EPID 550
Clinical Economics and Decision Making

January 17, 2020

Registration

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Schedule

Classes are held Wednesdays and Fridays, 10:00 AM - 11:45 in room 418 Blockley Hall.

Spring recess begins at the end of classes on Friday, March 6 and ends at 8:00 a.m. on Monday, March 16

The expected schedule for lecture topics, readings, and quizzes is provided in the SYLLABUS which can be found under the “Pages” tab on Canvas (NOT under the Syllabus tab on Canvas)

Grades

Grades will be based on class participation, homework, two quizzes, and a final examination.

Quizzes and exams will be "open book." Quizzes will be take place in class; the final will be "take home."

Assigned Materials

Course materials including the syllabus, lecture notes, readings, homework, quizzes, examinations, and recordings will be distributed through the Internet-based Canvas website. These materials can be accessed at the following address:

http://upenn.instructure.com/

Special software (TreeAge) and material from the book by Glick et al. titled *Economic Evaluation in Clinical Trials*, *2nd edition* are the only exceptions.

(Nearly) Everything is in the Pages Section

- **Lecture notes, homework, and the final** are provided under a tab labeled Course Handouts/Homework on the "Pages" tab Front Page.
- **Course readings** that are listed in the syllabus are provided under a tab labeled Course Readings on the "Pages" tab Front Page.
- **Critical appraisal and other articles** that are not listed in the syllabus will be provided in the "Course Handouts/Homeworks" tab under the "Pages" tab Front Page along with any notes for the critical appraisals.
- **Recordings of lectures** will be available under the tab labeled "Recordings of Lectures" under the "Pages" tab Front Page.
- **Instructions about how to use Canvas** are available here: https://infocanvas.upenn.edu/guides/canvas-for-students/ and under the "Pages" tab in Canvas.

Selected chapters from the following 3 books have been included under a tab labeled Course Readings on the "Pages" tab Front Page in Canvas. Students who are interested in learning more about the topics presented in this course should consider reading all of these books:

Drummond M, et al. *Methods for the Economic Evaluation of Health Care Programmes, 4th Ed*. Oxford University Press, 2015

Neumann PJ, et al. *Cost Effectiveness in Health and Medicine, Second Edition*. Oxford University Press, 2016

Briggs A, et al. *Decision Modelling for Health Economic Evaluation*. Oxford University Press, 2006.

Purchases

- A copy of the book by Glick HA, Doshi JA, Sonnad SS, and Polsky D titled Economic Evaluation in Clinical Trials, Second Edition (published by Oxford University Press in 2015). Available on Amazon.
- Software (TreeAge Pro Suite for healthcare users)

TreeAge Pro Suite for Healthcare Users

As of 01/14/2020, TreeAge Pro Suite for healthcare users was available with a limited Student Course license for $55 at the following web site:

https://www.treeage.com/shop/

To purchase this software, select "Academic Use" for Treeage Pro Healthcare and then select "Purchase Student Course License ($55)" as the second option

DO NOT purchase TreeAge Pro Core.

Also, we do not expect to use this software until Wednesday March 4 (or Friday March 6) so plan to purchase it before Wednesday, March 4.

COURSE SUMMARY

The overall goal of this course is for students to learn quantitative tools that can be used to analyze and understand medical decisions.

- Diagnostic tests with dichotomous results
- Diagnostic tests with continuous results
- Prediction rules
- Introduction to cost-effectiveness analysis
- Mathematical modeling with decision trees
- Costing / Analysis of cost / Discounting
- Mathematical modeling with Markov techniques
- Measuring outcomes in "utility" terms
- Confidence intervals / sample size for cost-effectiveness analysis
- Economic assessment and policy analysis

EPID 550:Clinical Economics and Medical Decision Making

Introduction to
the Interpretation of Diagnostic Tests

A Patient with Sore Throat

A mother brings her 12-year-old daughter in to see you because the child has a sore throat.

What are your concerns?

Your examination finds a fever (103.1^{o}F), tonsillar membranes, and anterior cervical lymph nodes that are enlarged and tender. There is no cough or history of cough. The girl's brother had the same syndrome 3 days ago, and you cultured Group A beta-hemolytic streptococci from his throat.

What are your options? What do you do?

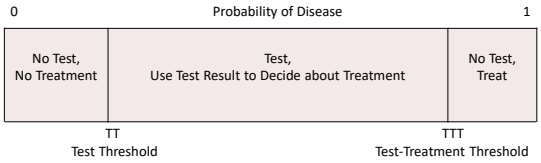
Another Patient with Sore Throat

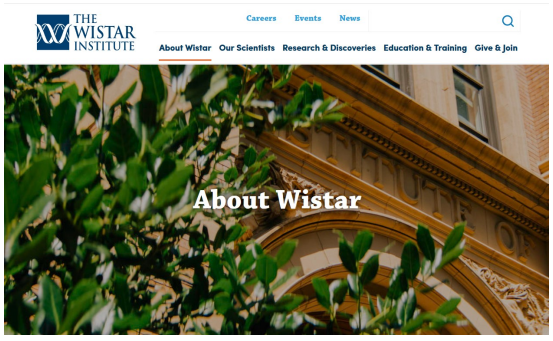
Another mother brings her 12-year-old daughter in to see you because the child has a sore throat.

