CHAPTER

75

Diagnostic Reasoning: Approach to Clinical Diagnosis Based on Bayes' Theorem

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Introduction

Doctors caring for patients in their everyday clinical practice are faced with decisions that are sometimes routine and simple, but may be complicated on other occasions. Sometimes, the decisions may be regarding the choice of investigation or intervention, on other occasions, the decisions may have to be taken regarding a therapeutic option. Either way, clinical decision making is challenging because, these decisions are not only unavoidable but also must be made under uncertain conditions. In this review, an attempt is being made to provide an overview regarding the applications of Bayes' theorem and clinical decision analysis in arriving at a diagnosis.

Basic Mathematics

In order to understand diagnostic reasoning, it is necessary to understand the basic mathematical language of probability and Bayes' theorem as applied to clinical medicine. Bayes' theorem, ascribed to Rev. Thomas Bayes (1701-1761) is a mathematical rule explaining how one should change existing beliefs in light of new evidence.[1] Bayes' paper on 'An essay towards solving a problem in the doctrine of chances'[2] posthumously, due to the efforts of his friend Richard Price.[3]

Probability

Probability as applied to clinical diagnostic reasoning may be regarded as a measure of one's strength of belief that an event will occur and range from 0.0 to 1.0.[4] In statistical notation, probability of an event A is written as P[A].

Summation principle

The summation principle states that the sum of probabilities of all possible outcomes of a chance event equals 1.0.[4] If there are four possible outcomes A, B, C, and D, then

$$P[A] + P[B] + P[C] + P[D] = 1$$

Joint probability

The concomitant occurrence of any number of events is defined as joint probability of those events.[4] In statistical notation, the joint probability of two events A and B is written as

$$P[A,B].$$

Conditional probability

The probability that an event A occurs, given that the event B is known to occur is defined as the conditional probability of event A given event B or P[A½B].[4]

The relationship between joint and conditional probabilities is given by the formula

$$P[A,B] = P[A½B] = P[B]$$

Figure 1 : Some important conditional probabilities: sensitivity and specificity

Test	Disease: Present (D+)	Disease: Absent (D-)
Positive (T+)	TP	FP
Negative (T-)	FN	TN

Variable	Probability notation	Estimate of probability
Sensitivity Equla to the true-positive rate; frequency of positive test reults in those with disease	P[T+ | D+]	TP/TP+FN)
Specificity Equal to true-negative rate; frequency of negative test results in those with disease	P[T- | D-]	TN (TN+FP)
False-negative rate Frequency of negative test results in those with disease	P[T- | D+]	FN/ (TP+FN)
False-positive rate Frequency of positive test results in those without disease	P[T+ | D-]	FP/ (TN+FP)
Predictive value of positive test Frequency of disease in those with a positive test result	P[D+ | T+]	
Predictive value of negative test Frequency of non-disease in those with a negative test result	P[D- | T-]	

TP =true positive; FP = false positive; TN = true negative; FN = false negative; D+ = disease present; D- = disease absent; T+ = positive test result; T- = negative test result

Independence

When the conditional probability of an event A, given event B, is the same as the unconditional probability of event A, then, events A and B are independent.[4]

Thus, if events A and B are independent,

$$P[A½B] = P[A]$$

The joint probabilities of independent events obey the "product rule".

$$P[A,B] = P[A] ´ P[B]$$

Figure 2 : Application of Bayes' theorem to estimate the probability of the disease given a positive or a negative test result

$$\text{Bayes' formula (positive test result)} = \frac{P[T+|\,D+] \times P[D+]}{P[T+|D+] \times P[D+] + P[T+|D-] \times P[D-]}$$

$$\text{Bayes' formala (negative test result)} = \frac{P[T+|\,D+] \times P[D+]}{P[T-|D+] \times P[D+] + P[T-|D-] \times P[D-]}$$

T+ = positive test result; D+ = disease present; T - = negative test result; D- = disease absent. Probability notation: P[T+½D+] should be understood as probability of the test being positive given the disease being present, and so on as detailed in the text under conditional probability

The *product rule* is not applicable for events that are not independent.

