Overview of Clinical Care

HST.956/6.793
Machine Learning in Healthcare
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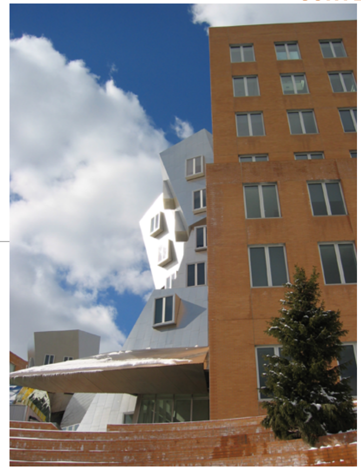
Example of diagnostic process
from Madhur Nayan,
NYU Urology



Massachusetts Institute of Technology

What do Clinicians Do?

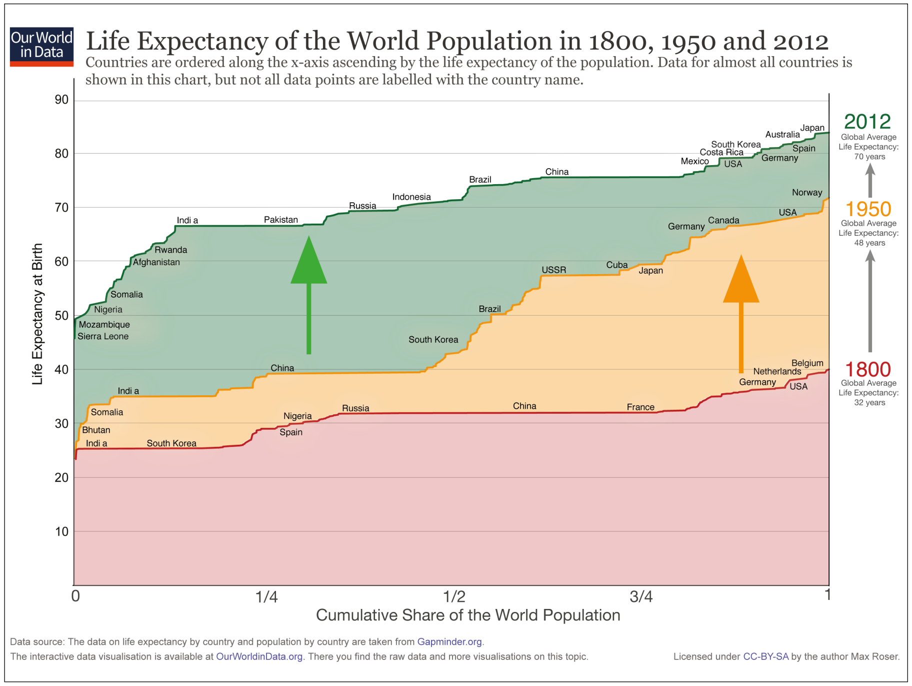
Outline

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

WHO Constitution defines “health”

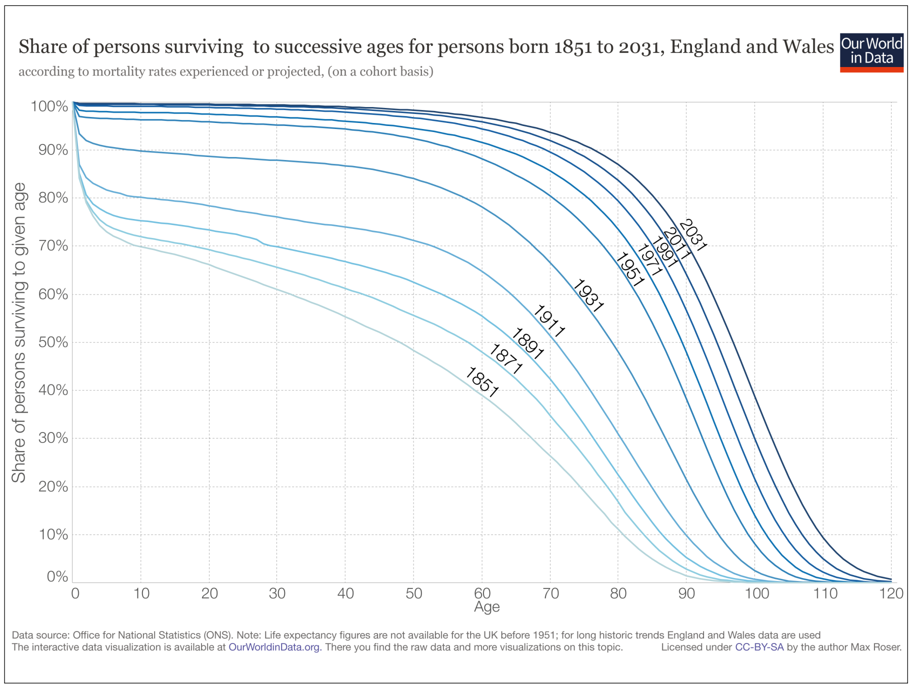
“a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”

- Physical
- Mental
- Social
  - —very hard to measure



Longevity at birth (CIA World Fact Book, 2001, 2024)

