Evidence Based Medicine: 
Articles of Diagnosis

Duke University School of Medicine 
EBM Course 
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Jamie Fox, MD 
David Ming, MD 
Departments of Internal Medicine and Pediatrics
Diagnosis
Why conduct diagnostic tests?

WE’LL DO AN MRI TO BE SURE, BUT I’M FAIRLY CERTAIN IT’S A SWANNOMA
Objectives

• To introduce key concepts for understanding articles of diagnosis

• To briefly review the validity criteria for the appraisal of articles of diagnosis

• To understand the concepts behind core statistical measures seen in articles of diagnosis

• To practice application of core statistical measures through review of real-world examples
DIAGNOSIS ARTICLES: CORE CONCEPTS
Probability Estimates

• Pre-test Probability
  – The probability of the target condition being present before the results of a diagnostic test are known.

• Post-test Probability
  – The probability of the target condition being present after the results of a diagnostic test are known.
Pre-test Probability

• An estimate of how likely it is that a patient has a specific disease *before any additional testing is done*

• Where does this come from?
  – Clinical judgment after H&P (and other tests)
  – Prevalence of disorder in your population
    • Epidemiologic data
  – Clinical manifestations of disease articles
  – Differential diagnosis articles

• Clinical presentation also influences our pretest probability of disease
  – Example: typical anginal symptoms increase the pretest probability for CAD
Diagnostic Tests Spur Action

Zone of Action

LR

Probability of Diagnosis

LR

Zone of Uncertainty

LR

Zone of Action

Test Threshold

0%

Probability below test threshold: no testing warranted

Probability between test and treatment threshold: further testing required

Probability above treatment threshold; testing completed; treatment commences

Treatment Threshold

100%
Treatment Threshold

- How certain you’d like to be of a diagnosis before proceeding with treatment

- Depends on:
  - Risk of not treating
  - Risk/cost/burden/scarcity of therapy
  - Patient preferences
Test Threshold

• AKA: Observation or “Do Nothing” Threshold

• How certain you’d like to be that a patient does not have a diagnosis before you are comfortable withholding treatment and/or doing no further testing

• Depends on:
  – Risk of not treating
  – Risk/cost/burden/scarcity of therapy
  – Patient preferences
Volunteer #1 please
Clinical Presentation
Differential Diagnosis
Pre-test Prob 30%

LR+ 25

LR- 0.2
Volunteer #2 please
Clinical Presentation

?
Differential Diagnosis
Pre-test Prob 20%

<table>
<thead>
<tr>
<th># correct</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
</tr>
</tbody>
</table>
DIAGNOSIS:

CASE DISCUSSION
The 5 A’s

Evidence-based Medicine Cycle

ASSESS

ASK

ACQUIRE

APPLY

APPRAISE
You are an ED physician and you’ve just evaluated a 5yoM brought in by his parents for evaluation of abdominal pain which began yesterday.

Pain began 36hrs ago and is located near his belly button. He developed a fever 12 hours ago and feels nauseated. No trauma. He’s vomited twice (NBNB) and diarrhea x 2 today. Previously healthy w/o abd surgery.

PE:
AFVSS. Appears ill but seems to move w/o discomfort.
CTAB
NABS, soft, diffuse abd TTP including RLQ
Rest of exam is unremarkable.

WBC 14K
75S/4B/20L
Urine normal
To Image or Not to Image??

1. NONE
2. US
3. CT
What is your best estimate (probability) that he has acute appendicitis?

1. 0-10%
2. 11-20%
3. 21-30%
4. 31-40%
5. 41-50%
6. 51-60%
7. 61-70%
8. 71-80%
9. ≥81%
Pre-test Probability

• An estimate of how likely it is that a patient has a specific disease *before any additional testing is done*

• Where does this come from?
  – Clinical judgment after H&P (and other tests)
  – Prevalence of disorder in your population
    • Epidemiologic data
  – Clinical manifestations of disease articles
  – Differential diagnosis articles

• Clinical presentation also influences our pretest probability of disease
  – Example: typical anginal symptoms increase the pretest probability for CAD
Let’s say he never had a fever and his WBC is 8K with 50S/0B/40L.
What is your best estimate (probability) that he has appy?