Summation principle for joint probabilities

If A is one event that can occur and B1, B2, B3, and B4 are mutually exclusive events, then,

$$P[A] = P[A,B1] + P[A,B2] + P[A,B3] + P[A,B4]$$

Averaging out is the method of computing the probability of an event from several conditional probabilities.

Bayes' Theorem

In arriving at a definitive clinical diagnosis, a diagnostic test is performed. The results that are obtained on performing such a diagnostic test are shown in Figure 1. The performance of the diagnostic test is assessed using a "gold standard" for categorisation of the subjects as "having disease" or "no disease".

Bayes' theorem can be applied in this situation to estimate the probability of the disease given a positive or a negative test result (Figure 2).

Odds

Let us assume that the probability of an event occurring is p. Then, the probability of that event "not occurring" will be (1-p). We can also compute the odds favoring the occurrence of the event = p/(1-p) the odds against the occurrence of the event = (1-p)/p

Figure 3 : Bayes' theorem expressed in the odds-likelihood ratio form

$$\frac{P[D+|R]}{P[D-|R]} = \frac{P[D]}{P[D-]} \times \frac{P[R+|D+]}{P[R|D-]}$$

Posterior odds	Prior odds	Likelihood ratio

D+ = disease present; D- = disease absent; R = test result

P[D+½R] should be understood as probability of the disease being present given the test result, and so on as detailed in the text under conditional probability

Likelihood Ratio

The likelihood ratio (LR) for a particular value of a positive test result is defined as the ratio of the probability of the test result in persons with disease to the probability of the test result in those without the disease.

LR for a positive test result = sensitivity / (1-specificity)

Similarly, LR for a negative test result = (1-sensitivity) /specificity

From the pre-test odds and LR, one can calculate the post-test odds by the relationship

Post-test odds = pre-test odds ´ LR

Bayes' theorem can also be expressed in terms of odds rather than probabilities (Figure 3).

Generalisation of Bayes' Theorem To Several Disease States

Till this time, the possibility of two disease states (disease present/absent) have been considered. Let us assume that the following disease states D1, D2, and so on up to Dn. We can apply Bayes' theorem to compute the revised probability of any one disease (Di) given the test result R as shown in Figure 4.

Applications

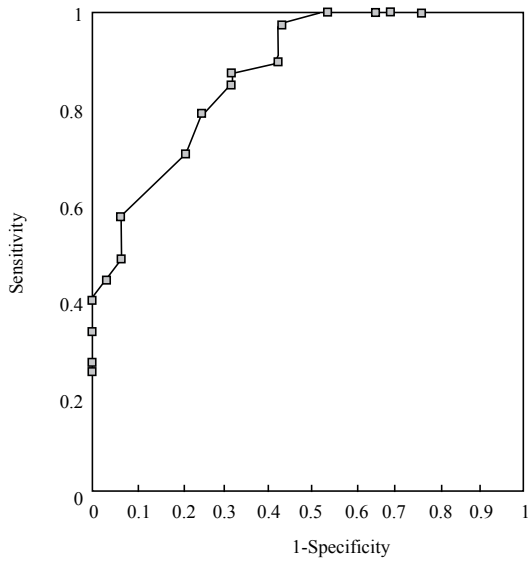
Several applications have been developed for use in clinical medicine for diagnostic reasoning and decision making basing on the mathematical principles described above.[3,5,6] Some of these applications are briefly outlined in this review.

