STATISTICS IN MEDICINE, VOL. 13, 201–209 (1994)

FOUNDATIONS OF MEDICAL DIAGNOSIS: WHAT ACTUALLY ARE THE PARAMETERS INVOLVED IN BAYES' THEOREM?

OLLI S. MIETTINEN

Montreal Neurological Institute, 3801 University St., Montreal, PQ, H3A 2B4, Canada

AND

J. JAIME CARO

Division of General Internal Medicine, Royal Victoria Hospital, McGill University, Montreal, Canada

SUMMARY

Three decades ago, the thesis was adduced that setting diagnostic probabilities requires, by the inherent nature of diagnosis-pertinent medical knowledge, the use of Bayes' theorem. That paper was both vague and inconsistent in its delineation of the nature of the parameters involved in this formulation, and subsequent authors have only added to the confusion. Nevertheless, that thesis has been, and continues to be, enthusiastically embraced by clinical scholars. We here posit what those parameters must be taken to represent in principle; and this explication reveals that their quantification poses generally unsurmountable epistemologic challenges. The implication of this is not that informed setting of diagnostic probabilities is generally infeasible. Our conclusion is, instead, that the seminal thesis was founded on an untenable pair of premises about the nature of scientifically attainable knowledge pertinent to diagnosis.

1. INTRODUCTION

Three decades ago, in a paper published in *Science*, Ledley and Lusted[1] adduced the thesis that setting diagnostic probabilities in medical practice requires the use of Bayes' theorem, and they also gave some delineation of the parameters involved in this formulation of them.

This paper has proved to have been quite seminal to the theory of diagnosis:[2,3] seemingly without exception (objection was expressed by Feinstein,[4] but subsequently this author has adopted the Bayes' theorem framework[5]), clinical scholars have come to embrace Bayes' theorem as an 'essential guidepost'[6] to diagnosis. This acceptance is evident not only in expository papers on the subject[6–11] but in chapters of textbooks of medicine as well.[12–16] Moreover, in accord with this, various calculational aids for the quantification of diagnostic probability in the Bayes' theorem framework have been published (References 17–19 among others).

Notwithstanding this acceptance of the thesis, even the inherent nature of the parameters involved in the Bayes' theorem formulation of diagnostic probabilities remains poorly understood, with several conflicting outlooks manifest in the literature.[20]

In this paper, we first restate, in most general terms Ledley and Lusted's thesis. We then set forth the first-order issues on which there needs to be clarity about the parameters involved, and we proceed to examine what is said about these in the seminal paper and in subsequent writings

0277–6715/94/030201–09$09.50

Received January 1992
Revised May 1992

on the subject. Finally, we posit resolutions of these issues and address their implications regarding the estimability of those parameters – with a view to understanding the feasibility of, and need for, deploying the Bayes' theorem framework in diagnosis, and the implications of this for research bearing on diagnosis.

2. THE SEMINAL THESIS

In setting a diagnosis, the challenge is, as set forth by Ledley and Lusted, to perceive the probability of the presence of a particular illness I_i given the clinical profile Cp of the patient – that set of known facts about the patient which have to do with potential manifestations of illness.

The point of departure for Ledley and Lusted was a pair of premises as to the nature of potentially available, diagnosis-relevant knowledge in medicine. The first one was that the direct probability $\Pr(I_i|Cp)$ cannot be a matter of general medical knowledge; and their second premise was that the inverse probabilities or 'likelihoods' – those of the clinical profile given various particular illnesses, $\Pr(Cp|I_j)$, $j = 1, 2, \ldots$ – can be. From these two premises they deduced their thesis that the use of general medical knowledge for deriving the direct, or 'posterior', probability of interest requires the deployment of Bayes' theorem. Specifically,

$$\Pr(I_i|Cp) = \frac{P_i' \Pr(Cp|I_i)}{P_i' \Pr(Cp|I_i) + \sum_j P_j' \Pr(Cp|I_j)}, \quad (1)$$

where the summation ranges over all other illnesses, and where the additional parameters P_i' and $P_j', j = 1, 2, \ldots$, are the 'prior' probabilities of the respective illnesses defined without regard to the clinical profile. The magnitudes of the latter are determined by the patients's non-clinical profile – the set of 'host' characteristics such as age and place of residence, together with the calendar time of the patient's presentation.

