Evidence Based Medicine

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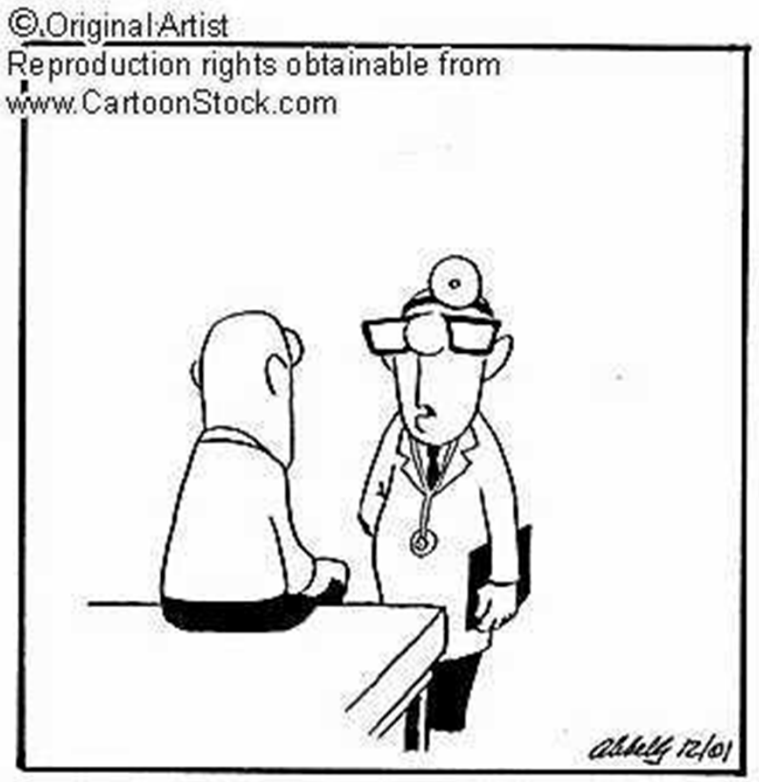
Clinical Epidemiology

Module 2: Applying EBM to Diagnosis



"I'm not really sure what it is but five or six thousand dollars of tests should help me figure it out."

Content

- 1. Phases of diagnostic research
- 2. Developing a new test for lung cancer
- 3. Thresholds
- 4. Critical appraisal of a diagnostic article

Potential new diagnostic test and treatment for lung cancer

- **The finance will enable Cizzle to progress its research into a potential new method of diagnosing and treating lung cancer, based on the discovery of the role that the protein Ciz 1 appears to play in triggering DNA replication and cell growth. As cancer is associated with abnormal cell growth, the Cizzle team ultimately hope to confirm that blocking the actions of this protein will prevent tumours from occurring or slow down the growth of existing tumours.**

http://www.news-medical.net/?id=18874

Using Ciz1 as a diagnostic tool ?

- How can you determine whether measuring Ciz1 in the blood can help you make the diagnosis of lung cancer ?

There are 4 phases in diagnostic research

1. Phases in Diagnostic Research

- Phase 1: Do patients with the target disorder have different test results from normal individuals?
- The answer requires a comparison of the distribution of test results among patients known to have the disease and people known not to have the disease.

Phases in Diagnostic Research

- Phase 2: Are patients with certain test results more likely to have the target disorder than patients with other test results
- This can be studied in the same dataset that generated the Phase I answer, but now test characteristics such as sensitivity and specificity are estimated.

Phases in Diagnostic Research

- Only if Phase I and Phase II studies, performed in “ideal circumstances”, are sufficiently promising as to possible discrimination between diseased and non-diseased subjects, it is worth evaluating the test under “usual” circumstances. Phase III and IV questions must then be answered.

Phases in Diagnostic Research

- Phase 3: Among patients in whom it is clinically sensible to suspect the target disorder, does the test result distinguish those with and without the disorder?
- To get the appropriate answer, a consecutive series of such patients should be studied.

Phases in Diagnostic Research

- The validity of Phase III studies is threatened when cases where the reference standard or diagnostic test is lost, not performed, or indeterminate, are frequent or inappropriately dealt with.
- Because of a varying patient mix, test characteristics such such as sensitivity, specificity and likelihood ratios may vary between different healthcare settings.