Your examination finds no fever (97.2ºF), no tonsillar membranes, and no anterior cervical lymph nodes. The girl coughs continuously during your examination. The girl's brother had the same syndrome 3 days ago, and your culture of his throat did not find any pathogenic bacteria.

What do you do?

The Threshold Approach to Medical Decision Making





"Wistar is a world leader in early-stage discovery science in the areas of cancer, immunology and infectious disease. The Institute is committed to accelerating research advances from bench to bedside through brilliant science and distinctive approaches to collaboration among scientific investigators and academic and industry partners. Wistar's single-minded focus is on making discoveries that will change the future of human health."

Wistar discoveries have led to vaccines for rabies and rubella, the identification of genes associated with breast, lung, and prostate cancer, and the development of monoclonal antibodies. Wistar is an independent research center that has close working relationships with the University of Pennsylvania, Children's Hospital of Philadelphia, and other organizations.

How do you measure how good a diagnostic test is?

What are the operating characteristics of a diagnostic test?

Diagnostic Tests with Dichotomous Outcomes

The Standard 2by2 Table

	Disease Present	Disease Absent	Total
Test Result Positive	True Positive (TP)	False Positive (FP)	TP + FP
Test Result Negative	False Negative (FN)	True Negative (TN)	FN + TN
Total	TP + FN	FP + TN	

Operating Characteristics 1

	Disease Present	Disease Absent	Total
Test Result Positive	TP	FP	TP + FP
Test Result Negative	FN	TN	FN + TN
Total	TP + FN	FP + TN	

$$\text{Sensitivity} = \frac{TP}{TP + FN} = \frac{TP}{\text{All with Disease}}$$

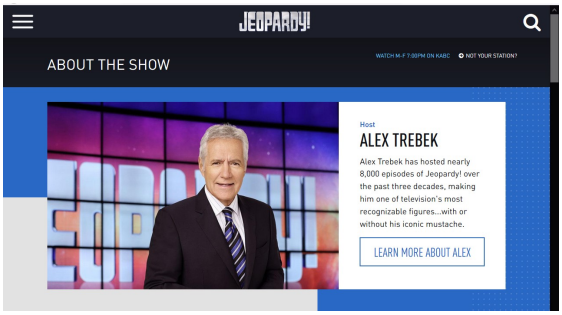
$$\text{Specificity} = \frac{TN}{FP + TN} = \frac{TN}{\text{All without Disease}}$$

An Example

	Disease Present	Disease Absent	
Test Result Positive	97	5	
Test Result Negative	3	95	
Total	100	100	

$$\text{Sensitivity} = \frac{97}{100} = 0.97$$

$$\text{Specificity} = \frac{95}{100} = 0.95$$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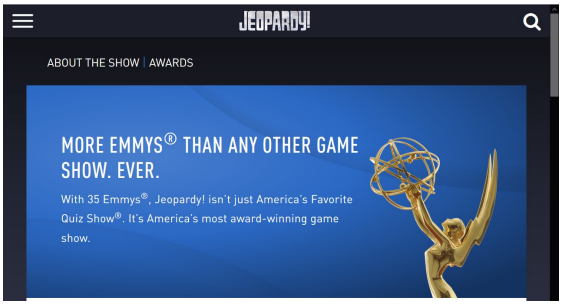
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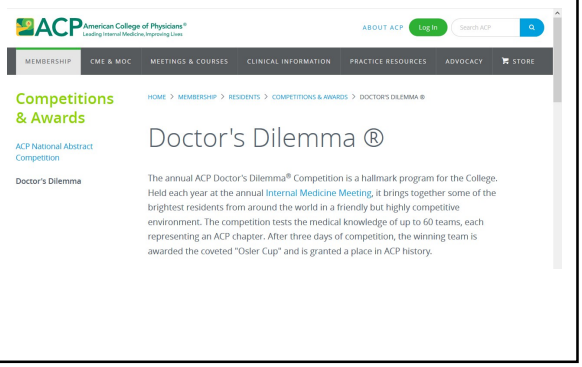
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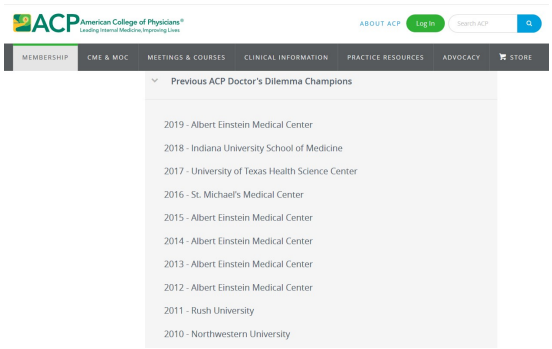
Doctor's Dilemma ®
The annual ACP Doctor's Dilemma® Competition is a hallmark program for the College. Held each year at the annual Internal Medicine Meeting, it brings together some of the brightest residents from around the world in a friendly but highly competitive environment. The competition tests the medical knowledge of up to 60 teams, each representing an ACP chapter. After three days of competition, the winning team is awarded the coveted "Osler Cup" and is granted a place in ACP history.



