Perspective Article

Bayesian Medicine: An Approach to Systematic Diagnosis

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Abstract

Faulty diagnosis is often at the heart of medical treatment gone wrong. The root cause of this is that the medical practitioner is averse to a lengthy diagnosis process and relies exclusively on intuition and prior experience to arrive rapidly at a diagnosis. The purpose of this article is to advance a method of scientific diagnosis that would yield the highest probability of success. The method relies on a notion of probability that was introduced a few centuries ago. Using this method, it is possible to quantitate the degree of confidence in one diagnosis relative to the degree of confidence in another differential diagnosis. The method provides an objective metric to differentiate between two competing diagnoses and select the correct diagnosis based on the strength of the evidence and findings. Adoption of the method would potentially improve the standards of medical treatment available in our country.

Key Words: Clinical diagnosis, Evidence-based medicine, Differential diagnosis, Bayes' theorem, Conditional probability, Likelihood ratios

Introduction

Thomas Bayes was an 18th century English theologian who laid down the foundations for an alternative, possibly authentic, interpretation of probability. Through the famous theorem that bears his name, he established a method for probability inference which factors the history of occurrence of the event in predicting the chances of its future occurrence. Using this interpretation, it is possible to update prior beliefs in the light of new relevant evidence in a precise manner. The Bayesian approach facilitates the quantitative integration of new sample information with old data to assess and refine our understanding of the states of nature.

Bayes' theorem is an elementary formula for calculating conditional probabilities, i.e, the probability of something given something else that has happened. For example, let us postulate a certain hypothesis H to explain some phenomena. Let the prior probability (before any measurement or observation has been made) of H being the true explanation be p(H). What is the posterior probability of the validity of hypothesis H in the light of acquisition of some new data D for the same phenomena? Following Bayes' theorem, this is given by:

$$p(H|D) = \frac{p(D|H)p(H)}{p(D)} \quad (1)$$

where p(H|D) is the required posterior probability, p(D|H) is the likelihood of the data D given the hypothesis H, and p(D) is the overall likelihood of the data D under any hypothesis. From this, the theorem's key insight emerges, namely that a hypothesis is strengthened by unbiased data that its truth renders objectively probable. This idea is the foundation of Bayesian inference, which is applied to estimate the posterior probability of a given hypothesis in the context of new evidence. In the following, we will see that the heart of evidence-based medicine follows Bayesian tenets.

Diagnostic Reasoning

The diagnostic process is based on the clinical interview between the doctor and the patient. The clinical interview is subject to the same difficulties that bedevil any dialogue, even with an empowered patient. When we communicate our thoughts to others, we use descriptive terms with shared meanings. It is this notion of shared meanings that makes possible the idea of human communication. A diagnosis is the title we attach to a portrait of affliction. This might be pictured with varying degrees of meaning by different medical professionals, depending on the interpretation of the available evidence recorded in a particular patient. There will be substantial variation between what medical professionals imagine when a diagnosis is discussed. This in turn depends on what they have read, their personal experience, and research experience. As a matter of convention, the label for a given disease is used to connote the essence of the disease as generally understood. This motivates the need to delineate diagnostic envelopes specific to each disease. In developing diagnostic labels, we translate the 'particular' evidence from a specific patient and generalise the findings to evidence for a generic diagnosis. The sum of evidence would be adducing of the probability of a diagnosis. Arguably (or inarguably) medicine is a probabilistic art, the aim being to maximise the probability of cure. As William Osler remarked, "Variability is the law of life, and as no two faces are the

same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease."

Intuitive Approach to Diagnosis

Most doctors use a non-transparent reasoning process. The diagnostic process need not involve conscious reasoning, it could be entirely intuitive. This seems to involve recognising combinations of signs and patterns of findings subconsciously and which suggest or confirm a diagnosis. When analysing the thought processes of doctors with long years of experience, it becomes evident that choosing a diagnostic lead (called a 'pivot') was key to the explanations of senior physicians in making a diagnosis. In a team setting, the team's consensus opinion might have been recorded. The way that one's own mind (or a colleague's) worked to reach the diagnosis might be impossible to explain. The intuitive approach to diagnosis emphasizes the subconscious aspect of the diagnostic method. It is a skill that could be trained and improved by experience. Practice confers a degree of automaticity to rapidly recognise the constellation of signs, symptoms and findings as suggesting a diagnosis. Over time, this could become second nature just like recognising someone's face. However attractive this approach, it has its limitations, namely that it tends to calcify with time and fails to keep pace with the advances in medical knowledge. Over-reliance on this approach would subject the diagnostic process to unintentional, sometimes grave, slips. These considerations motivate the need for a 'transparent' reasoning process.

