Mini-Max Procedure versus Bayes Formula to Calculate Probabilities of Medical Diagnoses*

*The mini-max procedure is the core of our practical computer program that diagnoses diseases in actual patients, which complete details can be found in our more theoretical book [6] or more practical book [8]. Other partial aspects of this diagnostic system will be published separately: Best Cost-Benefit Clinical Datum Next to Investigate, Recommended Set of Best Cost-Benefit Clinical Data Next to Investigate, and Complex Clinical Presentations and their Models.

CARLOS FEDER, MD, Internal Medicine; TOMAS FEDER, PhD, Computer Sciences

In the 18th century, Thomas Bayes, a theologian and mathematician, proposed his formula for calculating conditional probabilities, which was posthumously published in 1763. To our knowledge, Ledley and Lusted [1], in 1959, committed the original sin to apply this formula to calculate the probability of a specific diagnosis, given the manifestations—clinical data—of a disease. After that, Bayes formula gained widespread dissemination in the field of medical diagnosis. The inaccuracy of Bayes formula for calculating the posterior probability of a diagnosis given clinical data that are not independent has been recognized by many researchers. Their excuse for using Bayes despite this realization is that they consider the introduced error not to substantially affect the final result [2]. Our novel mini-max procedure, meant for computerized diagnosis, calculates the probability of a specific diagnosis, processing clinical data present—favoring the diagnosis—and clinical data absent—disfavoring the diagnosis. It is more accurate than Bayes formula and has remarkable additional properties, which enable diagnosis of concurrent diseases and recommendation of the best cost-benefit *set* of clinical data further to investigate to reach end of diagnostic quest through the most efficient and less costly pathway.

Bayes formula is accurate only when three conditions are fulfilled [3] [4] [5]:

1. Clinical data used for calculation of the conditional probability of a diagnosis must be **independent**: that is, a specific clinical datum—symptom, physical sign, diagnostic test result, or diagnostic procedure result—should neither favor nor disfavor any other clinical datum of the same disease. In other words, the probability that one clinical datum is manifested by a specific disease, should not depend on the presence of another clinical datum. This is not true for actual clinical cases, where clinical data result from a chain of reactions that originate in a common cause or lesion and are necessarily related. These clinical data configure syndromes that by definition are associations of related clinical data (*e.g.*, jaundice, increased blood bilirubin, and dark urine.)

2. The diseases must be **incompatible,** which means that clinical data justified by one disease cannot be justified by another disease. When concurrent diseases occur, some clinical data may be caused by more than one of them. Because Bayes formula is only capable to calculate probabilities of competing diagnosis, which are incompatible because only one can become a final diagnosis, it is unsuitable to handle concurrent diseases. To solve the problems of independence and incompatibility, so-called Bayesian networks have been devised, but their application to diagnostic algorithms is excessively complicated and hard to compute. We created the mini-max procedure (to be explained later), which identifies concurrent diagnoses despite manifesting shared clinical data, and calculates the probability (P) of such diagnoses independently, circumventing the *incompatibility* condition of Bayes' formula.

3. The number of diseases processed by Bayes must be **exhaustive**: all known diseases must be included in the database, enabling inclusion in the denominator of the formula of all corresponding diagnoses that manifest a clinical datum. If this condition is violated, some clinical datum originated by a disease not included in the formula will distort the calculated result. Accordingly, the calculated

probability of the diagnosis under consideration will be incorrect and will adversely affect the differential diagnosis. Still worse, the excluded disease will never be included in the differential diagnosis. This is why computer programs based on Bayes formula but circumscribed to a restricted area of diseases—such as congenital cardiopathies or nephropathies—are inherently inaccurate.

Our novel mini-max procedure is able to calculate the probability of a specific diagnosis, processing simultaneously clinical data present—favoring the diagnosis—and clinical data absent—disfavoring the diagnosis. It is more accurate than Bayes formula and has remarkable additional properties:

- It identifies and processes concurrent diseases.
- It precludes reduction of great probability of a confirmed diagnosis (strongly supported by clinical data present) by some relatively unimportant clinical datum absent.
- It facilitates the recommendation, at each diagnostic stage, of the best cost-benefit clinical datum next to investigate in the patient, and even a **set** of such clinical data to be investigated simultaneously.

The mini-max procedure became the core of our diagnostic algorithm, which is discussed in great detail in our book: *A Practical Computer Program that Diagnoses Diseases in Actual Patients* [8].

To understand how our mini-max procedure works, we must first review the principles upon which it is based.

PRINCIPLES OF OUR DIAGNOSTIC COMPUTER PROGRAM

DISEASE MODEL

A **disease model** (Table 1), as defined in this study, is an abstract concept that comprises all clinical data that can be manifested by all patients with a specific disease. A single patient typically never manifests all clinical data that the disease potentially can provoke. Integration of a specific disease model with all of its possible manifestations requires statistical study of a large patient population. *Each clinical form, stage, degree, or complication of a disease has its own disease model*. Because death and iatrogenic diseases are diagnoses that must be established clinically, the corresponding disease models must also be created.

Each disease model is stored in the database, listing all the clinical data that a given disease potentially can manifest.