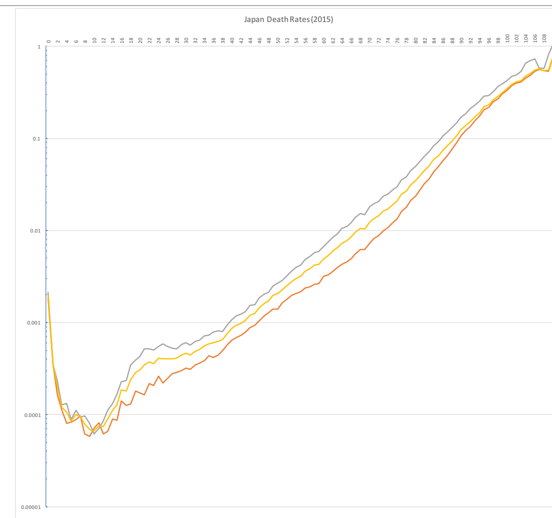
Country	*Male*		*Female*	
	2024	2001	2024	2001
Rwanda	64.6	38.4	68.6	39.7
Kenya	68.6	46.6	72.2	48.4
South Africa	70.3	47.6	73.5	48.6
Cambodia	69.6	54.6	73.3	59.1
Brazil	72.6	59.0	80.1	67.7
Russia	67.4	62.1	77.4	72.8
Turkey	74.4	68.9	79.2	73.7
Albania	77.3	69.0	82.8	74.9
USA	78.7	74.4	83.1	80.1
France	79.8	75.0	85.5	83.0
Israel	81.1	76.7	85.1	80.8
Japan	82.3	77.6	88.2	84.2



Distribution of Death Rates by Age

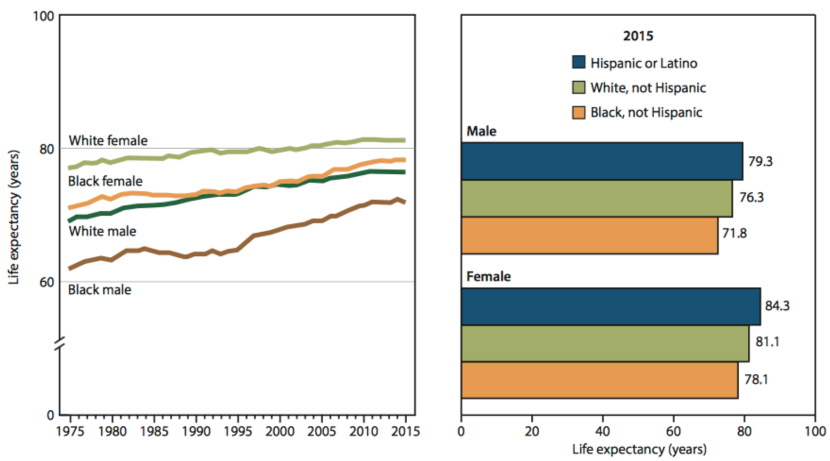
- Life table deaths by year (Japan, 2015)

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



https://www.cdc.gov/nchs/data/hus/hus16.pdf#019

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
OTHER	*215.8*	*26.2*
TOTAL	823.7	100.0

https://www.medicalnewstoday.com/articles/282929.php

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?

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

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)

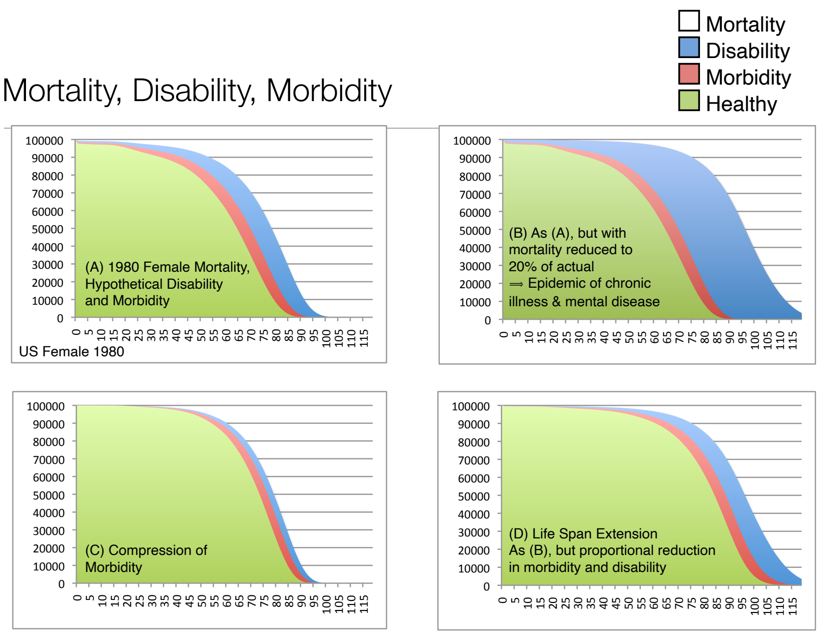
Instrumental

- 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



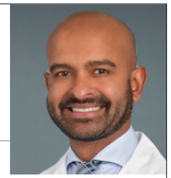
Societal quality of life

- Aggregation of individual qualities

\+ Equity (distributions)

- Is more better? (Population control)
- Is less better?
- How much to spend?