Answer: **Sensitivity**

Question 1

- What is the probability that the patient will have disease when the test result is positive?

Question 2

- What is the probability that the test result will be positive when the patient has disease?

Answer: **Specificity**

Question 1

- What is the probability that the patient will not have disease when the test result is negative?

Question 2

- What is the probability that the test result will be negative when the patient does not have disease?

Operating Characteristics 2

	Disease Present	Disease Absent	Total
Test Result Positive	TP	FP	TP + FP
Test Result Negative	FN	TN	FN + TN
Total	TP + FN	FP + TN	

$$\text{Positive Predictive Value (PPV)} = \frac{TP}{TP + FP} = \frac{TP}{\text{All Positives}}$$

$$\text{Negative Predictive Value (NPV)} = \frac{TN}{FN + TN} = \frac{TN}{\text{All Negatives}}$$

Compare Sensitivity and Specificity

	Disease Present	Disease Absent	Total
Test Result Positive	TP	FP	TP + FP
Test Result Negative	FN	TN	FN + TN
Total	TP + FN	FP + TN	

$$\text{Positive Predictive Value (PPV)} = \frac{TP}{TP + FP} = \frac{TP}{\text{All Positives}}$$

$$\text{Negative Predictive Value (NPV)} = \frac{TN}{FN + TN} = \frac{TN}{\text{All Negatives}}$$

$$\text{Sensitivity} = \frac{TP}{TP + FN} = \frac{TP}{\text{All with Disease}}$$

$$\text{Specificity} = \frac{TN}{FP + TN} = \frac{TN}{\text{All without Disease}}$$

What is the probabily of cancer in a 65 year old man who has 40 pack-years of cigarette smoking, a 6-month history of 30 lb weight loss and worsening of his chronic cough?

An Example

	Disease Present	Disease Absent	Total
Test Result Positive	97	5	102
Test Result Negative	3	95	98
Total	100	100	200

$$\text{Positive Predictive Value (PPV)} = \frac{97}{102} = 0.95$$

$$\text{Negative Predictive Value (NPV)} = \frac{95}{98} = 0.97$$

What is the probability of cancer in people shopping at King of Prussia Mall, excluding those who already know they have cancer?

Another Example: Screening

	Disease Present	Disease Absent	Total
Test Result Positive	97	4,995	5,092
Test Result Negative	3	94,905	94,908
Total	100	99,900	100,000

$$\text{Positive Predictive Value (PPV)} = \frac{97}{5,092} = 0.02$$

$$\text{Negative Predictive Value (NPV)} = \frac{94,905}{94,908} = 0.99$$

Why did the positive predictive value change so much?

Original Example

	Disease Present	Disease Absent	Total
Test Result Positive	97	5	102
Test Result Negative	3	95	98
Total	100	100	200

Positive Predictive Value (PPV) = 97 / 102 = 0.95

Negative Predictive Value (NPV) = 95 / 98 = 0.97

Screening Example

	Disease Present	Disease Absent	Total
Test Result Positive	97	4,995	5,092
Test Result Negative	3	94,905	94,908
Total	100	99,900	100,000

Positive Predictive Value (PPV) = 97 / 5,092 = 0.02

Negative Predictive Value (NPV) = 94,905 / 94,908 = 0.99

Compare

Sensitivity and Specificity

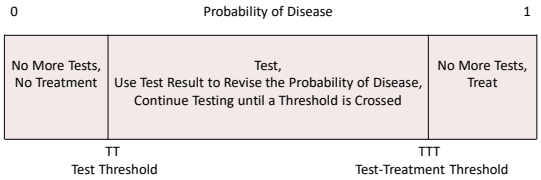
- Have the same numerators as predictive values, but the denominators are disease status
- Are calculated vertically in the standard 2by2 table
- Do not change with disease prevalence or disease probability
- Answer questions that are clinically irrelevant

Predictive values

- Have the same numerators as sensitivity and specificity, but the denominators are test results
- Are calculated horizontally in the standard 2by2 table
- Do change with disease prevalence and disease probability
- Answer questions that are clinically relevant

Does a positive test result mean the patient has disease? Does a negative test result mean the patient does not have disease? What do test results mean?

A Refinement to The Threshold Approach for Medical Decision Making



What the first part of this course is about.

How to revise the probability of disease after the test result is known.

What the first part of this course is really about.

How to calculate predictive values.

Definitions

- The "prior probability" of disease and the "pretest probability" of disease are the probability of disease before doing a diagnostic test.
- The "posterior probability" of disease and the "post-test probability" of disease are the revised probability of disease after doing a diagnostic test and combining information from the test result with the pretest probability of disease.