Phases in Diagnostic Research

- Phase 4: Do patients who undergo the diagnostic test fare better (in their ultimate health outcomes) than similar patients who do not?
- These questions have to be answered by randomising patients to undergo the test of interest or some other (or no) test.

2. Using Ciz1 as new diagnostic test for lung cancer (hypothetical)

- 100 patients with proven lung Cancer (group 1)
- 100 patients without known lung Cancer (group2)

Phase 1

- You find Ciz1 positive in 80% of group1 and 10% of group 2
- You feel you have answered a Phase 1 question and that you need to continue

Phase 2

	Lung Cancer	No Lung Cancer	
Ciz1 positive	80	10	90
Ciz1 negative	20	90	110
	100	100	

	Lung Cancer	No Lung Cancer	
Ciz1 positive	80	10	90
Ciz1 negative	20	90	110
	100	100	

1. What % of tests are positive in those with lung cancer ?

2. What % of tests are negative in those without lung cancer ?

1. What is 1 called ?
2. What is 2 called ?

Phase 3

- You are so impressed with the results that you now use your venture capital to do a Phase 3 study
- All patients referred to the lung unit for suspected lung cancer get a Ciz 1 blood test and a full workup for lung cancer (the gold standard is histology of a biopsy specimen of a lung mass noted on X ray)

Your findings in Phase 3

	Lung Cancer	No Lung Cancer	
Ciz1 positive	140	80	220
Ciz1 negative	60	320	380
	200	400	

Your questions answered

- % of test positive in those with disease
- (sensitivity or true positives) =140/200=70%
- % of test negatives in those without disease
- (specificity of true negatives)=320/400=80%

- How useful is sensitivity and specificity ?

Sensitivity and Specificity

- This tells you how the test would perform if you knew if the patient had cancer or not.
- The problem is that as the physician at the lung clinic you do not know the disease status of the patient
- Sens = P (T+/D+) Spec=P(T-/D-)
- You want P (D+/T+) or P(D-/T-)

Sens and Spec

- You want P (D+/T+) or P(D-/T-) !!!!
- However all is not lost
- Sensitivity and Specificity is useful using SPin and Snout
- A positive specific test rules IN disease
- A negative sensitive test rules OUT disease
- BUT you still don't know how likely is disease if you test positive (what is the chance that I have cancer doctor?)

- You want P (D+/T+) or P(D-/T-)
- What is this called ?
- P (D+/T+) = Positive Predictive value
- = 140/220=64%
- P(D-/T-)= Negative Predictive value
- =320/380=84%

	Lung Cancer	No Lung Cancer	
Ciz1 positive	140	80	220
Ciz1 negative	60	320	380
	200	400	

PPV and NPV

- So this means that if Ciz1 comes back positive the patient has a 64% chance (probability) of having lung cancer
- (also called post test probability)
- If it comes back negative you can tell the patient that there is a 84% chance that he does not have lung cancer
- You feel this is of much greater value

PPV and NPV

- BUT PPV and NPV is greatly influenced by Prevalence
- What is the prevalence in your study ?
- = 200/600=33%

	Lung Cancer	No Lung Cancer	
Ciz1 positive	140	80	220
Ciz1 negative	60	320	380
	200	400	

PPV and NPV

- What would happen if you use Ciz1 for screening for lung cancer in the general population where the prevalence of lung cancer may be so low as 1% ??
- The sensitivity (70%) and specificity(80%) of Ciz1 stays exactly the same

PPV and NPV

	Lung Cancer	No Lung Cancer	
Ciz1 positive	7	198	205
Ciz1 negative	3	792	795
	10	900	1000

PPV and NPV

- What happens to the PPV and NVP now ?
- PPV=7/205= 3.4%
- NPV= 99.6%
- So what happens if we move from a high prevalence to a low prevalence setting ?