Extended Example of Clinical Care
Madhur Nayan, NYU Urology



- 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

- Nurse determines triage level
  - 1. Immediate risk of death
    - pulse, respiratory rate, capillary refill time, presence of bleeding, the patient's ability to follow commands
  - 2. Serious immediate medical need — no waiting
    - high risk, confused/lethargic/disoriented mental status, severe pain, deteriorating condition
  - 3, 4, 5 determined by number of hospital resources needed
    - 2+ ⇒ 3, 1 ⇒ 4, 0 =>5
    - e.g., lab tests, imaging, parenteral or nebulizer medications, consultations, simple procedures such as a laceration repair, or a complex procedure
- For kids:
  - Airway
  - Breathing
  - Circulation/Coma/Convulsion
  - Dehydration

https://www.ncbi.nlm.nih.gov/books/NBK557583/

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

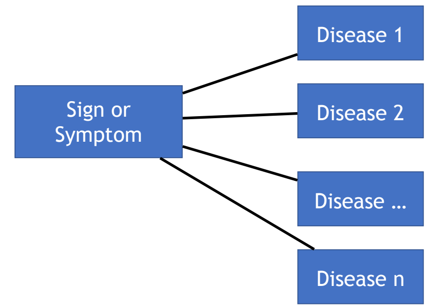
Diagnostic process

- 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."**

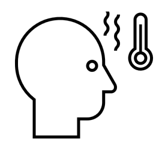
Differential Diagnosis



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**

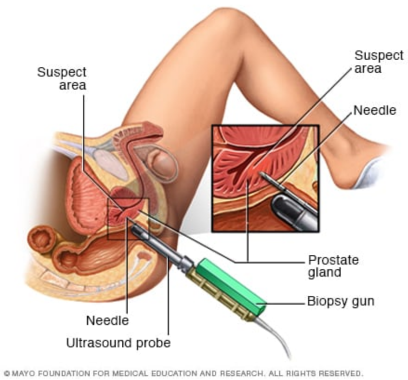
- Malignant
  - Anywhere along the urinary tract
    - Kidney
    - Ureter
    - Bladder
    - Prostate
    - Urethra
- Non-malignant
  - Infection
  - Stone
  - Trauma
  - Benign prostatic hyperplasia (BPH)
  - Etc.

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



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/

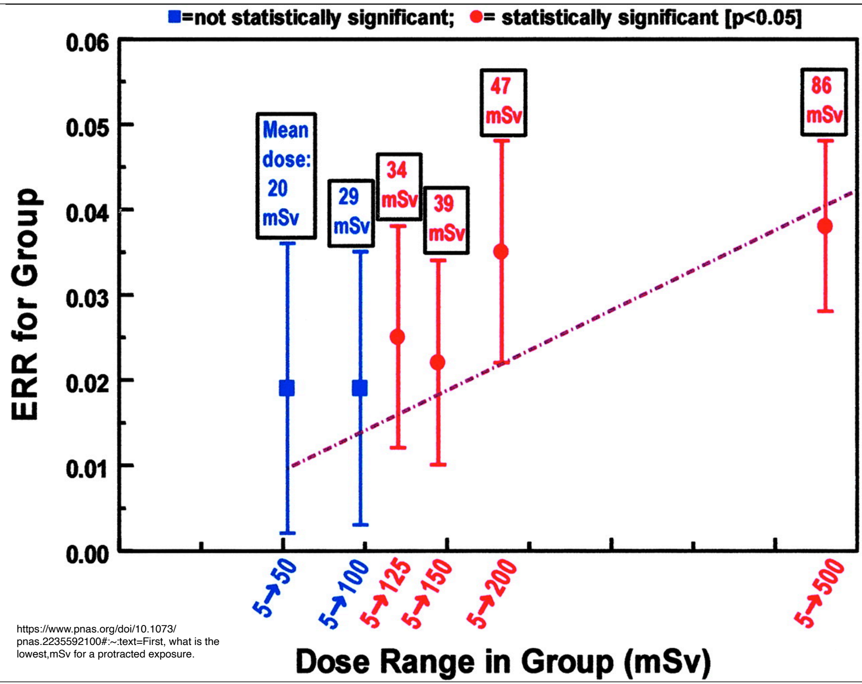
Radiation exposure from CT scan

- 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.

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



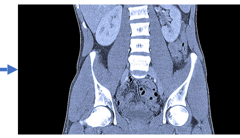
https://www.pnas.org/doi/10.1073/pnas.2235592100#:~:text=First, what is the lowest,mSv for a protracted exposure.

