Diagnostic testing revisited: pathways through uncertainty

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To aid physicians who may be having difficulty applying the principles of decision analysis to diagnostic data according to the methods published in the past several years, the authors of this paper set out a few principles and schemes for using and interpreting diagnostic data obtained from dichotomous tests. They also present a simple BASIC program for calculating post-test probabilities from likelihood ratios and pretest probabilities that a particular disease is present in a particular patient; the program can be adapted for use on microcomputers.

Physicians have at their disposal a vast arsenal of diagnostic tests that continues to expand at a geometric rate. The use and costs of these tests, both the financial and the health costs, increase in a similar fashion. Despite the need for restraint in the face of this uncontrolled growth, diagnostic test use continues to be excessive; in many instances the test is ordered carelessly and its results may be ignored or misinterpreted. Lundberg has likened the process of test ordering to a form of perseveration, and Wong and Lincoln have aptly described the sequence of events in diagnostic test utilization as “Ready! Fire! . . . Aim!”.

Fortunately, as evidenced by these articles, there is at the same time the growing recognition that greater rigour must be applied to the use of diagnostic tests and the interpretation of their results and that rational individualized testing must supplant the traditional process of routine testing. Along these lines, Reuben recently applied some of the factors that cause us to carry diagnostic testing beyond what is necessary for optimal patient management, calling upon academic generalists and epidemiologists to “take an active, even aggressive, role in teaching students, clinicians, and teachers to use tests more discriminately”.

Methods for the use and interpretation of diagnostic data have been developed over the past several years and have received considerable attention. In general these methods centre on the application of principles of decision analysis, including the use of concepts such as predictive values, to diagnostic data. Despite these efforts, it is our experience that the medical community continues to have difficulty understanding and using these methods. As Reuben stated: “Although the influence of such researchers is spreading, they still represent an eclectic minority. Unfortunately, the statistics and epidemiology that have become tools of their trade are beyond the grasp of many clinicians.” Regrettably, some clinicians tend to conclude from their lack of comprehension that these concepts must be esoteric and clinically irrelevant. Nothing could be further from the truth. For example, Morgan recently applied epidemiologic concepts to suggest ways of dealing with an issue of crucial importance to everyday clinical practice; that is, the waste associated with ruling out unlikely diagnoses.

To help those who may have had difficulty grasping the basics of the use and interpretation of diagnostic data, we set out here a few principles and schemes. We hope that they can serve both as a guide for utilization in clinical practice and as a foundation for further study. For simplicity we will concentrate our

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CURRENT REVIEWS
attention on dichotomous tests; that is, those whose result is simply positive or negative. Readers who wish a more detailed review or who wish to carry out further study should refer to an excellent and comprehensive series on this topic that appeared recently in CMAJ.14

Principles (Table I) and schemes

Principle 1: In the diagnostic context, patients do not have disease, only a probability of disease.

To understand this statement, let us consider a patient who is to undergo a diagnostic test meant to detect a certain target disease. If one is absolutely certain that the disease is present prior to the test (i.e., the pretest probability is 1), then the test need not be done. Conversely, if one is absolutely certain that the disease is not present prior to the test (i.e., the pretest probability is 0), then again the test need not be done. Since in most instances the pretest probability is thus not 0 or 1, it must lie somewhere in between. Thus, the principle asserts that prior to diagnostic testing, patients should not be considered to have or not to have disease but simply to have a pretest probability of disease. To utilize principle 1 effectively, one need only assign to patients a pretest probability of disease that reflects one's level of confidence that the target disease is actually present. This can be based on the history and the results of physical examination, previous tests and consultations, combined with one's cumulative clinical experience in similar situations.

Principle 2: Diagnostic tests are merely revisions of probabilities.

One of the great failings of current medical training has resulted in the widespread misconception that diagnostic tests confer certainty with their results; that is, that positive test results imply that patients are diseased and that negative ones imply that they are not. Since virtually all tests have false-positive and false-negative results, a moment's reflection should persuade the reader that this cannot be so. In fact, even after diagnostic tests, principle 1 still applies: patients still do not have disease, only a probability of disease.

What the test has accomplished is to revise the probability of disease as follows: The patient enters the test with a pretest probability (P) as discussed earlier. If the test result is positive, the probability of disease should now be higher than prior to the test; in fact, the probability is revised upwards to the post-test probability of a positive test result, denoted as PTL(+). If the test result is negative, the probability is revised downwards to the post-test probability of a negative test result, denoted as PTL(−).

