AMIA
INFORMATICS PROFESSIONALS. LEADING THE WAY.

2A-1: Clinical Decision-making

Bimal R. Desai, MD, MBI, FAAP, FAMIA
Children's Hospital of Philadelphia

Clinical Informatics
Board Review Course

Clinical Informatics Subspecialty Delineation of Practice (CIS DoP)

Domain 1: Fundamental Knowledge and Skills (no Tasks are associated with this Domain which is focused on fundamental knowledge and skills)

Clinical Informatics

K001. The discipline of informatics (e.g., definitions, history, careers, professional organizations)
K002. Fundamental informatics concepts, models, and theories
K003. Core clinical informatics literature (e.g., foundational literature, principle journals, critical analysis of literature, use of evidence to inform practice)
K004. Descriptive and inferential statistics
K005. Health Information Technology (HIT) principles and science
K006. Computer programming fundamentals and computational thinking
K007. Basic systems and network architectures
K008. Basic database structure, data retrieval and analytics techniques and tools
K009. Development and use of interoperability/exchange standards (e.g., Fast Health Interoperability Resources [FHIR], Digital Imaging and Communications in Medicine [DICOM])
K010. Development and use of transaction standards (e.g., American National Standards Institute X12)
K011. Development and use of messaging standards (e.g., Health Level Seven [HL7] v2)
K012. Development and use of ancillary data standards (e.g., imaging and Laboratory Information System[LIS])
K013. Development and use of data model standards
K014. Vocabularies, terminologies, and nomenclatures (e.g., Logical Observation Identifiers Names and Codes [LOINC], Systematized Nomenclature of Medicine --Clinical Terms [SNOMED-CT], RxNorm, International Classification Of Diseases[ICD], Current Procedural Terminology [CPT])
K015. Data taxonomies and ontologies
K016. Security, privacy, and confidentiality requirements and practices
K017. Legal and regulatory issues related to clinical data and information sharing
K018. Technical and non-technical approaches and barriers to interoperability
K019. Ethics and professionalism

The Health System

K020. Primary domains of health, organizational structures, cultures, and processes (e.g., health care delivery, public health, personal health, population health, education of health professionals, clinical research)
K021. Determinants of individual and population health
K022. Forces shaping health care delivery and considerations regarding health care access
K023. Health economics and financing
K024. Policy and regulatory frameworks related to the healthcare system
K025. The flow of data, information, and knowledge within the health system

Domain 2: Improving Care Delivery and Outcomes

K026. Decision science (e.g., Bayes theorem, decision analysis, probability theory, utility and preference assessment, test characteristics)
K027. Clinical decision support standards and processes for development, implementation, evaluation, and maintenance
K028. Five Rights of clinical decision support (i.e., information, person, intervention formats, channel, and point/time in workflow)
K029. Legal, regulatory, and ethical issues regarding clinical decision support
K030. Methods of workflow analysis
K031. Principles of workflow re-engineering
K032. Quality improvement principles and practices (e.g., Six Sigma, Lean, Plan-Do-Study-Act [PDSA] cycle, root cause analysis)
K033. User-centered design principles (e.g., iterative design process)
K034. Usability testing
K035. Definitions of measures (e.g., quality performance, regulatory, pay for performance, public health surveillance)
K036. Measure development and evaluation processes and criteria
K037. Key performance indicators (KPIs)
K038. Claims analytics and benchmarks
K039. Predictive analytic techniques, indications, and limitations
K040. Clinical and financial benchmarking sources (e.g., Gartner, Healthcare Information and Management Systems Society [HIMSS] Analytics, Centers for Medicare and Medicaid Services [CMS], Leapfrog)
K041. Quality standards and measures promulgated by quality organizations (e.g., National Quality Forum [NQF], Centers for Medicare and Medicaid Services [CMS], National Committee for Quality Assurance [NCQA])
K042. Facility accreditation quality and safety standards (e.g., The Joint Commission, Clinical Laboratory Improvement Amendments [CLIA])
K043. Clinical quality standards (e.g., Physician Quality Reporting System [PQRS], Agency for Healthcare Research and Quality [AHRQ], National Surgical Quality Improvement Program [NSQIP], Quality Reporting Document Architecture [QRDA], Health Quality Measure Format [HQMF], Council on Quality and Leadership [CQL], Fast Health Interoperability Resources [FHIR] Clinical Reasoning)
K044. Reporting requirements
K045. Methods to measure and report organizational performance
K046. Adoption metrics (e.g., Electronic Medical Records Adoption Model [EMRAM], Adoption Model for Analytics Maturity [AMAM])
K047. Social determinants of health
K048. Use of patient-generated data
K049. Prediction models
K050. Risk stratification and adjustment
K051. Concepts and tools for care coordination
K052. Care delivery and payment models

Domain 3: Enterprise Information Systems

K053. Health information technology landscape (e.g., innovation strategies, emerging technologies)
K054. Institutional governance of clinical information systems
K055. Information system maintenance requirements
K056. Information needs analysis and information system selection
K057. Information system implementation procedures
K058. Information system evaluation techniques and methods
K059. Information system and integration testing techniques and methodologies
K060. Enterprise architecture (databases, storage, application, interface engine)
K061. Methods of communication between various software components
K062. Network communications infrastructure and protocols between information systems (e.g., Transmission Control Protocol/Internet Protocol [TCP/IP], switches, routers)
K063. Types of settings (e.g., labs, ambulatory, radiology, home) where various systems are used
K064. Clinical system functional requirements
K065. Models and theories of human-computer (machine) interaction (HCI)
K066. HCI evaluation, usability engineering and testing, study design and methods
K067. HCI design standards and design principles
K068. Functionalities of clinical information systems (e.g., Electronic Health Records [EHR], Laboratory Information System [LIS], Picture Archiving and Communication System [PACS], Radiology Information System [RIS] vendor-neutral archive, pharmacy, revenue cycle)
K069. Consumer-facing health informatics applications (e.g., patient portals, mobile health apps and devices, disease management, patient education, behavior modification)
K070. User types and roles, institutional policy and access control
K071. Clinical communication channels and best practices for use (e.g., secure messaging, closed loop communication)
K072. Security threat assessment methods and mitigation strategies
K073. Security standards and safeguards
K074. Clinical impact of scheduled and unscheduled system downtimes
K075. Information system failure modes and downtime mitigation strategies (e.g., replicated data centers, log shipping)
K076. Approaches to knowledge repositories and their implementation and maintenance
K077. Data storage options and their implications
K078. Clinical registries
K079. Health information exchanges
K080. Patient matching strategies
K081. Master patient index
K082. Data reconciliation
K083. Regulated medical devices (e.g., pumps, telemetry monitors) that may be integrated into information systems
K084. Non-regulated medical devices (e.g., consumer devices)
K085. Telehealth workflows and resources (e.g., software, hardware, staff)

Domain 4: Data Governance and Data Analytics

K086. Stewardship of data
K087. Regulations, organizations, and best practice related to data access and sharing agreements, data use, privacy, security, and portability
K088. Metadata and data dictionaries
K089. Data life cycle
K090. Transactional and reporting/research databases
K091. Techniques for the storage of disparate data types
K092. Techniques to extract, transform, and load data
K093. Data associated with workflow processes and clinical context
K094. Data management and validation techniques
K095. Standards related to storage and retrieval from specialized and emerging data sources
K096. Types and uses of specialized and emerging data sources (e.g., imaging, bioinformatics, internet of things (IoT), patient-generated, social determinants)
K097. Issues related to integrating emerging data sources into business and clinical decision making
K098. Information architecture
K099. Query tools and techniques
K100. Flat files, relational and non-relational/NoSQL database structures, distributed file systems
K101. Definitions and appropriate use of descriptive, diagnostic, predictive, and prescriptive analytics
K102. Analytic tools and techniques (e.g., Boolean, Bayesian, statistical/mathematical modeling)
K103. Advanced modeling and algorithms
K104. Artificial intelligence
K105. Machine learning (e.g., neural networks, support vector machines, Bayesian network)
K106. Data visualization (e.g., graphical, geospatial, 3D modeling, dashboards, heat maps)
K107. Natural language processing
K108. Precision medicine (customized treatment plans based on patient-specific data)
K109. Knowledge management and archiving science
K110. Methods for knowledge persistence and sharing
K111. Methods and standards for data sharing across systems (e.g., health information exchanges, public health reporting)

Domain 5: Leadership and Professionalism

K112. Environmental scanning and assessment methods and techniques
K113. Consensus building, collaboration, and conflict management
K114. Business plan development for informatics projects and activities (e.g., return on investment, business case analysis, pro forma projections)
K115. Basic revenue cycle
K116. Basic managerial/cost accounting principles and concepts
K117. Capital and operating budgeting
K118. Strategy formulation and evaluation
K119. Approaches to establishing Health Information Technology (HIT) mission and objectives
K120. Communication strategies, including one-on-one, presentation to groups, and asynchronous communication
K121. Effective communication programs to support and sustain systems implementation
K122. Writing effectively for various audiences and goals
K123. Negotiation strategies, methods, and techniques
K124. Conflict management strategies, methods, and techniques
K125. Change management principles, models, and methods
K126. Assessment of organizational culture and behavior change theories
K127. Theory and methods for promoting the adoption and effective use of clinical information systems
K128. Motivational strategies, methods, and techniques
K129. Basic principles and practices of project management
K130. Project management tools and techniques
K131. Leadership principles, models, and methods
K132. Intergenerational communication techniques
K133. Coaching, mentoring, championing and cheerleading methods
K134. Adult learning theories, methods, and techniques
K135. Teaching modalities for individuals and groups
K136. Methods to assess the effectiveness of training and competency development
K137. Principles, models, and methods for building and managing effective interdisciplinary teams
K138. Team productivity and effectiveness (e.g., articulating team goals, defining rules of operation, clarifying individual roles, team management, identifying and addressing challenges)
K139. Group management processes (e.g., nominal group, consensus mapping, Delphi method)

Knowledge Statements from the DoP

K026. Decision science (e.g., Bayes theorem, decision analysis, probability theory, utility and preference assessment, test characteristics)

Making Healthcare Decisions

All medical decisions involve uncertainty, many involve risk

- Diagnosis, testing, natural course of disease, effects of treatment are rarely “certain”
- Choosing which variables to consider when making a decision is a challenge

Some factors have characterizable / measurable risk → appeal of decision analysis

Sources of Decision Bias

Diagnostic inference is a problem of “revising opinion with imperfect information” (Hunink, p151)

Blois’ Funnel: Breadth of diagnostic considerations are refined, restricted over course of interaction between patient and practitioner (Blois, 1984)

Making decisions based on opinion is subject to **predictable patterns of bias** based on how humans think

Decision-Making Heuristics and Cognitive Bias

Heuristic: An approach to problem-solving that relies on a practical or simplified method, e.g., a “rule of thumb.” It is not always accurate, which is how heuristics can introduce cognitive bias.

Example: “I” before “E” except after “C” or when sounded like “A” as in “Neighbor” or “Weigh.”

It’s a great heuristic…except for words like "foreign," "counterfeit," "weird," "feisty," etc.