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

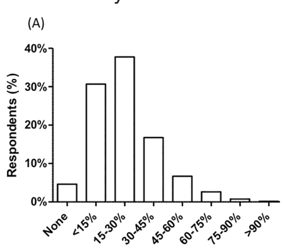
↑ risk of cancer 1 in 2000

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

- ≈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

		DISEASE (GROUND TRUTH)		
		Present	Absent	
TEST RESULT	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) PPV = a / (a + b)

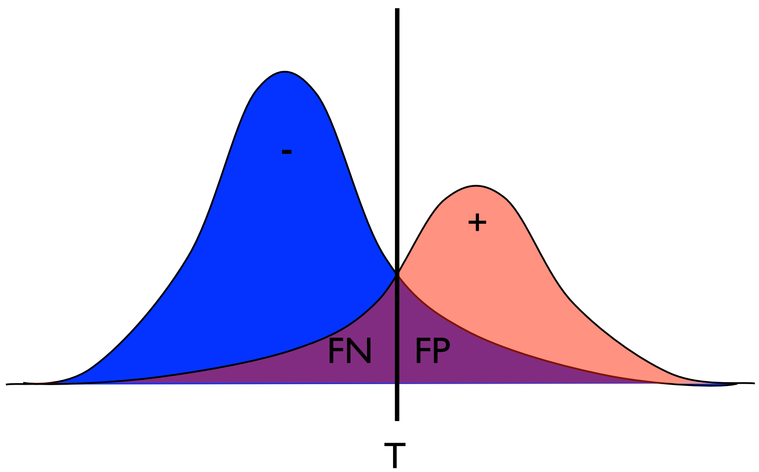
Specificity = d / (b + d) NPV = d / (c + d)

Low sensitivity means lots of false negatives
Low specificity means lots of false positives

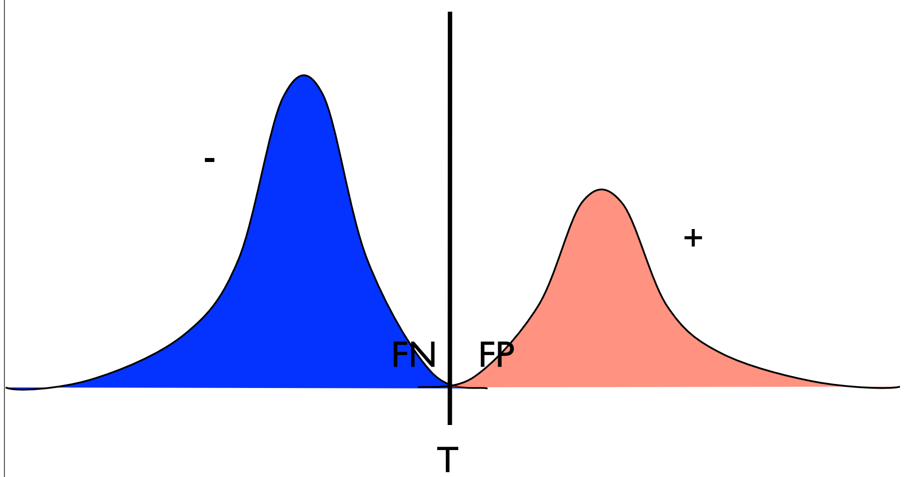
Test Characteristics in Healthcare

- 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?