1. 0-10%
2. 11-20%
3. 21-30%
4. 31-40%
5. 41-50%
6. 51-60%
7. 61-70%
8. 71-80%
9. ≥81%
No fever, nl WBC, diffuse abd TTP including RLQ

1. NONE
2. US
3. CT
Let’s say he is febrile in the ED, has focal TTP in RLQ, and WBC 25K.
What is your best estimate (probability) that he has appy?

1. 0-10%
2. 11-20%
3. 21-30%
4. 31-40%
5. 41-50%
6. 51-60%
7. 61-70%
8. 71-80%
9. ≥81%
Febrile with focal RLQ TTP and WBC 25K

1. NONE  2. US  3. CT
How certain do you need to be to consult your friendly Pediatric surgeon to have him/her **CUT** open this child’s abdomen?

1. 50-60%
2. 61-70%
3. 71-80%
4. 81-90%
5. 91-99%
6. 100%
Treatment Threshold

• How certain you’d like to be of a diagnosis before proceeding with treatment

• Depends on:
  – Risk of not treating
  – Risk/cost/burden/scarcity of therapy
  – Patient preferences
How low would your suspicion of acute appendicitis need to be in order to discharge this patient home?

1. <1%
2. 1%
3. 5%
4. 10%
5. 20%
Observation/Test Threshold

• AKA: Observation or “Do Nothing” Threshold

• How certain you’d like to be that a patient does not have a diagnosis before you are comfortable withholding treatment and/or doing no further testing

• Depends on:
  – Risk of not treating
  – Risk/cost/burden/scarcity of therapy
  – Patient preferences
Study Architect

Validity criteria for a Diagnostic Test Article

1. Physicians faced diagnostic uncertainty

2. Every patient underwent reference (gold) standard

3. The test being evaluated didn’t influence the decision to perform reference (gold) standard

http://www.crutcherstudio.com/architect_services.htm
Searching  ......
Your sessions with the medical librarians pay off!

**Effectiveness of a Staged US and CT Protocol for the Diagnosis of Pediatric Appendicitis: Reducing Radiation Exposure in the Age of ALARA**

<table>
<thead>
<tr>
<th>Purpose:</th>
</tr>
</thead>
<tbody>
<tr>
<td>To evaluate the effectiveness of a staged ultrasonography (US) and computed tomography (CT) imaging protocol for the accurate diagnosis of suspected appendicitis in children and the opportunity for reducing the number of CT examinations and associated radiation exposure.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Materials and Methods:</th>
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</thead>
<tbody>
<tr>
<td>This retrospective study was compliant with HIPAA, and a waiver of informed consent was approved by the institutional...</td>
</tr>
</tbody>
</table>
DIAGNOSIS MATH:
SENSITIVITY AND SPECIFICITY
A Few Ground Rules

• No jargon
  – Define stats using “real English”

• No formula memorization
  – Focus on the principles behind the calculations
The 2x2 Table!!
### “The Truth”

Allah, Buddha, God

Reference Standard Test

<table>
<thead>
<tr>
<th>Test</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>+</td>
<td>+ True Positive</td>
</tr>
<tr>
<td>-</td>
<td>- False Negative</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference Standard Test</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
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</tr>
<tr>
<td>-</td>
<td>- False Negative</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>True Positive</th>
<th>False Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Negative</td>
<td>True Negative</td>
</tr>
</tbody>
</table>
Sensitivity

Of all patients with disease, the proportion with a positive test

<table>
<thead>
<tr>
<th></th>
<th>Disease</th>
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<tbody>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- **True Positive**: True Positive + False Negative

- **False Positive**: False Positive

- **False Negative**: False Negative

- **True Negative**: True Negative

“Positive in Disease” (PID)
Specificity

Of patients without disease, the proportion with a negative test

<table>
<thead>
<tr>
<th></th>
<th>Disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>True Negative</strong></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>True Negative + False Positive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>False Positive</strong></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>False Negative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>True Negative</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“Negative in Health”

NIH
Limitations of Sensitivity and Specificity

• Our question isn’t really:
  “If my patient has an appy, what is his chance of having a (+) US?”