Decision-Making Heuristics and Cognitive Bias

Availability

- Overestimating probability of unusual events because of recent or memorable instances
- “The last patient I saw with symptom X had disease Y, so we should test for Y”

Representativeness

- Overestimating rare diseases by matching patients to “typical picture” of that disease.
- “representative heuristic is insensitive to pretest probabilities” (Hunink, p.151)
- “He has features of the rare disease X, so we should test for it”
- The medical adage “when you hear hoofbeats, think horses, not zebras” is a warning against errors due to this heuristic

Decision-Making Heuristics and Cognitive Bias

Ascertainment bias

- Thinking is shaped by prior expectation
- Examples include stereotyping or gender bias

Confirmation bias

- Tendency to look for confirming evidence rather than disconfirming evidence to refute it.
- “Cherry-picking” results from a large set of negative results

Diagnosis momentum

- Things that are initially diagnostic considerations, as they are passed from clinician to clinician, become “stickier” and more certain

Decision-Making Heuristics and Cognitive Bias

Anchoring

- Failure to adjust probability of a disease or outcome based on new information
- “I was told in sign-out that he had condition X, so I didn’t consider it might be condition Y, despite lab result Z”

Premature closure

- Tendency to accept a diagnosis before it’s fully confirmed
- “When the diagnosis is made, the thinking stops”

Value-induced bias

- Overestimate probability of an outcome based on value associated with that outcome
- Ex: “It would be horrible to miss a brain tumor in this patient with new onset headache, so we should get a head CT”

Defending Against Cognitive Bias

Strategy
Develop insight/awareness
Consider alternatives
Meta-cognition (“thinking about how you think”)
Decrease reliance on memory
Specific training
Simulation
Cognitive forcing strategies
Make task easier
Minimize time pressures
Establish accountability
Feedback about diagnostic errors

Education about cognitive bias is an important defense

Some of these can be aided through EHR design / CDS

- **Decrease reliance on memory** (e.g. orderset for diagnosis of rheumatologic disorders)
- **Cognitive forcing strategies** (e.g. CDS for clinical pathways)
- **Make task easier** (e.g. display of complex information to highlight trends and outliers)

Expected Value vs. Expected Utility

You have a 1:80 chance of winning $1000

- If you gamble and win, you get $1000
- If you gamble and lose, you get nothing.
- If you don't gamble, you are guaranteed $10

Expected value of gambling:

- ($1000 x (1/80)) + ($0 x (79/80)) = **$12.50 (favors gambling, on average)**

Expected utility is a function of value and also risk aversion, personal preferences / circumstances

- If you desperately need $10, you might choose not to gamble
- If you are a risk-taker or have lots of money, you might choose the gamble

Can You Calculate the Expected Value?

Q: What is the expected value of a dice game with the following rules: rolling a single die, you lose $1 if you roll a 1,2,3,4, or 5; but you win $10 if you roll a 6.

A. $0.83
B. $1.50
C. $1.83
D. $2.50

A: The correct answer is "A". The average payout is (5/6 x -1) + (1/6 x 10) = $0.83. Note that there is no way to win $0.83 in a single game – the expected value represents the **prevalence-weighted average** in a range of possible outcomes.

Decision Analysis

Sum of probabilities for outcomes in a given scenario must = 1

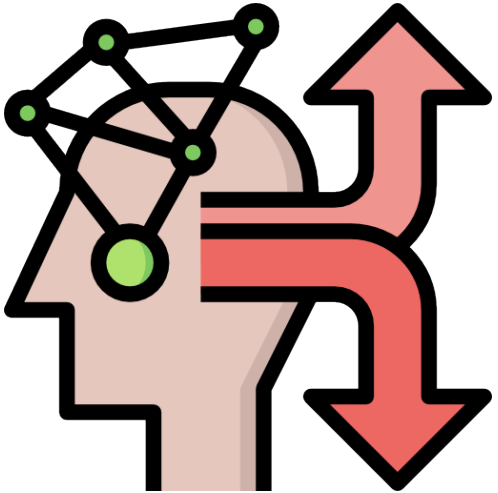
- P(Pregnant) + P(not Pregnant) = 1

Conditional probabilities (“probability of X **given** Y”) notated with vertical pipe

- P(“HIV” | “IV drug use”) = “probability of HIV given IV drug use”

Sequential events can be described as a **chance tree** or graph

This tree can be used to **model a decision** using the sum of the conditional probabilities



Decision Tree Conventions

Decision node is a **square**

Chance node is a **circle**

- each branch assigned a probability (P)
- All branches at a node must add to P = 1

Outcome node is a **triangle**

- Assigned a “value” (cost, utility, QALY, relative value)
- If life or death are the outcomes of interest: life = 1, death = 0

“Rollback analysis” – multiplying the conditional probabilities and comparing the expected value of each branch of a decision node

For a finance example, check out this excellent YouTube tutorial by Joshua Emmanuel

Decision Analysis: Clinical Scenario

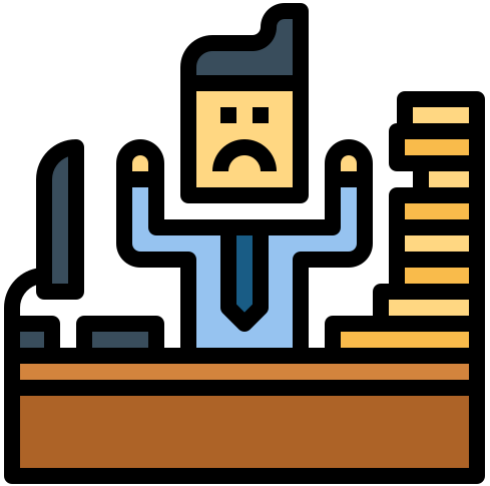
Your patient has Acquired Information Overloadosis

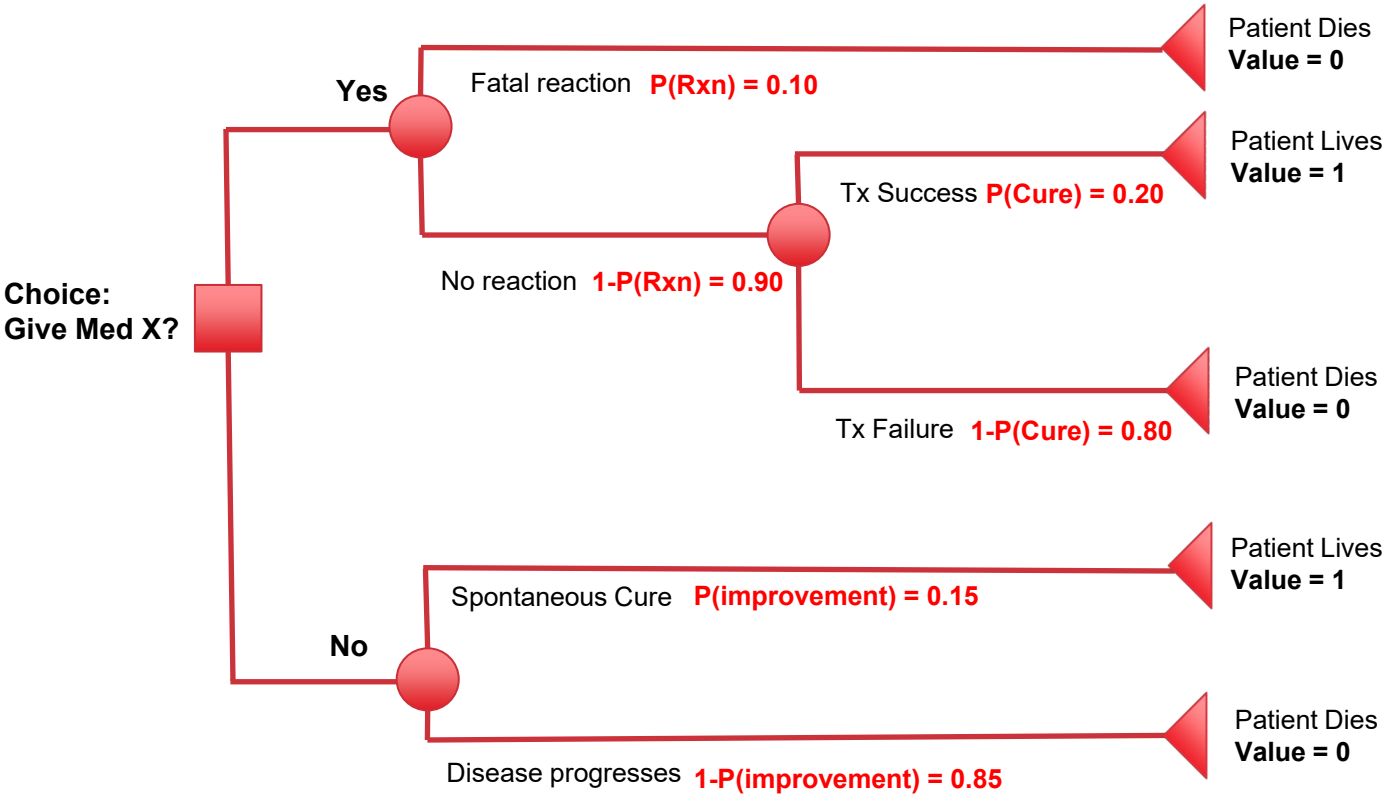
- The disease is fatal in 85% of untreated patients
- The remaining 15% have spontaneous improvement and cure

Treatment X confers modest improvement in outcomes

- When treated with X, survival improves from 15% to 20%
- However, 10% of treated patients have a fatal reaction

Question: Is treatment better than non-treatment?




Choice:
Give Med X?
Yes
Fatal reaction P(Rxn) = 0.10
Patient Dies
Value = 0
No reaction 1-P(Rxn) = 0.90
Tx Success P(Cure) = 0.20
Patient Lives
Value = 1
Tx Failure 1-P(Cure) = 0.80
Patient Dies
Value = 0
No
Spontaneous Cure P(improvement) = 0.15
Patient Lives
Value = 1
Disease progresses 1-P(improvement) = 0.85
Patient Dies
Value = 0

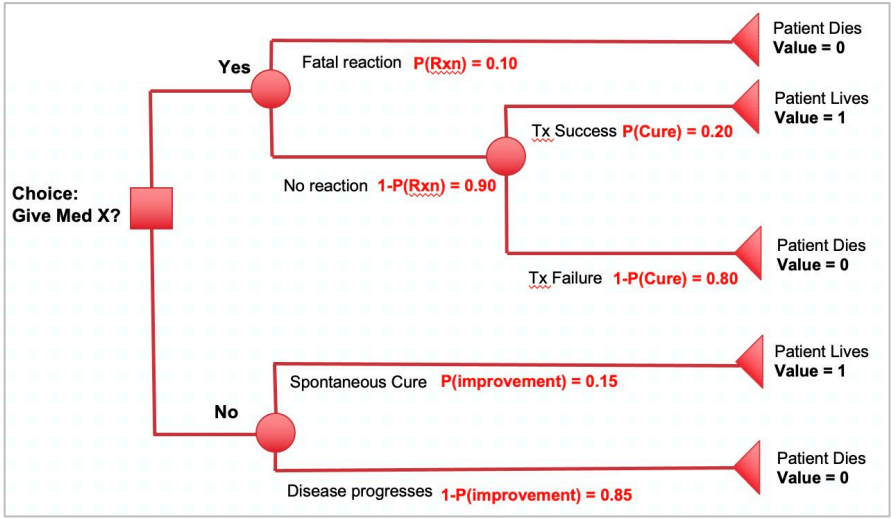
Worked Example

Expected Value of "Yes" branch = 0.18

- Fatal rxn = 0 x 0.1 = 0
- No reaction = ((1 x 0.2) + (0 x 0.8)) x 0.9 = 0.18
- Sum of both = 0 + 0.18 = **0.18**

Expected Value of "No" branch = 0.15

- Cure = 1 x 0.15 = 0.15
- Progression = 0 x 0.85 = 0
- Sum of probabilities of both = 0.15 + 0 = **0.15**



