

THERAPEUTIC REASONING

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Objectives:

- 1) Learn how to answer the question: What do you do with the post-test probability once you've calculated it?
- 2) Learn when it is best to do nothing (observe), to test, or to treat empirically without testing.

Notes:

- 1) The underlying principle of treatment decisions: treat only if it does more good than harm. We will determine when it is appropriate to treat someone based on this principle.
- 2) The underlying principle of testing decisions: do not test unless it has the potential to change management. We will determine when it is appropriate to test someone based on this principle.

Treating and the Action Threshold

Case # 1: Disease is known for certain

For some patients, the presence of a particular disease is known for certain and the only question is whether treating the disease does more good than harm. Consider the following simple example. Suppose a new disease emerges. Fifty percent of people who develop the disease will die within a few weeks. A new drug is created to combat the new disease. Patients who have the disease and are treated with the new drug have only a 20% chance of dying.

Disease	Treat	Die	Live
present	no	50%	50%
present	yes	20%	80%

The benefit of treatment can be expressed as the difference in survival between the treated and untreated groups: $80\% - 50\% = 30\%$. This means that 30% of all diseased patients would have died if you hadn't treated them. The Net Benefit is therefore 30%. Under this simple scenario, it is obvious that treatment is indicated, since the Net Benefit is greater than zero and there does not appear to be any harm to taking the drug.

Case # 2: Presence of disease is not known for certain

Sometimes we suspect that a patient has a particular disease but we do not know for certain. Suppose that patients with the disease have the same outcomes (with and without treatment) as for Case # 1. But also suppose that treating patients who do not have the disease (you thought they had the disease but they really didn't) causes some harm. In this case, let's say that 10% of patients who do not have the disease but who are given the drug will die as result of side effects from the drug.

(Case # 2, continued)

Disease	Treat	Die	Live
present	no	50%	50%
present	yes	20%	80%
absent	yes	10%	90%
absent	no	0%	100%

Net Benefit of treating diseased patients: $80\% - 50\% = 30\%$

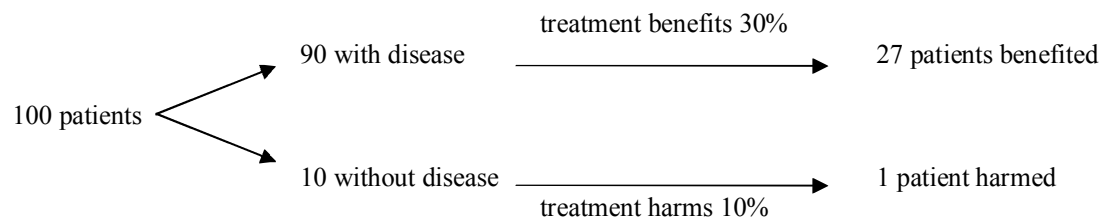
Net Harm of treating nondiseased patients: $100\% - 90\% = 10\%$

Questions

- If a patient had a 90% probability of disease and there were no other tests that could be done, would you treat or not treat? (Use intuition to answer this question)
- If a patient had a 10% probability of disease, would you treat or not treat? (Use intuition)
- Above what probability of disease is treatment indicated? In other words, above what probability of disease would treatment produce more good than harm?

Answer to (a):

If you had 100 patients, each with a probability of disease of 90%, then:



Since benefits outweigh harms, it is appropriate to treat a patient with a 90% probability of disease.

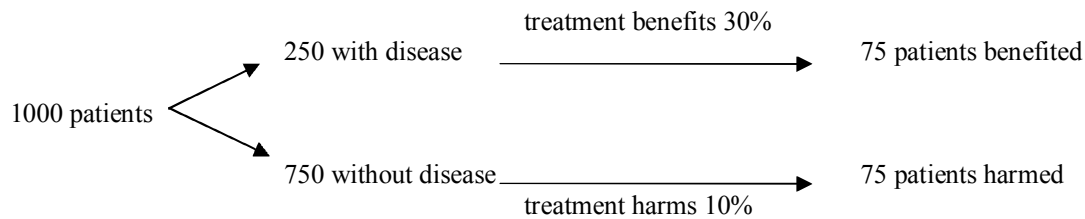
Answer to (b):

If you had 100 patients, each with a probability of disease of 10%, then:



Since harms from treating nondiseased patients outweigh the benefits of treating diseased patients, treatment should not be given to a patient with a 10% probability of disease.