Evidence-Based Approach

If a few or handful of differential diagnoses do not spring to mind readily, it is a paramount ethical obligation to employ a 'transparent' reasoning process. At the end of it, one might examine the outcomes of the non-transparent and transparent thought processes and see if they agree or not. If they are at variance, the doctor might wish to revise his/her opinion of the possible diagnoses. Unfamiliar situations frequently arise however experienced one becomes, which means that the transparent approach will be of permanent value. Transparent reasoning is a directed approach to solving diagnostic problems. It involves identifying an aggregate of specific which could be matched with a certain diagnosis. This could be initiated by selecting one diagnostic lead but not necessarily be the presenting complaint or the first finding the doctor sees. Multiple diagnoses would be consistent with the lead. All the diagnoses consistent with a lead are called differential diagnoses. The key duty of the physician's art is to arrive at the correct diagnosis from the set of several competing differential diagnoses. By practising evidence-based medicine, the doctor would be validating the proposed diagnosis with an orthogonal mental procedure, just as we would double-check a calculation by permuting the symbols in an allowed manner. The transparent evidence-based approach verifies the clinical diagnosis and could take either the passive form or the stronger active diagnosis.

Evidence-Based Passive Diagnosis

Evidence-based passive approach involves thinking about each of the patient's findings in turn and to consider if there is only one diagnosis that is common to each list of differential diagnoses[1]. If there is only a single diagnosis common to a number of findings, it follows that the diagnosis will be probable, i.e it will occur very frequently in a group of patients with those findings. Zeroing in on the diagnosis involves the identification of evidence confirmatory of a single diagnosis. A diagnosis could be confirmed in different ways. Here it is useful to distinguish between necessary and sufficient criteria. To illustrate with an example, in order to make a diagnosis of ectopic pregnancy, it is obvious that the subject is female and not male. If the patient is not female, then the patient lies outside the diagnostic envelope. Such an invariable diagnostic finding is termed a 'necessary' criterion. But the finding of necessary criteria may not be sufficient for confirming a diagnosis. If at least one sufficient criteria of a diagnosis is present, then the diagnosis becomes a candidate diagnosis. A confirmatory finding delineates the envelope of patients with the diagnosis. The multiple confirming findings present the 'definitive criteria' of the diagnosis, which are both sensitive and specific to those with the diagnosis. In other words, they are necessary as well as sufficient for the diagnosis. The evidence-based approach to diagnostic confirmation requires us to choose the 'confirmatory' test which could be shown superior to rival tests based on the balance of responder patients and those not responding to the treatments directed at the diagnosis. Essentially we would like to optimize the response rates in patients, the critical component of which is the determination of the correct diagnosis.

The best findings are those that maximise the frequency of successful diagnosis. The balance of probability of the finding modifies the likelihood of the diagnosis. If the finding is indicative of the pursued diagnosis but less so of another competing diagnosis, the pursued diagnosis becomes more probable relative to the competing, alternative diagnosis. In tandem with the earlier findings, the combined set of evidence would adduce correspondingly more weight to the pursued diagnosis. The same arguments hold for the finding that is not very representative of the pursued diagnosis. In this case, one of the competing diagnoses might gain in favour, and eventually replace the earlier pursued diagnosis.