DISREGARD QUALITIES OF CLINICAL DATA

Clinical data, especially subjective symptoms, typically have diverse non-exclusive qualities. For example, chest pain of angina pectoris typically is retrosternal, radiating to the neck, jaw, and upper extremities; is oppressive, lasting only a few minutes; is exertion related and relieved by nitroglycerine. Some authors confer values to these pain qualities, their chronology, and their evolution. This is correct, when such qualities, powerfully suggest a diagnosis. Nevertheless, our algorithm purposely *does not consider such clinical data qualities*; we believe that computation of clinical datum qualities is not critical for calculation of probability of a diagnosis. Reasons are: clinical data qualities and chronology are subjective and widely variable; chest pain of angina pectoris sometimes is mild, referred to the upper

DISEASE MODEL FOR ACUTE APPENDICITIS				
Symptoms	**S**	**PP value**	**Cost**	**Masked by**
Anorexia	0.93	0.20	none	
Pain in right lower abdomen	0.95	0.30	none	‡ (analgesics, antibiotics)
Vomiting	0.66	0.16	none	‡ (antiemetics)
Nausea	0.64	0.15	none	
Fever/chills	0.29	0.07	none	‡ (antipyretics, antibiotics)
Constipation	0.70	0.02	none	
⋮	⋮	⋮	⋮	
Signs				
Rebound tenderness	0.86	0.18	none	‡ (analgesics, antibiotics)
Fever (>37.5 C)	0.36	0.08	none	‡ (antitermics, antibiotics)
⋮	⋮	⋮	⋮	
Laboratory				
Increased white blood cell count	0.96	0.21	small	
Albumin in urine	0.19	0.04	small	
⋮	⋮	⋮	⋮	
Abdominal ultrasound				
Swollen appendix or abscess	0.60	0.95	intermediate	
⋮	⋮	⋮	⋮	
Laparotomy finding	1.00	1.00	great	

TABLE 1. Example of disease model; S, sensitivity; PP value, positive predictive value; cost of obtaining the clinical datum; ‡, interacting drugs. The numeric values for S and PP value in the above examples were not obtained from actual statistics or calculations.

abdomen, not radiating, is burning, or even absent in patients with diabetes. Accordingly, these qualities may not be reliable. Anxious or hypochondriac patients can imagine such qualities. To confirm angina pectoris, more reliable tests, such as stress ECG and sometimes angiogram are needed, which provide clinical data with greater supporting value that anyway will supersede the oppressive quality of chest pain that has a lesser supporting value. Disregarding these unreliable qualities simplifies the diagnostic process without losing accuracy. It would be difficult, if not impossible, to determine the sensitivity, necessary to calculate the supporting positive predictive value of each diverse quality that thousand of known clinical data and diseases can manifest. In the especial case where the quality of a clinical datum is essential, such as the case of prolonged retrosternal pain for myocardial infarction, this quality can be included as a separate clinical datum in the corresponding disease model.

DISREGARD DISEASE PREVALENCE

Prevalence of a disease is the number of existing cases in a given population at a specific time. Prevalence statistics are of epidemiological importance. However, it may be harmful to include prevalence values when calculating the probability of a patient having a rare disease. This happens because the small prevalence value for such a rare disease could considerably reduce the probability of the corresponding diagnosis, causing it to be improperly ruled out. If a patient has a disease afflicting only one in a million persons, the probability of that diagnosis would be very small, but for him it

represents one hundred percent. A perfect program should diagnose every possible disease, including those that are rare. After all, we do not need a computer to diagnose a common cold during an epidemic. Furthermore, accurate epidemiological information is difficult to obtain because many disease cases remain unreported. Accordingly, our diagnostic algorithm purposely does *not* take prevalence into account; this is equivalent to assuming that all diseases occur with the same probability.

INDICES OF CLINICAL DATA

In our database, three **indices** are associated with each clinical datum: *sensitivity*, *positive predictive value*, and *cost*.

Indices

1. *Sensitivity* (S)

Sensitivity is defined as the conditional probability P of a clinical datum C, given a disease D:

$$S = P(C|D) \tag{1}$$

Where: S = sensitivity of clinical datum C for disease D

A practical way to calculate S of a specific clinical datum for a given disease is to determine statistically the fraction of patients afflicted by this disease who manifest the clinical datum:

$$\text{Sensitivity (S)} = \frac{\text{Number of disease cases manifesting the clinical datum}}{\text{Total number of disease cases}} \tag{2}$$

Sensitivity can be expressed either as a decimal (*e.g.*, 0.30), or as a percentage (*e.g.*, 30%.)

A given clinical datum can be manifested by more than one disease. Accordingly, both the clinical datum and the disease that manifests it, determine the value of S. This value is stored in the database linked to the corresponding clinical datum and disease model.

If the numerator and denominator of equation 2 are equal, the sensitivity (S) of the datum will equal 1, which is unlikely, as it requires that all clinical cases so far reviewed manifested the clinical datum. Otherwise, the numerator will always be smaller than the denominator, S will be smaller than 1, and an additional clinical case will increase S if the clinical datum is present, or reduce it if the datum is absent. Accordingly, the computer recalculates the sensitivity of each clinical datum each time the database is updated with new cases. The greater the number of cases analyzed, the greater the accuracy of S. If a clinical datum never is manifested by a specific disease, its S equals 0 for this disease. When sufficient number of cases have been reviewed, the disease model will include all the clinical data this disease can potentially manifest, and the sensitivities will approach their true values.