This formulation can be recast, as is well known, in terms of mere relative likelihoods, or likelihood ratios:

$$\Pr(I_i|Cp) = \frac{1}{1 + \sum_j \frac{P_j'}{P_i'} \frac{1}{LR_j}}, \quad (2)$$

where $LR_j = \Pr(Cp|I_i)/\Pr(Cp|I_j)$, the likelihood ratio contrasting the illness at issue, I_i, to the jth alternative illness, and where the summation ranges again over all other illnesses.

In brief, the use of Bayes' theorem was posited as essential for setting diagnostic probabilities in the light of general medical knowledge, specifically for 'updating' the prior probability based on *ad hoc* (extrascientific) information specific to the non-clinical profile, with the updating based on general (scientific) knowledge about the likelihoods (relative) of the patient's clinical profile in various conceivable illnesses, independent of the non-clinical profile.

3. THE ISSUES

3.1. The juncture of application

The pivotal issue in this type of formulation of diagnostic probability is the separation of the totality of known facts about the patient into those that bear on the *ad hoc* prior probabilities and those that are involved in the science-based updating of these – the separation which we think of as forming the *juncture* of application of Bayes' theorem. The choice of juncture has, of course,

major implications on what the component parameters are in principle; and this, in turn, determines the suitability of the use of Bayes' theorem in the actual practice of medical diagnosis, depending on how estimable the prior probabilities and the likelihoods (relative) actually are from *ad hoc* and scientific sources respectively.

One possible juncture is, of course, the *non-clinical/clinical* juncture considered by Ledley and Lusted themselves.

The main alternative subsequently adduced to this is the *pre-test/post-test* juncture. In this one, the entire set of facts (clinical as well as non-clinical) known before the diagnostic test serve to set the prior ('pre-test') probabilities, directly, and only the test result is dealt with by the use of Bayes' theorem.

A third principal possibility that has been considered is the *ignorance/facts* juncture. In this one, the prior probabilities are based on nothing known about the particular patient (excepting the practice to which he presents himself and the time at which he does so), and all of the relevant facts on the patient (inclusive of, for example, age) are involved in the updating.

Any remaining option is but a variation of these principal ones.

3.2. The parameters involved

Whatever the juncture of application of Bayes' theorem, there needs to be clarity about the prior probabilities and likelihoods as to the meanings of the frequencies at issue – about their respective domains and their particular meanings within those domains. With respect to the prior probabilities, the issue of domain is that of what the 'universe' is for which these probabilities represent the relative frequencies of the various illnesses; and whatever the domain, exactly what type of frequency of illness is at issue (prevalence, incidence, ...?). As for the likelihoods (their ratios) the respective domains are, in some sense, the various particular illnesses; but are these to be thought of in the abstract, as they occur regardless of their manifestations, or what?

4. THE LITERATURE

4.1. The juncture

The various possible junctures delineated above for the application of Bayes' theorem were not addressed by Ledley and Lusted. They, as is apparent from what is said above (Section 2), seemingly took the non-clinical/clinical juncture to be the only appropriate one to consider. They seemingly were driven by the (highly tenable) principle that general medical knowledge is to be deployed maximally in setting diagnostic probabilities, together with the premise that the likelihoods of the entire clinical profile not only can be (Section 2), but in fact are, knowable from general (scientific) sources, while those of profiles involving non-clinical facts are not (Section 2).

Various subsequent authors, however, tend to focus on the pre-test/post-test juncture as though this were the only appropriate one to consider.[13] They do not, however, clearly explain the basis for this modification of the Ledley and Lusted outlook – whether they view the likelihoods of the pre-test clinical profiles as, in fact, unavailable from general sources, or whether, instead, they believe the pre-test probabilities to be knowable from general sources after all, despite the involvement of non-clinical facts in their quantification (Section 4.2).

