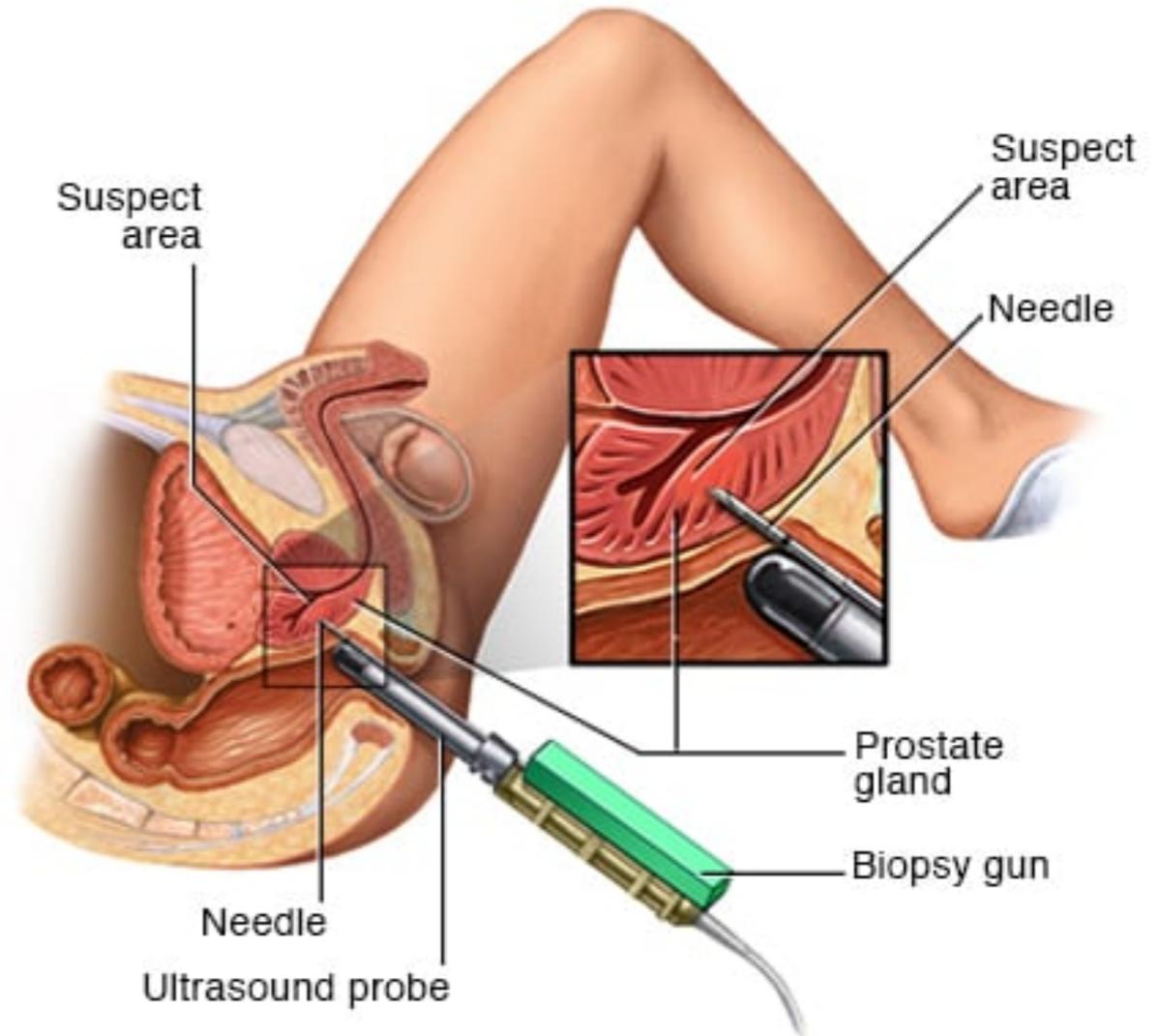
- Malignant
 - Anywhere along the urinary tract
 - Kidney
 - Ureter
 - Bladder
 - Prostate
 - Urethra
- Non-malignant
 - Infection
 - Stone
 - Trauma
 - Benign prostatic hyperplasia (BPH)
 - Etc.

Narrow the Differential Diagnoses

- Obtain **data** to narrow differential diagnoses
 - Malignant
 - Anywhere along the urinary tract
 - Kidney - CT scan
 - Ureter - CT scan
 - Bladder - Cystoscopy
 - Prostate - Digital rectal exam (DRE), PSA, Prostate biopsy
 - Urethra - Cystoscopy
 - Non-malignant
 - Infection - History, urine culture
 - Stone - CT scan
 - Trauma - History
 - Benign prostatic hyperplasia (BPH) - History, DRE
 - Etc.
- **Testing can be invasive, associated with risks, and costly**
 - **Selective testing is needed to minimize these**

Invasive

- Prostate biopsy
 - Patient discomfort



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<https://www.mayoclinic.org/tests-procedures/prostate-biopsy/about/pac-20384734>

Risks of CT scan

1. Increased possibility of cancer induction from x-ray radiation exposure.
2. May demonstrate a benign or incidental finding, leading to unneeded, possibly invasive, follow-up tests that may present additional risks
 - 20-30% of small renal masses are benign



<https://www.fda.gov/radiation-emitting-products/medical-x-ray-imaging/what-are-radiation-risks-ct>

<https://www.hindawi.com/journals/au/2008/415848/fig9/>

Radiation exposure from CT scan

- Radiation exposure measured in millisieverts (abbreviated mSv)

Diagnostic Procedure	Typical Effective Dose (mSv) ¹
Chest x-ray (PA film)	0.02
Lumbar spine	1.5
I.V. urogram	3
Upper G.I. exam	6
Barium enema	8
CT head	2
CT chest	7
CT abdomen	8
Coronary artery calcification CT	3
Coronary CT angiogram	16

Radiation dose from CT procedures varies from patient to patient.

Risk of cancer with a CT scan

Overall risk
of cancer

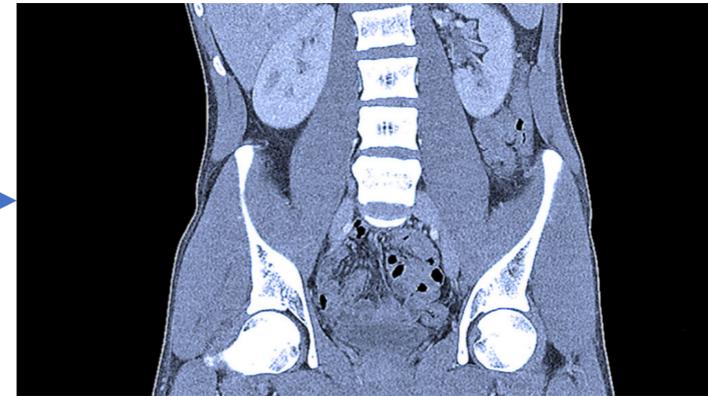
Baseline risk of
fatal cancer:

1 in 5

400 in 2000

1 CT = ≈ 10 mSv

401 in 2000



↑ risk of cancer 1 in 2000

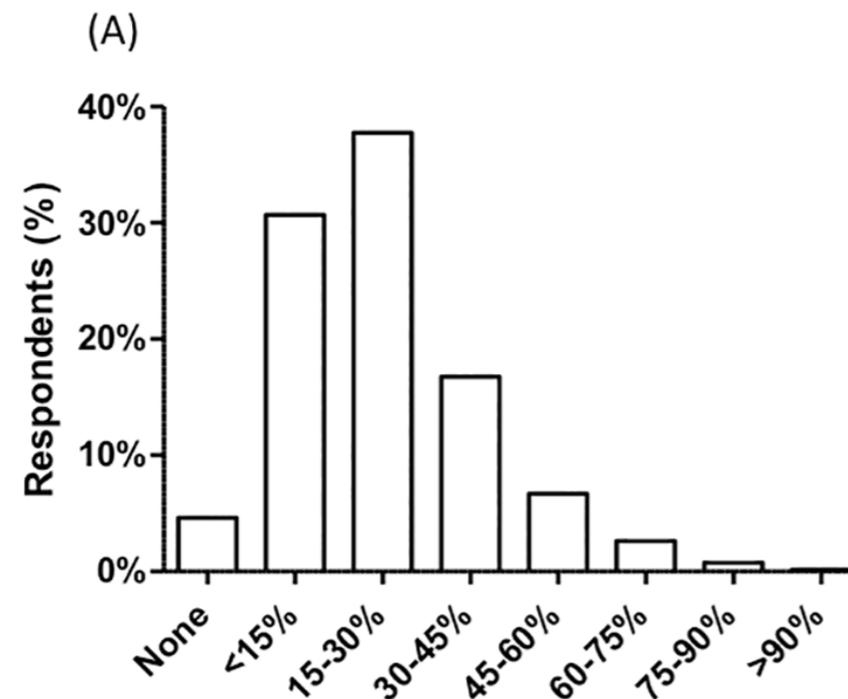
<https://www.fda.gov/radiation-emitting-products/medical-x-ray-imaging/what-are-radiation-risks-ct>

<https://www.medicalnewstoday.com/articles/abdominal-ct-scan>

Costs of Unnecessary Tests

- $\approx 30\%$ of US health spending in 2009 (\$750 billion) was wasted on unnecessary services, excessive administrative costs, fraud, and other problems
- Survey of 2,106 physicians from the American Medical Association

In your specialty, what percent of overall care do you think is unnecessary?



- **20% of overall care unnecessary**
 - Most common cited reasons for overtreatment
 - Fear of malpractice (84.7%)
 - Patient pressure/request (59.0%)
 - Difficulty accessing medical records (38.2%)

McGinnis, J. Michael, et al., eds. "Best care at lower cost: the path to continuously learning health care in America." (2013).
Lyu, Heather, et al. "Overtreatment in the united states." *PloS one* 12.9 (2017): e0181970.

Characteristics of an ideal test

- Non-invasive
- Low-risk
- Inexpensive
- **Reflect the truth**
 - **Sensitivity**
 - **Specificity**
 - **Positive predictive value**
 - **Negative predictive value**

Test Performance Characteristics

		<u>DISEASE (GROUND TRUTH)</u>		
		Present	Absent	
<u>TEST RESULT</u>	Positive	a (true pos)	b (false pos)	a+b
	Negative	c (false neg)	d (true neg)	c+d
		a+c	b+d	N