2. *Positive predictive value* (PP value)

Next, it is necessary to define an index that represents the strength with which each clinical datum present in the patient supports a specific diagnosis. S cannot be used directly because it only expresses how frequently a disease manifests a clinical datum, but not how often it occurs with other diseases. We

consider that positive predictive value (PP value) best accomplishes this function. PP value is defined as the conditional probability P of a disease D, given a clinical datum present C:

$$\text{PP value} = P(D|C) \tag{3}$$

Let's start with Bayes formula, which calculates conditional probabilities:

$$P(D_i|C) = \frac{P(D_i)\,P(C|D_i)}{P(D_1)\,P(C|D_1) + \ldots + P(D_i)\,P(C|D_i) + \ldots + P(D_n)\,P(C|D_n)} \tag{4}$$

Where: $P(D_i)$ = probability of disease D_i; also called *prior probability* because it is the probability of the disease *before* considering clinical datum C

$P(D_i|C)$ = probability of disease D_i, given specific clinical datum C; also called *posterior probability* of the disease because it is the result of the equation *after* considering clinical datum C

$D_1 \ldots D_n$ = all diseases that manifest clinical datum C, including D_i

$P(C|D)$ = probability of clinical datum C, given a disease D; it equals the sensitivity (S) of the clinical datum for this disease D: $P(C|D) = S$. This is valid for any disease ($D_1 \ldots D_n$) that manifests clinical datum C

We explained earlier the reasons why we purposely do not take into account prevalence of diseases, called prior probability of diseases here in Bayesian context. This is equivalent to assuming that all diseases have the same prior probability [P (D)]; accordingly, we can simplify equation 4 by deleting the prior probability of all diseases [$P(D_1) \ldots P(D_i) \ldots P(D_n)$]. Then, if we replace P (D|C) with PP value (according to equation 3), and P (C|D) with S (according to equation 1), we obtain the following equation:

$$\text{PP value}_i = \frac{S_i}{S_1 + \ldots + S_i + \ldots + S_n} \tag{5}$$

Where: PP value_i = positive predictive value of the clinical datum for the disease i under consideration

S_i = sensitivity of the clinical datum for the disease i under consideration

$S_1 \ldots S_n$ = sensitivities of the *same clinical datum* for corresponding diseases*

* "Corresponding diseases" could either refer only to diseases that manifest the clinical datum, or alternatively to all known diseases. For either of these alternatives, the resulting PP value will be identical, because S of a clinical datum for a disease that never manifests such datum is zero. Adding zeros to the value of the denominator established by S of the diseases that manifest the clinical datum will neither change the value of the denominator nor the result of the equation.

Equation 5 shows that S_i (numerator of the right member) and PP value_i are directly proportional.

This equation is convenient because it expresses PP value as a function of sensitivities (S), being S the cornerstone of our algorithm.

PP value = 1 when the clinical datum is manifested only by the disease under consideration (that is, when for all other diseases S = 0); conversely, PP value approaches 0 when the clinical datum is always

manifested in all other diseases (that is, when for all other diseases S = 1), a theoretical situation. In remaining situations, PP value takes an intermediate value between 0 and 1.

PP value quantifies how characteristic or exclusive a clinical datum is for a specific disease or diagnosis. According to equation 5, the fewer the number of diseases that manifest a given clinical datum (number of S terms in the denominator) and the fewer this clinical datum is manifested by each of these diseases (the smaller each S value in the denominator), the greater the PP value of the clinical datum and the probability of the specific diagnosis or disease. For example, the presence of *Mycobacterium tuberculosis* in sputum is pathognomonic of pulmonary tuberculosis because no other disease manifests this clinical datum; accordingly PP value = 1. We believe that *PP value is the most accurate index of how strongly a clinical datum present supports a diagnosis or disease*.

Calculated PP values are linked to the corresponding clinical data in the disease models. Because PP values are based on statistically established sensitivities stored in the database, they do not depend on specific clinical cases, and therefore can be pre-calculated (before the diagnostic program is applied to actual clinical cases) saving computing real time. These values remain fixed unless new disease models are added to the database or revised statistics change the values of the sensitivities upon which PP values are based. Should such changes occur as a result of an occasional update, all PP values must be recalculated. Our program, with a limited number of disease models in the database, recalculates at each diagnostic step the PP value of each clinical datum present related to the diagnoses in the differential diagnosis list.

Definition of PP value based on equation 5 is rational, simple, accurate, practical, and novel.