Testing Spinal Fluid for Alzheimer's Disease

Cerebrospinal Fluid Biomarker Signature in Alzheimer's Disease.
Ann Neurol 2009;65:403–413

Leslie M. Shaw, PhD*, Hugo Vanderstichele, PhD, Malgorzata Knapik-Czajka, PhD*, Christopher M. Clark, MD*, Paul S. Aisen, MD, Ronald C. Petersen, MD, Kaj Blennow, MD, PhD, Holly Soares, PhD, Adam Simon, PhD, Piotr Lewczuk, MD, PhD, Robert Dean, MD, Eric Siemers, MD, William Potter, MD, **Virginia M.-Y. Lee, PhD*, John Q. Trojanowski, MD, PhD*, and the Alzheimer's Disease Neuroimaging Initiative**

*Names in bold font indicate people who were at the University of Pennsylvania when this article was published.

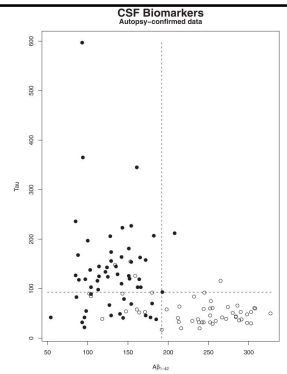


Fig 2. Plot of cerebrospinal fluid (CSF) tau concentration versus CSF amyloid-β 1 to 42 peptide ($A\beta_{1-42}$) concentration for the autopsy-confirmed Alzheimer's disease (AD) cases (*solid circles*) and elderly cognitively normal (NC) subjects (*open circles*).

	Disease Present	Disease Absent	
Test Result Positive	54	11	
Test Result Negative	2	41	
Total	56	52	

$$\text{Sensitivity} = \frac{54}{56} = 0.964^*$$

$$\text{Specificity} = \frac{41}{52} = 0.788^*$$

*Remember these numbers

Problem

About 3 percent of men and women ages 65 to 74 who have no symptoms of dementia have Alzheimer's Disease.

1. What is the probability that a 70-year-old woman who has no symptoms of dementia has Alzheimer's Disease if the test result for $A\beta_{1-42}$ is positive?

2. What is the probability that such a person does not have Alzheimer's Disease if the test result is negative?

Five Ways to Revise the Probability of Disease Once the Test Result Is Known

1. Two-by-Two Table Method

Step 1: Assume that there are 1000 people and the prevalence of disease is 3%. Insert the appropriate column totals.

	Disease Present	Disease Absent	Total
Test Result Positive			
Test Result Negative			
Total	30	970	1000

Step 2: Use the known sensitivity (0.964) and specificity (0.788) of the test to calculate the number of true positives and true negatives.

	Disease Present	Disease Absent	Total
Test Result Positive	29		
Test Result Negative		764	
Total	30	970	1000

Step 3: Subtract the true positives and true negatives from the column totals to give the number of false negatives (FN) and the number of false positives (FP).

	Disease Present	Disease Absent	Total
Test Result Positive	29	206	
Test Result Negative	1	764	
Total	30	970	1000

Step 4: Calculate the total number of positive test results and the total number of negative test results.

	Disease Present	Disease Absent	Total
Test Result Positive	29	206	235
Test Result Negative	1	764	765
Total	30	970	1000

Step 5: Calculate PPV and NPV

	Disease Present	Disease Absent	Total
Test Result Positive	29	206	235
Test Result Negative	1	764	765
Total	30	970	1000

PPV = 29/235 = .123*

NPV = 764/765 = .999*

*Remember these numbers

Five Ways to Revise the Probability of Disease Once the Test Result Is Known

1. Two-by-Two Table Method

Use the standard 2by2 table.

Step 1: Assume that there is some proportion of people who have the disease of interest. Pick a total number, and insert the other column totals .

Step 2: Use the known sensitivity and specificity of the test to calculate the number of true positives and true negatives.

True positives = sensitivity x prevalence

True negatives = specificity x (1 – prevalence)

Step 3: Subtract the true positives and true negatives from the column totals to give the number of false negatives (FN) and the number of false positives (FP).

Step 4: Calculate the total number of positive test results and the total number of negative test results (row totals).

Step 5: Calculate PPV and NPV

Five Ways to Revise the Probability of Disease Once the Test Result Is Known

2. Bayes Theorem Method

Reverend Thomas Bayes, 1702-1761

LII. *An Eſſay towards ſolving a Problem in the Doctrine of Chances. By the late Rev. Mr.* Bayes, *F. R. S. communicated by Mr.* Price, *in a Letter to* John Canton, *A. M. F. R. S.*

Dear Sir,

Read Dec. 23, 1763. I Now ſend you an eſſay which I have found among the papers of our deceaſed friend Mr. Bayes, and which, in my opinion, has great merit, and well deſerves to be preſerved. Experimental philoſophy, you will find, is nearly intereſted in the ſubject of it; and on this account there ſeems to be particular reaſon for thinking that a communication of it to the Royal Society cannot be improper.