Most authors are quite liberal about the juncture of use of Bayes' theorem, allowing for its use even in the ignorance/facts juncture (References 7, 21 among others). Some even recommend the use of Bayes' theorem sequentially over the component facts about the patient, with the posterior probability after any given fact becoming the prior probability when addressing the next.[22,23]

4.2. The prior probabilities

According to Ledley and Lusted, the prior probability for any given illness at the non-clinical/clinical juncture is 'the total probability that the patient has the disease complex in question, irrespective of any symptoms', 'the ratio of the number of patients that have ... [the illness] ... to the total number of patients from which the random selection is made'. They left the 'random selection' unspecified as to both the population to be sampled and the process of sampling. Elsewhere in their paper prior probabilities are said to refer to 'already-diagnosed cases' within the practice; and, in accord with this, the authors suggest estimating each of them as the proportion known to have the illness at issue among all securely diagnosed patients in the practice at issue. The denominator in this relative frequency is not said to be limited according to the illnesses involved, nor is it said to be specific to any of the non-clinical facts on the patient. On the other hand, such limitation and specificity are apparent in their example.

Wulff,[11] concerned with the same juncture, appears to agree with Ledley and Lusted's instructions for estimating the prior probabilities. Thus to him the prior probability of lung cancer, in the context of a patient presenting with haemoptysis, is the relative frequency of lung cancer among the diagnostician's patients – without any restriction according to their illnesses, or any based on the patients's non-clinical characteristics.

Those who focus on the pre-test/post-test juncture in the use of Bayes' theorem take the prior probability of a given illness to be the relative frequency of this illness among patients so tested. This referent for the frequency is generally left without further specification. Typically, illustrations of this concept involve taking the prior probability as the proportion of patients who in some study of the diagnostic value of the test at issue had the illness at issue,[10] with no restrictions on the set of illnesses or express conditionality of these probabilities on the set of known pre-test facts about the patient. On the other hand, Goldman, in accord with some others, states that the pre-test probability should be based on 'key historical questions, findings on physical examination, and [previous laboratory test results]' and 'must be derived from relevant patient populations ... so that the results can be extrapolated to local medical practice'.[13]

To authors who contemplate the use of Bayes' theorem for updating prior probability in the ignorance/facts juncture, the prior probability of a given illness is its frequency in the patient's community, with the particulars of this, again, only loosely specified.[21] For example, in reference to a young person presenting with fever and sore throat, the prior probability for streptococcal infection has been said to be 'the prevalence of streptococcal pharyngitis in the community at that time'.[7]

4.3. The likelihoods

Ledley and Lusted said nothing on the level of theory about the nature of the likelihoods, but they gave instructions for estimating these on the basis of a practice's securely diagnosed cases. This implies, first, that they took them to refer to the respective illnesses as they manifest themselves in clinical settings. From these instructions it can also be inferred that they view the likelihoods as independent of the non-clinical profile, as all cases of a given illness regardless of their non-clinical profiles were to be used for estimating the corresponding likelihood to be deployed in the context of whatever non-clinical profile.

No other writers have addressed the likelihoods of the entire clinical profile as such, only those of its components. No explicit theoretical distinctions have been made among different types of fact in the clinical profile, and each set of component likelihoods is taken to refer to the respective illnesses as they manifest themselves in clinical settings. A few writers have recognized that these likelihoods do tend to depend on the pre-test profile.[24–28]

5. PROPOSITIONS REGARDING NON-CLINICAL/CLINICAL JUNCTURE

5.1. Restriction of the set of illnesses

When applying Bayes' theorem in the non-clinical/clinical juncture, the first challenge is the identification of the set of illnesses that need to be considered. Although on the level of theory, all illnesses need to be considered, in practice an initial restriction is commonly provided for by the known non-clinical patient characteristics such as age and gender, implying zero prior probabilities for various illnesses. Further restriction is provided for by the clinical profile: among the remaining illnesses consideration can be restricted to the small subset for which the likelihood $\Pr(Cp|I_j)$ is non-zero.