3. *Cost*

Cost to obtain each clinical datum is another index that is attached to this datum. In our context it involves not only expense, but also risk and discomfort resulting from the required test or procedure. *Expense* is quantifiable in dollars or any other currency. *Risk* can be statistically quantified by outcomes of the procedure, although it also depends on operator skill. *Discomfort* is a subjective feeling that depends in part on the invasiveness of the procedure and in part on patient apprehension, although the latter can be controlled with sedation or anesthesia. Discomfort cannot be expressed as an exact numerical value, but only can be assigned an estimated qualitative level such as none, small, intermediate, or great. Expense, risk, and discomfort—like apples and oranges—cannot be arithmetically combined into an exact overall cost. However, expense and risk can be qualitatively expressed in levels similar to discomfort, to make the latter comparable to the former two. It is practical to consider the maximum qualitative level of expense, risk, and discomfort, as representative of overall cost level.

$$\text{Cost} = \max(\text{expense}, \text{risk}, \text{discomfort})$$

Because cost does not participate in the calculation of the probability of diagnoses, its inexactness is not critical; it is considered only when selecting the most suitable clinical datum next to investigate in the patient.

We assign to each clinical datum one of four overall cost categories: no cost (clinical data typically obtained through medical history and physical examination), small cost (*e.g.*, obtained through routine laboratory analysis, ECG, and other ancillary studies), intermediate cost (*e.g.*, colonoscopy, lymph node excision biopsy), and great cost (*e.g.*, liver biopsy, laparoscopy, laparotomy).

Cost must be compared to the *benefit* expected to result from acquiring a clinical datum. Benefit has two components: a quantitative component and a qualitative component. The *quantitative component* depends on the positive predictive value (PP value) and sensitivity (S) of the clinical datum, which in turn determine the probability (P) of the corresponding diagnoses. PP value of a clinical datum present in a patient tends to increase the P of the corresponding diagnoses; S of a clinical datum absent tends to reduce the P of the corresponding diagnoses. The clinical datum that has the greatest PP value or the greatest S will result in the greatest P change. The magnitude of increment of P, produced by PP value, or decrement of P, produced by S, approaching P respectively to the confirmation or deletion threshold quantifies the benefit of the clinical datum that produces it. The quantitative component of benefit can be determined before actually investigating a clinical datum for presence or absence in the patient, by virtually testing with the computer program both possible outcomes.

The *qualitative component* of benefit cannot be quantified; it depends on multiple factors such as patient health status and ability to tolerate the procedure, patient financial condition, insurance company approval, prognosis, involved physician liability, and existence of efficacious and available treatments for the diseases listed in the differential diagnosis. Benefit must equal or exceed cost. The evaluation of cost-benefit of a clinical datum and the decision to implement a procedure to obtain it must be discussed with and approved by the patient. If the patient is wealthy, is not discouraged by the risk, or can tolerate discomfort, a procedure that incurs a greater cost may be acceptable. Confirmation of an uncertain diagnosis of a potentially life-threatening but treatable disease also may justify implementation of a more costly procedure.

Because cost and benefit cannot be accurately quantified, neither can cost-benefit ratio. If all of the aforementioned qualitative factors could be given an empiric value, it might be possible to devise an algorithm to assist the physician in better evaluating cost-benefit.

Summarizing how the three indices of clinical data—S, PP value, and cost—are determined: S depends on the clinical datum and corresponding disease; it is determined statistically with equation 2. PP value depends on S of the clinical datum for the disease under consideration and S of the same clinical datum for all diseases that manifest this datum; it is determined with equation 5. Cost—expense, risk, and discomfort—depends on the nature of the test or procedure needed to obtain the clinical datum; it is assigned one of four empirical categories: none, low, intermediate, or great.

Before explaining how our algorithm relates to sensitivity, positive predictive value, and cost, we must discuss the ruling in and ruling out of diagnoses.

RULING IN AND RULING OUT DIAGNOSES

A diagnosis is *ruled in* when it is included in the differential diagnosis (a list of potential diagnoses); this occurs whenever a patient clinical datum matches a clinical datum in the respective disease model.

A diagnosis is *ruled out* when it is deleted from the differential diagnosis; this occurs whenever the probability of the diagnosis falls below an empirical threshold. Clinical data that reduce the probability of a diagnosis favor this deletion.

These statements imply that a diagnosis must be ruled in before it can be ruled out.

When a new patient, for whom no clinical data are known, comes to our attention, we first collect clinical data manifested by the patient. These clinical data *present*, when matched with diseases model clinical

data, introduce the respective diagnoses in a differential diagnosis list, gradually incrementing the number of such potential diagnoses; this process is called *ruling in diagnoses*. The greater PP value of a clinical datum that is *present*, the more likely the corresponding diagnosis. For example, microhemagglutination for *Treponema pallidum* test (MHA-TP) is a clinical datum of great PP value for syphilis; accordingly, if positive, it rules in this disease with great probability, because few other diseases manifest this clinical datum. A clinical datum that is present, with great PP value, strongly rules in the diagnosis, even if its S is small, meaning that this clinical datum is not frequently found; but as it is already present in this case, S is irrelevant. For example, filarias present in a blood sample is a clinical datum with great PP value for filariasis, confirming this diagnosis, despite a small S.