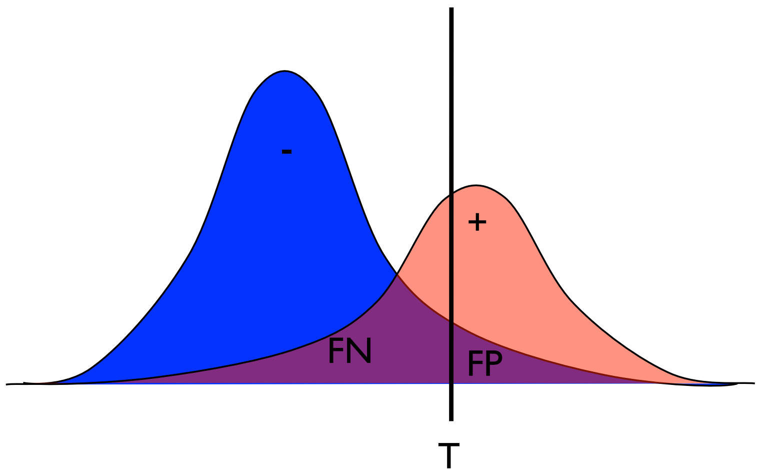
Test Thresholds



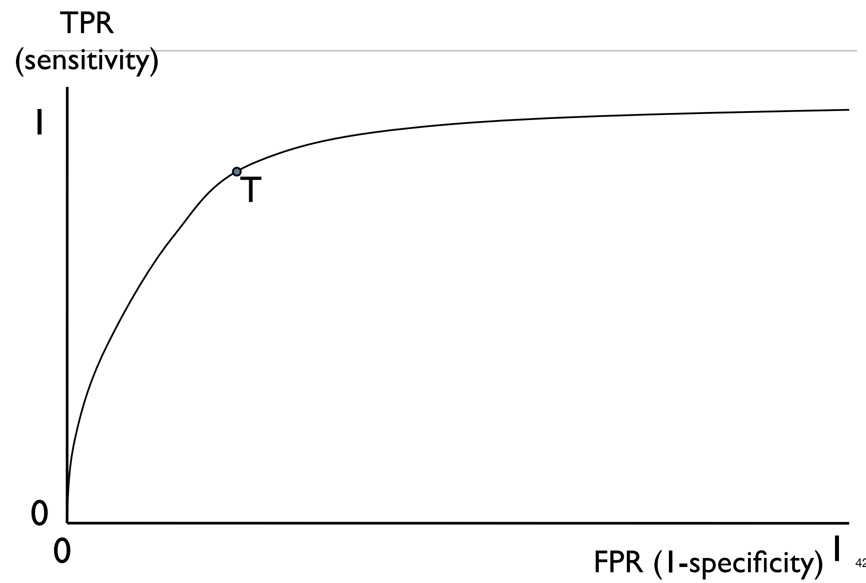
Wonderful Test



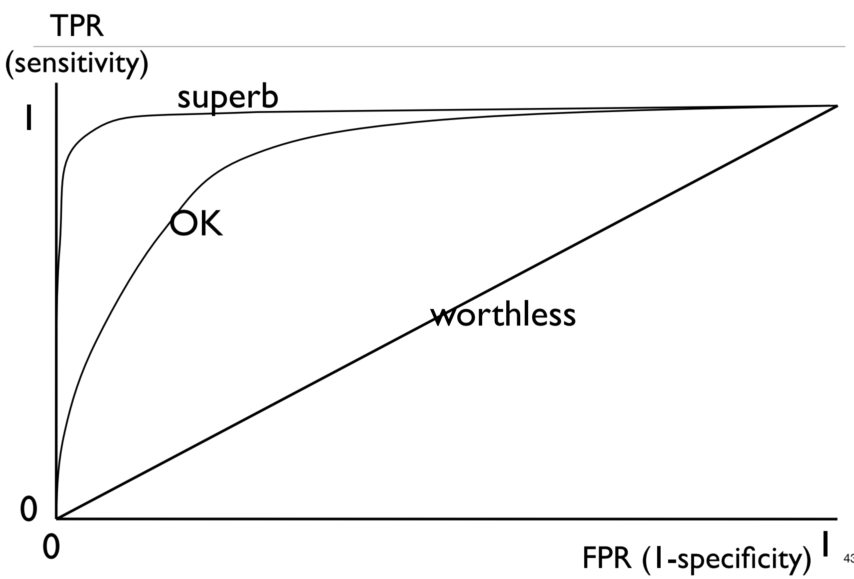
Test Thresholds Change Trade-off between Sensitivity and Specificity



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

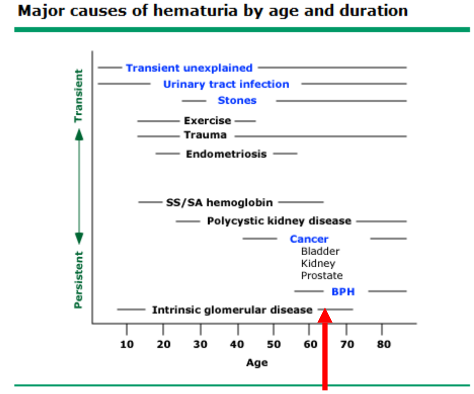
- P(disease|test) = P(disease) x P(test|disease) / P(test)
- P(disease|symptom) = P(disease) x P(symptom|disease) / P(symptom)
- What is the probability that a patient from the ER at this hospital with gross hematuria has
  - Prostate cancer? *prior* = 30%
    - P(PC|GH) = P(PC) P(GH|PC) / P(GH)
    - = 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(BC|GH) = P(BC) P(GH|BC) / P(GH)
    - = 0.05 * 0.8 / (0.3 * 0.01 + 0.05 * 0.8) = 0.93
  - (We ignored BPE)

Hall, G. H. "THE CLINICAL APPLICATION OF BAYES' THEOREM." *The Lancet* 290.7515 (1967): 555-557.

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



Mostly likely diagnosis varies by Age

UpToDate®

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	*p* value	AUC (%)	OR	95 % CI	*p* 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	

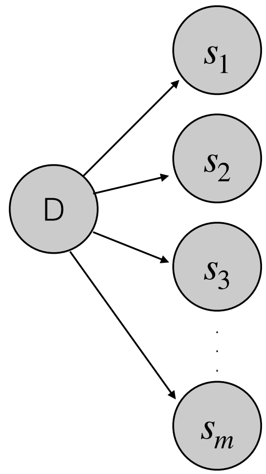
AUC estimates are based on internal validation using 200 bootstrap samples

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.

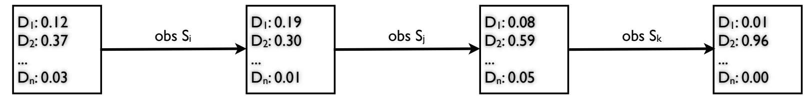
Formalizing Madhur's Reasoning Process: Naïve Bayes

- $D = \{d_j\}$ represents an exhaustive and mutually exclusive set of n possible diseases d_j; we know prevalences $p(d_j)$, and $\sum_{j=1}^{n} p(d_j) = 1$
- s_i are possible signs, symptoms, lab results, etc., conditionally independent given a particular value of D; we know the conditional probabilities $p(s_i \mid d_j)$
- Goal: ask for results s_i to minimize the entropy $H(p(D)) = -\sum_{j=1}^{n} p(d_j)\,\log p(d_j)$ while minimizing number of results requested (or risk of tests)



Diagnostic Reasoning with Naive Bayes

- Exploit assumption of conditional independence among symptoms
  $P(S_1, S_2, \ldots, S_n|D_i) = P(S_1|D_i)P(S_2|D_i)P(S_n|D_i)$
- Sequence of observations of symptoms, S_i, each revise the distribution via Bayes' Rule