The diagnostic test and its results may be pictorially represented by a tree diagram, as shown in Fig. 1. This type of representation is a fundamental tool in the science of structuring clinical decisions, known as clinical decision analysis.15

The amount by which the probability rises in the case of a positive test result is a measure of how much more confident one can now be about the presence of disease. The magnitude of this rise measures, in a sense, what a positive result accomplishes in terms of "ruling in" the disease. Similarly, the amount the probability falls in the case of a negative result is a measure of how much more confident one can now be about the absence of disease. The magnitude of this fall measures what a negative result accomplishes in terms of "ruling out" the disease.

Consider, for example, a hypothetical diagnostic test with a sensitivity of 0.65 and a specificity of 0.90, and suppose this test is applied to patients with a pretest probability of the target disease of 0.20. A diagnostic tree for this situation is shown in Fig. 2. If the test result is positive, the probability of disease rises from 0.20 to 0.62. If the result is negative, the probability falls from 0.20 to 0.09. Methods for the calculation of the post-test probabilities will be discussed shortly. A sensitivity and a specificity of 0.65 and 0.90 respectively suggest that the diagnostic test will yield an abnormal result in about 65 of every 100 diseased patients and a normal result in about 90 of every 100 nondiseased patients. It is difficult to see how these observations can help one directly to make predic-

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**Table I—Principles of diagnostic decision analysis**

<table>
<thead>
<tr>
<th>Principle</th>
<th>Description</th>
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<tbody>
<tr>
<td>Principle 1:</td>
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<td>Principle 2:</td>
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<td>Test interpretation should precede test ordering.</td>
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<td>Principle 4:</td>
<td>In general, if the revisions in probabilities caused by a diagnostic test do not entail a change in subsequent management, use of the test should be reconsidered.</td>
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**Fig. 1**—Diagnostic "tree" for a diagnostic test. The patient enters the test, at the left, with a pretest probability of the target disease of P. If the test result is positive, the probability rises to PTL(+), the post-test probability of a positive result. If the result is negative, the probability falls to PTL(−), the post-test probability of a negative result.

**Fig. 2**—Diagnostic tree for a test with a sensitivity of 0.65 and a specificity of 0.90 in a patient with a pretest probability of the target disease of 0.20.
tions about patients in whom the presence or absence of the target disease is still uncertain. That is why one considers post-test probabilities.

It is worth while at this point to introduce the likelihood ratios as an aid to the interpretation of diagnostic data. The positive likelihood ratio and the negative likelihood ratio, which we shall denote as LR(+) and LR(−) respectively, have several advantages in describing the capabilities of a diagnostic test. First, they are simple to calculate:

- \( LR(+) = \frac{\text{sensitivity}}{(1 - \text{specificity})} \)
- \( LR(−) = \frac{(1 - \text{sensitivity})}{\text{specificity}} \)

Second, and most important, they provide clear measures of the “ruling-in” and “ruling-out” capabilities of a test.

LR(+), for example, is a quantity greater than or equal to 1.0, and the magnitude by which it exceeds 1.0 is a measure of the test’s ability to revise probabilities upward when the test result is positive. An LR(+) of 2.0 to 5.0 should be considered as poor to fair, while one exceeding 10.0 might be considered good. Conversely, LR(−) is a quantity less than or equal to 1.0, and the magnitude by which it falls below 1.0 is a measure of the test’s ability to revise probabilities downward when the test result is negative. An LR(−) of 0.5 to 0.2 should be considered as poor to fair, while one below 0.1 might be considered good.

The third advantage of the likelihood ratios lies in their use in the calculations of post-test probabilities. To derive PTL(+) and PTL(−) one need only employ the pretest probability \( P \) in the following paired formulas:

- \( PTL(+) = \frac{P \cdot LR(+) \cdot (1 - P)}{P \cdot LR(+) + (1 - P) \cdot LR(−)} \)
- \( PTL(−) = \frac{P \cdot LR(−) \cdot (1 - P)}{P \cdot LR(−) + (1 - P) \cdot LR(+) \cdot (1 - P)} \)

This is a form of Bayes’ theorem. Several other methods for calculating post-test likelihoods have also been described,⁶ these include a simple nomogram, first proposed by Fagan,⁷ that allows direct reading of post-test probabilities from a scale using likelihood ratios and avoids the need for the calculations entailed by the use of these formulas. As an additional aid we have provided a simple BASIC program (see the Appendix) that performs these calculations and can be adapted for use on microcomputers.