	Lung Cancer	No Lung Cancer	
Ciz1 positive	7	198	205
Ciz1 negative	3	792	795
	10	900	1000

Prevalence

- The background prevalence in the group of people you are testing is also called the
- Pre test probability
- (Important later)
- In the lung unit there is a high pre test probability and in the community a low pre test probability

Likelihood ratios

- Is there some other parameter we can use that is not dependent on the prevalence ?
- Yes: likelihood ratio
- We will use Likelihood ratio of a positive test

Likelihood ratios

- LR + = P(T+/D+)/P(T+/D-)
- = Sens/(1-Spec) !
- =(140/200)/(80/400)
- = 3.5
- You are 3.5 times more likely to have Ciz1 positive if you have lung cancer than if you don't have lung cancer

	Lung Cancer	No Lung Cancer	
Ciz1 positive	140	80	220
Ciz1 negative	60	320	380
	200	400	

Advantages of LR

- Used in Bayesian reasoning
- eg.Post test odds of having a disease
- = pretest odds of disease x LR
- eg. Easier to use Fagan`s nomogram

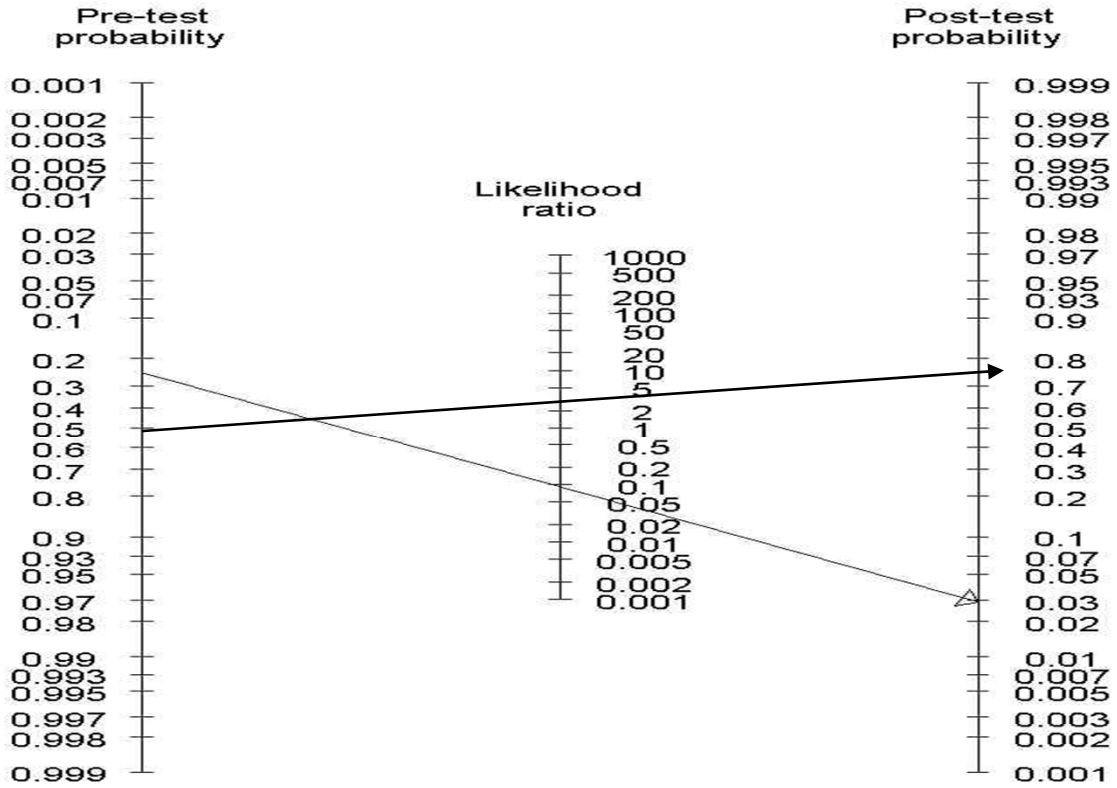
Likelihood ratio and Rev Bayes

- Lung Cancer
- Prevalence = 50% = *pretest probability*
- Pretest odds = 1 = (0.5/1-0.5)
- We have a + Ciz1, LR =3.5
- = 1 x 3.5 = post test odds
- 3.5/(1+3.5) = 78% = *post test probability* of having lung cancer

Likelihood ratio	Change in Probability in disease
10	+45
9	+40
6	+35
5	+30
4	+25
3	+20
2	+ 15
1	No change
0.5	-15
0.4	-20
0.3	-25
0.2	-30
0.1	-45