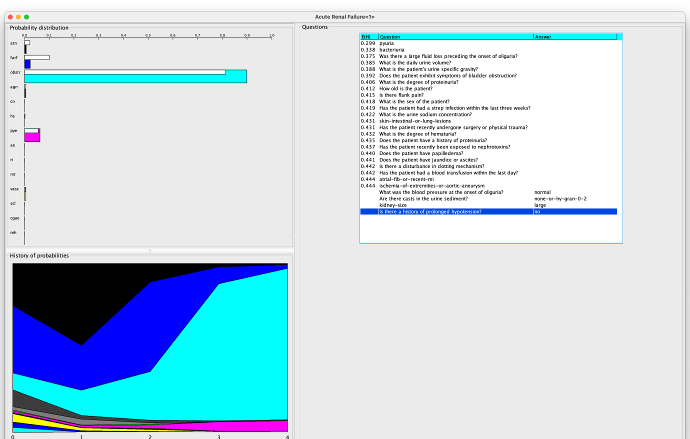


- After the j-th observation,

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

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

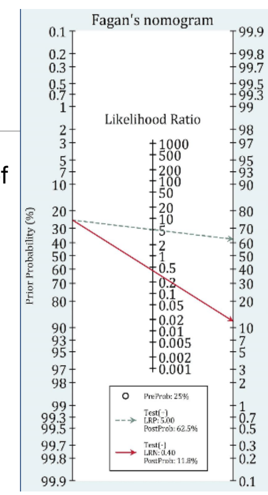
Sequential Diagnosis of Acute Renal Failure



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

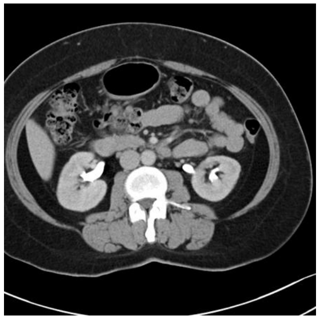


- In gambling, "3-to-1" odds means 75% chance of success
  $O = P/(1-P) = P/\neg P$
- P = 0.5 means O=1
- Likelihood ratio
- Odds-likelihood form of Bayes rule
  $L(S|D) = P(S|D)/P(S|\neg D)$
- Log transform
  $O(D|S_1, \ldots, S_n) = O(D)L(S_1|D)\ldots L(S_n|D)$

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

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

Imaging



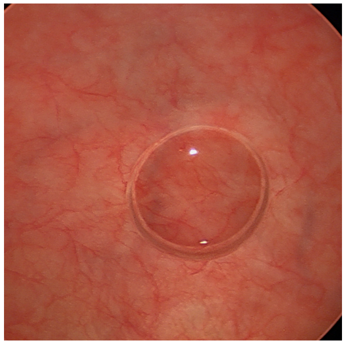
- Sensitivity for stones: 98%
- Sensitivity for kidney cancer: 75%
- Sensitivity for bladder cancer: 2%

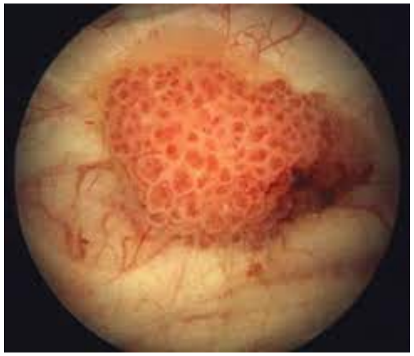
- **How do you explain this to a patient?**

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

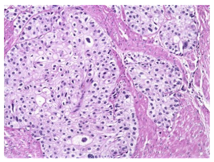
Date of surgery (TURBT)

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:

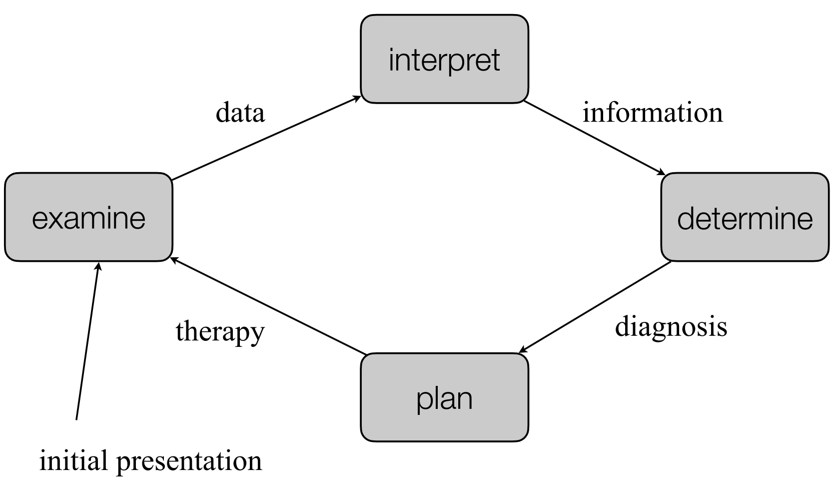
1. Complete staging: CT chest
2. Medical oncology consult

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)
- ≈ 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…