He had, you know, the honour of being a member of that illuſtrious Society, and was much eſteemed by many in it as a very able mathematician. In an introduction which he has writ to this Eſſay, he ſays, that his deſign at firſt in thinking on the ſubject of it

Five Ways to Revise the Probability of Disease Once the Test Result Is Known

2. Bayes Theorem Method

Where:

p = the prior probability of disease
sens = the sensitivity of the test
spec = the specificity of the test
PPV = positive predictive value
NPV = negative predictive value

$$PPV = \frac{(p)(sens)}{[(p)(sens)] + [(1-p)(1-spec)]}$$

$$PPV = \frac{0.03 \times 0.964}{0.03 \times 0.964 + (0.97 \times 0.212)} = 0.123$$

$$NPV = \frac{(1-p)(spec)}{[(1-p)(spec)] + [(p)(1-sens)]}$$

$$NPV = \frac{0.97 \times 0.788}{0.97 \times 0.788 + (0.03 \times 0.036)} = 0.999$$

	Disease Present	Disease Absent	Total
Test Result Positive	(p)(sens)	(1-p) - [(1-p)(spec)] or (1-p)(1-spec)	
Test Result Negative	p - [(p)(sens)] or (p)(1 – sens)	(1-p)(spec)	
Total	p	1 - p	1

$$PPV = \frac{(p)(sens)}{[(p)(sens)] + [(1-p)(1-spec)]}$$

(p)(sens) = probability of true-positive results

(1-p)(1-spec) = probability of false-positive results

PPV = probability of true positives / probability of all positives

	Disease Present	Disease Absent	Total
Test Result Positive	(p)(sens)	(1-p) - [(1-p)(spec)] or (1-p)(1-spec)	
Test Result Negative	p - [(p)(sens)] or (p)(1 – sens)	(1-p)(spec)	
Total	p	1 - p	1

$$NPV = \frac{(1-p)(spec)}{[(1-p)(spec)] + [(p)(1-sens)]}$$

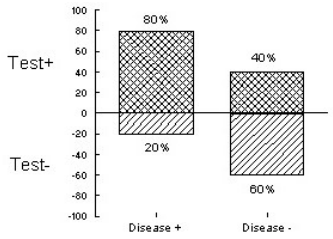
(1 – p)(spec) = probability of true-negative results

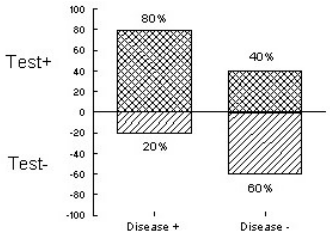
(p)(1-sens) = probability of false-negative results

NPV = probability of true negatives / probability of all negatives

Likelihood Ratios

- Likelihood ratios report the number of times those with disease have the test result for every 1 time those without disease have the test result
- If the LR is 5 (or 5 to 1), then the test result occurs 5 times among diseased individuals for every 1 time it occurs among non-diseased individuals (e.g., if it is positive 50% of the time among diseased individuals, it is positive 10% of the time among non-diseased individuals).
- If the LR is 0.2 (or 0.2 to 1), then the test result occurs 0.2 times among diseased individuals for every 1 time it occurs among non-diseased individuals (e.g., if it is negative 2% of the time among diseased individuals, it is negative 10% of the time among non-diseased individuals).





LR+ = 80%/40% = 2

LR- = 20%/60% = 0.33

Calculating the Likelihood Ratio

$$LR+ = \frac{\text{Probability of positive test in patients with disease}}{\text{Probability of positive test in patients without disease}}$$

LR+ = (sens) / (1 - spec)

$$LR- = \frac{\text{Probability of negative test in patients with disease}}{\text{Probability of negative test in patients without disease}}$$

LR- = (1 - sens) / (spec)

	Disease Present	Disease Absent	
Test Result Positive	54	11	
Test Result Negative	2	41	
Total	56	52	

Sensitivity = 54/56 = 0.964
Specificity = 41/52 = 0.788

LR+ = Sensitivity/(1-Specificity) = 0.964/0.212
LR+ = 4.547*
LR- = (1-Sensitivity)/Specificity = 0.036/0.788
LR- = 0.046*

*Remember these numbers

Interpreting Odds in Horse Racing

1. If your horse wins, you collect the amount of money you bet plus the amount of money you bet times the odds.

Interpreting Odds in Horse Racing

1. If your horse wins, you collect the amount of money you bet plus the amount of money you bet times the odds.
2. $$\text{Odds} = \frac{\text{Chances of losing}}{\text{Chances of winning}}$$

Odds are **NOT** probabilities

$$\text{Odds} = \frac{\text{Chances of losing}}{\text{Chances of winning}}$$

$$\text{Probability} = \frac{\text{Chances of losing}}{\text{Chances of losing plus chances of winning}}$$

If you have probabilities, and you want odds

odds = probability/(1 – probability)

Probability	Prob/(1-Prob)	Odds
60%	60%/40%	1.5
75%	------/-------	-------
½	------/-------	-------
0.25	------/-------	-------

If you have odds, and you want probabilities

probability = odds/(1 + odds)

Probability	Odds/(1+Odds)	Odds
0.2	(1/4)/(5/4)	1/4
------	------/-------	1/3
------	------/-------	4/1
------	------/-------	0.5

Why do you need to know about likelihood ratios and odds?

The posterior odds of disease equal the prior odds of disease times the likelihood ratio (either positive or negative).