Clearly, the ability of a test to revise probabilities up or down is the key to the test’s potential contribution to the clinical situation. Unfortunately, the concepts of sensitivity and specificity that have been adopted by convention as the measures of test validity do not directly describe this ability. To see this readily, consider the example of a test with a specificity of only 0.2 but a sensitivity of 0.8. While the test is not very specific, it possesses fairly good sensitivity. Is this an excellent test that should always be used, a good test that should often be used, a mediocre test that may sometimes be used or a worthless test that should never be used? Choose one of these four options before reading further. From our informal survey of over 200 faculty and residents it appears that the vast majority of physicians choose the third option, feeling that such a test could be of value in selected clinical situations.

Fig. 3 shows that the test is, in fact, worthless. A diagnostic tree for this test for a patient with a pretest probability of 0.5 is shown. The probability of disease remains 0.5 regardless of whether the test result is positive or negative, or whether the test is even performed at all. The three probabilities \( P \), PTL(+) and PTL(−) will be identical no matter what the pretest probability is assumed to be. This can be seen immediately by noting that in this case both LR(+) and LR(−) are equal to 1.0. Despite a sensitivity of 80%, the test provides absolutely no information. In general, consideration of the sensitivity and specificity alone in the assessment of a diagnostic test, as is so often the case, will not suffice to determine the test’s clinical utility.

Let us, by way of illustration, consider the example of radionuclide angiography (RNA) for the detection of coronary artery disease (CAD). A recent assessment by Austin and colleagues⁸ demonstrated a sensitivity and a specificity for the RNA test of 0.87 and 0.54 respectively. One can now obtain an LR(+) of 1.9 and an LR(−) of 0.24 for this test. The LR(+) of only 1.9 indicates immediately that the test will perform poorly at increasing the probability of disease when its result is positive. The LR(−) of 0.24 suggests that the test is only somewhat better at lowering the probability of disease when its result is negative.

To see this, let us consider the test as applied to several patients. The first is a 40-year-old woman with a chest pain syndrome that is not consistent with angina, so that her pretest probability of CAD is low, say 0.1. The second patient is an elderly man with a classic history of exertional angina responsive to nitrates who has several coronary risk factors, so that the pretest probability of CAD is extremely high, say 0.9. Finally, let us consider a 55-year-old man with a syndrome of atypical angina during a period of high stress. He is a smoker and has a 10-year history of well controlled hypertension, so he is at an elevated risk of CAD, but the history is somewhat suspicious. For purposes of illustration we estimate his pretest probability to be 0.5.

Diagnostic trees for these three patients are presented in Fig. 4. The post-test probabilities were calculated with the formulas presented earlier involving the likelihood ratios and the pretest probability. Just as predicted from the likelihood ratios, the RNA test does perform better at revising probabilities downwards when its result is negative than it does at revising them upwards when its result is positive.

Principle 2 implies that diagnostic
tests should not be considered as providing absolute conclusions about the presence or absence of disease depending on their results; rather, they should be viewed as adjustments of our level of confidence in making conclusions about individual patients. While the likelihood ratios measure the capabilities of the test at performing such adjustments, it is the diagnostic tree that maps a particular patient's pathway through uncertainty. As shown by Fig. 4, the conclusions provided by a test depend not only on the test's capabilities but also, and much more heavily, on the individual patient to whom the test is applied.

**Principle 3: Test interpretation should precede test ordering.**

In considering the interpretation of diagnostic data discussed thus far, it is important to recognize that there is nothing to dictate that this method must be applied after the diagnostic test. Since the likelihood ratios and pretest probability are known prior to the test, the diagnostic tree can be constructed prior to it as well. This can be done not only for purposes of interpretation but also in consideration of whether the test should be ordered at all. In the language of Wong and Lincoln1 this would correspond to “aiming” the test before “firing”. If one views the diagnostic tree as the patient’s “response” to a diagnostic test, then Fig. 4 illustrates that patients “respond” to a given diagnostic test in as varied a fashion as they might respond to a specific therapy. In the test situation, however, the “response” is not idiosyncratic: it can be mapped out in advance of the test by using the methods we have outlined.