• Really what we want to know is:
  “If my patient has a (+)US what is the chance he has an appy?”

  OR

  “If my patient has a (-)US what is the chance he has an appy?”
LIKELIHOOD RATIOS
Likelihood Ratios...better than Sensitivity and Specificity

• Combine components of Sens and Spec

• “Portable” calculation
  – Applicable for individual patients
  – Useful at the bedside

• Help to move us from uncertainty into “zones of action”
Likelihood Ratio - Concept

• How likely is it that a patient with disease will have a given test result, compared to how likely is it that a patient without disease will have the SAME test result?

• Both positive and negative likelihood ratios compare the likelihood of the SAME test result in the presence of disease versus in the absence of disease.
Likelihood Ratio - Concept

\[
\text{Likelihood Ratio (LR)} = \frac{\text{Test Result Disease (+)}}{\text{Test Result Disease (-)}}
\]

- \( LR > 1 \rightarrow \) Test result more likely present in \( \text{Dz (+)} \)
- \( LR < 1 \rightarrow \) Test result more likely present in \( \text{Dz (-)} \)
- \( LR = 1 \rightarrow \) Test results equally likely in \( \text{Dz (+)} \) and \( \text{(-)} \)
## Positive vs Negative LR - Concept

### Positive Likelihood Ratio

<table>
<thead>
<tr>
<th>Proportion of patients with disease with positive test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients without disease with positive test</td>
</tr>
</tbody>
</table>

### Negative Likelihood Ratio

<table>
<thead>
<tr>
<th>Proportion of patient’s with disease with negative test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patient’s without disease with negative test</td>
</tr>
</tbody>
</table>
Positive vs Negative LR – Practice

Positive Likelihood Ratio

Proportion of patients **with** Strep throat with **positive** rapid strep

Proportion of patients **without** Strep throat with **positive** rapid strep

Negative Likelihood Ratio

Proportion of patient’s **with** strep throat with **negative** rapid strep

Proportion of patient’s **without** strep throat with **negative** rapid strep
Likelihood Ratio
continuous variables

Compares a given test result in the presence of disease versus in the absence of disease

LR for WBC > 15 in diagnosing appendicitis

Proportion of patient’s with appendicitis with WBC > 15

Proportion of patient’s without appendicitis with WBC > 15
Test = rapid flu   Disease = influenza

**LR+**

Proportion of patients **with** Influenza with **positive** rapid flu

Proportion of patients **without** Influenza with **positive** rapid flu

**LR-**

Proportion of patient’s **with** influenza with **negative** rapid flu

Proportion of patient’s **without** influenza with **negative** rapid flu
Test = high prob VQ  Disease = PE

\[ LR_{\text{high prob VQ}} \]

Proportion of patients \textbf{with} PE with high prob VQ

\[ \frac{\text{Proportion of patients with PE with high prob VQ}}{\text{Proportion of patients without PE with high prob VQ}} \]

Proportion of patients \textbf{without} PE with high prob VQ
**Definitions**

**Likelihood ratio of a positive test:** Proportion of patients with disease who have a positive test compared to the proportion of patients without disease who have a positive test.

\[
\text{Sensitivity} = \frac{TP}{TP + FN} \\
1 - \text{specificity} = \frac{FP}{FP + TN}
\]

<table>
<thead>
<tr>
<th>Disease</th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>TP</td>
<td>FP</td>
</tr>
<tr>
<td>-</td>
<td>FN</td>
<td>TN</td>
</tr>
</tbody>
</table>
Quick Understanding Check

• Do you want the LR+ to be?
  – As high as possible
  – As close to 1 as possible
  – As low as possible
Definitions

Likelihood ratio of a **negative** test: Proportion of patients with disease who have a **negative** test compared to the proportion of patients without disease who have a **negative** test.

\[
\frac{FN}{TP + FN} \times \frac{FP + TN}{TN} = 1 - \text{sensitivity}
\]

\[
\frac{TN}{FP + TN} = \text{Specificity}
\]
Quick Understanding Check

• Do you want the LR- to be?
  – As high as possible
  – As close to 1 as possible
  – As low as possible
LR Impact