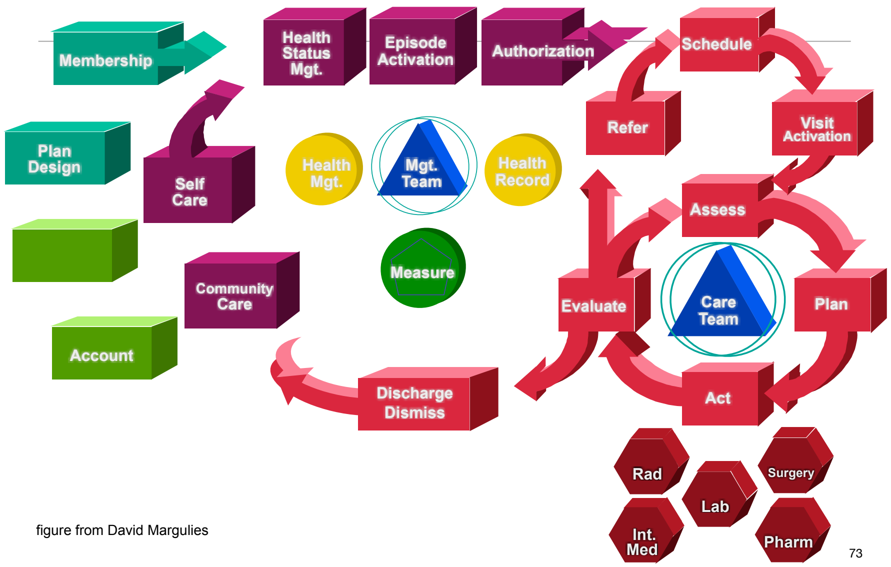
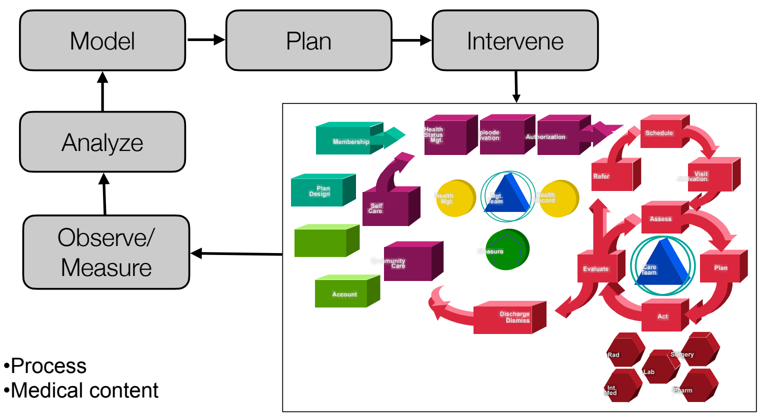


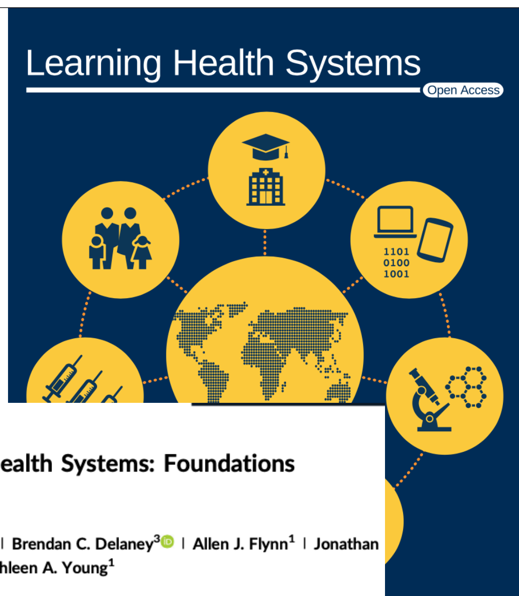
figure from David Margulies

The "Learning Health Care System"



•Process
•Medical content

Volume 1, Issue 1
January 2017



COMMENTARY

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

Charles P. Friedman[1] | Nancy J. Allee[2] | Brendan C. Delaney[3] | Allen J. Flynn[1] | Jonathan C. Silverstein[4] | Kevin Sullivan[5] | Kathleen A. Young[1]

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[2] Taubman Health Sciences Library, University Library and Department of Learning Health Sciences, Medical School, University of Michigan, Ann Arbor, Michigan
[3] Medical Informatics and Decision Making, Imperial College, London, UK
[4] Medical Informatics, Tempus and Kanter Health Foundation, Chicago, Illinois
[5] Department of Computer Science, School of Engineering and Applied Science, University of Virginia, Charlottesville, Virginia

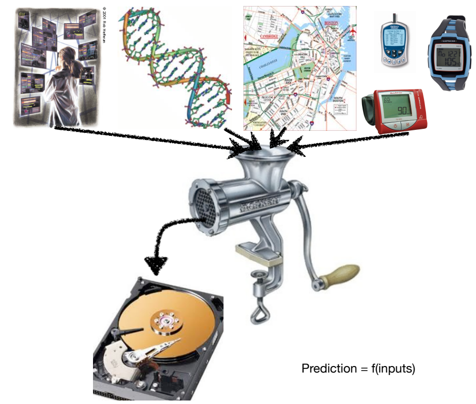
How Does the Health System Learn?