(Mc. Gee S . Simplifying likelihood ratios. J Gen Intern Med 2002, 17:646 – 649)

FAGAN Nomogram



Odds ratio

- Sometimes we use sophisticated statistics such as logistic regression to determine the association between a test (or patient characteristic such as age) and disease
- Advantage=we can use all the information we have (age gender history and test)
- Example: Odds ratio for Ciz1 positive in lung cancer=4

Odds ratio

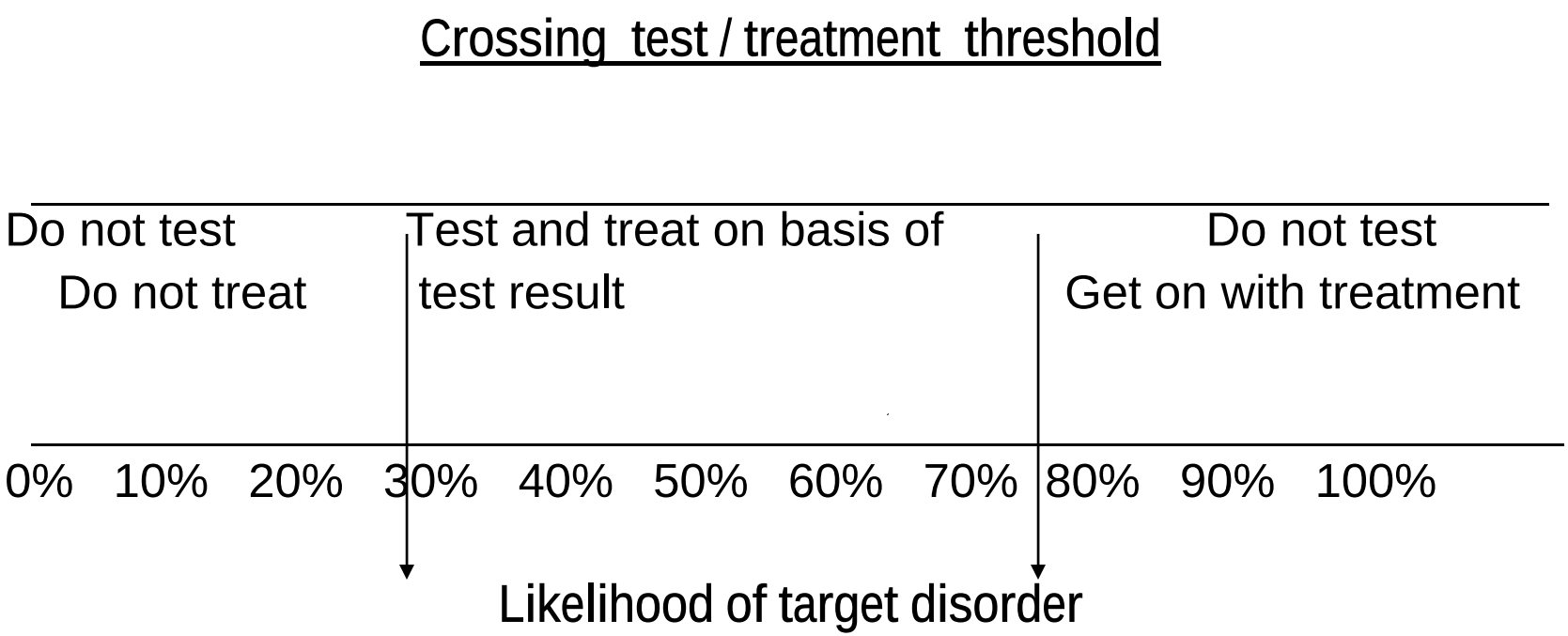
- OR = 4
- This means that you are 4 times more likely to have lung cancer if you test positive than if you test negative
- (NB!!!! Careful, this is different from a LR+, what`s the difference?)

4. Thresholds:

- The whole reasoning behind the diagnostic process is that you gather information until a certain threshold is reached (at which stage you either treat or send home!)