In other words, the set of illnesses to be addressed in the Bayes' formulation of diagnostic probability (equations (1), (2)) can be restricted to those which not only can occur in the context of the non-clinical profile but also are capable of explaining the clinical profile.

5.2. Prior probabilities

The restriction of the set of illnesses even by the clinical profile has a simplifying implication for the prior probabilities. It is not necessary to consider the absolute prior probabilities of all illnesses conceivable in the context of the patient's non-clinical profile – probabilities which add up to unity over all of those illnesses. It suffices to consider the *relative* prior probabilities within the set of illnesses restricted by the clinical profile as well – probabilities which, while proportional to the absolute ones, add up to unity over this clinically restricted set.

The meaning of the prior probability (relative) of a particular one of the illnesses I_i, I_j must be that of the proportion of people who have this illness – in a properly defined population of people. The specific referent population – the domain – of this proportion is, of course, one whose members have one of the restricted set of illnesses; and membership in it is further restricted by the non-clinical profile of the patient at hand. It is, thus, a subpopulation, in these two regards, of whatever the properly defined general referent population of prior probabilities is in principle. On the other hand, the subpopulation must not be restricted, unwittingly even, in terms of the clinical profiles of the members of the general referent population, because this aspect is reserved for use in updating the prior probability implied by membership in the specific referent population of prior probabilities.

The challenge is, then, proper definition of the general referent population of prior probabilities. It cannot properly be taken to be the 'population' (aggregate of instances) of patient presentations in the practice at issue, or anywhere else. For such a 'population' is inherently selected according to the clinical profiles that were to be reserved for deployment in the updating of the prior probabilities, as patients present themselves for diagnosis to a large measure because of (some aspects of) their clinical profiles, not independently of these. The requisite clinical unselectiveness is achieved by taking the general referent population to be that of all people alive anywhere at the time of the diagnosis – the contemporaneous world population.

Despite the enormousness of this general referent population, the specific referent population within it, upon restrictions such as place of residence, can be very small. As a consequence, the prevailing proportion of its members with any given one of the set of illnesses can be too unstable to be meaningful. This means that the prior probabilities cannot properly be taken to be the respective, actually prevailing proportions – the actual relative prevalences – in the specific referent population. Rather, they must be taken to be the corresponding 'expected' proportions based on suitable lateral patterns in place, time, and/or the non-clinical person characteristics taken into account on the patient.

In short, then, the prior probability of a particular illness at the non-clinical/clinical juncture is to be thought of as the expected proportion of people with that illness, at the time of diagnosis, among all people who share the patient's non-clinical profile and who have one of the illnesses capable of explaining the patient's clinical profile.

5.3. The likelihoods

With the *ad hoc* prior probabilities thus understood, understanding of the domains of the corresponding general likelihoods follows: the likelihoods must refer to illness-specific subdomains of the domain of the prior probabilities. The strict requirement of shared overall domain can, however, be relaxed insofar as it is believed – in accord with Ledley and Lusted – that the distributions of clinical profile conditional on particular illnesses are more or less invariant over various circumstances, specifics of which are incorporated in the non-clinical profile which determines the prior probabilities.

Thus, the likelihoods at the non-clinical/clinical juncture represent probabilities (or probability densities) of the known clinical profile in the abstract domains of the respective illnesses – not among cases of these seen in clinical practices – possibly restricted further according to some aspects of the non-clinical profile. These domains, like that of the prior probabilities, are ones defined independently of possible manifestations of the illnesses, thus including asymptomatic cases together with symptomatic ones – in contrast to the relative overrepresentation of symptomatic cases in the clinical domain (Section 5.2).