Let us, therefore, interpret the RNA test results for our three patients with CAD (Fig. 4) prior to ordering the test. For the first patient the “response” to the test will be poor, and the test's use in this case would be inappropriate and potentially harmful. A positive result will move the probability from 0.10 to only 0.17, hardly a major boost to our confidence in the presence of CAD. It is difficult to argue that the further management of the patient would be different if the probability of CAD was 17% as opposed to 10%, so that a positive test result should entail no change in subsequent management. Unfortunately, the reality of current clinical practice is such that this type of interpretation prior to test ordering is not often carried out. Many clinicians will order such a test in just this situation and worry about the results later. Often this approach reflects a desire to be thorough or simply to follow a test-ordering protocol; in addition, there is often the motivation that one “might just pick up” a case of CAD. Once a test is carried out, unfortunately, one is invariably confronted with the results and must deal with them. For patients who do not have CAD, about half (46%) will have abnormal RNA test results since the specificity is 0.54, and these abnormal results must be explained. Thinking that he or she has “picked up” a case of CAD, the physician may so advise the patient, causing unnecessary anxiety, and may feel compelled to order further, more invasive testing. In fact, all that has been “picked up” is about seven percentage points of chance that the patient truly has CAD. Examples such as this illustrate the pitfalls associated with the practice of ruling out unlikely diagnoses.

For the second patient there are several reasons why the RNA test would be inappropriate for diagnostic purposes. First, setting a pretest probability of 0.9 is equivalent to stating that one is virtually certain of the diagnosis and that further diagnostic maneuvers are unnecessary. Such a patient can go directly to treatment or to staging procedures such as coronary angiography in anticipation of possible bypass surgery. Second, the RNA test will not lead to any change of management anyway. Even if the result is negative, the probability of disease is still 68%. Although this is an appreciable drop from 90%, it is probably not enough to warrant a change in management. Unfortunately, clinicians may overestimate the meaning of a negative result and think that CAD is unlikely, when, in fact, it is probably still present. This illustrates the problems associated with the practice of ruling in likely diagnoses.

It is only for the third patient that there appears to be a rationale for the use of the RNA test. Here, in planning whether or not to order it, we see that the results will lead to changes in management. A positive result will cause a modest rise in probability, from 50% to 66%, where further testing is clearly warranted, while a negative result entails a significant drop in probability, from 50% to 19%, a level at which one may feel sufficiently confident to just observe the patient.

Thus, the diagnostic test serves a meaningful discriminatory function here, separating patients into two groups that should be managed in different ways. Only for the third patient does the test appear to satisfy the final principle.

![Fig. 4](image-url) — Diagnostic trees for radionuclide angiography for three patients with possible coronary artery disease.
Principle 4: In general, if the revisions in probabilities caused by a diagnostic test do not entail a change in subsequent management, use of the test should be reconsidered.

Conclusion

If one synthesizes the principles discussed thus far, one can envisage the following type of diagnostic procedure: Given an individual patient and a target disease, one begins by estimating the probability that the target disease is present. In the screening situation, for example, when the patient is asymptomatic, one might very well use the prevalence of the target disease in the source population as an estimate of the pretest probability. In the diagnostic situation, where additional evidence for the presence of the target disease exists, one must rely on the history and the results of physical examination, previous tests and consultations, together with one's clinical experience. In addition, with the increasing availability and decreasing cost of computing facilities, it is hoped that more data will be collected, stored and made available for analysis to provide better estimates of these probabilities.

Instead of ordering a panel of tests for the patient and then interpreting the results, one can first consider the capabilities of the various tests available and map out diagnostic trees of the patient's response to these tests. The likelihood ratios, as we have discussed, provide an immediate measure of the tests' capabilities at revising probabilities. For each test and each post-test probability, one can then consider what the appropriate management should be in that eventuality. Only those tests that significantly alter subsequent management need be considered, and a strategy for serial testing can be developed in advance.