Prevalence = $(a + c) / N$

Sensitivity = $a / (a + c)$

Specificity = $d / (b + d)$

PPV = $a / (a + b)$

NPV = $d / (c + d)$

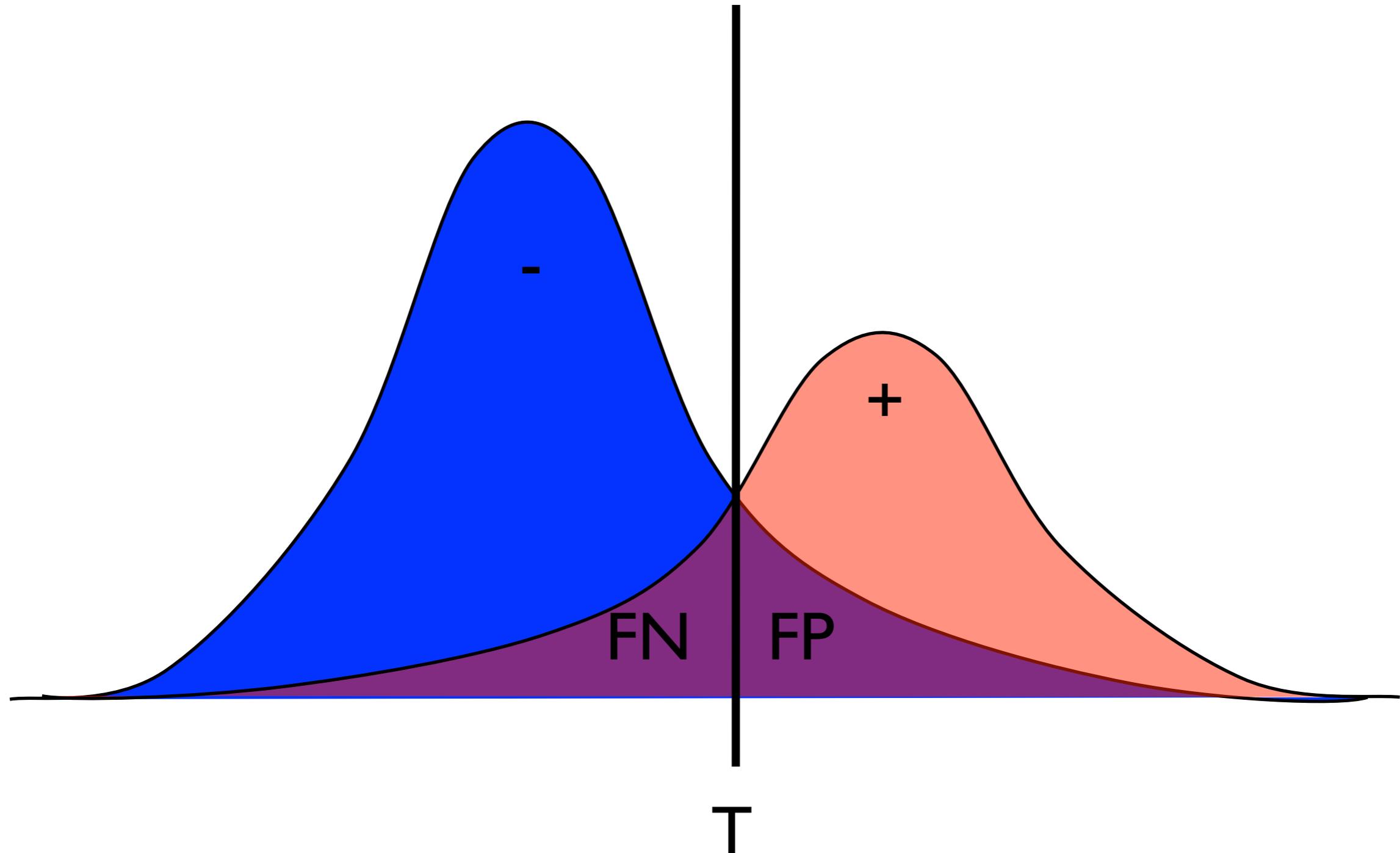
Low sensitivity means lots of false negatives

Low specificity means lots of false positives

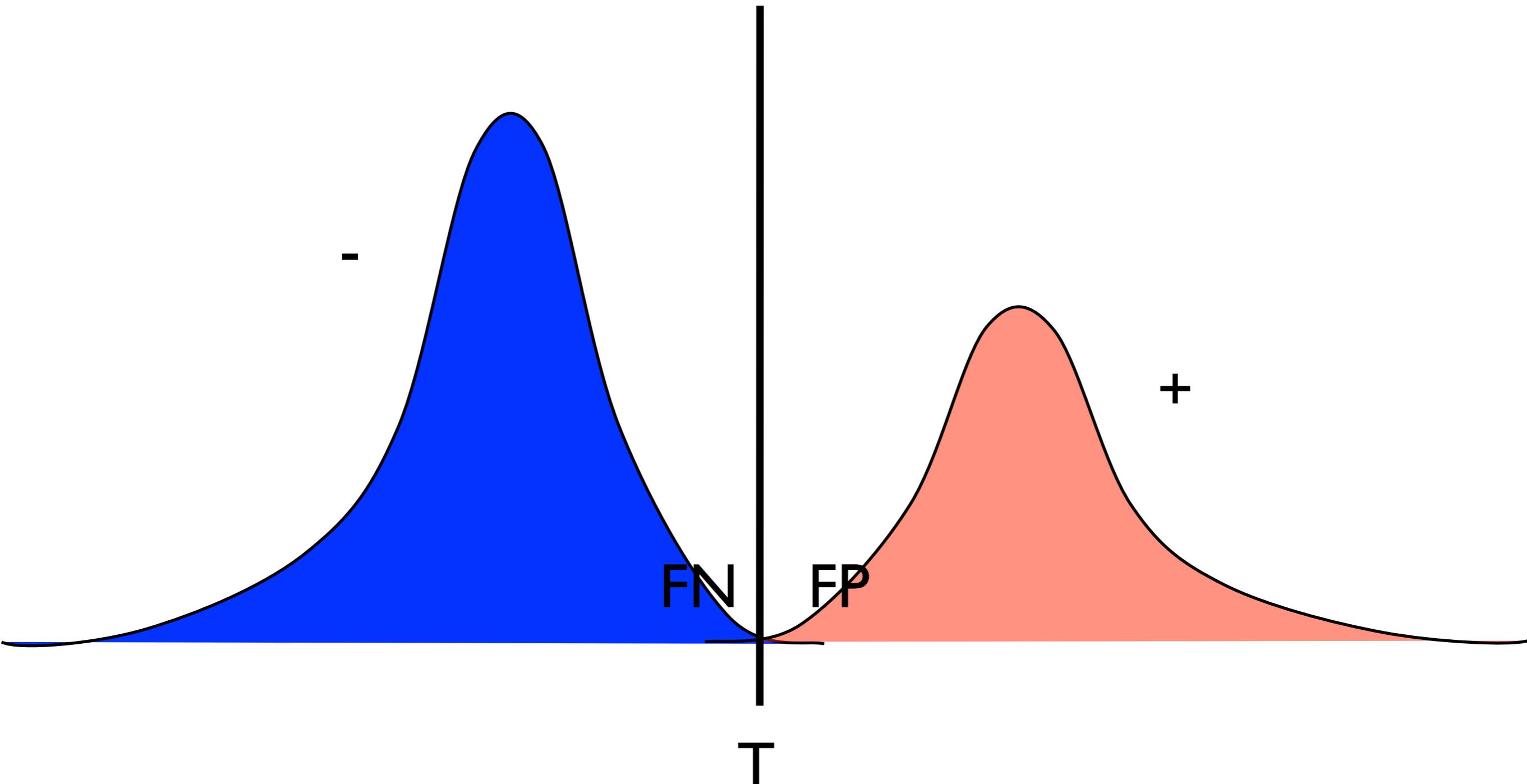
Test Characteristics in Healthcare

- In healthcare, when would you want a sensitive test?
- In healthcare, when would you want a specific test?
- What happens if the test result is continuous?
- How does prevalence of disease influence test characteristics?