On the other hand, a clinical datum present, typically would not favor a diagnosis only because it has a great S; it simply tells that this clinical datum is frequently manifested by the specified disease, but many other diseases also may manifest it (small PP value). For example, weight loss has a great S for hyperthyroidism, but a small PP value; therefore, to rule in hyperthyroidism, a clinical datum with a greater PP value, such as suppressed thyroid stimulating hormone (TSH) must be investigated. A clinical datum that is present, with small S, typically would not rule in a diagnosis, because it simply means that this clinical datum is rare for the disease, which is not a reason *per se* to rule in the disease; for example, diarrhea (small S and small PP value) for duodenal ulcer. Accordingly, *ruling in a diagnosis relies on a clinical datum that is present and the greater the PP value* the more it will support this diagnosis. *S is irrelevant* if the clinical datum is present.

Once some diagnoses have been ruled in, integrating the differential diagnosis list, we consider clinical data absent in the patient. For example, when we notice that he is a male, we realize that he cannot have an ovarian cancer; because he is young, prostate cancer is unlikely, and so forth. This process is called *ruling out* potential *diagnoses*. To *rule out* a potential diagnosis, we rely on the *sensitivity* of *clinical data* that are *absent* in the patient. The greater the S of a clinical datum that is absent, the less likely the corresponding diagnosis, even if the PP value is great, because the clinical datum is absent. For example, microhemagglutination test for *Treponema pallidum* (MHA-TP) is a clinical datum of great S for syphilis; accordingly, if negative, it rules out this disease because it is positive in essentially all cases of syphilis (false negative tests are rare). As mentioned in the previous paragraph, weight loss is a clinical datum with great S for severe hyperthyroidism, because it is manifested in all such cases; accordingly, if this clinical datum is absent, this diagnosis tends to be ruled out. A clinical datum that is absent, with small S, has little influence on the probability of the diagnosis, even if PP value is great; for example, filarias negative in blood (great PP value, but small S) for filariasis. Small sensitivity of an absent clinical datum does not rule out the corresponding diagnosis because it only means that the clinical datum is rare for the disease; absence of a rare clinical datum does not exclude a diagnosis. For example diarrhea with small S and small PP value for duodenal ulcer, if absent, does not rule out this diagnosis. Accordingly, *ruling out a diagnosis relies on clinical data that are absent and with great S*; *PP value is irrelevant* if the clinical datum is absent.

In summary: A clinical datum present rules in the corresponding diagnosis with strength proportional to its positive predictive value (PP value). A clinical datum absent rules out the corresponding diagnosis with strength proportional to its sensitivity (S).

Table 2 shows how PP value and S of a clinical datum affect the probability (P) of a diagnosis, and ruling in or ruling out of a diagnosis according to whether the datum is present or absent in the patient.

Clinical datum	PP value	S	P	Effect on Diagnosis	Example	Comments
Present	Great	Great	Increased	Strongly ruled in	MHA-TP test for syphilis	Ruling in a diagnosis relies on clinical data present, with great PP value; S is irrelevant
	Great	Small	Increased	Strongly ruled in	Filariae in blood for filariasis	
	Small	Great	Unchanged	Weakly ruled in	Weight loss for hyperthyroidism	
	Small	Small	Unchanged	Weakly ruled in	Diarrhea for duodenal ulcer	
Absent	Great	Great	Decreased	Strongly ruled out	MHA-TP test for syphilis	Ruling out a diagnosis relies on clinical data absent, with great S; PP value is irrelevant
	Great	Small	Slightly changed according to value of S	Weakly ruled out	Filariae in blood for filariasis	
	Small	Great	Decreased	Strongly ruled out	Weight loss for hyperthyroidism	
	Small	Small	Slightly changed according to value of S	Weakly ruled out	Diarrhea for duodenal ulcer	

TABLE 2. MHA-TP, microhemagglutination for *Treponema palladium*, a highly exclusive and sensitive test for syphilis; PP value, positive predictive value; S, sensitivity; P, probability of diagnosis.

Eight combinations are possible—clinical datum *present with great PP value* and great S, clinical datum *present with great PP value* and small S, clinical datum present with small PP value and great S, clinical datum present with small PP value and small S, clinical datum *absent with* great PP value and *great S*, clinical datum absent with great PP value and small S, clinical datum *absent with* small PP value and *great S*, and clinical datum absent with small PP value and small S. Of these eight combinations, only two are useful—clinical datum present with great PP value and clinical datum absent with great S—because only they can significantly change the P of the corresponding diagnosis; all other combinations are discarded.

OPERATION OF OUR DIAGNOSTIC PROGRAM

INITIAL CLINICAL DATA COLLECTION

The diagnostic process begins with collection of initial clinical data gleaned from the patient's history, physical examination, and previous consultations. These *initial* clinical data, entered in the computer, are unrefined because we do not know yet their PP value or S. Each of these values depend on the clinical datum collected, but also on the corresponding as yet not ruled in diagnosis. Initially, collection is focused primarily on clinical data *present* because only these can rule in diagnoses. At this early phase, clinical data processing is purely categorical because we have not yet applied any probabilistic calculation; the diagnostic process is called *ill structured* [7]. Any clinical datum present may be significant because it selects diseases, regardless of its as yet undetermined PP value or S. Only after potential diagnoses are selected can S and PP value of clinical data be determined, a differential diagnosis list be created, and the probability (P) of each diagnosis be calculated; the diagnostic process then is said to be *well structured*. Once P of diagnoses are established, only clinical data with great PP value or great S are able to significantly change this P. Then, if warranted, diagnoses can be ruled out by processing clinical data absent.