Five Ways to Revise the Probability of Disease Once the Test Result Is Known

3. Revising the Probability of Disease with the LR, Method A

Step 1: Change the prior probability of disease into the prior odds of disease.

Step 2: Calculate the posterior odds of disease by multiplying the likelihood ratio (either positive or negative) times the prior odds.

Step 3: Change the posterior odds of disease into the posterior probability of disease.

Our Example

Probability of disease = 0.03, LR+ = 4.547, LR- = .046

Step 1. Change the prior probability of disease into the prior odds of disease

Odds = .03 / .97 = .031

Step 2. To calculate the posterior odds of disease, multiply the likelihood ratio (positive or negative) times the prior odds

Posterior odds of disease =

(LR+ * .031) = (4.547*.031) = .141

(LR- * .031) = (.046*.031) = .001

Our Example

Step 3. Change the posterior odds of disease into the posterior probability of disease

Posterior probability of disease = .141/1.141 = .124
Posterior probability of disease = .001/1.001 = .001

The second result (for LR-) is the probability of disease in a patient with a negative test result. One minus this number, or 0.999, is the probability of no disease in a person with a negative test result, which is the NPV and the value we want.

Five Ways to Revise the Probability of Disease Once the Test Result Is Known

4. Revising the Probability of Disease with the LR, Method B

Henry derived a new equation by replacing the numbers in the steps for the traditional method with algebraic expressions, as follows. Note that LR indicates either LR+ or LR-.

- Change the prior probability into the prior odds of disease
  Prior odds = (Prior probability) / (1 - Prior probability)
- Calculate the posterior odds by multiplying the prior odds times the likelihood ratio.
  Posterior odds = ((Prior probability) / (1 - Prior probability)) × LR
- Change the posterior odds into the posterior probability by dividing the posterior odds by (1 + Posterior odds)

$$\frac{((\text{Prior probability}) / (1 - \text{Prior probability})) \times LR}{1 + [((\text{Prior probability}) / (1 - \text{Prior probability})) \times LR]}$$

4. Revising the Probability of Disease with the LR, Method B, continued

- Multiply numerator and denominator times (1 - (Prior probability)) , which results in:

$$\text{Posterior Probability of Disease} = \frac{\text{Prior Probability} \times LR}{(1 - \text{Prior probability}) + (\text{Prior probability} \times LR)}$$

- Rearrange the terms in the denominator:

$$\text{Posterior Probability of Disease} = \frac{\text{Prior Probability} \times LR}{(\text{Prior probability} \times LR) + (1 - \text{Prior probability})}$$

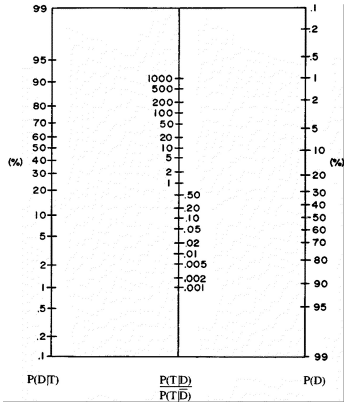
Our Example
Probability = .03, LR+ = 4.547, LR- = .046

Posterior Probability of Disease (PPD) = Prior Probability x LR / Prior probability x LR + (1 – Prior probability)

$$PPD \mid \text{Test result} + = \frac{0.03 \times 4.547}{0.03 \times 4.547 + (1 - 0.03)} = .123$$

$$PPD \mid \text{Test result} - = \frac{0.03 \times .046}{0.03 \times .046 + (1 - 0.03)} = .001$$

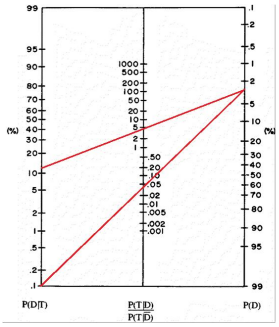
The second result (using LR-) is the probability of disease in a patient with a negative test result. One minus this number, or 0.999, is the probability of no disease in a person with a negative test result, which is the NPV and the value we want.



Five Ways to Revise the Probability of Disease Once the Test Result Is Known

5. Revising the Probability of Disease with the LR, Method C

- Locate the prior probability of disease on the right vertical axis of the nomogram P(D)
- Locate the LR on the middle vertical axis of the nomogram
- Draw a straight line between these 2 points, and extend it until it intersects the left vertical axis of the nomogram P(D|T)
- If the test result is positive, read the posterior probability of disease from the left vertical axis
- If the test result is negative, the posterior probability of no disease (NPV) is 1 minus the value on the left vertical axis of the nomogram



Five Ways to Revise the Probability of Disease (Calculate the Predictive Value of the Test Result) Once the Test Result Is Known

1. Two-by-Two Table Method
2. Bayes Theorem Method
3. LR, Method A, Traditional Method
4. LR, Method B, Henry's Equation
5. LR, Method C, Nomogram

Homework 1.

Due at the Beginning of Class
Wednesday January 22, 2020

Wharton junior Owen Thomas (40) was a second-team All-Ivy player in 2009. He recorded 29 tackles and finished second in the league with six sacks. He was elected one of the captains of the team for his senior year.