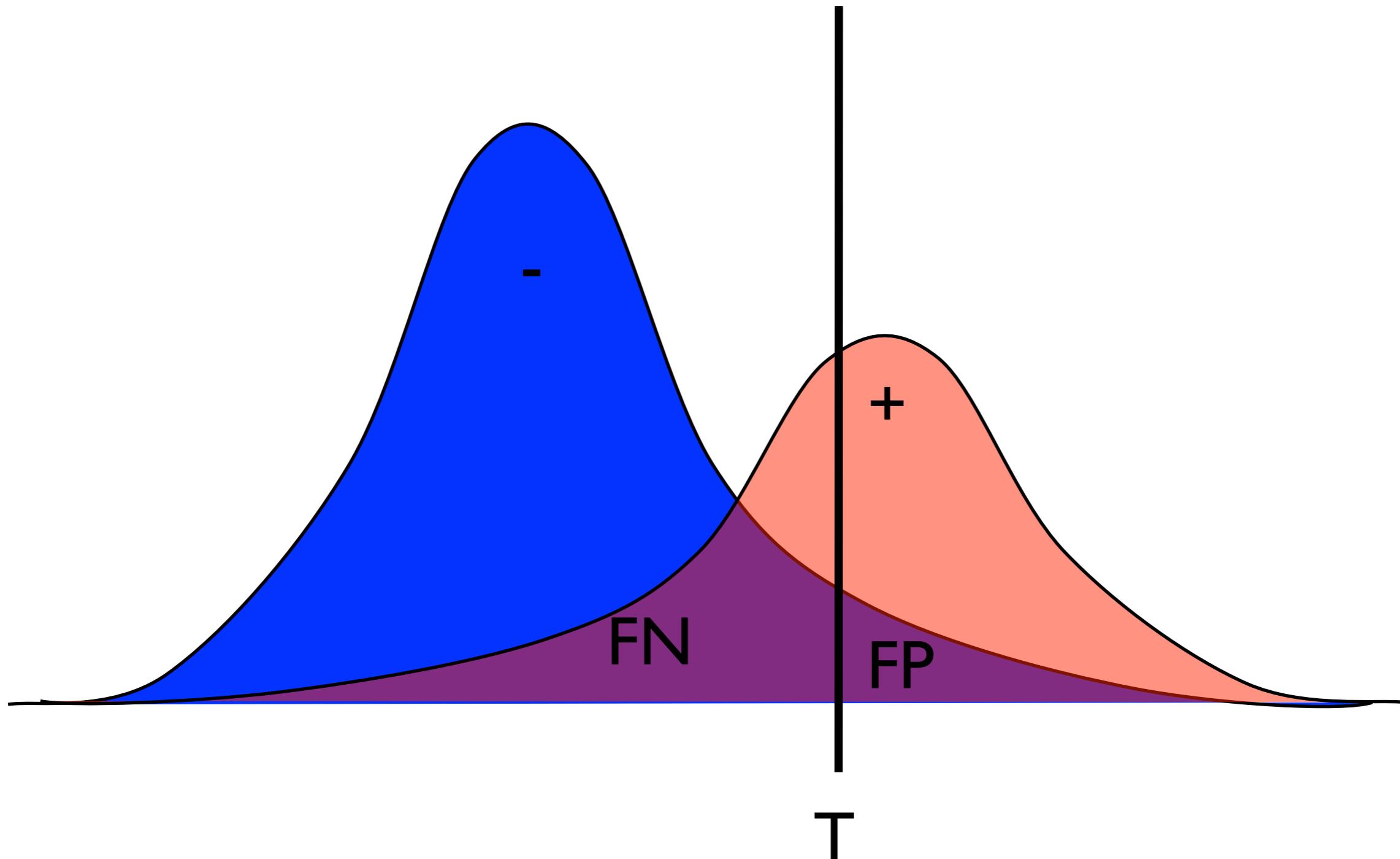
Test Thresholds



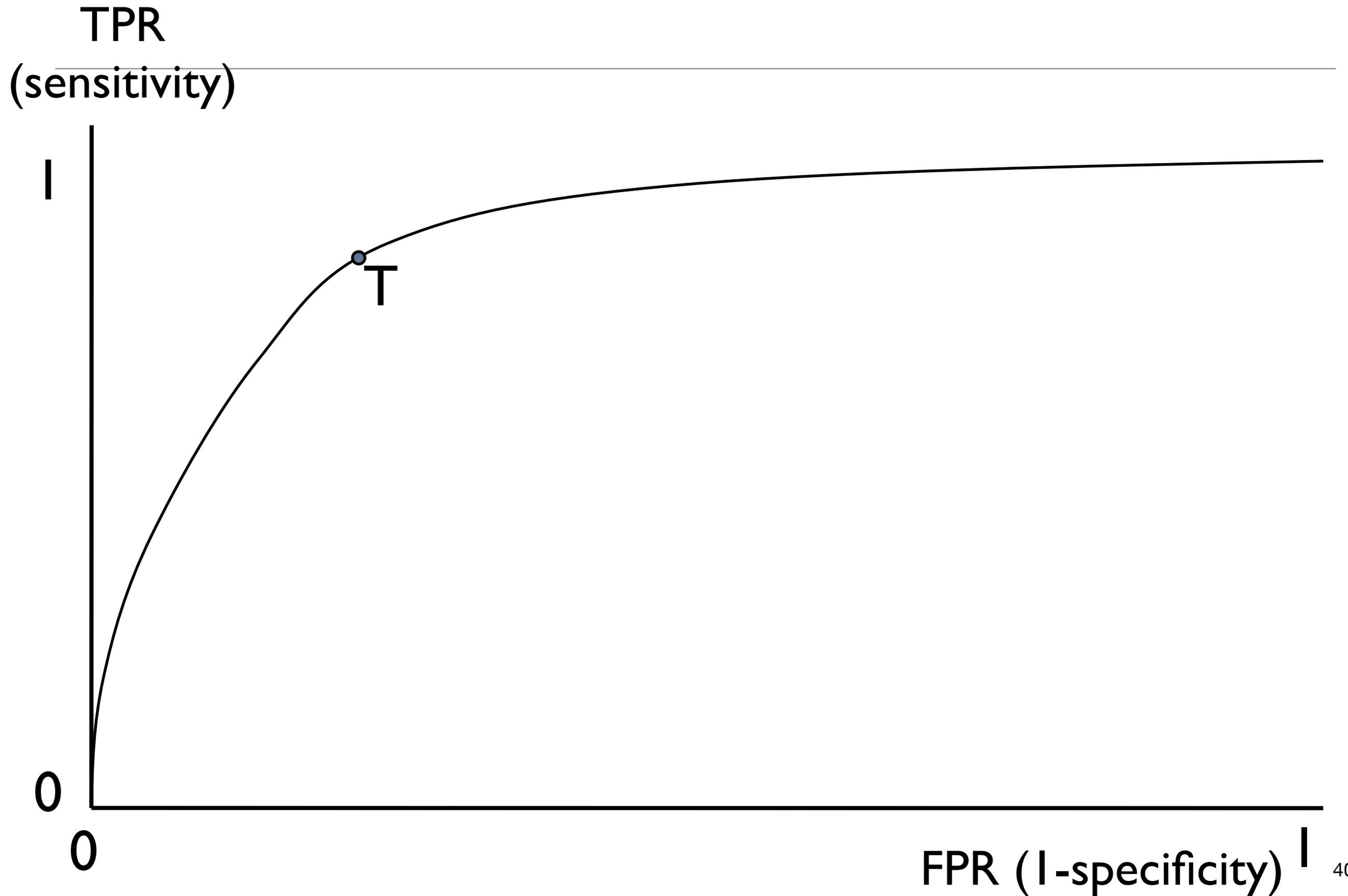
Wonderful Test



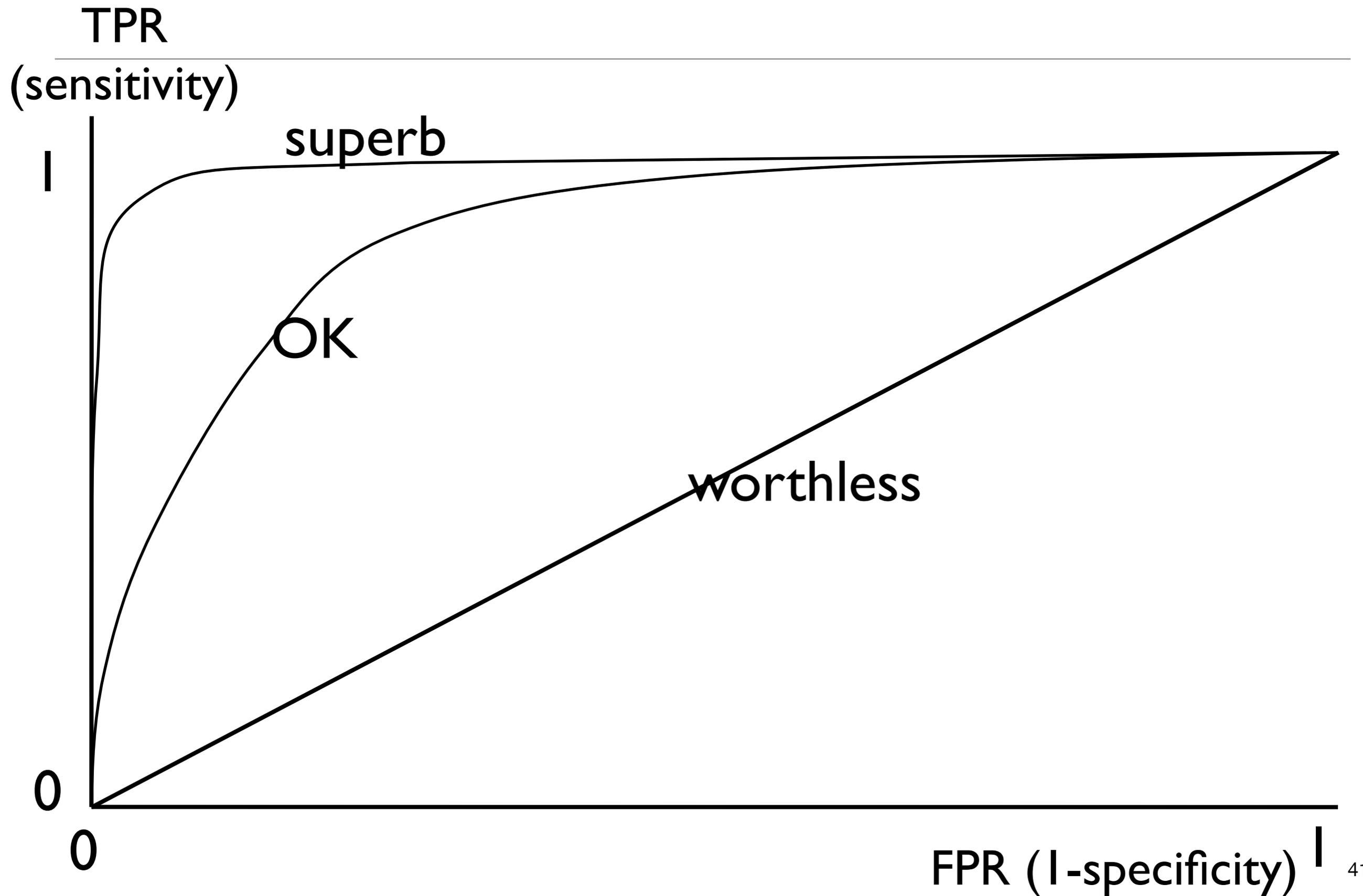
Test Thresholds Change Trade-off between Sensitivity and Specificity



Receiver Operator Characteristic (ROC) Curve



What makes a better test?



Narrowing the Differential Diagnoses

- **Selected testing is important**

- Consider invasiveness, safety, cost, and ability to reflect truth when selecting tests

- **Other important considerations?**

- Most likely diagnosis (highest probability)
 - In the population (of my clinical setting)
 - In this patient
- Most serious diagnosis
 - “Cost” of delayed/missed diagnosis
- Most informative test
 - Reduces entropy of the resulting probability distribution

**Cause of diarrhea?
Resource-rich
country
vs.
Resource-poor
country**

Differential Diagnosis of Gross Hematuria

	Prevalence
Kidney cancer	+
Ureteral cancer	+
Bladder cancer	+
Prostate cancer	+++++++
Urethral cancer	+
Infection	+++++++
Stones	+++++++
Trauma	+
BPE	+++++

+ not to scale, for illustrative purposes
BPE: benign prostatic enlargement

Differential Diagnosis of Gross Hematuria

	Prevalence	Associated with GH
Kidney cancer	+	+
Ureteral cancer	+	+++
Bladder cancer	+	++++++
Prostate cancer	++++++	+
Urethral cancer	+	+
Infection	++++++	++++
Stones	++++++	+
Trauma	+	+++
BPE	+++++	++++

+ not to scale, for illustrative purposes
 BPE: benign prostatic enlargement

Updating the differential diagnosis

- A study of the ER population at this hospital has shown that
 - Prevalence of prostate cancer and bladder cancer are 30% and 5%, respectively
 - 1% of patients with prostate cancer present with gross hematuria, compared to 80% of patients with bladder cancer
- What is the probability that a patient from the ER at this hospital with gross hematuria has
 - Prostate cancer?
 - Bladder cancer?

values for illustrative purposes

Bayes' Theorem

- $P(\text{disease} | \text{test}) = P(\text{disease}) \times P(\text{test} | \text{disease}) / P(\text{test})$
- $P(\text{disease} | \text{symptom}) = P(\text{disease}) \times P(\text{symptom} | \text{disease}) / P(\text{symptom})$
- What is the probability that a patient from the ER at this hospital with gross hematuria has
 - Prostate cancer? *prior* = 30%
 - $P(\text{PC} | \text{GH}) = P(\text{PC}) P(\text{GH} | \text{PC}) / P(\text{GH})$
 - $= 0.3 * 0.01 / (0.3 * 0.01 + 0.05 * 0.8)$
 - $= 0.003 / (0.003 + 0.04) = 0.07$
 - Bladder cancer? *prior* = 5%
 - $P(\text{BC} | \text{GH}) = P(\text{BC}) P(\text{GH} | \text{BC}) / P(\text{GH})$
 - $= 0.05 * 0.8 / (0.3 * 0.01 + 0.05 * 0.8) = 0.93$
- (We ignored BPE)

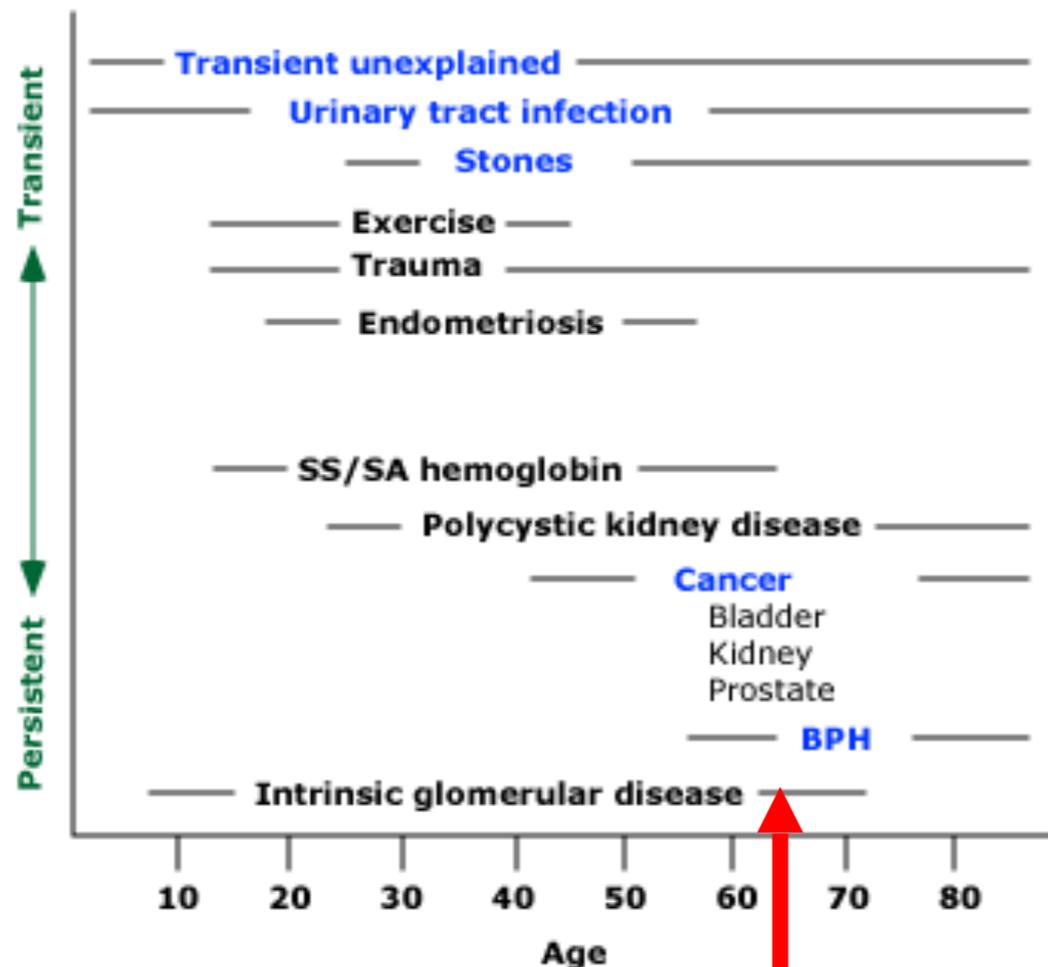


Narrowing the Differential Diagnoses

- A **65 year old male** is referred to you for **gross hematuria**?
- What **data** has already been provided to narrow the differential diagnosis in this patient?
 - Age
 - Sex
 - Symptom = gross hematuria