Model very slightly favors giving X despite 10% chance of fatal reaction

Other Applications

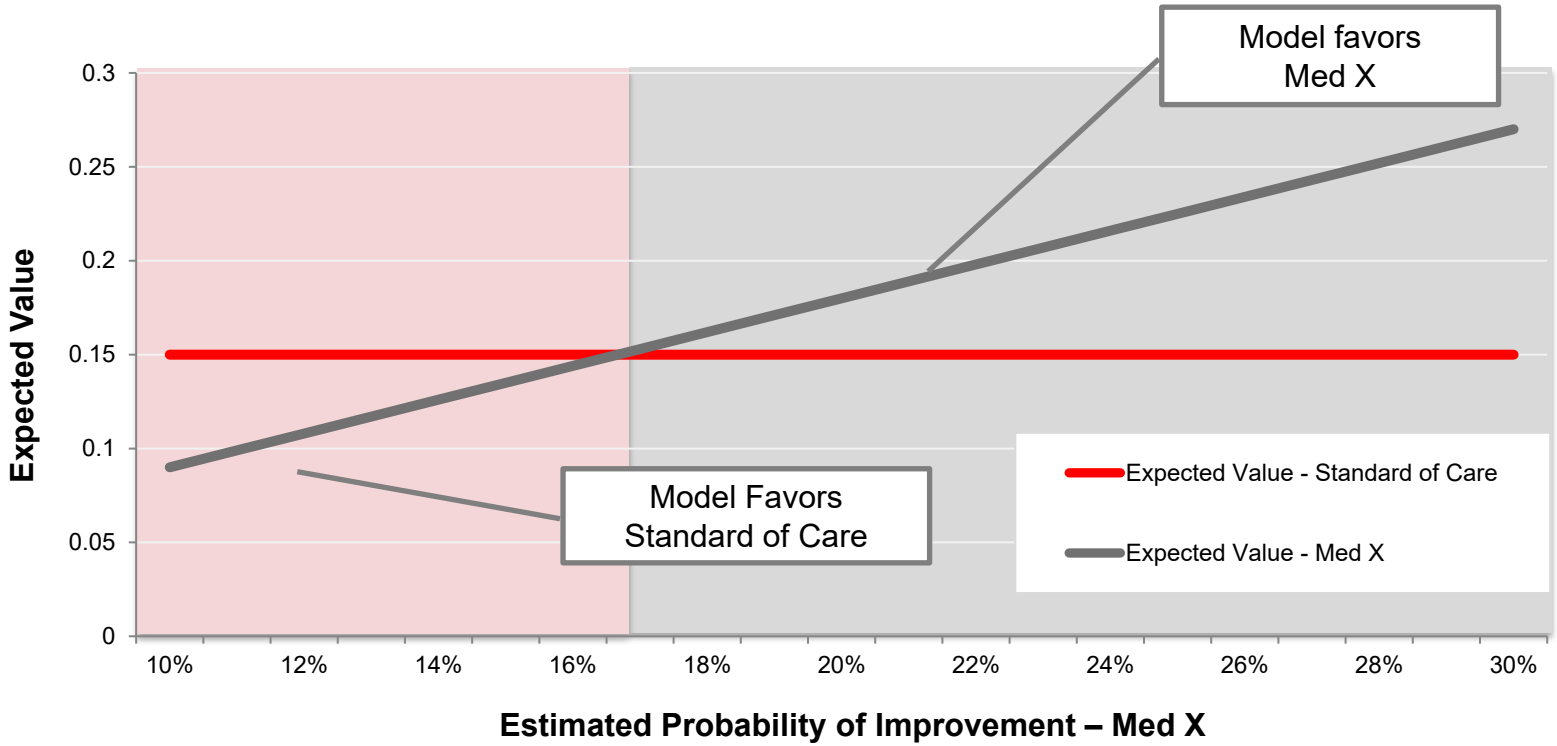
“What-if” or sensitivity analysis

- Use a range of values to see how model changes
- “What if the probability of treatment success due to med X is somewhere between 10% and 30%? At what threshold does the therapy become too risky?”

Cost effectiveness analysis

- The “value” of outcome nodes becomes units of cost instead of the values used in our example (Life = 1 / Death = 0)

Sensitivity Analysis



Incorporating Patient Preferences and Utility

Often required to assign values to outcomes – two outcomes may not have same effectiveness or impact on quality of life (eg: surgical debulking vs. chemotherapy vs. palliation)

The numerically favorable therapy is not the one the patient always prefers.

- **Therapy A:** 50% chance of 10-year survival
  - Expected value = 5 years
- **Therapy B:** 90% chance of 2-year survival
  - Expected value = 1.8 years
- **Therapy C:** 100% chance of 6-month survival with severe, debilitating pain
  - Expected value = -1 year

Quantifying Patient Utility

Can be used in decision analysis to define the “value” of an outcome node. You adjust the value of the outcome based on the perceived utility of that outcome for that patient.

Common approaches:

- **Standard gamble**
  - Choose between X time in state of illness vs. therapy with a known risk of cure or death
- **Time trade-off**
  - Choose between X time in state of illness vs. Y time in state of perfect health
- **Visual analogue**
  - Rate different health states on a scale where 0 = death, 100 = perfect health

Quality-Adjusted Life Year (QALY)

QALY are often calculated using **Time Trade-off**

- Ask the patient “Imagine living 10 years in your current state of health. Now imagine living for less than 10 years, but in a perfect state of health. How many years of perfect health do you believe are equal to 10 years of your current state of health?”
- Another way of asking “how many years of your current life would you trade to live in perfect health?”, which is a way to ascertain what utility they assign their current state of health
- Suppose patient says 4 years of perfect health = 10 years of current illness. TTO = 0.4
- Therefore, 3 years in current state = 3 x 0.4 = **1.2 QALY**
- **For many patients, there are states of health that are worse than death, so it is possible for QALY to have a negative value**

Cost Effectiveness Analysis

How do health systems / governments choose which therapies to cover?

One example: UK – National Institute for Health and Clinical Excellence (NICE) uses QALY as part of cost-effectiveness analysis to choose pharmaceutical options

Knowing cost and utility/value of an outcome allows you to calculate the **Incremental Cost/Effectiveness Ratio (ICER)**

- Compare calculated ICER to the "willingness to pay" to determine if a therapy is cost effective and worth implementing.

Is specialist management +/- natriuretic peptide testing recommended for treatment of acute heart failure?

"a specialist heart failure management service was cost-effective compared with standard management for patients presenting to the emergency department with acute dyspnoea.

- *In a context of NP testing: ICER= £3,159 per QALY gained*
- *In a context of no NP testing: ICER= £3,047 per QALY gained"*

Note: both are below the NICE definition of willingness to pay for 1 QUALY, roughly £20,000 – £30,000

Incremental Cost Effectiveness Ratio (ICER)

ICER is a measure of the change in cost with change in a unit of effectiveness (like 1 QALY or 1 avoided admission)

ICER = (C1 – C2) / (E1 – E2) ← *note that this is the formula for the slope of a line*

- *Steep positive slope = expensive intervention*
- *Relatively flat slope = inexpensive intervention*
- *Negative slope = cost-saving intervention*

Ex: Isetta V et al. **Cost-effectiveness of a new internet-based monitoring tool for neonatal post-discharge home care.** J Med Internet Res. 2013 Feb 18;15(2):e38. [Abstract]

- Comparing hospital-based neonatal follow-up to web-based follow-up with screening tool

ICER / Cost Effectiveness Example

Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	ICER
Internet Follow-up	€86.1		0.944		
Hospital Visit	€182.1	**€+96.0**	0.842	**-0.102**	**€-941.2**

- One unit of effectiveness was defined as one avoided visit to the ED within the first month of life.
- Hospital is €96 more expensive and 0.102 units less effective than Internet, so ICER is **negative €941, a cost-saving intervention compared to standard of care.**
- i.e., using the internet strategy, society would save **€**941 per avoided ED visit in the 1st month of life.

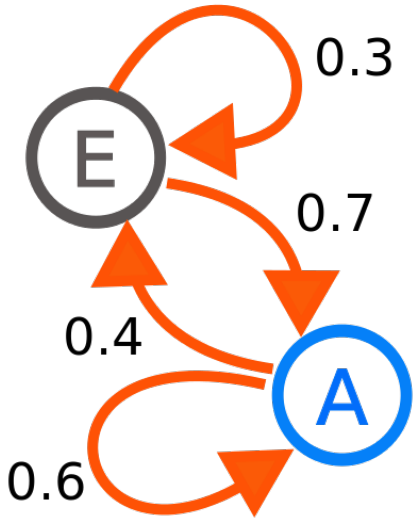
Markov Models

Decision tree assumes a linear sequence – you only move in one direction on the tree.

What if transitions between states are bidirectional or recursive?

Markov Chain

- Chain of events, each with a known, fixed probability of transition in a defined time period (aka “discrete time Markov Chain”)
- “stochastic” (random)
- 1st order chain is “memoryless” (next state doesn’t depend on prior state, only depends on present state)



Two-state Markov chain, courtesy Wikipedia

Markov Models and the Hungry, Sleepy Colony

In this example, there are two discrete states “E” and “A”, visualized as a directed graph, in which the sum of transition probabilities (the “outbound arrows” from each state) = 1

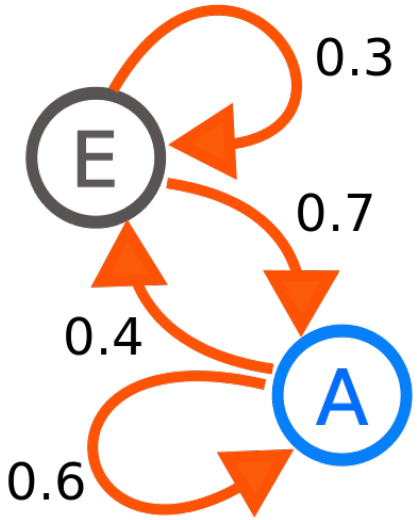
Imagine an animal that spends its life in 1 of 2 states: either Eating (E) or Asleep (A)

Now imagine you have 100 of these creatures, all eating at one point in time (t_0)

How many would be eating (E) and asleep (A) after one period of time (t_1)?

It’s intuitive that at time “t_1” there will be roughly 30 eating, 70 asleep

What about “t_2” and beyond?

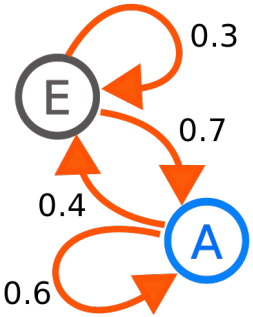


Two-state Markov chain, courtesy Wikipedia

Markov Models and Matrix Math

Represent the states transitions as a 2x2 Markov (aka stochastic) matrix

	$E(t_{n+1})$	$A(t_{n+1})$
$E(t_n)$	0.3	0.7
$A(t_n)$	0.4	0.6



This matrix represents our 2-state graph

Rows must add to 1 and values must be non-negative

Rows labels represent state at time “n”, columns labels represent state at time “n+1”

Values represent probability of transition from one state to another in the discrete time period

- 1st row show probability that E→E (which is 0.3) and E→A (which is 0.7)
- 2nd row shows probability that A→E (which is 0.4) and A→A (which is 0.6)

Matrix Math: Calculating the State Vector for t_1

We define a 1x2 state vector that represents a starting state where 100% of animals are eating (E) and 0% are asleep (A)

$E(t_0)$ $A(t_0)$

$[\mathbf{1} \quad \mathbf{0}]$ at time "t_0"

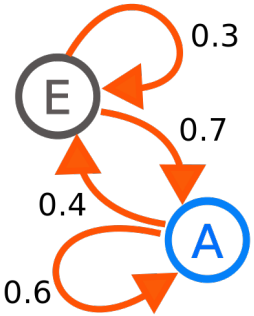
Multiplying our **state vector** by the **stochastic matrix** gives us a vector with the probability of the next state (t_1).

Multiply each row value in the state vector by the column value in the stochastic matrix

$$[1 \quad 0] \times \begin{bmatrix} 0.3 & 0.7 \\ 0.4 & 0.6 \end{bmatrix} =$$

$$[(1 * 0.3) + (0 * 0.4) \quad (1 * 0.7) + (0 * 0.6)] = [\mathbf{0.3} \quad \mathbf{0.7}] \text{ at } \mathbf{t_1}$$

So at t_1, there's a 30% probability the animals will be eating and a 70% probability they will be asleep. For t2 and beyond, we repeat the calculation, starting with the new vector.



Matrix Math: Calculating the State Vector for t2, t3

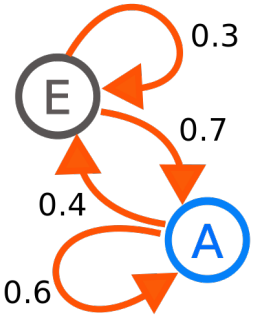
Multiply probability vector at each time "t_n" to get probability at "t_{n+1}"

$$\begin{bmatrix} 0.3 & 0.7 \\ 0.4 & 0.6 \end{bmatrix} \text{x} [0.3 \quad 0.7] =$$

$$[(0.3 * 0.3) + (0.7 * 0.4) \quad (0.3 * 0.7) + (0.7 * 0.6)] = [0.37 \quad 0.63] \text{ at } t_2$$

$$\begin{bmatrix} 0.3 & 0.7 \\ 0.4 & 0.6 \end{bmatrix} \text{x} [0.37 \quad 0.63] =$$

$$[(0.37 * 0.3) + (0.63 * 0.4) \quad (0.37 * 0.7) + (0.63 * 0.6)] = [0.36 \quad 0.64] \text{ at } t_3$$



So after 3 cycles (t_3), **P(E)=0.36, and P(A)=0.64** – note that this model converges at a steady state

What are the applications to healthcare and informatics?