Answer to (c):



A patient with a probability of disease of exactly 25% is equally as likely to get benefit from the treatment as to be harmed by the treatment. Therefore any patient with a probability of disease greater than 25% deserves treatment, as the likelihood of benefit for that patient will exceed the likelihood of harm. This is the same as saying that a patient with an odds of disease greater than 1/3 (probability of 25% → 25% / 100-25%) deserves treatment.

This probability (or odds) that marks the point above which action (treatment) is appropriate, and below which inaction (withholding treatment) is appropriate is called the action threshold (AT). Notice that this odds of disease (the action threshold) is related to the ratio of the Net Harm to the Net Benefit:

$$\text{AT (expressed in odds)} = \frac{1}{3} \qquad \frac{\text{Net Harm}}{\text{Net Benefit}} = \frac{10\%}{30\%} = \frac{1}{3}$$

This relationship should make sense. If the Net Benefit (among those with the disease) is 3 times as great as the Net Harm (among those without the disease), then the break-even point (the action threshold) should be when people without the disease are 3 times more common than people with the disease (i.e., when the odds of disease are 1/3). In a different scenario, with a different disease and a different treatment, if the Net Benefit among those with the disease is 7 times as great as the Net Harm among those without the disease, then the break-even point should be when people without the disease are 7 times more common than people with the disease (when odds of disease are 1/7 or probability of 12.5%).

Testing and the observe/test threshold and the test/treat threshold

Case # 3: Disease uncertain but a diagnostic test is available

When a clinician has a test available, there are three options the clinician can use: observe the patient (without testing or treating), use the test, or treat empirically without testing. Remember the underlying principle of testing decisions: do not test unless it has the potential for changing management.

For the following questions, use the data about disease and treatment from Case # 2. Suppose a simple test for the disease is available with a sensitivity of 90% and specificity of 70%.

- a) If a patient's pretest probability of disease is 99%, should we observe the patient (without testing or treating), use the test, or treat empirically without testing? You can check your intuitive answer by calculating the posttest probability of disease if the test is negative. Is that probability above or below the action threshold?

- b) If a patient's pretest probability of disease is 1%, should we observe, test or treat empirically? Again, check your intuition by calculating the probability of disease after a positive test. With that posttest probability, and given your action threshold, would it be appropriate to treat or not to treat? Does testing have the potential to change your management when starting at such a low pretest probability?
- c) Below what probability (or odds) of disease is it best just to observe (and not test or treat)? This is known as the observe/test threshold.
- d) Above what probability (or odds) of disease is it best to treat empirically (and not even test)? This is known as the test/treat threshold.
- e) Over what range of probabilities should we test? This is the range between the observe/test threshold and the test/treat threshold.

Answer to (c):

The probability (or odds) of disease below which testing is no longer helpful is when a positive test (LR+) cannot increase the probability (or odds) of disease above the action threshold. Since pretest odds x LR = posttest odds, the observe/test threshold (expressed in odds) can be calculated by the formula below:

$$\text{Observe/test}_{\text{odds}} \times \text{LR}^+ = \text{AT} \quad (\text{again, the observe/test threshold and the AT must be expressed in odds})$$

$$\text{Observe/test}_{\text{odds}} \times 90\% / 100 - 70\% = 1/3$$

$$\text{Observe/test}_{\text{odds}} = 1/9 \quad (\text{this is the observe/test threshold expressed in odds})$$

$$\text{Observe/test}_{\text{probability}} = 1 / (1+9) = 1/10 = 10\% \quad (\text{this is the observe/test threshold probability})$$

This means that when the pretest probability of disease is exactly 10%, the posttest probability after a positive test will be exactly at the action threshold. Therefore, when the pretest probability of disease is below 10%, it is best simply to observe the patient (don't test or treat), because for any pretest probability below 10% a positive test would not yield a posttest probability greater than the action threshold. (Remember, the action threshold marks the point above which the benefit of treatment exceeds the harms of treatment.) Even if the test were positive, it would still be best not to treat.