Narrowing the Differential Diagnoses

Major causes of hematuria by age and duration



Mostly likely diagnosis varies by Age

Differential Diagnosis of Gross Hematuria

	Incidence	Associated with GH	Age 65	Male
Kidney cancer	+	+	+++	+++
Ureteral cancer	+	+++	+++	+++
Bladder cancer	+	+++++	+++	+++++
Prostate cancer	+++++++	+	+++	+++++
Urethral cancer	+	+	++	
Infection	+++++++	+++++	+	-
Stones	+++++++	+	+	+
Trauma	+	+++		
BPE	+++++	+++++	+++	+++++

Narrowing the Differential Diagnoses

- A **65 year old male** is referred to you for **gross hematuria**?
- What more **data** do you want?
 - History
 - Physical exam
 - Labs
 - Imaging
 - Other

History (abbreviated)

- HPI: GH x 1 day, no LUTS*, no pain, no trauma.
- PMHx: none
- Current smoker: 1ppd x 10 yrs

Physical exam

- Digital rectal exam: smooth, non-tender prostate, estimated size 20g

* LUTS = Lower Urinary Tract Symptoms

Differential Diagnosis of Gross Hematuria

	Incidence	Associated with GH	Age 65	Male	Smoker
Kidney cancer	+	+	+++	+++	+++
Ureteral cancer	+	+++	+++	+++	+++++
Bladder cancer	+	++++	+++	+++++	+++++
Prostate cancer	+++++	+	+++	+++++	+
Urethral cancer	+	+	++		+
Infection	+++++	++++	+		
Stones	+++++	+	+	+	
Trauma	+	+++			
BPE	+++++	++++	+++	+++++	

- Most likely diagnosis: bladder cancer

Labs

- PSA 1.2 ng/mL*

* PSA < 4.0 is often considered “normal”, though it’s a highly imperfect relationship

Multivariable Models

Table 1 Univariable and multivariable logistic regression analyses assessing the association between predictor variables and the presence of bladder cancer in 1,182 patients

Predictors of bladder cancer	Univariable				Multivariable			
	OR	95 % CI	<i>p</i> value	AUC (%)	OR	95 % CI	<i>p</i> value	AUC (%)
Age (continuous)	1.04	(1.03, 1.06)	<0.0001	64.7	1.03	(1.02, 1.05)	<0.0001	83.1 %
Gender (male vs. female)	1.49	(1.04, 2.15)	0.03	52.3	1.10	(0.72, 1.68)	0.66	
Smoker (past/current vs. never)	3.38	(2.49, 4.58)	<0.0001	64.6	3.72	(2.58, 5.37)	<0.0001	
Hematuria (gross vs. microscopic)	2.47	(1.85, 3.30)	<0.0001	60.3	1.71	(1.21, 2.41)	0.002	
Cytology (positive vs. negative)	16.12	(10.98, 23.66)	<0.0001	70.6	14.71	(9.70, 22.28)	<0.0001	

AUC estimates are based on internal validation using 200 bootstrap samples

AUC area under the curve, CI confidence interval, OR odds ratio

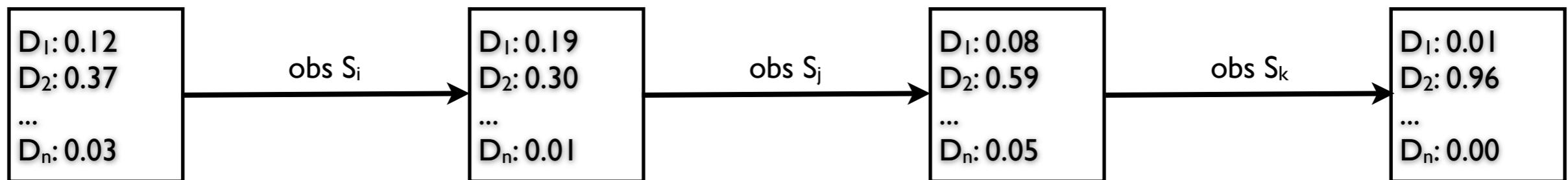
Cha, Eugene K., et al. "Accurate risk assessment of patients with asymptomatic hematuria for the presence of bladder cancer." *World journal of urology* 30.6 (2012): 847-852.

Diagnostic Reasoning with Naive Bayes

- Exploit assumption of conditional independence among symptoms

$$P(S_1, S_2, \dots, S_n | D_i) = P(S_1 | D_i) P(S_2 | D_i) P(S_n | D_i)$$

- Sequence of observations of symptoms, S_i , each revise the distribution via Bayes' Rule

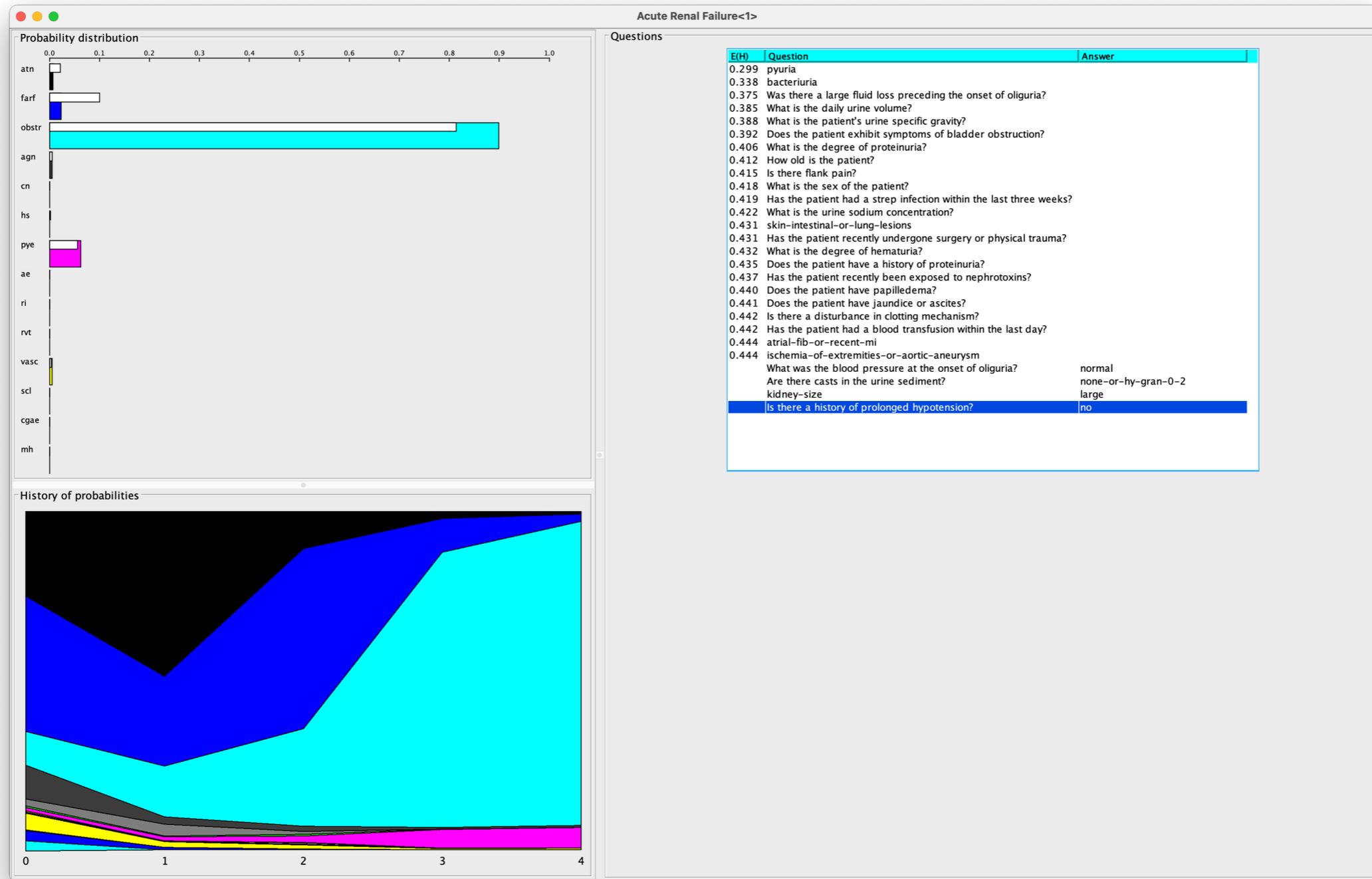


- After the j -th observation,

$$P^j(D_i | S_1, \dots, S_j) = \frac{P^{j-1}(D_i)P(S_j | D_i)}{P^{j-1}(S_j)} = \frac{P^{j-1}(D_i)P(S_j | D_i)}{\sum_{i=0}^n P^{j-1}(D_i)P(S_j | D_i)}$$

- Demo of Acute Renal Failure program
 - Based on technique from 1960s and (bad) data from the 1970s.

Sequential Diagnosis of Acute Renal Failure



1.

Based on:
 Gorry GA, Kassirer JP, Essig A, Schwartz WB. Decision analysis as the basis for computer-aided management of acute renal failure. *The American journal of medicine.* 1973 Oct;55(3):473-84.