Figure 4 : Application of Bayes' theorem to compute the revised probability of any one disease (Di) given the test result.

$$\frac{P[R|Di] \times P[Di]}{P[R|D1] \times P[D1] + \ldots\ldots + P[R|Di] \times P[Di] + \ldots\ldots + P[R|Dn] \times P[Dn]}$$

P = probability; D1, and so on up to Dn = disease states. R = test result. Probability notation: P[R½D1] should be understood as probability of the test result given disease 1 being present, and so on as detailed in the text under conditional probability

Figure 5 : Receiver-operator characteristic (ROC) curve for pleural fluid ADA showing 1-specificity on the X-axis and the sensitivity on the Y-axis



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Receiver-operator characteristic curve

The receiver-operator characteristic (ROC) curve, that is obtained by plotting sensitivity against 1-specificity, shows the trade-off between sensitivity and specificity depending on the chosen criterion of positivity for the test result.4 The ROC curve facilitates the identification of the optimum cut-off value. The concept of ROC curve can be illustrated by considering the following example. Estimation of the adenosine deaminase (ADA) levels in the pleural fluid has been used to diagnose tuberculous pleural effusion. The choice of the most appropriate cut-off level of the ADA in the pleural fluid can be

arrived at by plotting the ROC curve for pleural fluid ADA with 1-specificity on the X-axis and the sensitivity on the Y-axis (Figure 5).[7] Using a cut-off level of 35 IU/l, the sensitivity and specificity of pleural fluid ADA in the diagnosis of TB was estimated to be 83.3% and 66.6% respectively. This value was chose because, above or below this value, there were significant losses in the sensitivity and specificity without a significant corresponding gain in the specificity or sensitivity. Furthermore, at a cut-off level of 35 IU/l, pleural fluid ADA could be used to classify the pleural effusion as tuberculosis or non-tuberculosis with reasonable certainty. Using a cut-off value of 100 IU/l, pleural fluid ADA was found to have a sensitivity 40% and specificity 100%. This analysis shows that, at a cut-off pleural fluid ADA level using 100 IU/l as the cut-off, the diagnosis of TB can be ascertained in as much as 40% of the patients and it is possible to avoid pleural biopsy in these patients.

Decision analysis

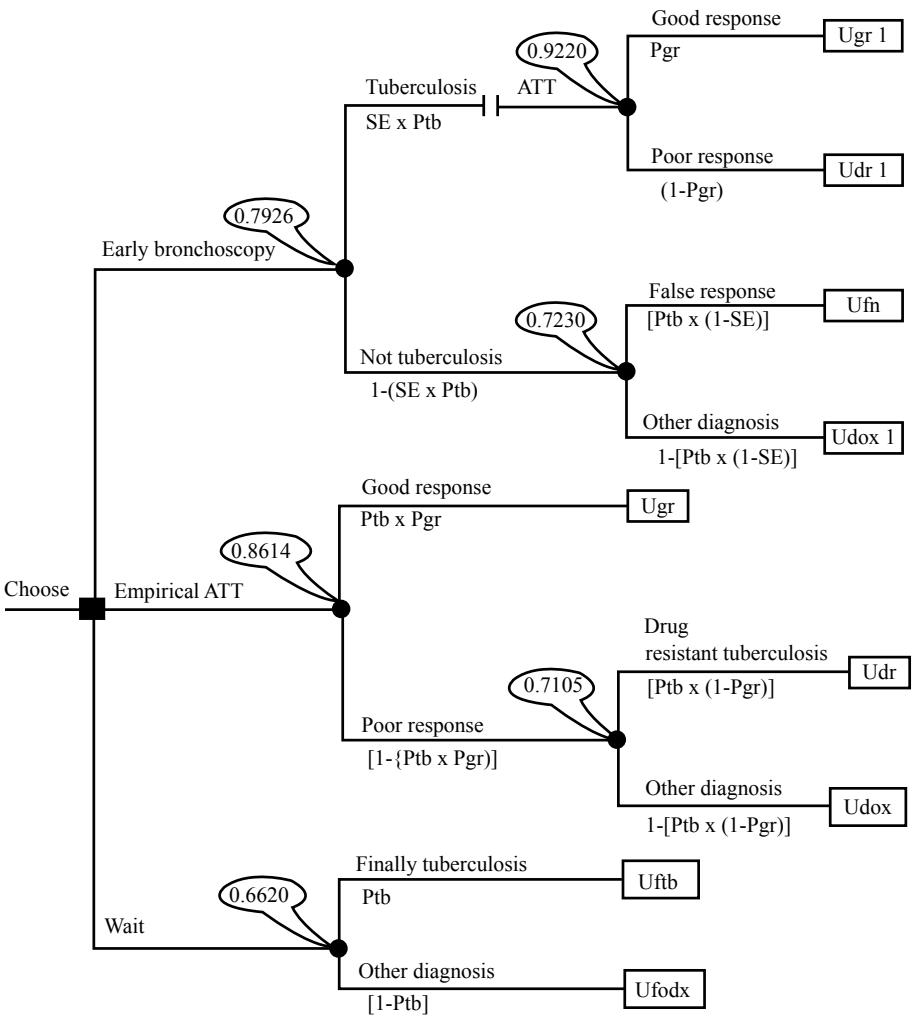
In order to arrive at a diagnosis, the clinician takes into consideration the information obtained from the history, the key findings on physical examinations and decides on a line of investigations. Then, basing on the information obtained, a diagnosis is arrived at intuitively based on previous clinical experience. Though the intuitive approach to clinical reasoning has the advantage of being flexible, it is subjective and may vary from person to person. The intuitive approach also is fraught with various factors that contribute to the uncertainty. These include errors in obtaining clinical data, ambiguity and variations in interpretation of the data, variations in the relationship between the clinical or laboratory information obtained and the disease being evaluated, among others. However, the last three decades have witnessed the evolution of "Clinical decision analysis" approach to decision making under conditions of uncertainty.[4,8-10]