Evidence-Based Active Diagnosis

Diagnoses could be actively pursued by searching for findings that would gradually confirm the pursued diagnosis. Absent such confirming findings, the tentative diagnosis could be progressively discounted, and another candidate diagnosis could take its place. The process is initiated by looking at the chart of findings and selecting one lead with the minimal list of consistent differential diagnoses accounting for the maximum fraction of patients with the lead finding. The other findings from the total evidence are used in the process of refining the diagnosis. If a finding has been shown to have a small number of differential diagnoses and these diagnoses account for a very high proportion of patients with that finding, then this would be evidence

of its ability to act as a good lead during the differential diagnostic process. In order to differentiate between the diagnostic categories, the physician has to choose a diagnosis to chase, which is called the postulated diagnosis. This should be the most probable diagnosis or dangerous diagnosis (to avoid delay). To put this framework on a precise footing, a mathematical treatment is necessary. We seek a measure of the ability of a test/finding to function as a differentiator of a pair of competing diagnoses. If a finding increases the likelihood of one diagnosis while simultaneously decreasing the likelihood of a competing diagnosis, then intuitively that finding would help to discriminate between the diagnostic pair.

The evidence-based method is a quantitative approach to differentiate between the competing diagnoses so that some become more probable and others less probable. The index of this ability to discriminate between two diagnoses is measured as simply the ratio of the conditional likelihoods of the two diagnoses given the finding. This ratio is different from the plain 'likelihood ratio' which is defined as simply the frequency of a finding in patients with a confirmed diagnosis divided by the frequency of the same finding in all those confirmed not to have that diagnosis. This ratio refers to a specific pair of differential diagnoses, and is thus termed a 'differential likelihood ratio.' If this differential likelihood ratio (R) is significantly greater than one, then the finding could be said to improve the odds of the differential diagnosis under question. In general, if R is significantly different from one, then the finding favours one diagnosis over the other whereas if $R \approx 1$ the finding is neutral with respect to the two diagnoses. The relationship between empirical observations and the theoretical diagnosis is quantified using Bayes' theorem. Let $p(H_1)$ be the prior probability of the diagnosis (given the lead finding F_1), and $p(H_2)$ the prior probability of the differential diagnosis. Given another finding F_2, the corresponding posterior probabilities are calculated using Bayes' theorem:

$$p(H1|F2) = \frac{p(F2|H1)p(H1)}{p(F2)} \quad (2)$$

$$p(H2|F2) = \frac{p(F2|H2)p(H2)}{p(F2)} \quad (3)$$

The net effect of this procedure is to update the evidence for the diagnoses under consideration and identify those whose evidence has weakened in the light of the finding F_2 and the estimates of the prior probabilities of the diagnoses given the diagnostic lead. The differential likelihood ratio between the competing diagnoses is given by the ratio of equations (2)&(3):

$$Diff.\ Likelihood\ ratio = \frac{p(H1|F2)}{p(H2|F2)} \quad (4)$$

The differential likelihood ratio obtained above is an objective indicator of the fitness of the diagnosis being chased relative to the competing differential diagnoses in the context of a specific finding and certain prior findings. A single diagnosis would be a final diagnosis if it could explain all the patient's findings, otherwise at least two diagnoses would be needed, for example in comorbid conditions. A strong differential likelihood ratio provides general evidence of a finding's ability to perform well as a differentiator during the diagnostic process. Given this background, we could objectively characterise the diagnostic lead as that finding with the maximal differential likelihood ratio. Auxiliary findings used in the diagnostic process provide further confirmatory differential likelihood ratios (or progressively discount the putative diagnosis in favour of some competing diagnosis). Bayesian estimation provides an objective method to revise the confidence in a particular diagnosis, eventually resulting in treatment decisions with better outcomes.

Conclusions

It is clear that scientific methods of diagnosis are the best answer to the plague of misdiagnosis that dominates medicine today. In the current scenario where new diseases are emerging, chances are even greater for the physician to fall into a diagnostic trap. Scant attention paid to the diagnostic process could equate to medical negligence and malpractice, and would lead to harm to the patient. The evidence-based approach with its solid foundation in Bayesian analysis is the way forward to resolving the diagnosis in difficult cases. The art of diagnostic detection could nearly match forensic criminology in its complexity, a fact attested by the popular fictional detective whose character was modelled on the diagnostic prowess of the physician Joseph Bell[2]. Bayesian medicine holds the key to systematic diagnosis and captures the soul of evidence-based detection. It is the necessary criterion for the advancement of precision medicine.

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References

1) Llewelyn, H. Mathematical analysis of the diagnostic relevance of clinical findings. Clin Sci 1979;57:477-9.

2) Conan Doyle A. Adventures of Sherlock Holmes. Bantam Books.1986: 304 pp.