Odds-Likelihood form of Bayes' Rule

Basis for many additive scoring systems

- In gambling, “3-to-1” odds means 75% chance of success

$$O = P/(1 - P) = P/\neg P$$

- $P = 0.5$ means $O=1$
- Likelihood ratio
- Odds-likelihood form of Bayes rule

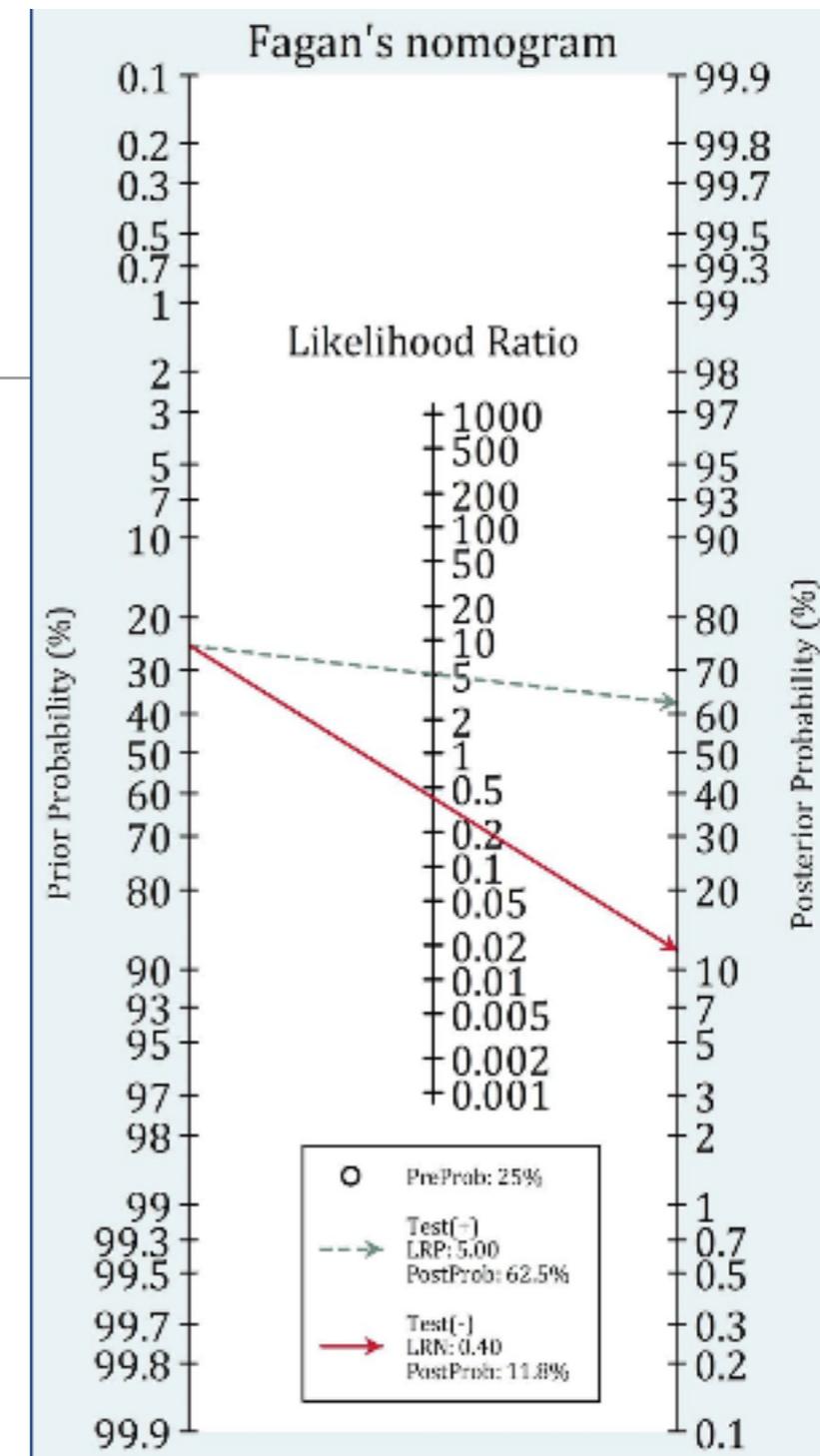
$$L(S|D) = P(S|D)/P(S|\neg D)$$

- Log transform

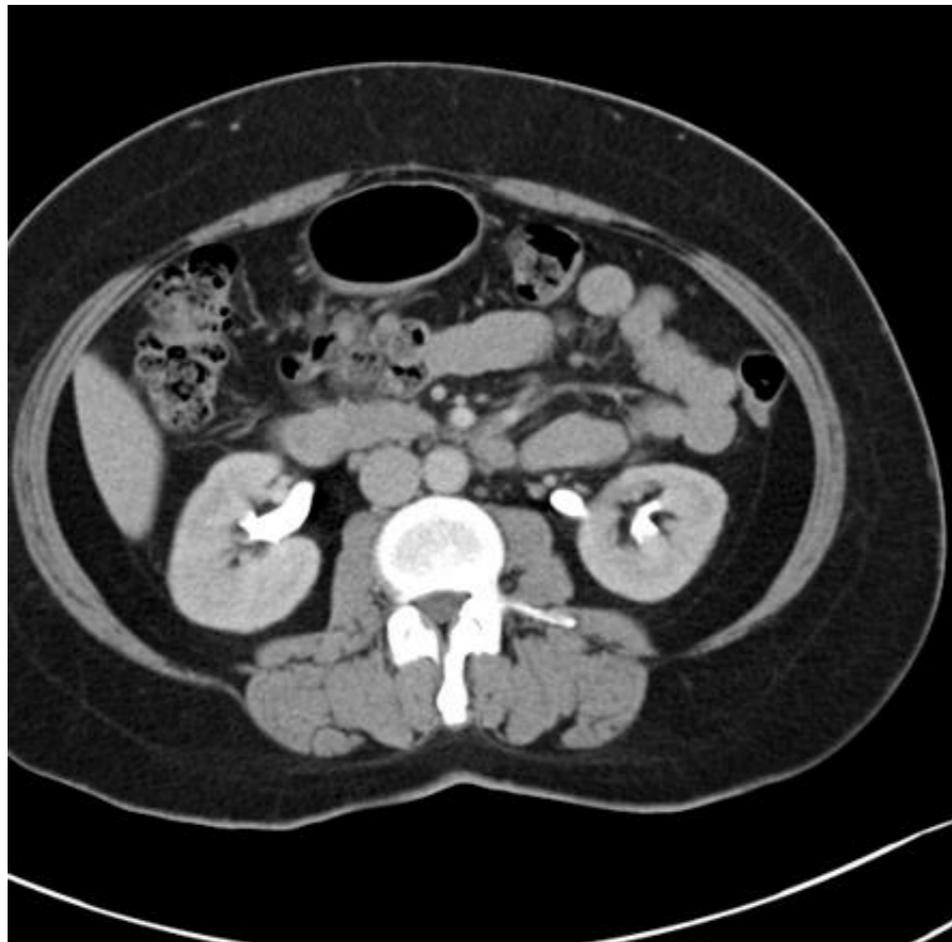
$$O(D|S_1, \dots, S_n) = O(D)L(S_1|D) \dots L(S_n|D)$$

$$\begin{aligned} \log O(D|S_1, \dots, S_n) &= \log[O(D)L(S_1|D) \dots L(S_n|D)] \\ &= \log[O(D)] + \log[O(S_1|D)] + \dots + \log[O(S_n|D)] \\ &= W(D) + W(S_1|D) + \dots + W(S_n|D) \end{aligned}$$

- Score = sum of scores for each feature; those are log likelihood ratios



Imaging

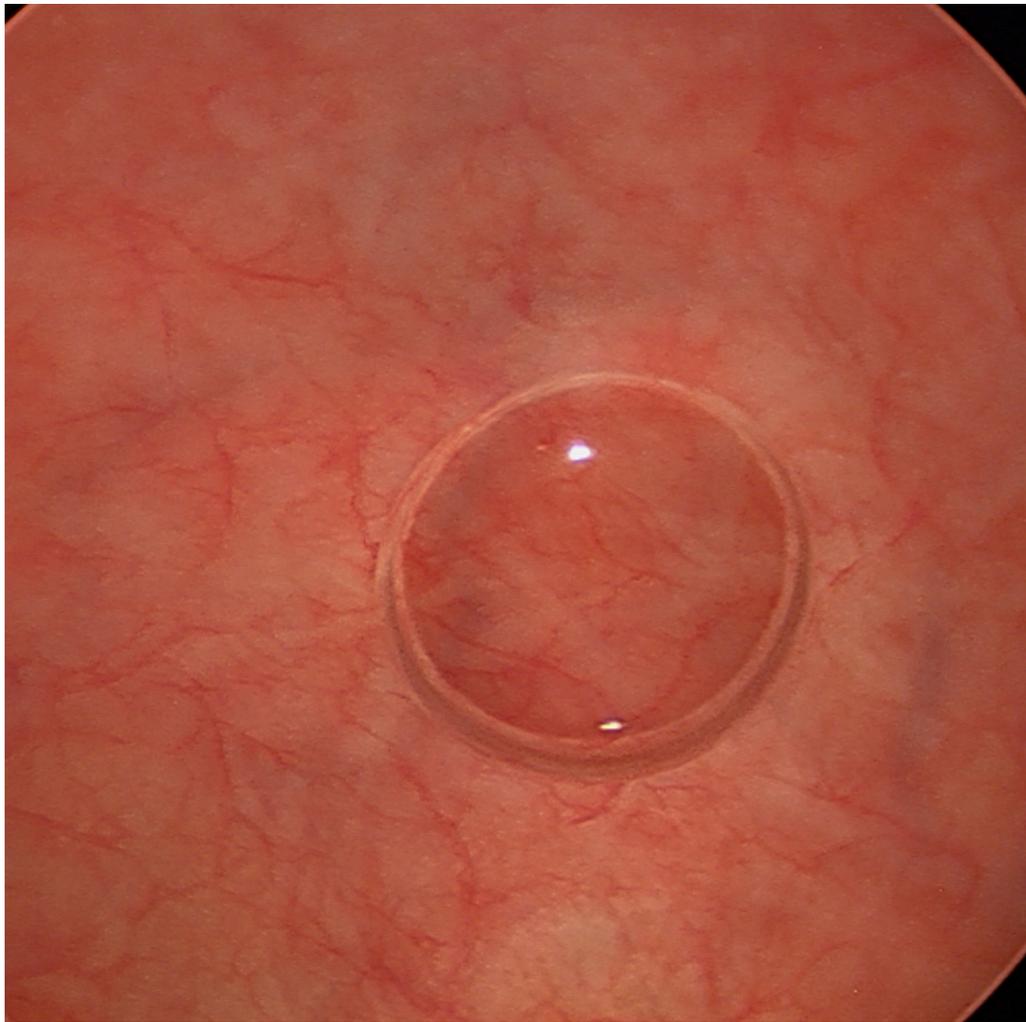


- Sensitivity for stones: 98%
- Sensitivity for kidney cancer: 75%
- Sensitivity for bladder cancer: 2%
- **How do you explain this to a patient?**

values for illustrative purposes

<https://radiopaedia.org/cases/normal-ct-intravenous-urogram?lang=us>

Cystoscopy



<https://vivwong.com.au/faqs/cystoscopy-procedures/>
<https://www.livescience.com/34701-bladder-cancer-symptoms-treatment.html>

A Provider's Perspective

Cystoscopy Note

- MRN, Name, DOB
- Clinical Note: Mr. Jones is a 65M who presented to the ER with a 1 day history of gross hematuria. A CT urogram was normal. He presents for cystoscopy.
- Procedure Note: A well lubricated flexible cystoscope was inserted into the urethra. The visualized anterior and posterior urethra were normal. The prostate demonstrated moderate lateral lobe enlargement. Upon entering the bladder, we performed cystoscopy. Both ureteric orifices were identified and normal. We noted 1 **papillary tumor** along the right lateral wall. The flexible cystoscope was then removed. The procedure was well tolerated and there were no immediate complications.

A Provider's Perspective

Cystoscopy Note Continued...

- Assessment: 1 papillary tumor along the right lateral wall. We discussed the role of TURBT* given the appearance of a bladder tumor. Specifically, we discussed the diagnostic and therapeutic role. We discussed the potential risks and complications of the procedure, including, ...The patient had an opportunity to ask questions and then signed the consent.
- Plan:
 1. TURBT with paralysis, post-operative gemcitabine
 2. PSA to assess risk of prostate cancer

* TURBT = trans urethral resection of bladder tumour

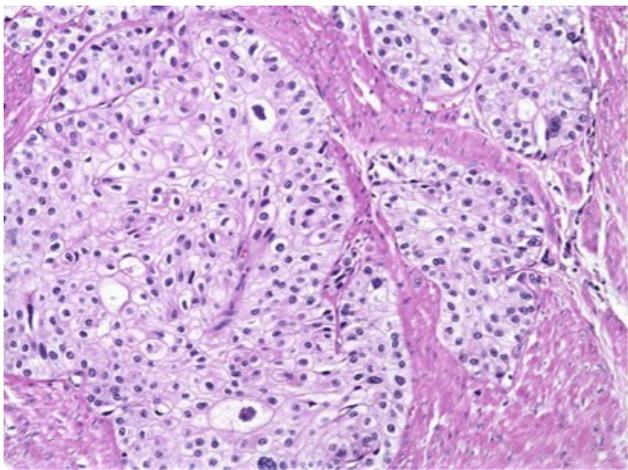
Date of surgery (TURBT)

A Patient's Perspective

- I had a bladder tumor resection today. The doctor thinks it's cancer. They said it will take a week for the pathology report to come back.

A Provider's Perspective

- Over the next few days, the specimen is processed and plated on slides
- The pathologist reviews the slides and initiates their diagnostic process



Compared with
knowledge
database

Diagnosis is reported
as observed pattern
most consistent with
knowledge database.

Report is generated

<https://www.nature.com/articles/modpathol200926>

Pathology Report

- Accession Number: AAAA1111
- Report Status: Final
- Type: Surgical Pathology
- Procedure Date: 02/05/2022
- Ordering Provider: Apprentissage Profond, M.D.
- CASE: AA-AA-1111
- PATIENT: Jim Jones
- Specimen(s) Received Bladder tumor, transurethral resection
- Data-driven Hospital Department of Pathology 1111 Main Street

Pathology Report

FINAL DIAGNOSIS: A. Bladder tumor, transurethral resection:

1. Poorly differentiated carcinoma, arising in an invasive papillary urothelial carcinoma with focal micropapillary differentiation, high grade (WHO 3 of 3). See comment.
2. Muscularis propria is present and involved by the tumor.