The Daily Pennsylvanian

Wharton Junior Found Dead Monday Afternoon
By Darina Shtrakhman
April 26, 2010, 8:41 pm

Wharton junior Owen Thomas was found dead at his off-campus residence around 2 p.m. Monday afternoon, University spokeswoman Lori Doyle and Director of Athletic Communication Mike Mahoney confirmed. He was a member of the football team.

Cause of death has not yet been determined, but “no foul play is suspected,” according to Doyle.

The New York Times

Suicide Reveals Signs of a Disease Seen in N.F.L.

By Alan Schwarz
September 13, 2010

ALLENTOWN, Pa. — A brain autopsy of a University of Pennsylvania football player who killed himself in April has revealed the same trauma-induced disease found in more than 20 deceased National Football League players, raising questions of how young football players may be at risk for the disease.

Owen Thomas, a popular 6-foot-2, 240-pound junior lineman for Penn with no previous history of depression, hanged himself in his off-campus apartment after what friends and family have described as a sudden and uncharacteristic emotional collapse. Doctors at Boston University subsequently received permission from the family to examine Thomas's brain tissue and discovered early stages of chronic traumatic encephalopathy, a disease linked to depression and impulse control primarily among N.F.L. players, two of whom also committed suicide in the last 10 years.

Thomas is the youngest and first amateur football player to be found with clear C.T.E.

The Washington Post

To Your Health

A hearing test may be able to identify a concussion

By Amy Ellis Nutt December 22, 2016

Call it the Telltale Brain. The first objective measurement for concussion may have been identified, according to a study published Thursday in the journal Nature, Scientific Reports.

By measuring the brain's electrical reactions to speech sounds, researchers at Northwestern University were able to identify children who had suffered a recent concussion with 90 percent accuracy and those who hadn't with 95 percent accuracy.

The study was small, with just 40 subjects, ages 8-15, recruited from the Institute for Sports Medicine at Ann & Robert H. Lurie Children's Hospital of Chicago. But the children who had been diagnosed with a concussion showed a distinct neural signature, compared with a control group of children with no concussion history.

Three sensors attached to the scalp measured the "frequency following response," electrical signals in the brain evoked by listening to speech. The brains of the concussed children registered smaller and slower responses to the pitch of a speaker's voice than the control group. The scientists also found that for 11 of the 20 concussed children who came for follow-up visits, auditory processing improved with recovery from the brain injury.

NATURE | NEWS

Brain scan hints at first simple test for concussion

Small study suggests long-sought biological marker for brain injuries.

Lisa Vincenz-Donnelly

22 December 2016

A biological marker for concussion could make it easier to diagnose the problem on the sports field, and track recovery.

www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

Auditory biological marker of concussion in children

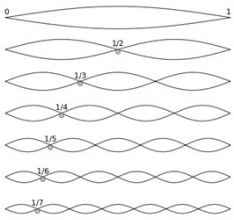
Nina Kraus[1,2,3,4], Elaine C. Thompson[1,2], Jennifer Krizman[1,2], Katherine Cook[5,6], Travis White-Schwoch[1,2] & Cynthia R. LaBella[5,6]

Received: 02 August 2016
Accepted: 14 November 2016
Published: 22 December 2016

Concussions carry devastating potential for cognitive, neurologic, and socio-emotional disease, but no objective test reliably identifies a concussion and its severity. A variety of neurological insults compromise sound processing, particularly in complex listening environments that place high demands on brain processing. The frequency-following response captures the high computational demands of sound processing with extreme granularity and reliably reveals individual differences. We hypothesize that concussions disrupt these auditory processes, and that the frequency-following response indicates concussion occurrence and severity. Specifically, we hypothesize that concussions disrupt the processing of the fundamental frequency, a key acoustic cue for identifying and tracking sounds and talkers, and, consequently, understanding speech in noise. Here we show that children who sustained a concussion exhibit a signature neural profile. They have worse representation of the fundamental frequency, and smaller and more sluggish neural responses. Neurophysiological responses to the fundamental frequency partially recover to control levels as concussion symptoms abate, suggesting a gain in biological processing following partial recovery. Neural processing of sound correctly identifies 90% of concussion cases and clears 95% of control cases, suggesting this approach has practical potential as a scalable biological marker for sports-related concussion and other types of mild traumatic brain injuries.

SCIENTIFIC REPORTS | 6:39009 | DOI: 10.1038/srep39009

The fundamental frequency is the lowest frequency of a periodic waveform. In music, the fundamental is the musical pitch of a note that is perceived as the lowest partial present.



Since the fundamental is the lowest frequency and is also perceived as the loudest, the ear identifies it as the specific pitch of the musical tone....The individual partials are not heard separately but are blended together by the ear into a single tone.

Background

- The fundamental frequency is one of the chief acoustic cues for everyday listening. The brain tracks the fundamental frequency to facilitate pitch perception and thus identify sounds.
- Sound processing is one of the most computationally-demanding tasks the nervous system has to perform, which means the auditory system is sensitive to neurological insults.
- Frequency following responses (FFRs) are electrical signals of brain activity associated with sound processing that are measured by scalp electrodes.
- The investigators predicted that children with a concussion would have poorer neural processing of the fundamental frequency as measured by frequency following responses (FFRs).