SELECTING POTENTIAL DIAGNOSES

Following initial clinical data collection, the algorithm must compare each clinical datum manifested by the patient with all clinical data listed in all disease models stored in the database, selecting those disease models that contain one or more matching clinical data. Such disease models represent potential diagnoses that will become the differential diagnosis list. This task involves important difficulties that are, in our opinion, a major reason why a satisfactory diagnostic algorithm has not earlier been achieved:

- A disease typically never manifests all clinical data listed in its disease model.
- The cost of obtaining some of these clinical data may be prohibitive.
- Diverse diseases can manifest similar clinical data; in other words, most clinical data are not exclusive or pathognomonic.
- After selection of potential diagnoses, the algorithm must establish whether they are *competing* for a single final diagnosis or whether they correspond to *concurrent* diseases.

Later on we will explain how our algorithm deals with these problems.

CLINICAL DATUM LISTS

Having selected the matching disease models that now represent potential diagnoses, the algorithm creates, for each clinical datum present, a list that has for heading this clinical datum and comprises all potential diagnoses able to manifest such clinical datum.

A CLINICAL DATUM LIST is a list of diagnoses (*e.g.*, bronchitis, asthma, lung cancer) that a single clinical datum (*e.g.*, cough) evokes in the mind of the physician, which is analogous to the matching of a single clinical datum with clinical data in disease models by the computer. Such diagnoses, as opposed to diseases, are in the mind of the physician; the patient is not afflicted by all of them. Each of these *potential diagnoses* has a probability to become a *final diagnosis*, the latter ideally being concordant with the disease that afflicts the patient. A proper denomination for clinical datum list would be **Potential Diagnoses List for a Single Clinical Datum**, which is lengthy and cumbersome. For that reason, we abbreviate it to **Clinical Datum List**, because despite being a list of diagnoses, the clinical

datum identifies the list and is its heading. Clinical Dat**um** List should not be mistaken with Disease Model, which has a disease as its heading and lists **all** clinical data that this disease can manifest.

Matching disease model 1 → Potential diagnosis 1
Matching disease model 2 → Potential diagnosis 2
⋮ ⋮
Matching disease model n → Potential diagnosis n

Examples of clinical datum lists: the sensitivity (S) and positive predictive value (PP value) of the clinical datum for each potential diagnosis is shown. The diagnoses are sorted by decreasing S and PP value.

Hemoptysis (bleeding from respiratory tract)	**S**	**PP value**
Tuberculosis	0.70	0.35 *
Lung cancer	0.40	0.20
Lung infarction	0.30	0.15
Bronchitis	0.05	0.025
Pneumonia	0.03	0.015
⋮	⋮	⋮

Dyspnea (difficulty to breathe)	**S**	**PP value**
Asthma	0.98	0.208
Congestive heart failure	0.80	0.17
Foreign body aspiration	0.80	0.17
Pneumonia	0.40	0.085
Emphysema	0.39	0.083
Carbon monoxide intoxication	0.22	0.047
Lung cancer	0.20	0.042
Lung infarction	0.19	0.04
Tuberculosis	0.17	0.036
Intense anemia	0.12	0.025
⋮	⋮	⋮

Cough	**S**	**PP value**
Foreign body aspiration	1.00	0.20
Bronchitis	0.98	0.196
Tuberculosis	0.70	0.14
Lung cancer	0.50	0.10
Lung infarction	0.40	0.08
Pneumonia	0.20	0.04
⋮	⋮	⋮

* The numeric values for S and PP value in the above examples were not obtained from actual statistics or calculations. Cost is omitted for the sake of simplicity.

In a complete clinical datum list, the sum of PP values equals 1. The fewer diagnoses a clinical datum list comprises, the more the clinical datum supports those diagnoses and the greater the corresponding PP values. When a clinical datum list contains only one diagnosis, PP value = 1, meaning the clinical datum is exclusive or pathognomonic for this diagnosis. Conversely, the more diagnoses a clinical datum list comprises, the less the clinical datum supports those diagnoses, and the smaller their corresponding PP values.

DIFFERENTIAL DIAGNOSIS LIST

This step creates a *differential diagnosis list* that comprises potential diagnoses transferred from the clinical datum lists.

The difference between clinical datum list and differential diagnosis list is that the former lists all diagnoses matched by a single clinical datum present, whereas the latter lists all diagnoses matched by all clinical data present in the patient.

Example of differential diagnosis list based on the previous clinical datum lists:

Differential diagnosis list	**P**
Tuberculosis	0.35
Asthma	0.208
Lung cancer	0.20
Foreign body aspiration	0.20
Bronchitis	0.196
Congestive heart failure	0.17
Lung infarction	0.15
Pneumonia	0.085
Emphysema	0.083
Carbon monoxide intoxication	0.047
⋮	⋮

PROBABILITY OF DIAGNOSES. MINI-MAX PROCEDURE

At this point we have a well-structured diagnostic problem with a differential diagnosis list. Next, the algorithm must determine which of these potential diagnoses will become one or more final diagnoses.