Answer to (d):

The probability (or odds) of disease above which testing is no longer useful is when the probability (or odds) of disease are so high that a negative test cannot lower the posttest odds below the action threshold.

$$\text{Test/Treat}_{\text{odds}} \times \text{LR}^- = \text{AT} \quad (\text{the test/treat threshold and the AT must be expressed in odds})$$

$$\text{Test/Treat}_{\text{odds}} \times 100 - 90\% / 70\% = 1/3$$

$$\text{Test/Treat}_{\text{odds}} = 7/3 \quad (\text{this is the test/treat threshold expressed in odds})$$

$$\text{Test/treat}_{\text{probability}} = 7 / (7+3) = 7/10 = 70\% \quad (\text{this is the test/treat threshold probability})$$

If we start with a pretest probability greater than 70%, even if the test is negative, the posttest probability will still be above the action threshold and the benefit of treatment will still exceed the harms of treatment. Since you would end up treating regardless of any test result, when the pretest probability of disease is above the test/treat threshold, it is best just to treat empirically without utilizing the test.

Answer to (e):

The testing range is the range of probabilities (or odds) between the observe/test threshold and the test/treat threshold. Based on the principle that a test is only useful if it has the potential to change management, any patient with a pretest probability of disease in the testing range can justifiably be tested. A patient with a pretest probability in this range should be treated if the test comes back positive and should not be treated if the test comes back negative (i.e., management will be different depending on test results). Patients with a pretest probability outside of this range (either below the observe/test threshold or above the test/treat threshold) should not be tested as the test result would not change management.

Points to remember:

- 1) An action threshold is based on the ratio of the net harms and net benefits of a disease and its treatment, but has nothing to do with any test characteristics.
- 2) The testing thresholds (observe/test threshold and test/treat threshold), on the other hand, depend on the test characteristics. They will be different for different tests. In addition to the characteristics of sensitivity, specificity and likelihood ratios, other aspects of a test (including the cost of the test, the risk of the test, and patient preferences) will affect the testing thresholds in ways that are beyond the scope of this handout.

Diagnostic and therapeutic reasoning: putting it all together

You have now completed the sessions on diagnostic and therapeutic reasoning. We hope the skills and tools you have learned will be useful as you continue to gain clinical knowledge and experience.

When a clinician is trying to determine the best way to manage a patient, he/she will have several variables in mind: how bad the disease is (harm of disease), how risky the treatment is (harm of treatment), how helpful the treatment is (benefit of treatment), how good (and costly, and risky) the test is, and how likely the patient is to have the disease in the first place (pretest probability). Ideally, the clinician will have access to accurate data for all these variables. The clinician can then plug all the numbers into the equations we have reviewed these sessions to come up with an action threshold and a treatment range. As you will observe, we often do not have the exact numbers on hand and clinicians usually do not explicitly calculate these thresholds. However, all clinicians, whether they know it or not, are using the above concepts whenever they make clinical decisions. The main reason to learn these concepts is to allow students (and clinicians) to become more conscious of the steps they are taking and the skills they are utilizing whenever they are making decisions. Bringing these concepts into the open facilitates the teaching and learning of clinical reasoning skills.

So, whenever you are participating in a clinical decision about patient management, try to formulate your thoughts using the terms and concepts from these sessions. For example, when you see a patient in the Emergency Department with chest pain, try to estimate a pretest (pre-history and physical) probability that the patient has coronary artery disease (or an aortic dissection, or a pulmonary embolism). Try to determine how much your history and physical has changed your pretest probability. Think about your threshold for ordering an EKG (or cardiac biomarkers) to evaluate the chest pain. Discuss to what degree an “abnormal EKG” or elevated biomarkers change your pretest probabilities. Appreciate subtle differences in each physician’s thresholds for admitting a patient to the hospital or for calling a cardiologist. Compare the different thresholds for giving nitroglycerin and for giving thrombolytics. For each of these decisions, you will be utilizing the concepts we have explored in these sessions. Keeping these concepts in the front of your mind as you are pondering these decisions will help to organize and reinforce your ever-growing clinical reasoning skills.