Clinical decision analysis is a systematic approach to decision making under conditions of uncertainity and can be helpful in choosing the best possible course of action in a given patient.[4,8-10] As opposed to intuitively choosing one of the available options, clinical decision analysis is an explicit, quantitative and prescriptive approach to decision making. In this approach, the ambiguity of clinical and investigational information, probabilities of arriving at a diagnosis from a given test, therapeutic options, utility of the outcome from each option in absolute and relative terms are taken into account to construct a logical structure of the decision problem. Then, the probability of each outcome is combined with its associated utility and the path with the highest expected value is chosen to make the decision.

The utility of clinical decision analysis can be illustrated by the following example, where the utility of bronchoalveolar lavage was evaluated in the diagnosis of sputum smear-negative pulmonary tuberculosis[11]. A hypothetical case scenario was considered where the patient presents with clinical history and chest radiograph evidence suggestive of pulmonary tuberculosis and is sputum smear-negative on three occasions or does not produce sputum. The sputum does not reveal malignant cells on cytopathological examination, there are no medication allergies or contraindications for bronchoscopy. When faced with this situation, clinicians may start antituberculosis treatment empirically, perform an early bronchoscopy to ascertain a diagnosis or to wait while monitoring the patient closely. With these options, various patient outcomes are possible and are shown in the Decision tree (Figure 6a).

Following early bronchoscopy the bronchoalveolar lavage may reveal acid-fast bacilli (AFB) on smear examination and the patient would be started on standard antituberculosis treatment. Following this, the patient could either show a good response to the treatment or a poor response (probably drug-resistant pulmonary tuberculosis). If an early diagnosis of tuberculosis could not be made on bronchoscopy, the result would either be "false negative" (patient would be having tuberculosis but the bronchoscopy has not

Figure 6a: Decision analysis tree for the evaluation of a patient with sputum smear negative pulmonary tuberculosis. Small squares indicate a decision node. Small circle indicates a chance node. Probability bindings are represented below each event. Utility bindings are depicted at the end of the path. Numbers in balloons indicate the averaged-out outcomes connected to each node. Reproduced with permission from "Mohan A, Pande JN, Sharma SK, Rattan A, Guleria R, Khilnani GC. Bronchoalveolar lavage in pulmonary tuberculosis: a decision analysis approach. QJM 1995;88:269-76" (reference 11)