We devised a procedure for calculating the probability (P) of a diagnosis by combining the PP value of clinical data when *present* (favoring a diagnosis) with the S of clinical data when *absent* (disfavoring a diagnosis). We call it the *mini-max procedure**. In successive steps, we will explain this procedure with examples.

* Our term mini-max is reminiscent of a similar term used in game theory, but not previously applied in combination with Bayes formula to calculate probability of medical diagnoses.

Step 1. Process clinical data present

To establish the value of P, other diagnostic programs add, subtract, multiply, or average the sensitivities, specificities, predictive values, estimated values of clinical data supporting a diagnosis, or iterate Bayes formula with each additional clinical datum. These approaches have flaws.

For example, jaundice, dark urine, light colored feces, and increased direct serum bilirubin are clinical data related by similar pathophysiologic mechanisms generated by a single lesion: biliary tract obstruction. Were we arithmetically to combine the individual PP values of these three equivalent and "redundant" clinical data, P of diagnosis biliary tract obstruction would be improperly increased thereby providing an undue advantage to this diagnosis, as compared to competing diagnoses. Furthermore, assume that an endoscopic retrograde cholangiopancreatography (ERCP) shows a biliary stone obstructing the common bile duct—a clinical datum that alone has a confirmatory PP value of 1 for biliary duct lithiasis. If we add the PP values of other supporting

clinical data, the P of the diagnosis obstructing gallstones would exceed 1, which is probabilistically impossible. If we average or multiply these PP values, the confirmatory PP value 1 would be unduly reduced.

With our algorithm, the PP value of gallstone obstruction, which equals 1, supersedes all other clinical data with smaller PP value (jaundice, dark urine, increased serum bilirubin) because—whether present or absent—they would not change the diagnosis of obstructing gallstones already confirmed by ERCP. Accordingly, we consider that the greatest PP value of these related clinical data better represents the P of the diagnosis than any arithmetical combination of the individual values.

For each diagnosis in the differential diagnosis list, our algorithm looks in the entire set of clinical datum lists and selects the greatest PP value that supports *this* diagnosis. The selected greatest PP value equals the P of this diagnosis.

$$P_i = \max (\text{PP value}_1 \ldots \text{PP value}_i \ldots \text{PP value}_n) \quad (6)$$

Where P_i = probability of the diagnosis under consideration

max = maximum of

$\text{PP value}_1 \ldots \text{PP value}_i \ldots \text{PP value}_n$ = positive predictive values of clinical data present, that support the diagnosis under consideration

The algorithm then iterates the same routine to determine the P of each diagnosis in the differential diagnosis list.

Example: a patient presents with cough, hemoptysis, dyspnea, expectoration, and *Mycobacterium tuberculosis* (*Mycobacterium TB*) in sputum. Five clinical datum lists are generated:

Cough	**S**	**PP value**
Pulmonary tuberculosis	0.80	0.276
Pulmonary embolism	0.50	0.172
Bronchiectasis	0.90	0.310
Lung cancer	0.70	0.241

Hemoptysis	**S**	**PP value**
Pulmonary tuberculosis	0.40	0.222
Pulmonary embolism	0.60	0.333
Bronchiectasis	0.30	0.167
Lung cancer	0.50	0.278

Dyspnea	**S**	**PP value**
Pulmonary tuberculosis	0.20	0.148
Pulmonary embolism	0.50	0.370
Bronchiectasis	0.05	0.037
Lung cancer	0.60	0.444

Expectoration	**S**	**PP value**
Pulmonary tuberculosis	0.80	0.417
Pulmonary embolism	0.02	0.010
Bronchiectasis	0.90	0.469
Lung cancer	0.20	0.104

Mycobacterium TB	**S**	**PP value**
Pulmonary tuberculosis	0.70	1.000
Pulmonary embolism	0.00	0.000
Bronchiectasis	0.00	0.000
Lung cancer	0.00	0.000

S values in the above example are for demonstration purposes only and do not represent actual statistics. PP values were calculated by applying equation 5 to these S values. We assume that only the four listed diagnoses exist and that any of them could account for the five clinical data. Highlighted values refer to clinical data that are not elements of a specific disease model; accordingly, their S and PP values equal 0. Such clinical data have no influence on calculated probabilities.

In the entire set of clinical datum lists, the greatest PP value for pulmonary tuberculosis is 1.000 and equals P for this diagnosis. Similarly, 0.370 for pulmonary embolism, 0.469 for bronchiectasis, and 0.444 for lung cancer.

A differential diagnosis list is created, with each diagnosis showing the respective P that competes with the P of the other diagnoses for a final diagnosis. The diagnoses are sorted by decreasing P values.