Thresholds

AIM: to use clinical and non clinical factors to cross thresholds



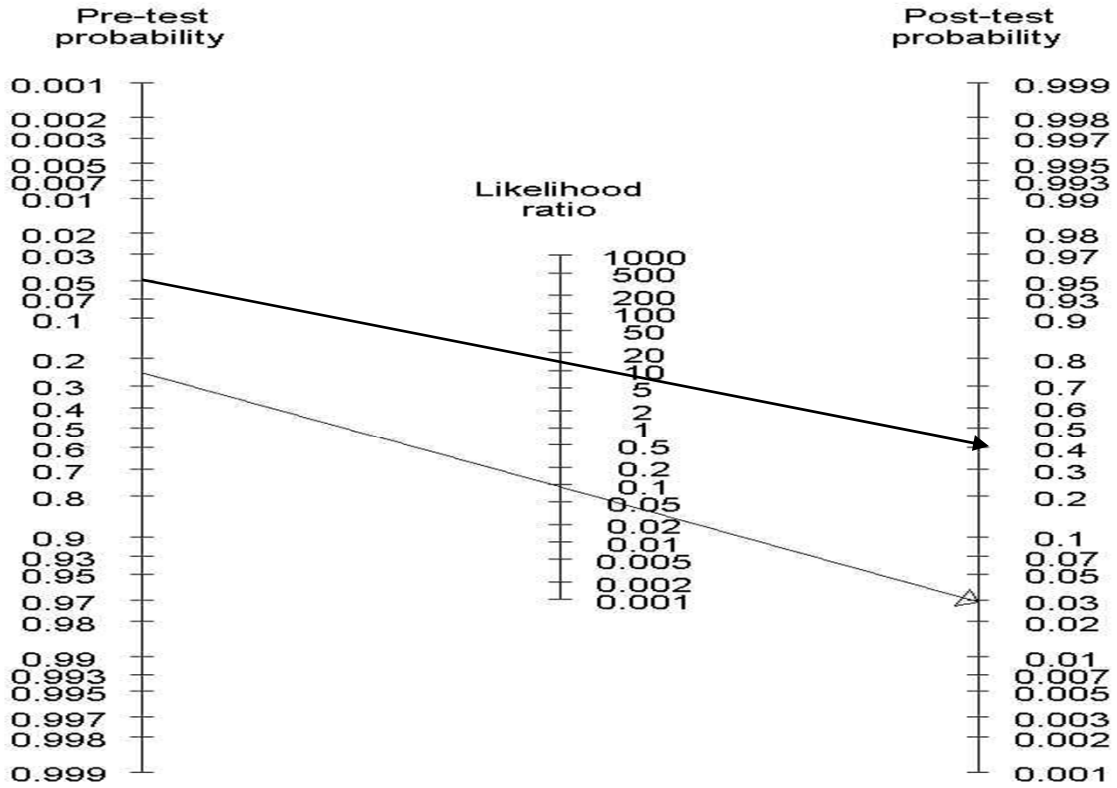
MCHUMOR.COM by T. McCracken

"Off hand, I'd say you're suffering from an arrow through your head, but just to play it safe, I'm ordering a bunch of tests."

Thresholds:

- Example:
- young female with chest pain
- Pre test probability low (<10%)
- History not typical of angina at all
- So post test probability even lower: send home
- What if you did a stress ECG and it seems positive ?? (stupid!)

Thresholds:


Pre-test probability
0.001
0.002
0.003
0.005
0.007
0.01
0.02
0.03
0.05
0.07
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
0.93
0.95
0.97
0.98
0.99
0.993
0.995
0.997
0.998
0.999
Likelihood ratio
1000
500
200
100
50
20
10
5
2
1
0.5
0.2
0.1
0.05
0.02
0.01
0.005
0.002
0.001
Post-test probability
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0.02
0.01
0.007
0.005
0.003
0.002
0.001