Methods 1

Two groups of children participated in this study. The concussion group (*N* = 20, mean age = 13.39 yr) met clinical diagnostic criteria for a concussion following medical evaluation by a sports medicine physician with expertise in concussion diagnosis and management. The control group (*N* = 20, mean age = 13.64 yr) was recruited through school flyers and word of mouth; none reported a history of brain injury.

Methods 2

Frequency-following responses (FFRs) were elicited by a 40 ms sound. Stimuli were delivered to the right ear through an earphone in the right ear.

Frequency-following responses (FFRs) were measured using 3 electrodes attached to the scalp.

Results

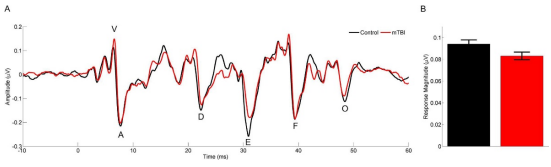


Figure 2. Children with a concussion have smaller and slower neural responses to speech.

Panel A compares the average frequency following responses (FFRs) for the concussion group (red) with the average frequency following responses (FFRs) for the control group (black). Panels A and B show that when compared with brain responses in control subjects, brain responses in concussed subjects were smaller over the consonant-vowel transition from peak D to peak E (peaks can be positive or negative). Error bars represent ± S.E.M. In addition, Panel A shows that brain responses of concussed children were slower by fractions of a millisecond than those of their non-concussed peers for 3 of the 6 peaks (peaks A, D, and E).

Logistic regression was used to convert these differences into a summary score. The investigators then selected a cutoff value for the summary score that best discriminated concussed from non-concussed children.

Operating Characteristics of the Summary Score

Test result	Concussion: Yes	Concussion: No	Total
Positive	18	1	19
Negative	2	19	21
Total	20	20	40

Sensitivity = 18/20 = 0.90
Specificity = 19/20 = 0.95

EPID 550 Homework Assignment 1

(Due at the beginning of class on Wednesday Jan 23)

Using the Auditory Test to Evaluate High School and College Football Players for Concussion

Background

High school and college football players are at risk for chronic traumatic encephalopathy, which can have devastating consequences. Most observers believe that recognizing concussion is an important step in preventing chronic traumatic encephalopathy. Traditional methods for recognizing concussion have uncertain accuracy and can be influenced by patient responses, and most of them take more time than is practical during game conditions. The Auditory test (*Scientific Reports*. 6:39009. DOI: 10.1038/srep39009) cannot be influenced by patient responses and may be brief enough to be used during game conditions.

Problem

Assume that the sensitivity of the Auditory test is 0.90 and the specificity is 0.95. Also assume that when a trainer suspects a football player might have a concussion, three-quarters of the players eventually have a concussion confirmed and one-quarter have a concussion ruled out during a subsequent evaluation by a neurologist that includes specialized testing. Finally, assume that a trainer uses the Auditory test during a game to examine a player who might have a concussion and then refers the player to a neurologist for further evaluation.

1. What is the probability that the player will eventually have a concussion confirmed if the Auditory test result is positive?

2. What is the probability that the player will eventually have a concussion ruled out if the Auditory test result is negative?

Use all 5 methods described in the first class session to answer these 2 questions. The 5 methods are the 2by2-table method, the Bayes' Theorem method, and the 3 methods that use the likelihood ratio (LR) -- the traditional method, Henry's modification of the traditional method, and the method using a nomogram. Use 4 decimal places for the answers. (In general, use 4 decimal places in this course for describing answers to questions on homework assignments, quizzes, and examinations, unless there is a good reason for using more or fewer decimal places.) Recognize that 4 decimal places in a probability, for example, 0.1234, is the same precision as 2 decimal places in a percentage, for example, 12.34%.

3. If the Auditory test result is negative, should the player be allowed to continue playing. Why? Or, why not?

A Quiz without Grades

Now that you know the basics, think about answers to the following questions

If sensitivity and specificity answer clinically irrelevant questions, why are they so often used to describe the operating characteristics of diagnostic tests? Why not use predictive values instead?

If you want to be confident that you can detect all the people with disease, should you use a test with a high sensitivity or a high specificity?

If you want to be confident that a positive test result means disease is present, should you use a test with a high sensitivity or a high specificity?

If you want to be confident that a negative test result means disease is absent, should you use a test with a high sensitivity or a high specificity?

You want to conduct a screening program of donated blood to identify units of blood that are infected with HIV, and you have two diagnostic tests with different sensitivities and specificities for HIV infection. How should you combine them?

- Test the donated blood first using the diagnostic test with higher sensitivity, and then test all the units that had a positive result using the diagnostic test with higher specificity
- Test the donated blood first using the diagnostic test with higher specificity, and then test all the units that had a negative result using the diagnostic test with higher sensitivity

What does the size of the predictive value (positive or negative) depend on?

Test sensitivity?

Test specificity?

Prevalence (or probability) of disease?