- Examples: Modeling of disease progression over time. Cost-effectiveness analysis.

Modeling Disease Progression Over Time

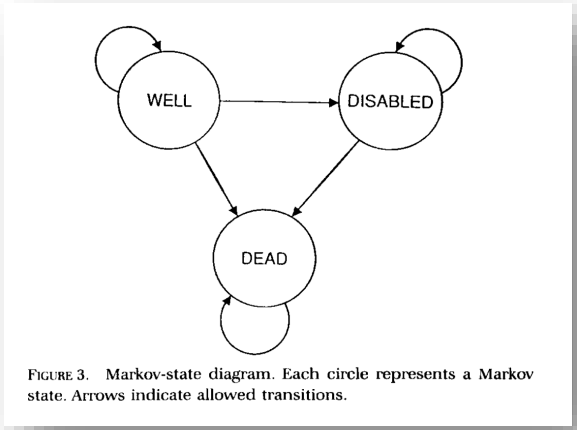


FIGURE 3. Markov-state diagram. Each circle represents a Markov state. Arrows indicate allowed transitions.

Table 1 • P Matrix

		To		
		WELL	DISABLED	DEAD
From	WELL	0.6	0.2	0.2
	DISABLED	0	0.6	0.4
	DEAD	0	0	1

Imagine a disease with 3 states, known probability of transition.

Death is an **"absorbing"** state (you can't move out of that state).

Disability is a **"tunnel"** state (you only move in one direction through this state).

Modeling Disease Progression Over Time

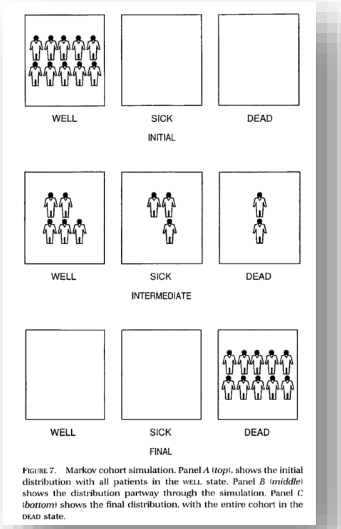


FIGURE 7. Markov cohort simulation. Panel *A* (*top*), shows the initial distribution with all patients in the WELL state. Panel *B* (*middle*) shows the distribution partway through the simulation. Panel *C* (*bottom*) shows the final distribution, with the entire cohort in the DEAD state.

Table 2 • Markov Cohort Simulation

Cycle	WELL	DISABLED	DEAD	Cycle Sum	Cumulative Utility
Start	10,000	0	0	—	—
1	6,000	2,000	2,000	7,400	7,400
2	3,600	2,400	4,000	5,280	12,680
•	•	•	•	•	•
•	•	•	•	•	•
23	0	1	9,999	7	23,752
24	0	0	10,000	<1	23,752
Total	15,000	12,500		23,752	23,752

We can simulate what happens to a cohort of 10,000 patients over time.

If you know the utility of each state, you can estimate the cumulative utility for things like QALY

Other Applications: User Interface Analysis

Research Article ■

An Interface-driven Analysis of User Interactions with an Electronic Health Records System

KAI ZHENG, PHD, REMA PADMAN, PHD, MICHAEL P. JOHNSON, PHD, HERBERT S. DIAMOND, MD

Abstract **Objectives:** This study sought to investigate user interactions with an electronic health records (EHR) system by uncovering hidden navigational patterns in the EHR usage data automatically recorded as clinicians navigated through the system's software user in

Design: A homegrown EHR was adapted to allow real-tir
These events, constituting time-stamped event sequences,
patient care settings. The study site is an ambulatory prim
medicine residents were the primary EHR users.

Measurements: Computer-recorded event sequences reflec
sequentially accessed.

Methods: We apply sequential pattern analysis (SPA) and
UI navigational patterns.

Results: Of 17 main EHR features provided in the system
Plan" and "Diagnosis," "Order" and "Medication," and "(
these paired features in a bundle together in a continuous
navigational pathway, suggesting an overall sequential or
followed by "Social History" and then "Assessment and P
navigational pathways commonly traversed by the EHR u

Conclusion: Users showed consistent UI navigational patt
designers or the clinic management. Awareness of such u
behavior as well as reengineering opportunities for impro

■ **J Am Med Inform Assoc.** 2009;16:228–237. DOI 10.1197

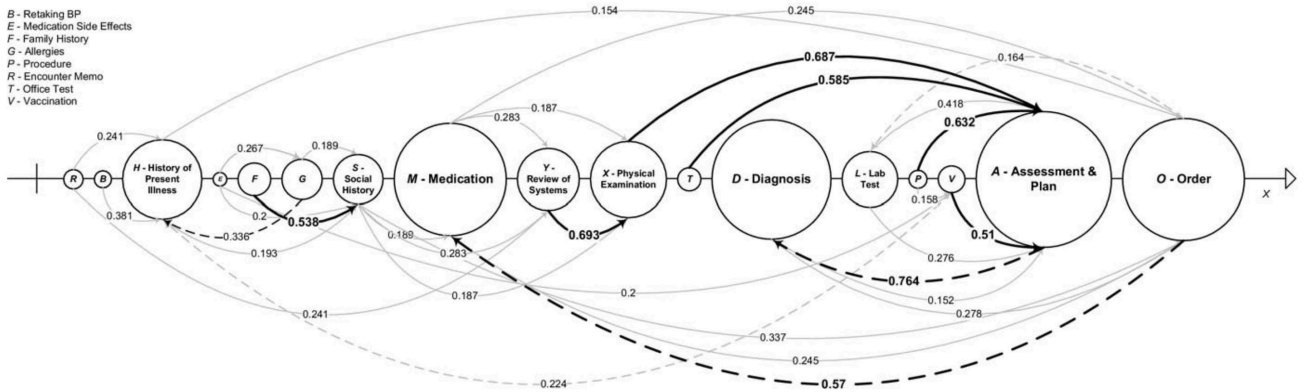


Figure 3. The feature transition probability matrix plotted as a network graph (the 17 features are horizontally positioned according to their sequential placement on the EHR's UI. Size of a node is proportional to the feature's overall frequency of use. Feature transitions with a probability lower than 0.15 are not shown. Bold arcs = transitions with a probability over 0.5; dashed arcs = nonadjacent feature transitions running counter to the default UI layout.

Other Applications: Modeling Vaccine Economics

Original Article

Economic evaluation for mass vaccination against COVID-19

Wei-Chun Wang [a], Jean Ching-Yuan Fann [b], Ray-E Chang [c], Ya-Chung Jeng [d], Chen-Yang Hsu [a,e], Hsiu-Hsi Chen [a], Jin-Tan Liu [f], Amy Ming-Fang Yen [d,*]

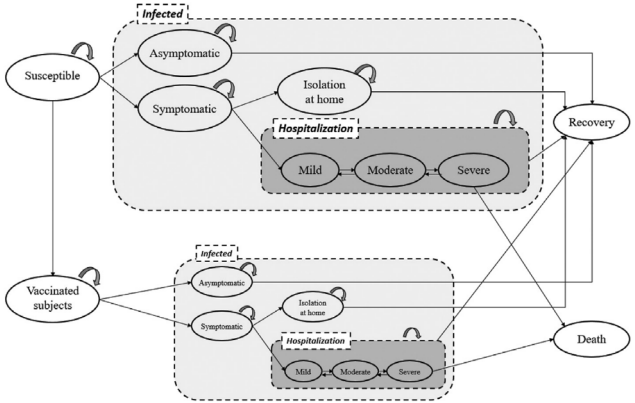


Figure 1 The structure of the Markov decision tree for the cost-effectiveness analysis for COVID-19 vaccination.

Table 1 Base-case estimates for cost-effectiveness analysis.

Variables	Base-case estimate	Distribution	Reference/source
Initial probability of state			
Initial probability of asymptomatic	0.000263798		
Initial probability of symptomatic	0.001055192		
Proportion of asymptomatic	17%	Beta(111,552)	Byambasuren et al., 2020
Transition probability of state			
Transmission duration (days)	7		
Proportion of hospitalization	15%		Jen et al., 2021
COVID-19 Clinical progression during hospitalization			
Low risk			Jen et al., 2021
Recovery	12.2%	Dirichlet*	
Medium risk	8.8%	(776,88,14,122,0.2)	
High risk	1.4%		
Death	0.02%		
Medium risk			
Recovery	2.6%	Dirichlet* (267,516,187,2	
Low risk	26.7%	6,4)	
High risk	18.7%		
Death	0.4%		
High risk			
Recovery	0.2%	Dirichlet*(17,76,871,2,34)	
Low risk	1.7%		
Medium risk	7.6%		
Death	3.4%		
Efficacy of vaccine (%)			
For symptomatic cases			
Moderna	94.1 (89.3–96.8)		Baden (2021)
Pfizer	95.0 (90.3–97.6)		Polack (2020)
AstraZeneca	70.4 (54.8–80.6)		Voysey (2021)
For asymptomatic cases			
Moderna	61.8 (30.7–78.9)		Baden et al. (2021)
Pfizer	52.4 (29.5–68.4)		Polack et al. (2020)
AstraZeneca (UK arm)	27.3 (−17.2 −54.9)		Voysey (2021)
Adverse effects of vaccine (%)			
Moderna	27.4	Beta(2281,12396)	Baden et al. (2021)
Pfizer	27.0	Beta(2619, 16241)	Polack et al. (2020)
AstraZeneca	33.6	Beta(4039,7982)	
Utility			
Isolation at home	0.81		Kohli et al. (2021)
Hospitalization			
Low risk	0.70		
Medium risk	0.50		
High risk	0.40		

Citation: Wang WC, Fann JC, Chang RE, Jeng YC, Hsu CY, Chen HH, Liu JT, Yen AM. Economic evaluation for mass vaccination against COVID-19. J Formos Med Assoc. 2021 Jun;120 Suppl 1:S95-S105.

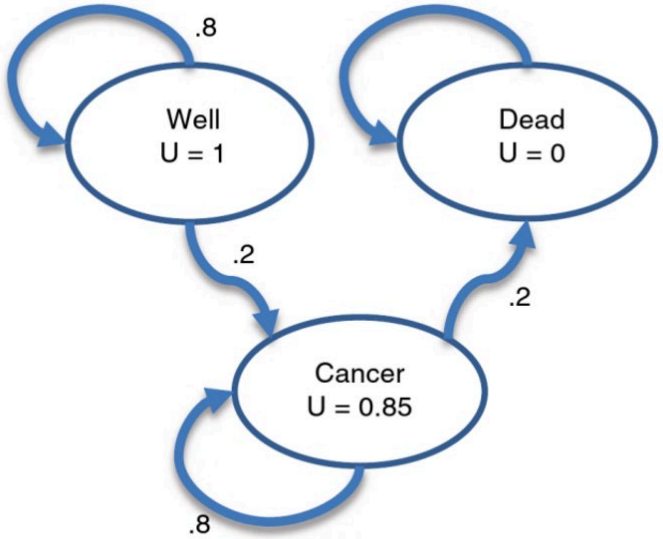
Class Exercise: Modeling Outcomes of Cancer Therapy

Here is a Markov model of patients treated for a specific type of cancer.

There are three possible outcomes after induction: remission (“Well”), relapse (“Cancer”), and death.

The Markov model shows probability of transition between these states in a time period of one year.