Comment: The tumor cells are negative for pancytokeratin, CK7, CK20, TTF-1, chromogranin and synaptophysin. Case also reviewed by a colleague (Dr. AB, M.D., who concurs.

Clinical History: Bladder cancer.

Gross Description: A. Bladder tumor, transurethral resection: Received in formalin are multiple friable, tan-white/brown tissue fragments measuring 3.0 x 2.6 x 1.5 cm in aggregate. The specimen is entirely submitted in cassettes A1-A5.

Final Diagnosis by AB, M.D.,

Electronically signed on Thursday February 8, 2022 at 06:40:43PM

A Provider's Perspective

- MRN
- Name
- DOB

- Urologic Oncology Clinic Note
- ID: Mr. Jones is a 65 year old male who underwent a TURBT on 02/05/2022. He returns today for follow-up.
- HPI: Patient reports that he is doing well since surgery. He denies any pain or lower urinary tract symptoms.
- Pathology: (copy/paste report)

A Provider's Perspective

Assessment: Mr. Jim Jones is a 65 year old male found to have muscle-invasive bladder cancer. We discussed that standard of care for this disease is neoadjuvant chemotherapy followed by radical cystectomy and urinary diversion.

We discussed the potential risks and complications of these, including ...

We also discussed alternative treatment options, including ...

The patient was given an opportunity to ask questions. They would like to proceed with neoadjuvant chemotherapy followed by radical cystectomy and creation of ileal conduit.

Plan:

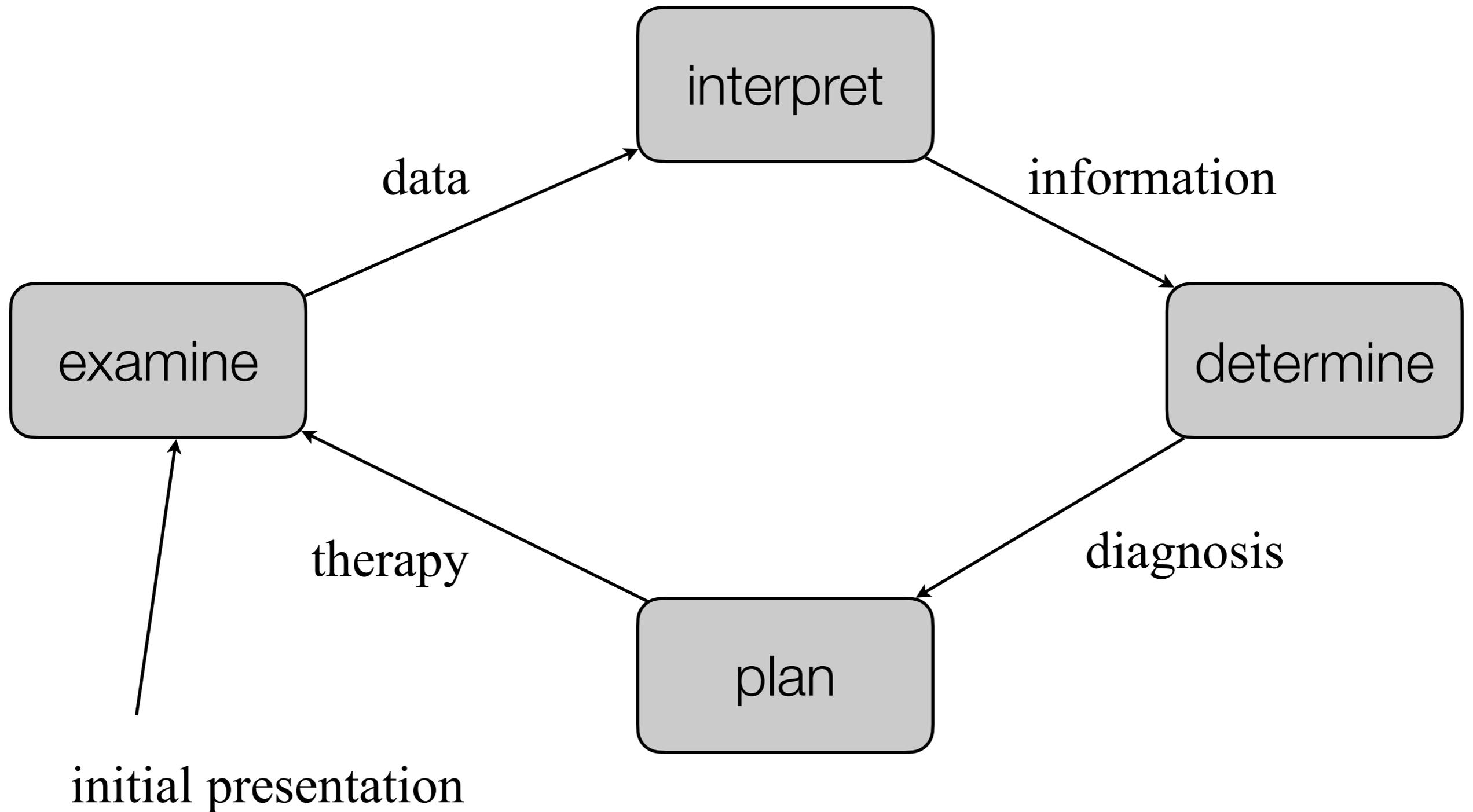
1. Complete staging: CT chest
2. Medical oncology consult

End of Case Presentation

Other Problems Demand Other Methods

- This case was a relatively straightforward, though serious, diagnostic and therapeutic problem
- Many disorders require management rather than one-time treatment

The Medical Cycle



Cognitive Theory of Diagnosis

- From initial complaints, guess suitable hypothesis
- Use current active hypotheses to guide questioning
- Failure to satisfy expectations is the strongest clue to a better hypothesis; differential diagnosis
- Hypotheses are activated, de-activated, confirmed or rejected based on
 - (1) logical criteria
 - (2) probabilities based on:
 - findings local to hypothesis
 - causal relations to other hypotheses (coherence)
- \approx Scientific Method

Pauker, S. G., Gorry, G. A., Kassirer, J. P., & Schwartz, W. B. (1976). Towards the simulation of clinical cognition. Taking a present illness by computer. *The American Journal of Medicine*, 60(7), 981–996.

Enterprise-level Clinical Process Automation...

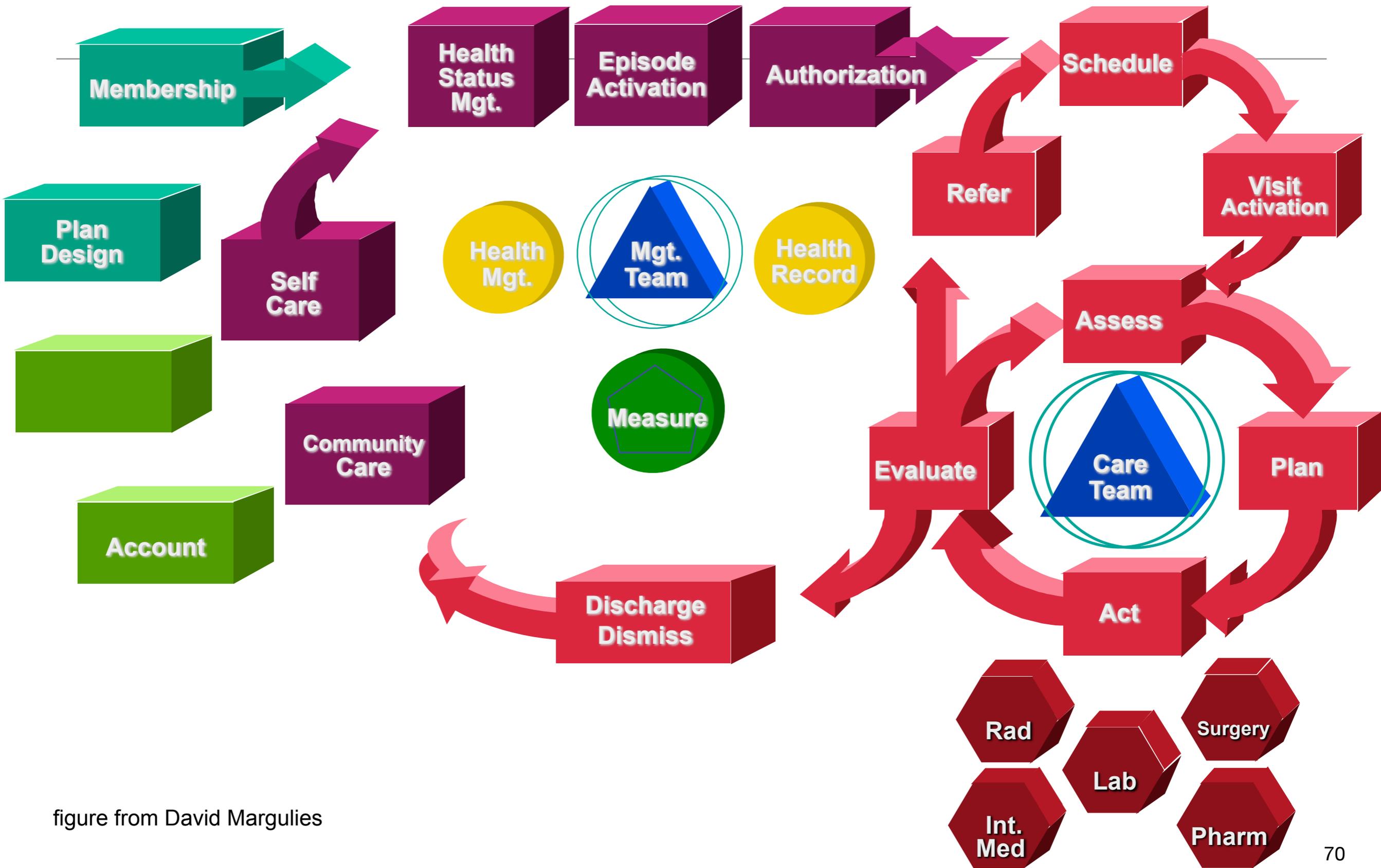
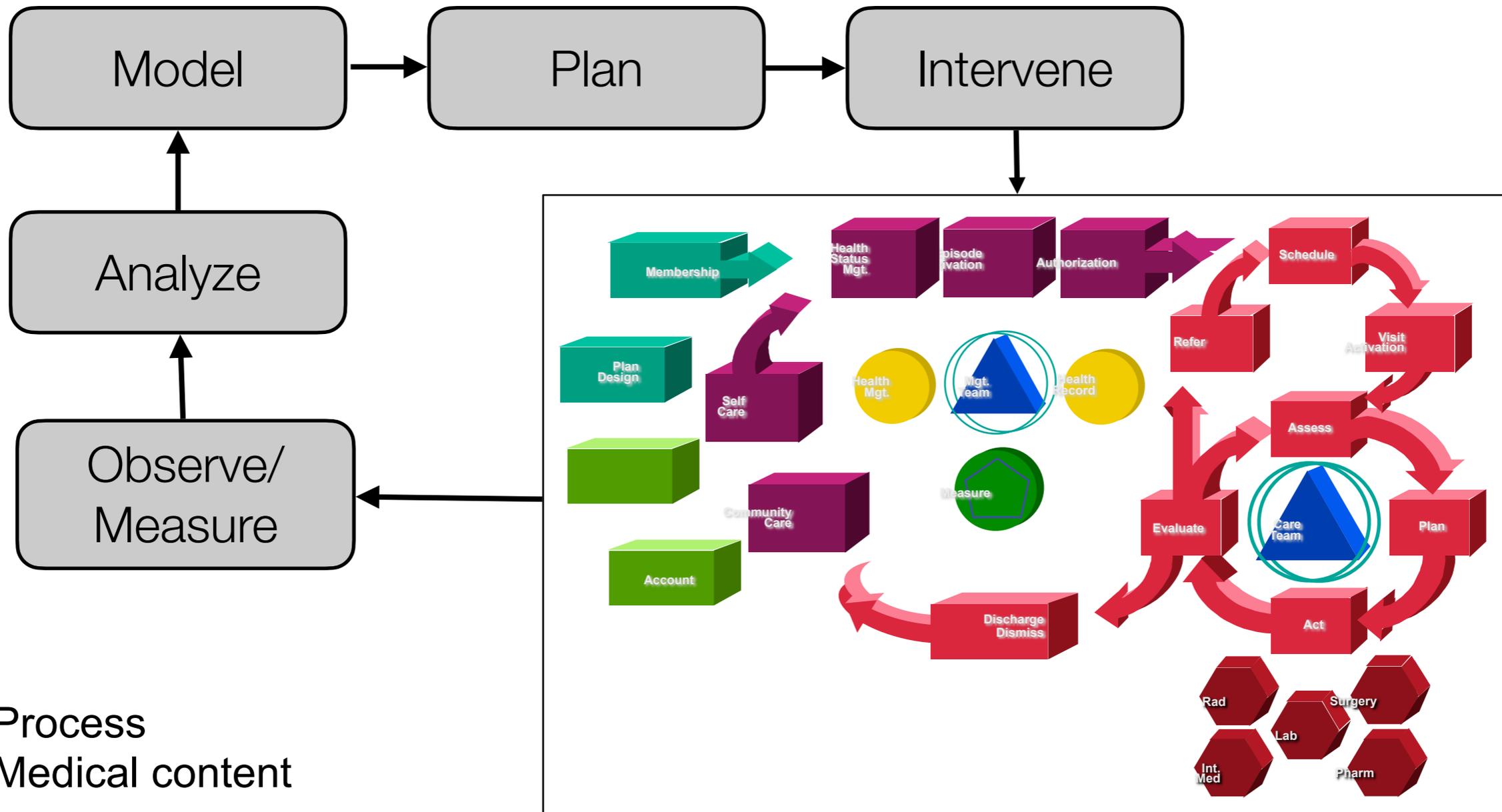