5.4. Estimability

As was argued above, the parameters involved in Bayes' theorem at the non-clinical/clinical juncture must be taken to refer to people at large having any one of the set of illnesses of diagnostic concern (prior probabilities) or various particular ones of them (likelihoods), irrespective of the clinical manifestations, if any, of these illnesses. Accessing the domain of the prior probabilities validly – independently not only of the clinical profiles but also of the underlying illness status within the set – requires secure ascertainment of the status with respect to each of the illnesses for all members of the current, local population of people, restricted in terms of the non-clinical profiles of its members. In studying the likelihoods, it is necessary to obtain, even if anywhere at any time, a series of cases of each of the illnesses by the use of facts that are uncorrelated with those in the clinical profiles considered in diagnostic practice.

Moreover, any given clinical profile is commonly a realization for quite a multidimensional random vector, with a multitude of other possible realizations, and this means that estimation of the relative likelihoods of a particular profile (conditional on particular illnesses) tends to require very large series of cases of each illness.

These requirements for estimation are, in general, formidable to say the least, and commonly downright unsurmountable.

5.5. Epilogue

As was noted in Section 4.2, Ledley and Lusted took the prior probabilities to refer to patients seen in the practice at issue. With this commitment, coherence of referents requires that the likelihoods also refer to this practice (cf. Section 5.3). Yet, with this shared referent, the likelihoods, or even their ratios, cannot be objects of general medical knowledge. For, their values depend on the local – and highly speciality dependent – roles of various elements in the clinical profile as determinants of patient presentations in the particular practice.

6. PROPOSITIONS REGARDING THE PRE-TEST/POST-TEST JUNCTURE

At the pre-test/post-test juncture, the restriction of the set of illnesses of concern is quite analogous to that in the non-clinical/clinical juncture (Section 5.1).

The proper prior probability of a particular illness again refers to its relative prevalence in a restricted segment of the general referent population of people at large (Section 5.2), but here the restrictions involve the pre-test clinical profile as well. As a consequence, these prior probabilities are subject to valid study among patients presenting themselves in clinical practices.

Similarly, the likelihoods of various test results are validly manifest in clinically encountered patients, so long as results of the test play no role in referral to the clinical realm.

Thus, in sharp contrast to the non-clinical/clinical juncture, the parameters involved in the use of Bayes' theorem in the pre-test/post-test juncture are estimable within the clinical realm.

On the other hand, the invariance premise about the likelihoods invoked by Ledley and Lusted for the non-clinical/clinical juncture cannot be retained for this juncture. The likelihoods of a particular test result are quite prone to depend on the pre-test clinical profile even if the likelihoods of the clinical profile, whether pre-test or post-test, do not depend on the non-clinical profile. Thus, the likelihoods corresponding to various particular pre-test profiles require estimations that account for their dependence on aspects of the non-clinical profile.

7. PROPOSITION REGARDING THE IGNORANCE/FACTS JUNCTURE

Nothing suggests that likelihoods for profiles involving non-clinical elements along with clinical ones are in principle invariant and, thus, subject to general medical knowledge. Thus, the idea of applying Bayes' theorem at this juncture is founded on a gross misunderstanding of Ledley and Lusted's thesis – or sheer ignorance of it.

8. PROPOSITION REGARDING SEQUENTIAL JUNCTURES

Sequential application of Bayes' theorem to the component facts on the patient – the posterior probability after one fact serving as the prior probability when taking account of the next – represents another misunderstanding. Even when applied to the clinical set of facts only, it is correct only insofar as the occurrence of each component fact is independent of the antecedent facts already accounted for.[20] In reality, though, clinical abnormalities tend to be positively correlated, so that this approach is conducive to exaggerated deviation of the computed posterior probability from the prior probability implied by the non-clinical profile.

9. DISCUSSION

Whereas Ledley and Lusted were, and subsequent authors have been, vague and inconsistent about the inherent nature of the parameters involved in Bayes' theorem formulation of diagnostic probabilities (Sections 4.2, 4.3), we find that they can be defined quite precisely (Sections 5.2, 5.3, 6).