- "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

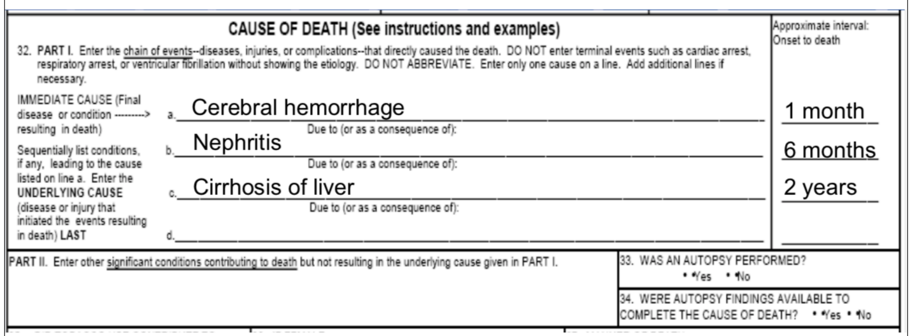
  (Note: pre-Pasteur)
- 1890s—Bertillon (Paris) classification: 161 titles, abstracted to 99, and 44
- 1920 International List of Causes of Death
- 1920s-40s—*Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*
- 1975—ICD-9
- 2015—ICD-10
- ICD-*n* are under 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

https://www.who.int/classifications/icd/en/HistoryOfICD.pdf

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)

32. PART I. Enter the chain of events--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.

		Approximate interval: Onset to death
IMMEDIATE CAUSE (Final disease or condition --------> resulting in death)	a. Cerebral hemorrhage Due to (or as a consequence of):	1 month
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	b. Nephritis Due to (or as a consequence of):	6 months
	c. Cirrhosis of liver Due to (or as a consequence of):	2 years
	d.	

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I.

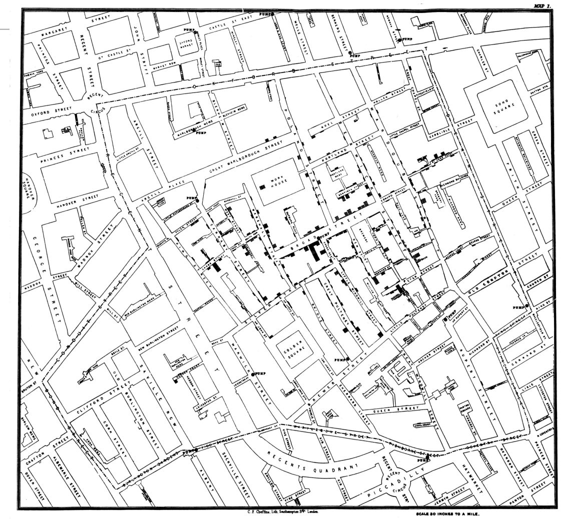
33. WAS AN AUTOPSY PERFORMED? • Yes • No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? • Yes • No

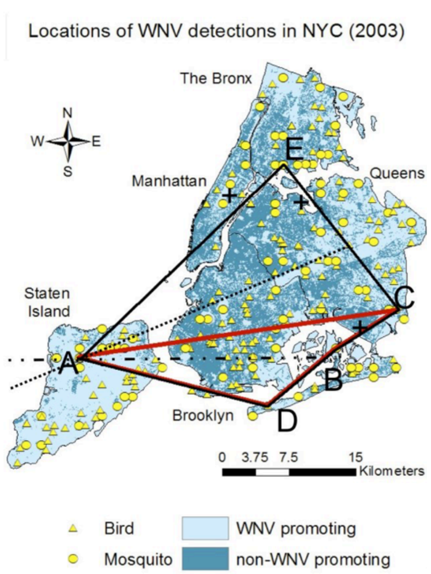
https://www.cdc.gov/nchs/ppt/nchs2012/li-14_minino.pdf

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



https://upload.wikimedia.org/wikipedia/commons/2/27/Snow-cholera-map-1.jpg



https://gisandscience.com/2013/02/11/decelerating-spread-of-west-nile-virus-by-percolation-in-a-heterogeneous-urban-landscape/

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

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

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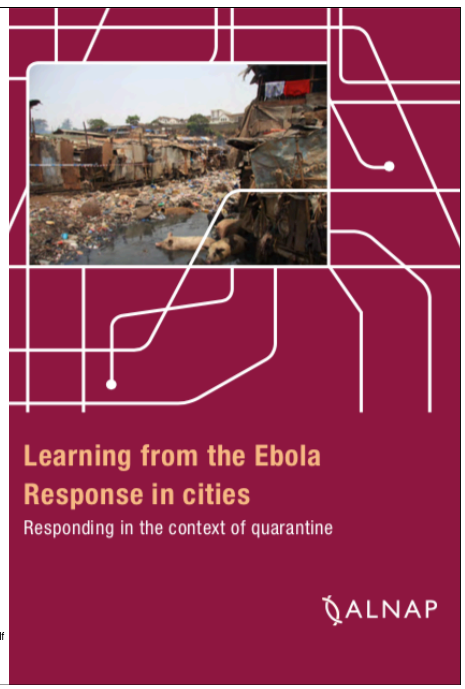
- Highly mobile populations make managing and enforcing quarantine more complex
- Large-scale quarantines result in equally large waste disposal needs and other water, sanitation and hygiene vulnerabilities



https://reliefweb.int/sites/reliefweb.int/files/resources/alnap-urban-2017-ebola-quarantine.pdf

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