LR = 0.01
Less Likely

LR = 0.1
Less Likely

LR = 0.2
Less Likely

LR = 1
No impact on likelihood of disease

LR = 5
More Likely

LR = 10
More Likely

LR = 100
More Likely

Increasing impact

0

Increasing impact

∞
LR Impact
“One, Five, Ten” Rule

<table>
<thead>
<tr>
<th>Value</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Not useful (no effect)</td>
</tr>
<tr>
<td>5 – 10</td>
<td>Moderately useful</td>
</tr>
<tr>
<td>0.2 (1/5) – 0.1 (1/10)</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>Very useful</td>
</tr>
<tr>
<td>&lt;0.1</td>
<td></td>
</tr>
</tbody>
</table>
**LR+:** Proportion of patients with appendicitis who have a positive US compared to the proportion of patients without appendicitis who have a positive US.

<table>
<thead>
<tr>
<th>U/S</th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>152</td>
<td>24</td>
</tr>
<tr>
<td>Equivocal</td>
<td>81</td>
<td>587</td>
</tr>
<tr>
<td>-</td>
<td>2</td>
<td>155</td>
</tr>
</tbody>
</table>

\[
\text{LR}_+ = \frac{\frac{152}{235}}{\frac{24}{766}} = 21
\]
**LR-**: Proportion of patients with appendicitis who have a negative US compared to the proportion of patients without appendicitis who have a negative US.

<table>
<thead>
<tr>
<th></th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>U/S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
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<td>24</td>
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<td>587</td>
</tr>
<tr>
<td>-</td>
<td>2</td>
<td>155</td>
</tr>
</tbody>
</table>

\[
\text{LR}_- = \frac{\frac{2}{235}}{\frac{155}{766}} = 0.04
\]
**LR_{Equiv}**: Proportion of patients with appendicitis who have an equivocal US compared to the proportion of patients without appendicitis who have an equivocal US.

<table>
<thead>
<tr>
<th>U/S</th>
<th>+</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendicitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>152</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>81</td>
<td>587</td>
</tr>
<tr>
<td>-</td>
<td>2</td>
<td>155</td>
</tr>
</tbody>
</table>

\[
\text{LR}_{\text{Equiv}} = \frac{81}{235} \div \frac{587}{766} = 0.45
\]
Likelihood Ratio Advantages

1. Can apply to individual patients

2. Incorporates test and treatment thresholds

3. Can calculate for different cut-offs of test result
You are an ED physician and you’ve just evaluated a 5yoM brought in by his parents for evaluation of abdominal pain which began yesterday.

Pain began 36hrs ago and is located near his belly button. He’s developed a fever 12 hours ago and feels nauseated. No trauma. He’s vomited twice (NBNB) and diarrhea x 2 today. Previously healthy w/o abd surgery.

PE:
AFVSS. Appears ill but seems to move w/o discomfort.
CTAB
NABS, soft, diffuse abd TTP including RLQ
Rest of exam is unremarkable.

WBC 14K
75S/4B/20L
Urine normal
Let’s use the LRs

http://www.cebm.net/index.aspx?o=1161

http://araw.medde.uic.edu/cgi-bin/testcalc.pl
\( \text{LR}^+ \ 21 \)

\( \text{LR}_{\text{Equiv}} \ 0.45 \)

\( \text{LR}^- \ 0.04 \)
Questions?
Summary

• To introduce key concepts critical for understanding diagnosis articles
  – Diagnostic tests move us from a “zone of uncertainty” to “zones of action” (crossing the test or treatment threshold)
  – Always assess the pre-test probability

• To summarize the validity criteria for the appraisal of diagnosis articles
  – Did every patient receive the diagnostic test under study and an appropriate reference (gold) standard?

• To understand concepts behind key statistical measures seen in diagnosis articles
  – “Truth lies in the heavens above” – always set up the 2x2 table the same way
  – “A Ratio is A Ratio is A Ratio,” ratios use division, and all ratios are >1/<1/=1
  – Remember the plain English definitions for sensitivity, specificity, and LR
  – High +LR and Low –LR are best

• To practice calculating core statistical measures in real-world examples
  – U/S for appy in 3 different cases w/ different pre-test probabilities