In the light of these definitions it becomes apparent, however, that the pursuit of empirical knowledge about them – about the *ad hoc* prior probabilities and also about the general likelihoods – tends to entail enormous, and indeed insurmountable, challenges in reference to the non-clinical/clinical juncture considered by Ledley and Lusted (Section 5.4). Thus, whereas we do not fault their logic in the context of their premises, we do have to call to question their second premise, the one that posits the inverse probabilities (likelihoods) as knowable from general

medical sources (Section 2). Moreover, even if we were to accept this premise, we would have to conclude that such general knowledge would not be well suited for application in diagnostic practice, given what it implies in terms of the requisite quantification of the associated, properly construed, prior probabilities (Section 5.4).

The implications of these definitions on the first premise of Ledley and Lusted – the one that posits the direct (Bayes' posterior) probabilities as not being knowable from general medical sources (Section 2) – are more subtle. Pertinent to this premise is the definition of prior probability in the pre-test/post-test juncture; for, setting this probability represents the general challenge of setting diagnostic probability in the light of a set of clinical facts on the patient, that is, the very challenge that Ledley and Lusted's thesis pertains to. That this probability is conditional on the clinical profile makes the domain of its referent frequency, in sharp contrast to those of the likelihoods of the profile (Section 5.4), accessible through clinical experience itself (Section 6). It is, thus, possible to pursue particularistic estimates of these, estimates specific to place and time. The particularism in these is, however, a matter of modification of the direct probability by relevant descriptors of place (climate, other aspects of environment, unspecified characteristics of people in it, etc.) and time (season, epidemicity, etc.); and the role of these particulars as modifiers of the probability is subject to general, scientific knowledge, in principle at least. The theoretical framework for research and knowledge of this direct sort is, of course, that of regression models in contrast to Bayes' theorem.

Those who now focus on the use of Bayes' theorem in the pre-test/post-test juncture only (Section 4.1) reflect implicit agreement with these conclusions – even if they still, without explicit rationale, proceed to advocate its use in deriving the post-test probability. Some others have indeed gone on to advocate the regression formulation throughout.[29–31] Yet no one, it seems, has up to now exposed the true inherent nature of the parameters involved in Ledley and Lusted's formulation of diagnostic probability – and the generally insurmountable epistemologic challenges that these parameters turn out to represent.

REFERENCES

1. Ledley, R. S. and Lusted, L. B. 'Reasoning foundations of medical diagnosis', *Science*, **130**, 9–21 (1959).
2. Beck, J. R., Pyle, K. I. and Lusted, L. B. 'A citation analysis of the field of medical decision making 1959–1982', *Medical Decision Making*, **4**, 449–468 (1984).
3. Lusted, L. B. 'The clearing "haze": a view from my window', *Medical Decision Making*, **11**, 76–88 (1991).
4. Feinstein, A. R. 'The haze of Bayes, the aerial palaces of decision analysis, and the computerized Ouija board', *Clinical Pharmacology and Therapeutics*, **21**, 482–496 (1977).
5. Feinstein, A. R. *Clinical Epidemiology: The Architecture of Clinical Research*, Little, Brown, Boston, 1985.
6. Sox, H. C. 'Probability theory in the use of diagnostic tests', *Annals of Internal Medicine*, **104**, 60–66 (1986).
7. Fletcher, R. H., Fletcher, S. W. and Wagner, E. H. *Clinical Epidemiology: the Essentials*, Williams and Wilkins, Baltimore, 1988.
8. Griner, P. F., Mayewski, R. J. *et al.* 'Selection and interpretation of diagnostic tests and procedures', *Annals of Internal Medicine*, **94**, 553–600 (1981).
9. Ingelfinger, J. A., Mosteller, F., Thibodeau, L. A. and Ware, J. H. *Biostatistics in Clinical Medicine*, Macmillan, New York, 1987.
10. Sackett, D. L., Haynes, R. B., Tugwell, P. and Guyatt, G. *Clinical Epidemiology: a Basic Science for Clinical Medicine*, Little, Brown, Boston, 1991.
11. Wulff, H. *Rational Diagnosis and Treatment: an Introduction to Clinical Decision-Making*, Blackwell, Oxford, 1981.
12. Pauker, S. G. in Wyngaarden, J. B. and Smith, L. H. (eds.), *Cecil Textbook of Medicine*, Saunders, Philadelphia, 1988, pp. 74–77.