figure from David Margulies

The “Learning Health Care System”



- Process
- Medical content



Volume 1, Issue 1

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Learning Health Systems

Open Access



COMMENTARY

The science of Learning Health Systems: Foundations for a new journal

Charles P. Friedman¹ | Nancy J. Allee² | Brendan C. Delaney³  | Allen J. Flynn¹ | Jonathan C. Silverstein⁴  | Kevin Sullivan⁵ | Kathleen A. Young¹

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⁴Medical Informatics, Tempus and Kanter Health Foundation, Chicago, Illinois

⁵Department of Computer Science, School of Engineering and Applied Science, University of Virginia, Charlottesville, Virginia

WILEY

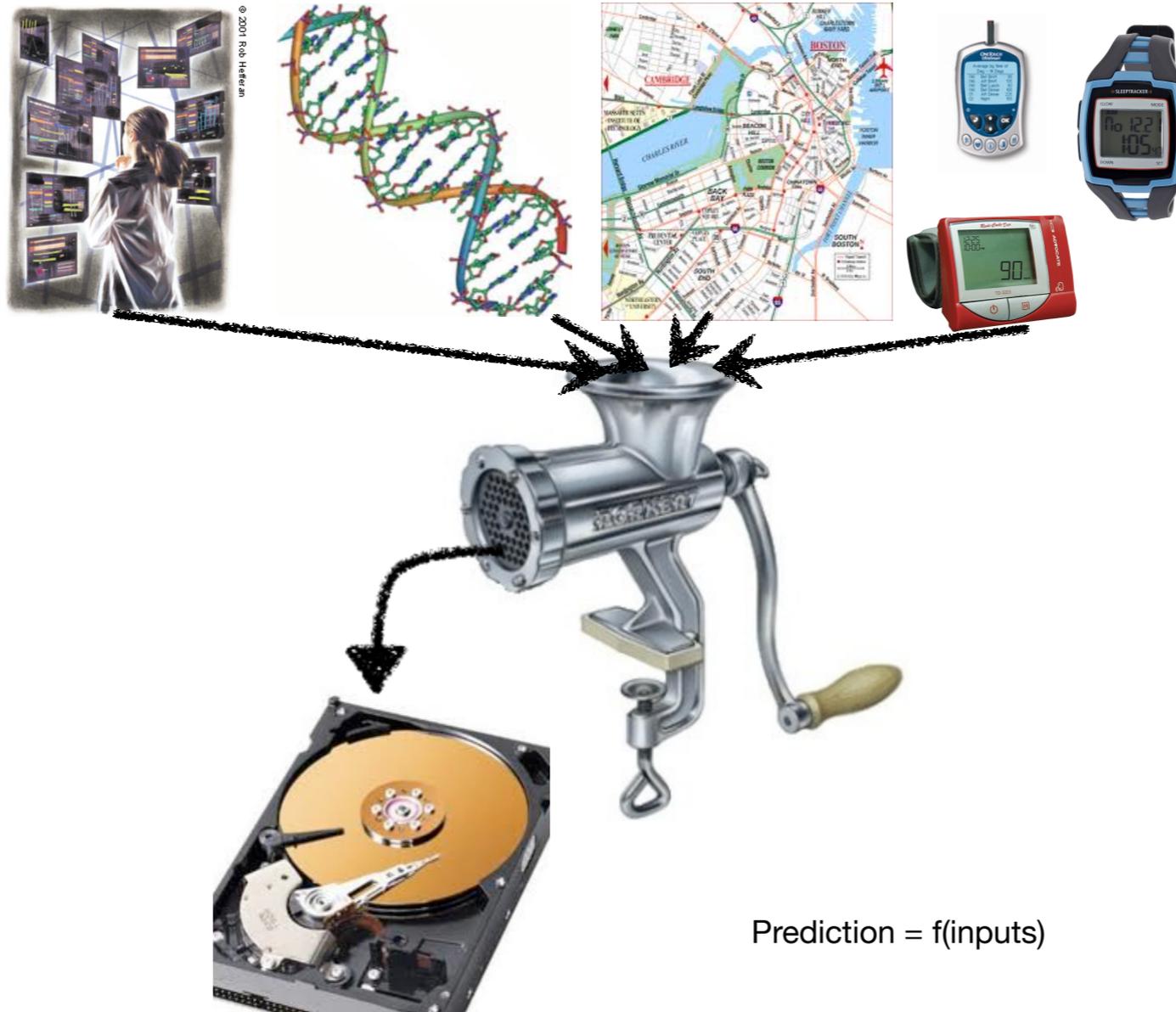
How Does the Health System Learn?

- “Evidence-Based Medicine”
 - Contrast with “Tradition-Based Medicine” — Apprenticeship
- Randomized Controlled Clinical Trial (RCT)
 - E.g., is drug A more effective than drug B for condition X?
 - Narrow selection of patient cases and controls
 - Careful collection of systematically organized data
 - Statistical analysis of outcomes
 - => Statistically significant conclusions
- But:
 - **Heterogeneity:** Most cases to which RCT results are applied do not fit trial criteria
 - **Short Follow-Up:** Trials run for limited times, but use is longer
 - **Small Samples:** Some effects are rare but devastating

“The Learning Health Care System”

- “one in which progress in science, informatics, and care culture align to generate new knowledge as an ongoing, natural by-product of the care experience, and seamlessly refine and deliver best practices for continuous improvement in health and health care” —IOM
- Needs not currently met:
 - Comprehensive collation of all clinical, social, demographic, behavioral, ... data that are now captured in the health care system
 - Routine capture of novel data sources:
 - genomes, gene expression, etc.
 - environmental factors (e.g., metagenomics)
 - physiological response to life situations
 - (related to fitness and wellness)
 - Technical infrastructure
 - Storage and analysis of truly “big data”
 - Incentives and demonstrations of utility

Use All Possible Data



Goals of Medicine: (2) Keep people healthy

- Public Health
 - Tracking disease prevalence
 - Tracing infections
 - Quarantine

Tracking disease prevalence by systematic classification

- 17th century: John Graunt on the London Bills of Mortality estimated mortality before age 6 at 36%
- 18th century: Sauvage, Linnaeus, Cullen made first attempts at systemic classification
- 1853—first International Statistical Congress led to Wm. Farr’s system:
 - epidemic diseases
 - constitutional (general) diseases
 - local diseases arranged according to anatomical site
 - developmental diseases
 - diseases that are the direct result of violence(Note: pre-Pasteur)
- 1890s—Bertillon (Paris) classification: 161 titles, abstracted to 99, and 44
- 1920 International List of Causes of Death
- 1920s-40s—*Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*
- 1975—ICD-9
- 2015—ICD-10
- ICD-*n* are under control of the World Health Organization (WHO)
- ICD-9CM, ICD-10CM are US “Clinical Modifications”, mainly to support billing
- ICD-11, published by WHO in 2022; not yet used in US for billing.
 - 14K codes in ICD-10 ⇒ 55K in ICD-11

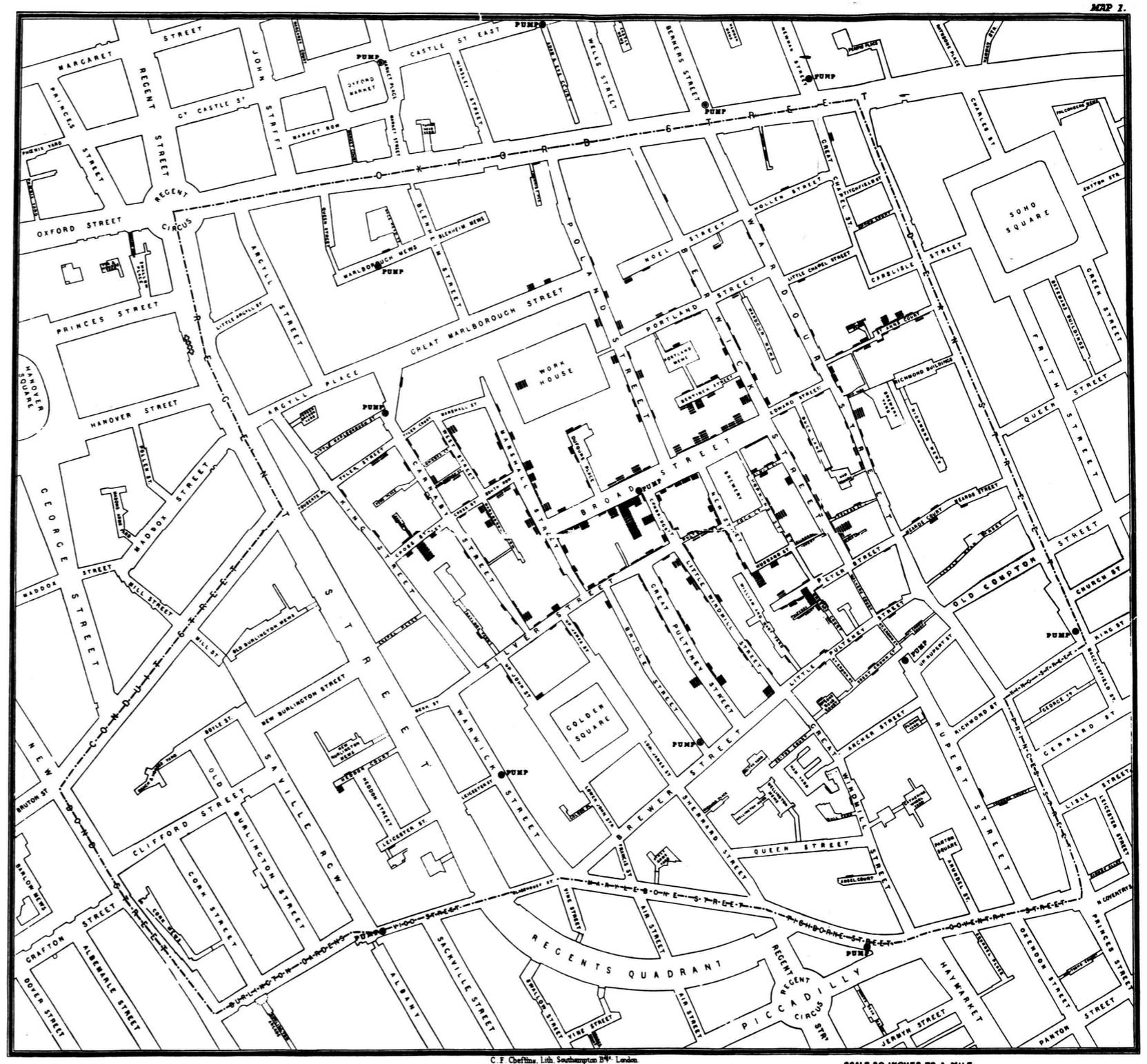
Centers for Disease Control and Prevention (CDC)

- Today, we collect death certificates that record direct & indirect causes of death
- Insurance payments are based on classifications of disease, severity, tests, intervention, ...