(coincidentally, the “U” refers to “utility” of each state, but we’re not using that in this example)

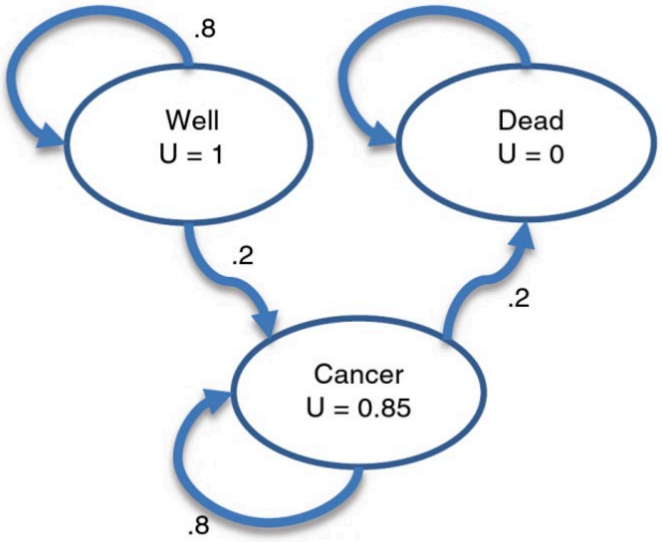


Question: In a cohort of patients, 90% are in remission (“Well”) and 10% have relapsed cancer (“Cancer”). After 2 years, what percent of patients are expected to have relapsed cancer?

Image credit: Downs SM and Johns LK in Clinical Informatics Study Guide. Finnell JT, Dixon BE Eds. Springer 2016

Class Exercise: Modeling Outcomes of Cancer Therapy

Cycle	State	Probability
t_0	Well	0.9
	Cancer	0.1
	Dead	0
t_1	Well	(0.9*0.8) = 0.72
	Cancer	(0.9*0.2)+(0.1*0.8) = 0.26
	Dead	(0.1*0.2)+(0*1.0)=0.02
t_2	Well	(0.72*0.8) = 0.576
	Cancer	(0.72*0.2)+(0.26*0.8)= **0.352**
	Dead	(0.26*0.2)+(0.02*1.0) = 0.072



Answer: after 2 years, 35% of the cohort is expected to have cancer.

Because they're memoryless…get it?

Q: Why do Markov Chains make the worst Christmas guests?

A: They only care about the present.

Monte Carlo Simulation

Mathematical models can be **deterministic** or **stochastic**

- **Deterministic** = variable states determined by parameters set in the model, so model always performs the same under given set of assumptions. The inputs determine the output.
- **Probabilistic / Stochastic** = variable states are determined by probability or random distributions, so model may produce different results each time you run the model

Monte Carlo Simulation is a **stochastic** model

- Technique involves running many simulations to estimate the variable state
- It's counterintuitive, but you can use randomness to measure things. See the **SUPPLEMENT** for an example of how you can measure the area of something using random ball drops.

Examples in Healthcare

Useful for disease simulation, especially in smaller populations where patients may not tend to the “average”

Variables used to simulate an individual patient’s pattern of disease progression and responsiveness to treatment

Output is a probability distribution (with confidence intervals) for things like functional status, QALY, cost, etc.

Source: Richter, A. and Mauskopf, J. (1998), MM1 Monte Carlo Simulation in Health Care Models. Value in Health, 1: 84–85. [Abstract]

Examples in Healthcare

A Monte Carlo simulation estimating US hospital cost reductions associated with hypotension control in septic ICU patients

Eric L. Keuffel, Mitali Stevens, Candace Gunnarsson, John Rizzo, Daniel I. Sessler & Kamal Maheshwari

Methods: A Monte Carlo simulation decision analytic model was developed that accounted for the probability of complications—acute kidney injury and mortality—in septic ICU patients and the cost of each health outcome from the hospital perspective. Probabilities of complications were calculated based on observational data from 110 US hospitals for septic ICU patients ($n = 8{,}782$) with various levels of hypotension exposure as measured by mean arterial pressure (MAP, units: mmHg). Costs for acute kidney injury (AKI) and mortality were derived from published literature. Each simulation calculated mean hospital cost reduction and 95% confidence intervals based on 10,000 trials.

Citation: Keuffel EL, Stevens M, Gunnarsson C, Rizzo J, Sessler DI, Maheshwari K. A Monte Carlo simulation estimating US hospital cost reductions associated with hypotension control in septic ICU patients. J Med Econ. 2019;22(4):383-389. doi:10.1080/13696998.2019.1576695

Smarter Than the “Average” Duck…

Three biostatisticians are out duck hunting when they suddenly see a duck!

The first biostatistician takes aim and fires, but the bullet misses by one foot to the left.

The second biostatistician takes aim and fires, missing the duck by one foot to the right.

The third biostatistician exclaims, “Nice job! We got him!”

Your well-earned moment of Zen…

Diagnostic Tests and 2x2 Contingency Tables

What questions do we care about related to diagnostic tests?

How to choose a diagnostic test

(is the test any good?)

- What is likelihood of positive test if disease is present?
- What is likelihood of negative test if disease is absent?

How to interpret a diagnostic test

(does the test have utility in clinical practice?)

- What is likelihood of disease if test is positive?
- What is likelihood of no disease if test is negative?

Understanding the 2x2 Contingency Table

2x2 contingency table allows us to answer these questions

		Disease State: Disease +	Disease State: Disease -	
Test Result	Test +	**A** True Positive	**B** False Positive	**(A+B)** Everyone with positive test
	Test -	**C** False Negative	**D** True Negative	**(C+D)** Everyone with negative test
		(A+C) Everyone with disease	**(B+D)** Everyone without disease	**(A+B+C+D)** Everyone

Understanding the 2x2 Contingency Table

- By convention, probability of an event **X** is noted as “P(**X**)”
- Probability of **X** given **Y** is noted as “P(**X** | **Y**)” – this is known as a “conditional probability”.

	D +	D -	
T +	**A** TP	**B** FP	**(A+B)**
T -	**C** FN	**D** TN	**(C+D)**
	(A+C)	**(B+D)**	**(A+B+ C+D)**

P(Disease) =

prevalence in sample population

(Everyone with disease)/ (Everyone in sample population)

(A+C) / (A+B+C+D)

Understanding the 2x2 Contingency Table

P(no disease) =

(B+D) / (A+B+C+D)

P(test +) =

(A+B) / (A+B+C+D)

P(test -) =

(C+D) / (A+B+C+D)

	D +	D -	
T +	**A** TP	**B** FP	**(A+B)**
T -	**C** FN	**D** TN	**(C+D)**
	(A+C)	**(B+D)**	**(A+B+ C+D)**

Understanding the 2x2 Contingency Table

What is the **True Positive Rate**?

P(test + | disease +) = TPR = A / (A+C)

What is the **False Negative Rate**?

P(test - | disease +) = FNR = C / (A+C) or 1-TPR

What is the **True Negative Rate**?

P(test - | disease -) = TNR = D / (B+D)

What is the **False Positive Rate**?

P(test + | disease -) = FPR = B / (B+D) or 1-TNR

	D +	D -	
T +	**A** TP	**B** FP	**(A+B)**
T -	**C** FN	**D** TN	**(C+D)**
	(A+C)	**(B+D)**	**(A+B+ C+D)**

Sensitivity = True Positive Rate

Sensitivity = True Positive Rate

- P(test + | disease +) = A / (A+C)
- Conditional probability: **“given the patient has disease, what is the likelihood the test will be positive?”**

1-sensitivity = False Negative Rate

- **Very sensitive tests have low false negative rate**
- Therefore, sensitive tests are good for **ruling out disease** (you can trust a negative result)
- Therefore, sensitive tests are good **screening tests**

SeNsitivity = rule OUT

“SNOUT”

	D +	D -	
T +	**A** TP	**B** FP	**(A+B)**
T -	**C** FN	**D** TN	**(C+D)**
	(A+C)	**(B+D)**	**(A+B+ C+D)**

Specificity = True Negative Rate

Specificity = True Negative Rate

- P(test - | disease -) = D / (B+D)
- Conditional probability: “given the patient has no disease, what is the likelihood the test will be negative?”

1-specificity = False Positive Rate

- **Very specific tests have low false positive rate**
- Specific tests are good for **ruling in disease** (you can trust a positive result)
- Specific tests are good **confirmatory tests**

SPecificity = rule IN

“SPIN”

	D +	D -	
T +	**A** TP	**B** FP	**(A+B)**
T -	**C** FN	**D** TN	**(C+D)**
	(A+C)	**(B+D)**	**(A+B+ C+D)**

Sensitivity and Specificity

- Both are **conditional probabilities**
- Both assume you know the **disease state**, not the test result.
- As such, they are measures of the **test performance**, not measures of test utility → used for test selection
- Sensitivity and specificity are **independent of rate of disease** in the population.
- There is a **tradeoff between sensitivity and specificity**: you can increase sensitivity at the expense of specificity and *vice versa*.

	D +	D -	
T +	**A** TP	**B** FP	**(A+B)**
T -	**C** FN	**D** TN	**(C+D)**
	(A+C)	**(B+D)**	**(A+B+ C+D)**

What if We Know the Test Result?

If you know the test result and are trying to determine disease state (e.g. how to interpret a result), Sensitivity and Specificity are not the correct measures.

Instead, you need a different set of conditional probabilities:

- What is likelihood of **disease** if test is **positive**?
- What is likelihood of **no disease** if test is **negative**?

•Fortunately, these are easy to derive, and they have their own names!

	D +	D -	
T +	**A** TP	**B** FP	**(A+B)**
T -	**C** FN	**D** TN	**(C+D)**
	(A+C)	**(B+D)**	**(A+B+ C+D)**

Positive Predictive Value

Positive Predictive Value

- P(disease + | test +) = A / (A+B)
- “given a positive test, what is the likelihood of disease”

Note that PPV depends on likelihood of disease in population

	D +	D -	
T +	**A** TP	**B** FP	**(A+B)**
T -	**C** FN	**D** TN	**(C+D)**
	(A+C)	**(B+D)**	**(A+B+ C+D)**

Negative Predictive Value

Negative Predictive Value

- P(disease - | test -) = D/(C+D)
- “given a negative test, what is the likelihood of no disease”

Note that NPV depends on likelihood of disease in population

	D +	D -	
T +	**A** TP	**B** FP	**(A+B)**
T -	**C** FN	**D** TN	**(C+D)**
	(A+C)	**(B+D)**	**(A+B+ C+D)**

Summary: Sensitivity, Specificity, PPV, NPV

Measures of Test Performance

Sensitivity = TPR = Recall

- Likelihood of positive test given disease
- Good for screening for disease
- Low false negative rate

Specificity = TNR

- Likelihood of negative test given no disease
- Good for confirming disease
- Low false positive rate

Measures of Clinical Utility of a Test

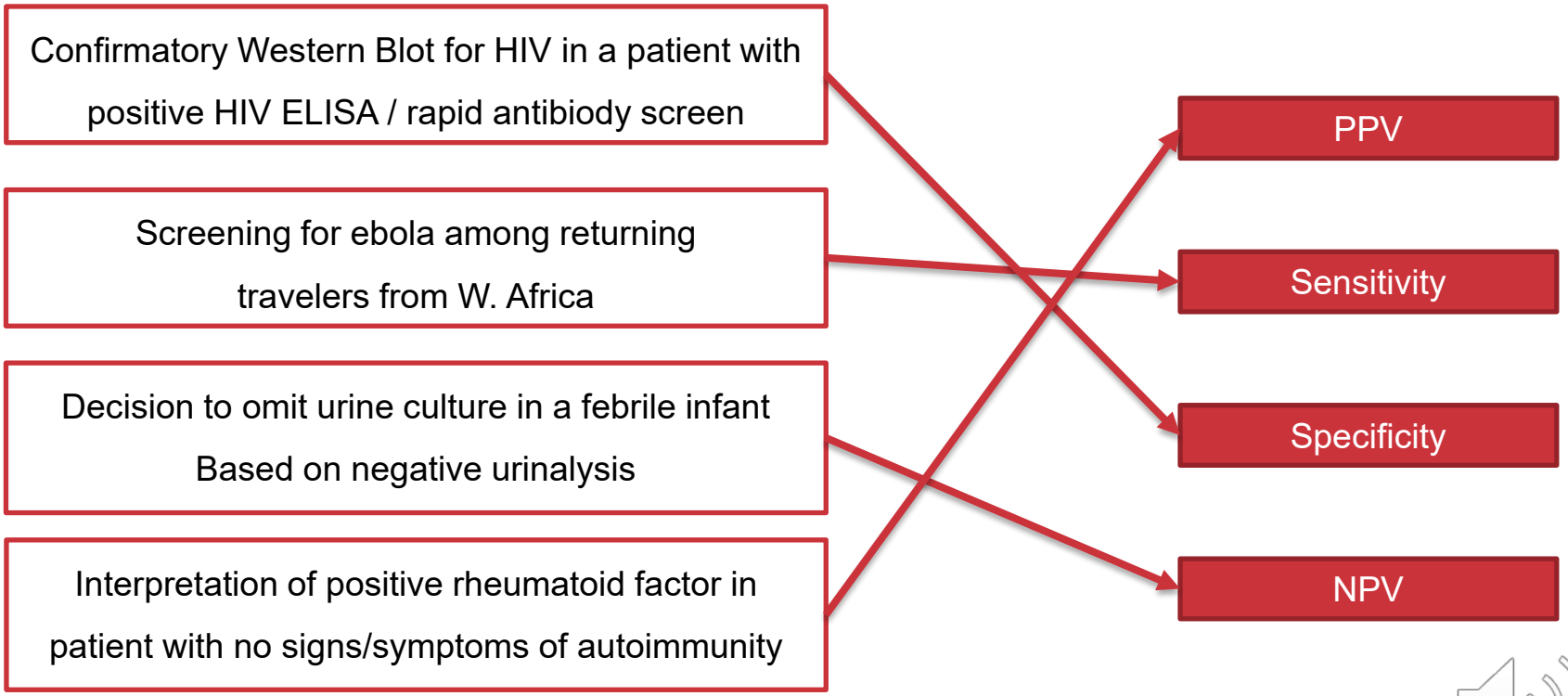
Positive Predictive Value = Precision

- Likelihood of disease given positive test

Negative Predictive Value

- Likelihood of no disease given negative test

Class Exercise:
Match the Scenario to the Relevant Statistic



Class Exercise: Interpreting Urinalysis Results

- 1998 study looking at performance of various UTI screening strategies in infants
- A “positive urinalysis” (defined as > trace Leukocyte Esterase OR + nitrites) had the following test characteristics:

	Total #	Positive Cx	Sensitivity	Specificity	PPV
>LE or +Nit	3394	95	79	97	?

- In this population, what was the **baseline prevalence**?
- In this population, what was the **rate of UTI in those with a positive dipstick**?

Shaw KN, McGowan KL, Gorelick MH, Schwartz JS. Screening for urinary tract infection in infants in the emergency department: which test is best? Pediatrics 1998 Jun;101(6):E1.

Class Exercise: Interpreting Urinalysis Results

		Urinary Tract Infection: Yes	Urinary Tract Infection: No	
Positive "dipstick" test	Yes	75	99	174
	No	20	3200	3220
		95	3299	**3394**

Shaw KN, McGowan KL, Gorelick MH, Schwartz JS. Screening for urinary tract infection in infants in the emergency department: which test is best? Pediatrics 1998 Jun;101(6):E1.

Class Exercise: Interpreting Urinalysis Results

What was the **baseline prevalence**?

95 / 3394 = 2.7%

What was the **rate of UTI among those with a positive dipstick**?

75 / 174 = 43%

		Urinary Tract Infection		
		Yes	No	
Positive "dipstick" test	Yes	75	99	174
	No	20	3200	3220
		95	3299	3394

So, in this population, a positive dipstick increases the probability of UTI from a pre-test (prior) probability of 2.7% to a post-test (posterior) probability of 43%.

With a positive dipstick, you are now **16x more certain** of the diagnosis.

Impact of Prevalence on Test Interpretation

Let's look at a commercially-available HIV rapid screening test:

- Published **sensitivity** (TPR) = 99.9%
- Published **specificity** (TNR) = 99.8%

False positive rate is 1 - 0.998 = 2 tests out of 1000

So, how does disease prevalence influence PPV and NPV?

Impact of Prevalence on Test Interpretation

PPV of HIV Tests in Populations with Differing HIV Prevalence

If HIV Prevalence is 10%

- **PPV = 98%**

If HIV Prevalence is 0.1%

- **PPV only 33%!**

Positive Predictive Value of HIV Tests in Populations with Differing HIV Prevalence Example: Testing 1,000 Persons			
HIV Prevalence	**True Positive (Number)**	**False Positive (Number)**	**Positive Predictive Value**
10%	100	2	98%
5%	50	2	96%
2%	20	2	91%
1%	10	2	83%
0.5%	5	2	71%
0.2%	2	2	50%
0.1%	1	2	33%

Source: “HIV Counseling with Rapid Tests”, available at https://aidsetc.org/sites/default/files/resources_files/6-DxTests.pptx

Class Exercise: Email Spam Filter Performance

You build an email filter to identify marketing spam, looking for key phrases like “opt-out” and “unsubscribe”

After a day, you find the following:

- 34 emails were trapped by the spam filter, of which 5 were not spam
- 2 spam emails were not caught by the filter and made it to your inbox

Two questions:

- Assuming an email is spam, what is the likelihood of being trapped by your filter?
- Assuming it is trapped by your filter, what is the likelihood of being spam?

Class Exercise: Email Spam Filter Performance

In our example, spam is the disease, and the email filter is a diagnostic test

- "Given the email is spam, likelihood of being trapped" = P(+ test | + disease) = **recall/sensitivity**
- "Given the email is trapped, likelihood of being spam" = P(+ disease | + test) = **precision/PPV**

Next, draw your 2x2 table:

		Manual Review: Spam	Manual Review: Not Spam	
Spam Filter	Trapped	29	5	34
	Not Trapped	2	?	?
		31	?	?

Class Exercise: Email Spam Filter Performance

If it is spam, what is the likelihood of being trapped?

- P(test + | disease +) = TPR = Sensitivity = **Recall**
- **Recall = 29/31 = 94%**
- False negatives: 6 of every 100 spam emails are missed by the spam filter

If it is trapped, what is the likelihood of being spam?

- P(disease + | test +) = PPV = **Precision**
- **Precision = 29/34 = 85%**
- False positives: 15 of every 100 trapped emails are not spam

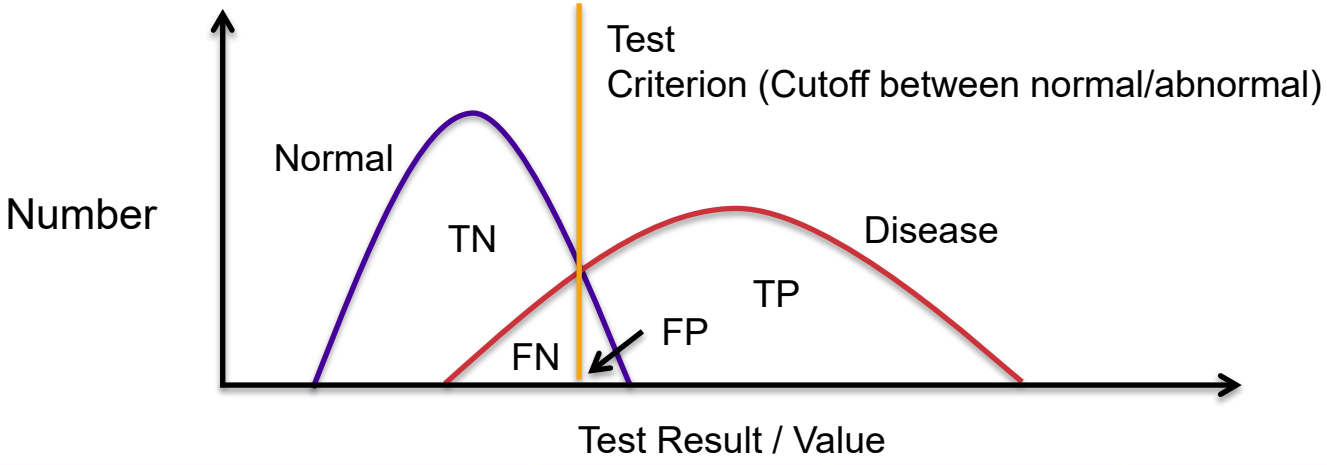
	Spam	Not Spam	
Trapped	29	5	34
Not Trapped	2	?	?
	31	?	?

Finding the Optimal Test Criterion / Cutoff

Test performed on patients with and without the clinical condition of interest (assuming you have a gold standard)

Will see a range of values about a mean, will likely see some overlap between those with and without the condition because few tests are perfect

As test criterion is changed, True Positive and False Positive rates will also change



Receiver Operating Characteristic (ROC) Curve

Visual representation of tradeoff between sensitivity and specificity – goal is to see how well the test can discriminate disease vs. no disease

Graph of sensitivity vs. 1-specificity (TPR vs. FPR)

The “shoulder” or inflection point can help to determine optimal threshold for a test with a range of possible results

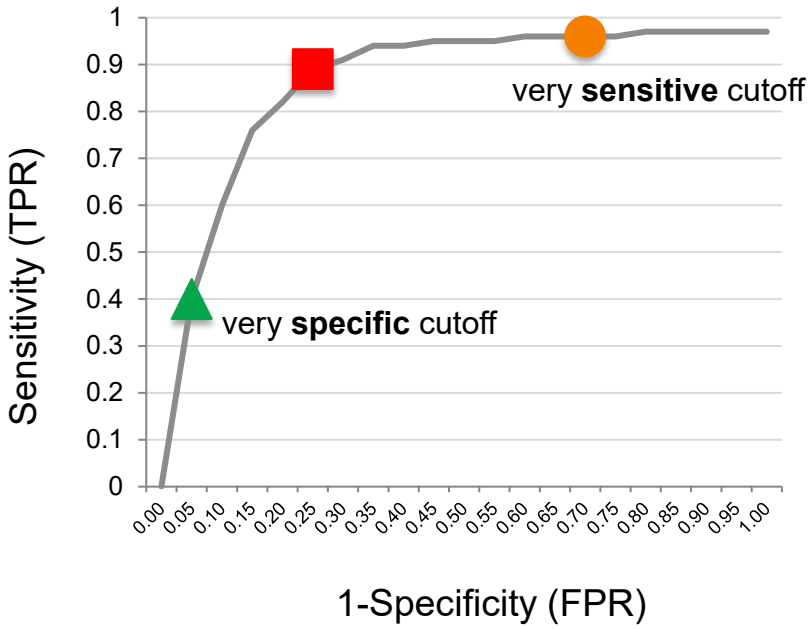
The area under the curve allows you to compare different tests to determine which is better at distinguishing disease from normal (optimize TPR, minimize FPR) – higher AUC is better

Receiver Operating Characteristic (ROC) Curve

Plot changes in TPR and FPR with changes in the test criterion

To identify optimal criterion for a given test, look for inflection point

- **Green** triangle: low TPR, low FPR
- **Red** square: best balance of TPR & FPR
- **Orange** circle: modestly higher TPR, but at expense of high FPR

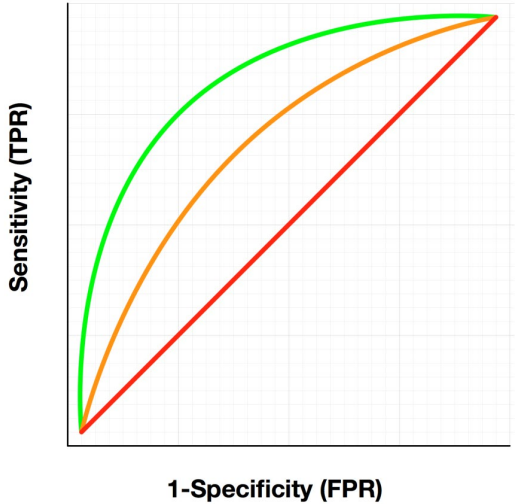


Receiver Operating Characteristic (ROC) Curve

Previous example showed different cutoff values for the same test.

What if you want to compare different tests?