13. Goldman, L. in Braunwald, E. *et al.* (eds.), *Harrison's Principles of Internal Medicine*, McGraw-Hill, New York, 1991, pp. 5–10.
14. Johns, R. J., Fortuin, N. J. and Wheeler, P. S. in Harvey, A. M., Johns, R. J., *et al.* (eds.), *The Principles and Practice of Medicine*, Appleton and Lange, Norwalk, 1988, pp. 4–8.
15. Gottfried, E. L. and Gerard, S. K. in Samiy, A. H., Douglas, R. G. and Barondess, J. A. (eds.), *Textbook of Diagnostic Medicine*, Lea and Fabiger, Philadelphia, 1987, pp. 23–32.
16. Sapira, J. D. *The Art and Science of Bedside Diagnosis*, Urban and Schwarzenberg, Baltimore, Munich, 1989.
17. Benish, W. A. 'Graphic and tabular expressions of Bayes' theorem', *Medical Decision Making*, **7**, 104–106 (1987).
18. McNeil, B. J. and Abrams, H. L. *Brigham and Women's Hospital Handbook of Diagnostic Imaging*, Little, Brown, Boston, 1986.
19. Griner, P. F., Panzer, R. J. and Greenland, P. *Clinical Diagnosis and the Laboratory: Logical Strategies for Common Medical Problems*, Yearbook Medical Problems, Chicago, 1986.
20. Begg, C. B. 'Statistical methods in medical diagnosis', *CRC Critical Reviews in Medical Information*, **1**, 1–22 (1986).
21. Kramer, M. S. *Clinical Epidemiology and Biostatistics*, Springer, Berlin, 1988.
22. Cebul, R. D., Hershey, J. C. and Williams, S. V. 'Using multiple tests: series and parallel approaches', *Clinical and Laboratory Medicine*, **2**, 871–890 (1982).
23. Lichtenstein, M. J. and Pincus, T. 'How useful are combinations of blood tests in "rheumatic panels" in diagnosis of rheumatic diseases?', *Journal of General Internal Medicine*, **3**, 435–442 (1988).
24. Lofgren, R. P. 'The dynamic nature of sensitivity and specificity', *Journal of General Internal Medicine*, **2**, 452–453 (1987).
25. Hlatky, M. A., Pryor, D. B., *et al.* 'Factors affecting sensitivity and specificity of exercise electrocardiography', *American Journal of Medicine*, **77**, 64–71 (1984).
26. Isenberg, D. A., Hammond, L., *et al.* 'Predictive value of SS-B precipitating antibodies in Sjogren's syndrome', *British Medical Journal*, **284**, 1738–1740 (1982).
27. Rozanski, A., Diamond, G. A., *et al.* 'The declining specificity of exercise radionuclide ventriculography', *New England Journal of Medicine*, **309**, 518–522 (1983).
28. Detrano, R., Guppy, K. H., Abbasi, N., *et al.* 'Reliability of Bayesian probability analysis for predicting coronary artery disease in a veterans hospital', *Journal of Clinical Epidemiology*, **41**, 599–605 (1988).
29. Anderson, J. A. 'Separate sample logistic discrimination', *Biometrika*, **59**, 1935 (1972).
30. Anderson, J. A. 'Diagnosis by logistic discriminant function: further practical problems and results', *Applied Statistics*, **23**, 397–404 (1974).
31. Dawid, A. P. 'Properties of diagnostic data distributions', *Biometrics*, **32**, 647–658 (1976).