In summary, we have outlined several principles (Table 1) and schemes that we hope will serve as an introduction to clinical decision analysis and as a stimulus for further reading. Owing to inadequacies in medical training and to a general lack of understanding in the medical community, most clinicians have serious misconceptions about the use and interpretation of diagnostic data, including an inability to quantitatively and judge the impact of diagnostic test results in individual patients. Diagnostic tests must be viewed not as infallible technologic tools providing definitive answers for all patients, but as aids with which we may revise probabilities in individual patients. It is the former view that gives rise to the reliance on test-ordering protocols and on conditioned test-ordering behavior. The latter view encourages us to tailor diagnostic procedures to the individual patient. To do this, we need to use elementary probability as a way of quantifying and not mystifying diagnostic uncertainty. The calculations and concepts involved, while foreign to some, are really no more involved than many physiological derivations in current clinical use (e.g., sodium replacement calculations and the arterial-alveolar gradient) and are clearly of equal or greater importance. This method would, in fact, be trivial if it were introduced in a fundamental way at an early stage of the medical curriculum.

The continued excessive and often inappropriate use of diagnostic tests should be a matter of concern to the entire medical community. From a wider perspective, these practices represent an important source of waste of limited resources in a time when such waste can no longer be tolerated. More important, from the perspective of individual patient care these behaviors lead to unnecessary morbidity and mortality, arising both from the tests themselves and from the misinterpretation of their results.

References

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14. Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ont.: Interpretation of diagnostic data [six parts]. Can Med Assoc J 1983; 129: 429-432; 559-564, 587: 705-710; 832-835; 947-954; 1093-1099
Appendix

Below is a program listing for a simple interactive MS-BASIC program that performs a likelihood analysis.

In the first phase the program elicits from the user the sensitivity, specificity and pretest probability, which must be entered as percentages (e.g., 80) and not as decimals (e.g., 0.8). The program then responds with a listing of these values together with the positive and negative likelihood ratios, LR(+) and LR(−), followed by a display of the diagnostic tree diagram similar in format to those in Figs. 1 to 4.

In the second phase the program produces a three-column table containing the post-test probabilities of both negative and positive test results, denoted as PTL(−) and PTL(+), for a range of pretest probabilities that includes 5%, 10%, 15%, 20% and so on up to 95%.

```
100 DEFINT A-J
110 DEFSNG L-S
120 DIM B(19), BP(19), BN(19)
130 PRINT:PRINT “DIAGNOSTIC LIKELIHOOD ANALYSIS”
140 PRINT:PRINT “ENTER SENSITIVITY(%), SPECIFICITY(%), PRE-TEST PROBABILITY(%)”
150 PRINT:PRINT “e.g. 90,60,15”
160 PRINT:INPUT SE,SP,P
170 LP=SE/(100!-SP)
180 LN=(100!-SE)/SP
190 DEF FNPOST(Q,L)=100!*Q*L/(100!-Q+Q*L)
200 PTLP=FNPOST(P,LP)
210 PTLN=FNPOST(P,LN)
220 PRINT “SENSITIVITY”, “SPECIFICITY”,SPC(1) “LR(+),” SPC(2) “LR(−)” ,SPC(2) “P”
230 PRINT SE,SP,LP,LN,P
240 PRINT:PRINT
250 TAB(20) “DIAGNOSTIC TREE DIAGRAM”
260 PRINT TAB(10) PTLP
270 FOR I=44 TO 20 STEP -6
280 PRINT TAB(I) “*”
290 NEXT I
300 PRINT SPC(10) P
310 FOR I=20 TO 44 STEP 6
320 PRINT TAB(I) “*”
330 NEXT I
340 PRINT TAB(50) PTLP
350 PRINT “TO CONTINUE, HIT ANY KEY”
360 XF=INKEY$: IF LEN(XF)=0 THEN 360
370 PRINT TAB(15) “PTL(−)”, TAB(33) “P”, TAB(45) “PTL(+)”
380 PRINT TAB(15) “-----”, TAB(33) “-”, TAB(45) “-----”
390 FOR J=1 TO 19
400 B(J) = 5*J
410 BP(J)=FNPOST(B(J),LP)
420 BN(J)=FNPOST(B(J),LN)
430 PRINT TAB(17) B(J), TAB(32) B(J), TAB(47) BP(J)
440 NEXT J
450 PRINT “TO START AGAIN, TYPE ‘YES’ - TO STOP, TYPE ‘NO’ ”
460 INPUT Y$ 470 IF Y$=“YES” THEN 130
480 IF Y$=“NO” THEN 490 ELSE 450
490 END
```

Disease label: The identity of the condition from which a patient suffers. It may be the name of a precisely defined disorder identified by a battery of tests, a probability statement based on consideration of what is most likely among several possibilities, or an opinion based on pattern recognition.