- Look for the one with highest area under the curve (AUC), which represents the test with the best ability to discriminate between true and false positives (you can achieve high TPR and still have low FPR).
- A “bad” test will be flat, a diagonal line with no clear inflection point
- In this example, the green test is better than the orange test. The red test cannot effectively discriminate between true and false positives



Example: Diagnosis of Pediatric Septic Shock

Q: Which test can best discriminate septic shock at the time of admission to the PICU:

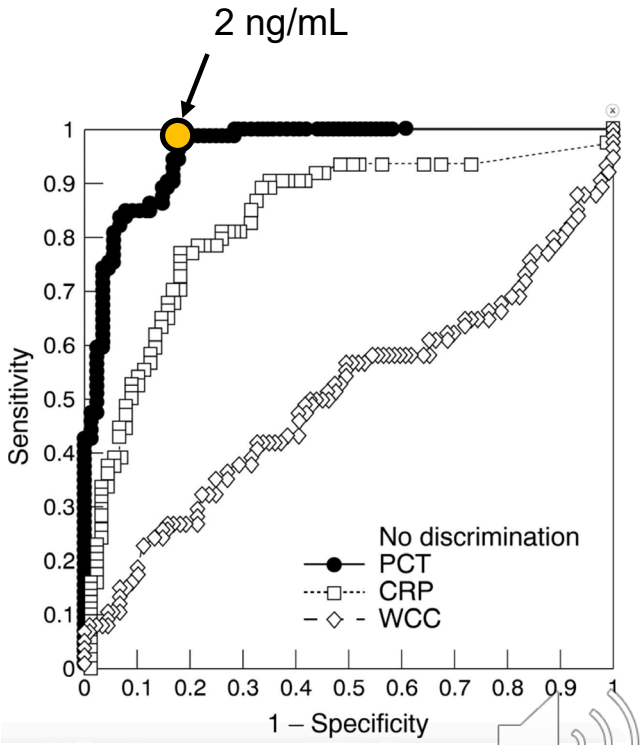
Procalcitonin (PCT) → AUC 0.96

C-Reactive Protein (CRP) → AUC 0.83

White Cell Count (WCC) → AUC 0.51

A: Procalcitonin, with a recommended cutoff of **2 ng/mL**. At that threshold, all patients with sepsis / meningitis were identified (100% sensitive).

What is the expected false positive rate at that cutoff value for procalcitonin?



Bayes Theorem

$$P(A|B) = \frac{P(B|A) * P(A)}{P(B)} \rightarrow P(D+|T+) = \frac{P(T+|D+) * P(D+)}{P(T+)}$$

Probability of disease given a positive test (PPV, posterior probability) equals:

- Probability of positive test given disease (sensitivity)
- Multiplied by probability of disease (prevalence)
- Divided by probability of a positive test (sum of true positive and false positive rates, or sensitivity + 1-specificity)

In simpler terms, you can adjust the posterior probability of an event in light of the prior probability and some new information (like the result of a test).

This is unwieldy and no fun to work with…

Using Likelihood Ratios to Calculate Posterior Probability

Manipulating the Bayes Theorem formula reveals an interesting relationship:

Posterior **odds** = prior **odds** x “likelihood ratio”

Likelihood Ratio has the unique property of being a value that reflects both the **sensitivity and specificity** of a test in a single number, doesn’t change with prevalence. LR is calculated from sensitivity / specificity

2 versions of “likelihood ratio”, corresponding to whether test is positive or negative

Likelihood ratio is derived from sensitivity / specificity

- **Positive likelihood ratio (LR+)** = sensitivity / 1-specificity = TPR/FPR → how much a positive test makes the diagnosis more likely
- **Negative likelihood ratio (LR-)** = 1-sensitivity / specificity = FNR/TNR → how much a negative test makes the diagnosis less likely

There’s one problem: ODDS and PROBABILITY are not the same!

Odds ≠ Probability

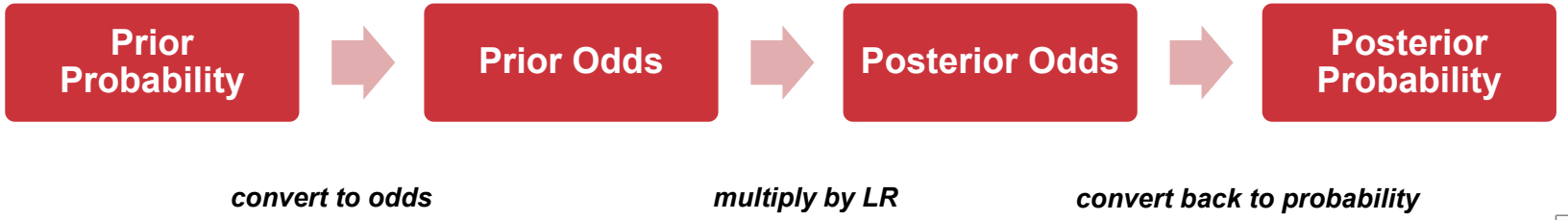
What is difference between ”Odds” and “Probability”?

Consider a coin toss:

- Odds of heads are 1:1. Probability of heads are ½
- Odds of X = P(X) / 1-P(X)
- Probability of X = odds / 1+odds

Event with 1:3 *(“1 to 3”)* odds has probability of 1/4 *(“1 in four”)* or 25%

So, to use LR+ / LR- to estimate **posterior probability** takes a few steps:



Worked Example: Probability of COPD Given History of Smoking

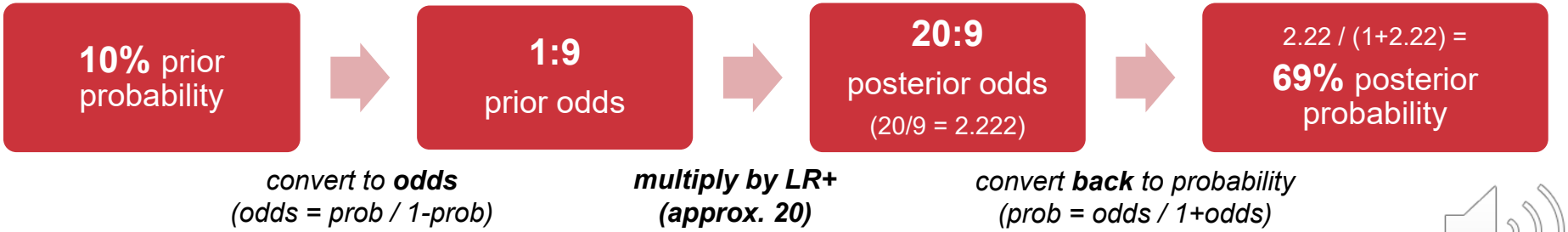
40 pack-years smoking history as predictor of risk of COPD (BMJ 2004):

- **Sensitivity: 28.4% and Specificity: 98.6%**

Q: can you calculate the **Positive and Negative Likelihood Ratios**?

- **LR+** = TPR / FPR = sens/(1-spec) = 0.284 / (1-0.986) = 0.284/0.014 = **20.3**
- **LR-** = FNR / TNR = (1-sens) / spec = (1-0.284) / 0.986 = 0.716/0.986 = **0.73**
- **In other words, history of 40PY smoking increases ODDS of COPD 20-fold**

Q: If a patient has 10% chance of COPD due to history of occupational exposure, and you learn she **also** has a 40 pack-year smoking history, what is her adjusted probability of COPD in light of this?



Fagan Nomogram

For most, odds are less intuitive, conversion is cumbersome

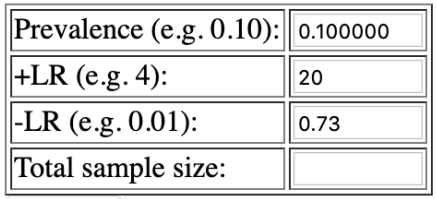
Fagan Nomogram allows you to determine post-test probability given the pre-test probability and LR+/LR-

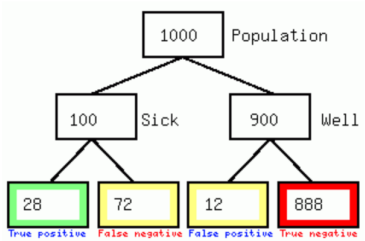
In our example, prior prob. was 10%, LR+ = 20.3, LR- = 0.73

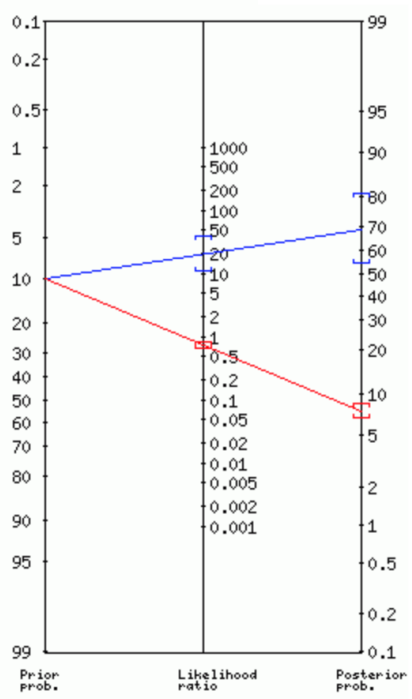
We can use the online Fagan Nomogram calculator hosted at U. of Illinois – Chicago

Q: Can you calculate our patient's risk using the nomogram?

Q: What if prior probability was only 1%? What about 20%?



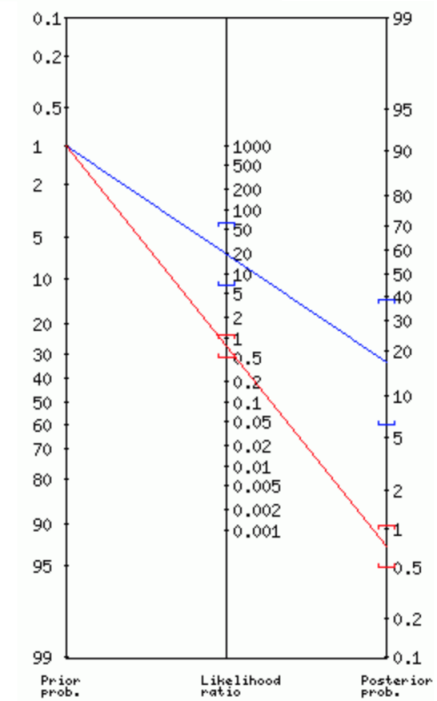




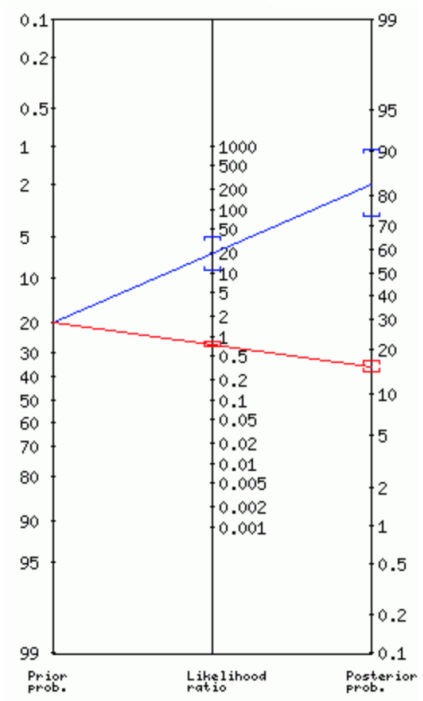
Source: Diagnostic Test Calculator, Alan Schwartz. Accessible at http://araw.mede.uic.edu/cgi-bin/testcalc.pl

Fagan Nomogram: 1% and 20% Prior Probability

1% Prior Probability



20% Prior Probability



Where Can You Find LR+ and LR-?

So that leaves deriving the LR+ / LR- as the “not-so-fun” part of this math

Thankfully, the LR+ and LR- are published and easily available for common signs, symptoms, and diagnostic tests:

- Ex: **Rapid Test** for Strep Throat: **LR+ = 15.2**
- Ex: Any **ST-segment elevation** on ECG for diagnosing MI: **LR+ = 11.2**
- Ex: **Pain radiating to both arms** for diagnosing MI: **LR+ = 7.1**

Source: Centre for Evidence-Based Medicine, Toronto, https://www.cebm.net/2014/02/likelihood-ratios/

Impact of LR+ / LR- on Disease Likelihood

Likelihood Ratio	Approximate* Change in Probability	Effect on Posttest Probability of disease
Values between 0 and 1 *decrease* the probability of disease		
0.1	- 45%	Large decrease
0.2	- 30%	Moderate decrease
0.5	- 15%	Slight decrease
1	- 0%	None
Values greater than 1 *increase* the probability of disease		
1	+ 0%	None
2	+ 15%	Slight increase
5	+ 30%	Moderate increase
10	+ 45%	Large increase

Source: https://en.wikipedia.org/wiki/Likelihood_ratios_in_diagnostic_testing

Class Exercise: Pediatric UTI

Clinical Scenario:

A 16-month female comes to your emergency department with high fever without an obvious source. You perform a urinalysis to determine if she may have a urinary tract infection.