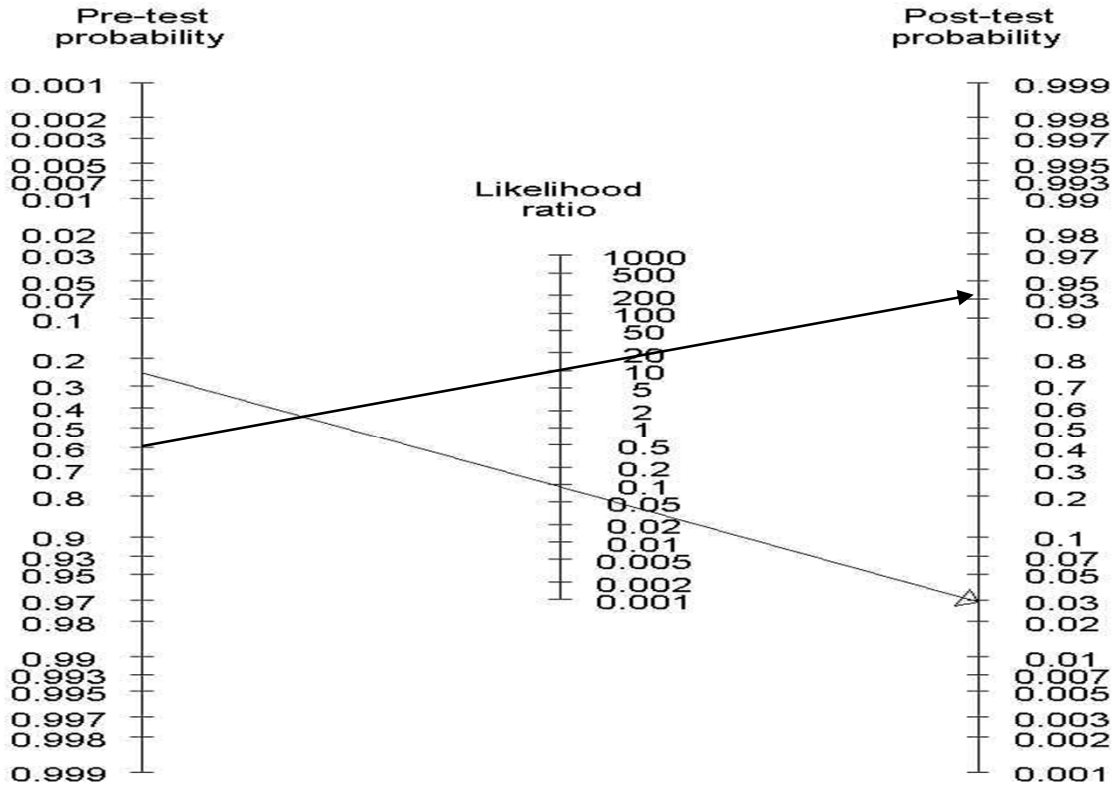
Thresholds:

- She still only has a post test probability < 40% (if we assume a positive stress has a LR of 10)

Thresholds:

- Male of 65 with DM and HT with chest pain
- pre test probability high (>50%)
- History typical of angina
- Post test probability now higher
- Need angiogram to decide on definitive treatment
- What is you did a stress ECG on him ?

Thresholds: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0.002
0.001

Thresholds:

- Now the Post test probability is >90%
- Thresholds depend on the type of disease and situation: in some instances you may want to start treatment at a threshold of 40% (eg giving medication) and in others you want >90% (eg doing a thoracotomy)

4. Critical Appraisal in Diagnostic research

- Remember in appraising any study
- 1. Is the study valid ?
- 2. What are the results ?
- 3. Can I apply it in my practice ?

1. Are the Results of this Diagnostic study Valid?

- Was there a comparison which was:
  - Independent
  - Blind
  - Gold standard reference
  - Applied to every patient/case
- Did the patient sample include an appropriate spectrum of patients?

1. Are the Results Valid? Cont.

- Did the results influence the decision to perform the Reference standard
  - Verification or workup bias
- Were the methods of performing the test described in sufficient detail to permit replication?

2. What Are the Results?

- In what form are the results presented and how useful are they?
  - Sensitivity /Specificity
  - Predictive values
  - Likelihood ratios
- How precise is the estimate?
  - CI

3. Will the Result Help Me Caring for My Patients?

- Will the test be reproducible and interpretable in my setting?
  - Interrater agreement
  - Required skill for interpretation
- Are the results applicable to my patients?
  - Different mix of disease severity
  - Different distribution of competing conditions

Will the Result Help Me Caring for My Patients?

- Will the test result change my management?
  - Test threshold
  - Treatment threshold
- Will my patients be better of as a result of the test?
  - Does it add to what is available?