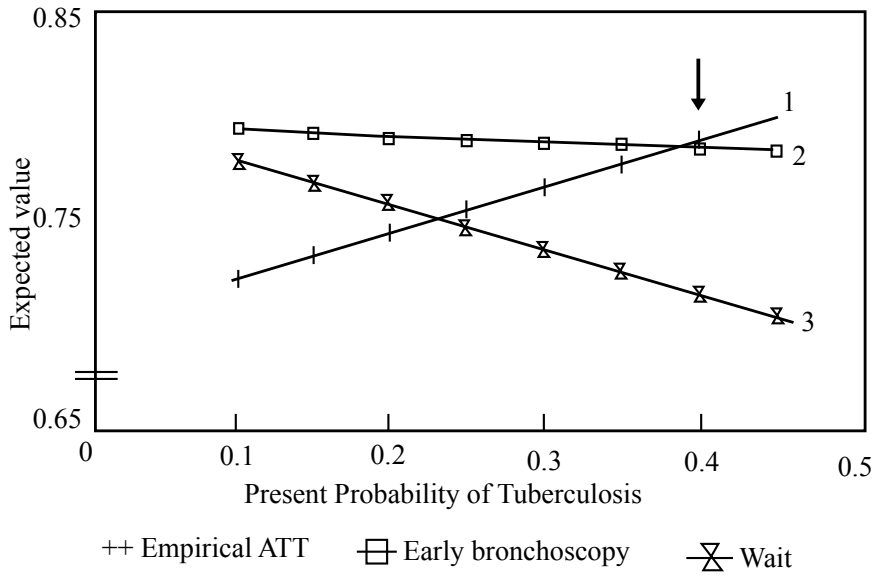


picked up the diagnosis) or the patient would be suffering from another disease ("true negative"). The further evaluation of such a patient was not included in the decision tree in order to simplify the analysis.

Following empirical treatment with antituberculosis drugs, the patient could either improve (good response) or ; remain stable or deteriorate further (poor-response). A patient who does not respond, could either have drug resistant tuberculosis or another diagnosis. The further evaluation of such a patient is not incorporated in the decision tree model in order to simplify the analysis. In waiting branch, the patient would finally develop tuberculosis or another diagnosis would finally be possible.

Each path was folded back to the starting point (fold back analysis). At a decision node the tree was folded back along the single best choice where as, at a chance node the probabilities were averaged out on all the branches emanating from that node and the best alternative course of action chosen.

Figure 6b : Univariate sensitivity analysis. at or above a threshold level of the pretest probability of the patient having tuberculosis of 0.4, the best alternative course of action switched from early bronchoscopy to empirical antituberculosis treatment (arrow). Reproduced with permission from "Mohan A, Pande JN, Sharma SK, Rattan A, Guleria R, Khilnani GC. Bronchoalveolar lavage in pulmonary tuberculosis: a decision analysis approach. QJM 1995;88:269-76" (reference 11)



Sensitivity analysis allows testing the stability of the conclusions over a wide range of values for each assumption. The baseline utilities and probabilities were subjected to a univariate sensitivity analysis over a wide range of clinically relevant values to see if it would alter the results and check the validity of the analysis which required so many assumptions and a multivariate (two-way) sensitivity analysis was done where relevant.

The authors[11] show that, at or above a threshold level of the pretest probability of the patient having tuberculosis of 0.4, the best alternative course of action switched from early bronchoscopy to empirical antituberculosis treatment (Figure 6b). In other words, it suggests that, when the pretest probability of having pulmonary tuberculosis is below the threshold level, it is worthwhile doing bronchoscopy to ascertain a diagnosis and at that probability, the sensitivity of the bronchoscope in picking up PT should be at least 0.5. If the pretest probability of the patient having tuberculosis is 0.4 or more, empirical antituberculosis treatment appeared to be the best course of action.

Limitations

While clinical decision analysis provides a more objective insight into what is subconsciously practiced as an intuitive decision making process, certain limitations must be kept in mind. When a patient like the one discussed in the example is encountered, whereever possible, an attempt must be made to confirm the diagnosis by microbiological or histopathological methods. The realistic risks and benefits of the interventions must be clearly explained to the patient and the patient must be actively involved in the decision making process.

Conclusions

Judicious application of the Bayes' theorem and diagnostic reasoning can help clinicians in arriving at the appropriate course of action in an objective way.

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