- How will a positive test influence your decision?
- How will a negative test influence your decision?

Class Exercise: Pediatric UTI

Ex: **Urinalysis** for detection of UTI in children

Published Positive Likelihood Ratio (LR+) = 5.6

Published Negative Likelihood Ratio (LR-) = 0.03

- Prevalence of UTI in febrile females 2 mo to 2 years presenting to an ED is 3.3% (i.e., prior probability in this population)
- Can we use the Fagan Nomogram to help us determine probability of UTI when the test is positive vs. negative?
- Do this using a printed Fagan nomogram or use the online calculator at http://araw.mede.uic.edu/cgi-bin/testcalc.pl to answer this question

Source: Centre for Evidence-Based Medicine, Toronto, https://www.cebm.net/2014/02/likelihood-ratios/

Class Exercise: Pediatric UTI

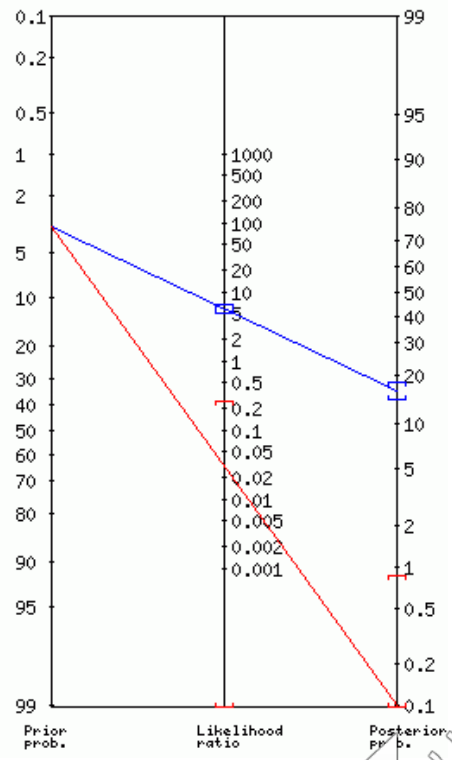
On left side of Fagan Nomogram, find your prior probability (aka pre-test probability). In our case, that's 3.3%

Draw a line across to the right that crosses the middle column at LR+ of 5.6

Note that it intersects the right column at ~16% (blue line)

Therefore, in this population, a positive test means there is a 16% probability the patient has a UTI

Do the same for LR- (red line), post-test probability after a negative test is 0.1% - **effectively ruling out disease**



Source: Diagnostic Test Calculator, Alan Schwartz. Accessible at http://araw.mede.uic.edu/cgi-bin/testcalc.pl

Relative Risk

Ratio of probability of an event in exposed group to probability of event in unexposed group

RR = P(disease | **exposure**) / P(disease | **no exposure**)

RR must be positive; RR of 1 means no association; RR < 1 means decreased risk

- Ex: Relative risk of lung cancer if you are a current smoker (>25 cig/day) = 10
- Ex: Relative risk of prostate cancer if you are Asian = 0.4

Strength	Decreased Risk (-)	Increased Risk (+)
Weak	RR 0.7 - <0.9	RR 1.1- <1.5
Moderate	RR 0.4 - <0.7	RR 1.5 - <3.0
Strong	RR 0.2 - <0.4	RR 3.0 - <7.0
Very Strong	RR <0.2	RR > 7.0

Class Exercise: MRSA Surveillance

Surveillance cultures in an ICU identify patients with MRSA colonization.

What is the relative risk of Skin/Soft tissue infection (SSTI) among patients with MRSA compared to those who do not have MRSA?

MRSA?	SSTI	Healthy	Total
Yes	12	77	89
No	4	279	283

RR= (12/89) / (4/283)
= 0.135 / 0.014
= 9.6

In this population, the relative risk of developing an SSTI if patient is colonized with MRSA is 9.6

End of Lecture

Supplemental Material: Mnemonic for 2x2 Terms

1. **Sensitivity** = “Given presence of disease, what is the probability of a positive test”

2. **Specificity** = “Given absence of disease, what is the probability of a negative test”

3. **PPV** = “Given a positive test, what is the probability of disease”

4. **NPV**= “Given a negative test, what is the probability of no disease”

IMPORTANT: In Information Retrieval

“Recall” = Sensitivity

“Precision” = PPV

Supplemental Material: Mnemonic for 2x2 Terms

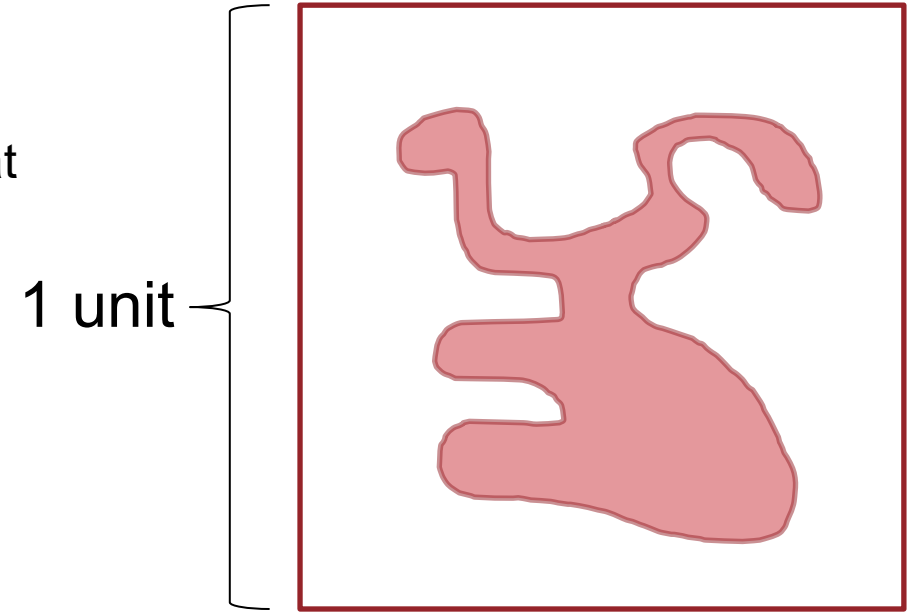
1. **Sensitivity** = P(+ test | + disease)
2. **Specificity** = P(- test | - disease)
3. **PPV** = P(+ disease | + test)
4. **NPV**= P(- disease | - test)

	Disease +	Disease -	
Test +	**A** True Positive	**B** False Positive	**(A+B)** Everyone with positive test
Test -	**C** False Negative	**D** True Negative	**(C+D)** Everyone with negative test
	(A+C) Everyone with disease	**(B+D)** Everyone without disease	**(A+B+C+D)** Everyone

Supplement: Using Randomness to Measure

Imagine an oddly-shaped object whose area we want to estimate

Difficult to measure directly, but what if we put it inside a box of known dimensions?



Hey! It's a bunny!

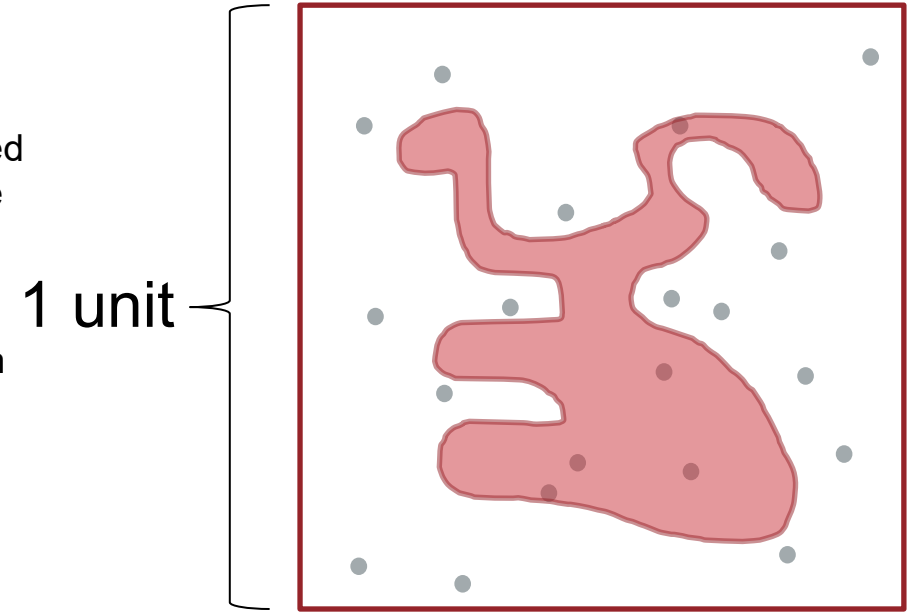
Supplement: Using Randomness to Measure

Now, let's randomly drop 20 balls onto the 1 unit square

It follows that the proportion of balls that landed inside the irregular object is an estimate of the proportion of the area of the object relative to the area of the square.

Since we know the area of the square, we can estimate the area of the object

Ex: if 25% of the balls falls inside the object, it has an estimated area of 0.25 square units (25% of area of the enclosing square)



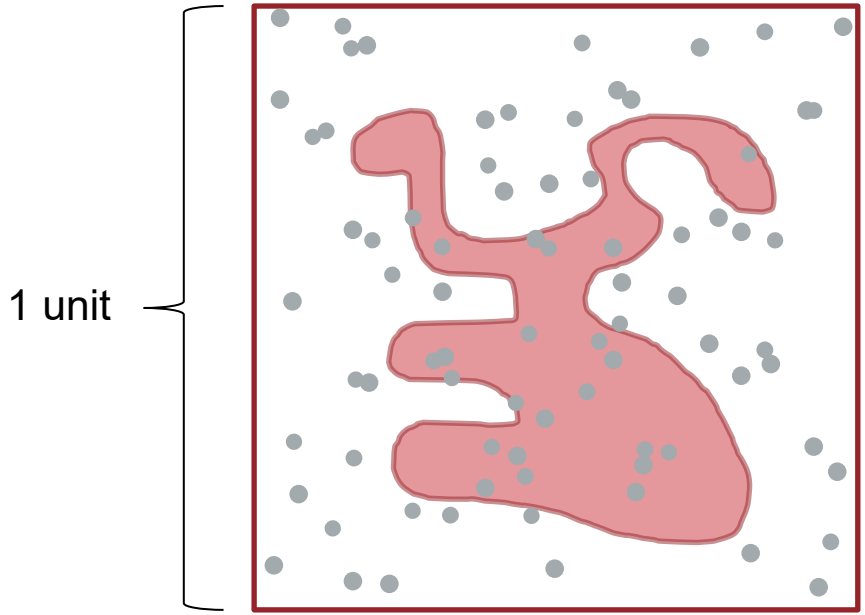
Q: How can we make our estimate more precise?

Supplement: Using Randomness to Measure

To improve precision of the estimate, you can:

1) Increase the number of balls
2) Run more simulations

This is the idea behind **Monte Carlo simulation**: using a stochastic/random process to estimate the value of something that is otherwise difficult to estimate using deterministic methods.



Additional Resources

Pagano M, Gauvreau K. **Principles of Biostatistics.** 2nd ed. Pacific Grove: Duxbury, 2000. 525 p.

Hunink M, Glasziou P. **Decision making in health and medicine.** 1st ed. Cambridge: Cambridge University Press, 2001. 388 p.

Blois MS. **Information and Medicine: The Nature of Medical Descriptions.** p. 160. University of California Press: Berkeley, 1984.

Fagan TJ. **Nomogram for Bayes's theorem** N Engl J Med Jul 31,1975; 293(5):257 [Abstract]

Sonnenberg FA, Beck JR. **Markov models in medical decision making**. Med Decis Making 1993;13:322-338. [link]

Croskerry P. **The importance of cognitive errors in diagnosis and strategies to minimize them**. Acad Med. 2003; 78(8):775-780 [link]

Additional Resources

Online Course: PennState STAT 507 “Epidemiological Research Methods”, Lesson 10.3: Sensitivity, specificity, positive predictive value, negative predictive value

Online statistics lectures by Rahul Patwari, MD

- Tradeoff between sensitivity and specificity
- Predictive values
- Screening tests
- ROC Curves