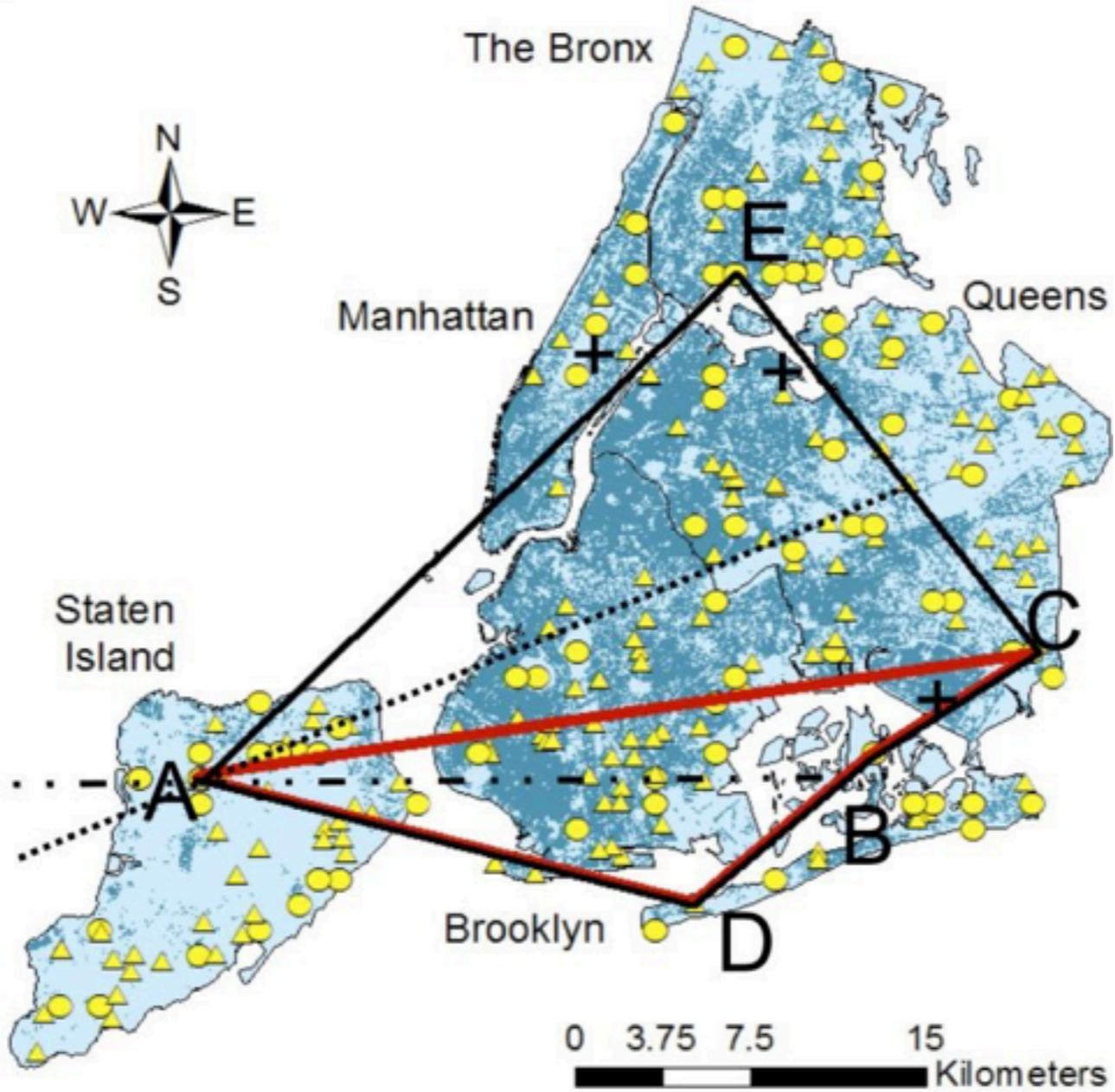
CAUSE OF DEATH (See instructions and examples)		Approximate interval: Onset to death
<p>32. PART I. Enter the <u>chain of events</u>--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.</p> <p>IMMEDIATE CAUSE (Final disease or condition -----> resulting in death)</p> <p>Sequentially list conditions, if any, leading to the cause listed on line a. Enter the UNDERLYING CAUSE (disease or injury that initiated the events resulting in death) LAST</p>		
a.	<u>Cerebral hemorrhage</u> Due to (or as a consequence of):	<u>1 month</u>
b.	<u>Nephritis</u> Due to (or as a consequence of):	<u>6 months</u>
c.	<u>Cirrhosis of liver</u> Due to (or as a consequence of):	<u>2 years</u>
d.	_____	
<p>PART II. Enter other <u>significant conditions contributing to death</u> but not resulting in the underlying cause given in PART I.</p>		<p>33. WAS AN AUTOPSY PERFORMED? • Yes • No</p>
		<p>34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? • Yes • No</p>

Cholera, John Snow, and the Broad Street Pump (1854)

- “germ-contaminated water was the source of cholera”
- Localization via mapping
- Led to sanitation improvements
- Snow also used:
 - Double-blind experimental technique
 - Voronoi diagrams to outline neighborhoods closest to each pump



Locations of WNV detections in NYC (2003)



- ▲ Bird
- Mosquito
- WNV promoting
- non-WNV promoting

Quarantine

- Isolation separates sick people with a contagious disease from people who are not sick.
- Quarantine separates and restricts the movement of people who were exposed to a contagious disease to see if they become sick.
- Mostly used at ports of entry, but sometimes to try to prevent epidemics
 - Ellis Island
 - “Typhoid Mary”
 - AIDS
 - Ebola

"TYPHOID MARY"

MOST HARMFUL



4 Landreem.

The Extraordinary Predicament of Mary Mallon, a Prisoner on New York's Quarantine Hospital

IT is probable that Mary Mallon is a prisoner for life—and yet she has committed no crime, has never been accused of an immoral or wicked act, and has never been a prisoner in any court, nor has she been sentenced to imprisonment by any judge.

Mary Mallon is a cook by profession. She has served in the kitchens of many New York millionaires with entire satisfaction for many years.

Mary Mallon for more than two years has been a prisoner on New York's quarantine island, along with the unfortunates who are from time to time removed to this isolated spot because they are suffering from smallpox,

scarlet fever or other contagious diseases.

But while Mary sees these unfortunate victims of various diseases come on the hospital boat and, in due time, return to their homes and friends—Mary stays on forever.

There is probably in the whole wide world no prisoner that can furnish a parallel to the extreme misfortune which has brought Mary Mallon to North Brother Island. Through no fault of hers, Mary Mallon is a living, walking incubator of typhoid fever germs. Every day for two years the officials of the New York Board of Health have examined Mary, and they have been discouraged to find a bountiful supply of new typhoid fever bacilli freshly

made each twenty-four hours by Mary.

Mary Mallon, in the five years before authorities got their hands on her, was the cause of twenty-six cases of typhoid fever—others. So far as is known, the woman had the disease, and is not now sick with it. But somewhere in her anatomy, perhaps in the gall duct, there is a never-failing typhoid fever germ. To the positive Board of Health Mary has been given typhoid bacilli for seven years. This they are able to trace her history

By Dr. Wm. H. Park, New York Board of Health.

MARY MALLON is the chief of fifty persons, fifteen of whom have been discovered within the past two years, in this country, whom we know in medical science as typhoid bacilli carriers. Her case is the most remarkable with which we are acquainted, because of the number of persons to whom she has communicated the disease.

Our study of the case leads us to believe that the typhoid germs lodge in the gall bladder, where they live indefinitely. From there they are carried through the body by the bile.

She is confined on North Brother Island, where she has been a prisoner for two years, and where, of course, she will remain indefinitely. She is a large, healthy looking woman, a typical cook, and there is nothing in her outward appearance to indicate that she is other than normal. She is, of course, segregated with the typhoid patients. When we consider that she has been spreading the contagion for many years, it is clear that she will be a prisoner on North Brother Island for a long time, perhaps for life; certainly until we are convinced that the typhoid germs and typhoid tendencies have been eliminated from her body.

Every effort has been made by the health authorities to cure the unfortunate woman, but so far without success. Examination is made each day, with the hope that some one of the various expedients we have tried may put an end to the discharge of bacilli. Nothing we have tried so far has proved effective. There is nothing at the present moment known to medical science which seems to reach a case like this. It is extremely unfortunate for the woman; but it is the plain duty of the health authorities to safeguard the public from such a menace.

The Extraordinary and Dis

The Official I

IN the Winter of 1906 I was called on to investigate a household epidemic of typhoid fever which had broken out in the latter part of August at Oyster Bay, N. Y. The epidemic had been studied carefully immediately after it took place, but its cause had not been ascertained with as much certainty as seemed desirable to the owner of the property.

The essential facts concerning the investigation follow:

At Oyster Bay, in the Summer of 1906, six persons in a household of eleven were attacked with typhoid fever. The house was large, surrounded with ample grounds, in a desirable part of the village, and had been rented for the summer by a New York banker.

The first person was taken sick on August 27 and the last on September 2. The diagnosis of typhoid was positive. Two of the patients were sent to the Nassau Hospital at Mineola. The others were attended by capable physicians at Oyster Bay. None of the subsequent cases apparently resulted from the first, although the interval from the first to the last might permit of this assumption. But whether the disease was transmitted from one person to another after the first case occurred was not a matter of great consequence. The most important question was how the first case occurred.

Germ Source a Mystery.

Typhoid fever is an unusual disease in Oyster Bay, according to the three physicians who share the medical practice there. At the time of the outbreak no other case was known. None followed.

The milk supply of this house was the same as used by most of the other persons in the village, all of whom remained well. The cream also was from a source which supplied several other families in the vicinity.

To the first investigators it seemed that the water must have been contaminated. They were



HELMS CALLS FOR AIDS QUARANTINE ON POSITIVE TESTS

By **United Press International**
CHICAGO TRIBUNE

JUNE 16, 1987 | WASHINGTON

A quarantine of people who test positive for **AIDS** infection is the way to halt the spread of the deadly disease, Sen. **Jesse Helms** (R., N.C.) said Sunday. Helms appeared on the CBS "Face The Nation" program after Education Secretary William Bennett, who suggested that prison inmates infected with the AIDS virus should be kept in custody after serving their sentences if they threaten to spread the disease to the general population to take "revenge on society."

Quarantine

- Quarantine is a controversial and debated issue. ... significant risks related to human rights, creating fear and confusion...
 - Quarantine should be used as a last resort
 - Quarantines in urban areas are complicated by the size and density of their populations
-
- Highly mobile populations make managing and enforcing quarantine more complex
 - Large-scale quarantines result in equally large waste disposal needs and other water, sanitation and hygiene vulnerabilities



Learning from the Ebola Response in cities

Responding in the context of quarantine

Quo Vadis?

- Anticipated improvements in health care should give us better information
 - Genomic medicine
 - Genome, transcriptome, proteome, epigenome, metabolome, meta genome, ...
 - Improved instrumentation, e.g.,
 - non-invasive examination of the body: ultrasound, MRI, CT, swallowable capsules, ...
 - continuous recording: MEMS implantable devices, ...
- Improved methods of data analysis, causal discovery, biology research, ... should give us better understanding
- New interventions can improve therapy
 - Gene editing: CRISPR-CAS9, ...
 - Targeted delivery of drugs to specific tissues