Differential diagnosis list	**P**
Pulmonary tuberculosis	1.000
Bronchiectasis	0.469
Lung cancer	0.444
Pulmonary embolism	0.370

Except for confirmed pulmonary tuberculosis, these P values do not yet satisfy thresholds that enable to rule out the other diagnoses or confirm some as concurrent final diagnosis. To satisfy this threshold requirement, our algorithm automatically determines which additional best cost-benefit clinical data should next be investigated for their presence or absence. Fever is first recommended, followed by pulmonary cavity lesion:

Fever	**S**	**PP value**
Pulmonary tuberculosis	0.70	0.636
Pulmonary embolism	0.30	0.273
Bronchiectasis	0.00	0.000
Lung cancer	0.10	0.091

Cavity	**S**	**PP value**
Pulmonary tuberculosis	0.60	0.600
Pulmonary embolism	0.00	0.000
Bronchiectasis	0.10	0.100
Lung cancer	0.30	0.300

Were fever and a pulmonary cavity lesion also *present* in the patient, we would now have a total of seven clinical datum lists. Were the PP value associated with any of the diagnoses in these 2 new clinical datum lists to exceed the P of the same diagnosis, that greater PP value would replace this existing P.

PP value of a clinical datum present can only **increase** the probability of a diagnosis (equation 6).

Step 2. Process clinical data absent

Only those clinical data absent that are related to diagnoses in the differential diagnosis list are processed.

We presented a rational explanation and example of why we believe that the greatest PP value of all the clinical data *present* that supports a specific diagnosis equals the P of this diagnosis. This is consequent to the fact that clinical data present are related by a common lesion or cause; adding the PP values of these clinical data would excessively increase this P. We discussed how the sensitivity (S) of a clinical datum *absent* typically reduces the P of the corresponding diagnosis. To reduce P of the corresponding diagnosis, some authors arithmetically combine S of all absent clinical data, or sequentially apply Bayes formula to each S of such clinical data. We observed that this procedure excessively decreases the P of the diagnosis to a value that might incorrectly rule out the corresponding disease. For this reason, to reduce the P of a diagnosis, we use only the greatest S of all clinical data absent. This approach for disfavoring a diagnosis is less intuitive than using the greatest PP value of clinical data present for supporting a diagnosis. Clinical data absent are not related by a common lesion or cause; however, they might be related by a specific characteristic of patient's body that is responsible for the failure to react, or the cause of diseases is too weak and the lesions too small to manifest all potential clinical data. This common denominator justifies considering only the datum absent of greatest S as the representative of all clinical data absent. The next example supports this approach:

Consider again a patient with a suspected common bile duct obstruction by gallstones. An endoscopic retrograde cholangiopancreatography (ERCP) in this case was negative—*i.e.*, *no* gallstones were present in the common

bile duct—an absent clinical datum of great S (close to 1) for the mentioned diagnosis. To rule out this diagnosis, it is unnecessary to consider additional clinical data absent of smaller S, such as right upper abdominal pain or vomiting.

So far, we have explained how clinical data present and their associated PP values determine the P of a diagnosis. Now we will explain how clinical data absent and their associated S values further influence this P. Originally, we tried this equation:

$$P = \text{PP value} \times (1-S) \tag{7}$$

Where PP value = probability of a diagnosis **before** considering the sensitivity of a clinical datum absent; this probability equals the greatest PP value of all clinical data present that support this diagnosis (equation 6)

P = probability of the this diagnosis **after** considering the S of a clinical datum absent pertaining to the same diagnosis

S = sensitivity of a clinical datum absent pertaining to the same diagnosis

With equation 7, the greater the S of a clinical datum absent, the more it reduces the P of a diagnosis.

Let's assume that fever and cavity in a previous example, were investigated and found *absent* and let's apply equation 7. *Mycobacterium tuberculosis* was found in the sputum, a clinical datum present with a PP value = 1, which confers a P = 1 to tuberculosis, confirming this diagnosis. Next, our example considers fever, a clinical datum absent with S = 0.7. Applying equation 7, we obtain:

$$P = \text{PP value} \times (1-S) = 1 \times (1-0.7) = 0.3$$

Notice that the absence of fever decreases tuberculosis P from 1 to 0.3. It is unacceptable that a relatively unimportant clinical datum absent, such as fever, should cause a substantial decrease in P, which tends to rule out the already confirmed diagnosis of tuberculosis.

To temper this unacceptable decrease in P caused by equation 7, we instead use:

$$P_i = \frac{\text{PP value}_i\,(1-S_i)}{\text{PP value}_1\,(1-S_1) + \ldots + \text{PP value}_i\,(1-S_i) + \ldots + \text{PP value}_n\,(1-S_n)} \tag{8}$$

Where P_i = probability of a diagnosis (*e.g.*, tuberculosis)

PP value_i = positive predictive value of the clinical datum present (*e.g.*, *Mycobacterium tuberculosis* in sputum for tuberculosis)

S_i = sensitivity of the clinical datum absent (fever for tuberculosis)

$\text{PP value}_1 \ldots \text{PP value}_i \ldots \text{PP value}_n$ = positive predictive value of the same clinical datum present (*Mycobacterium tuberculosis* in sputum) for each respective diagnosis in the differential diagnosis list (4 diagnoses per our example)

$S_1 \ldots S_i \ldots S_n$ = sensitivity of the clinical datum absent (fever) for each respective diagnosis in the differential diagnosis list (4 diagnoses per our example)

Notice that the numerator of equation 8 is identical to the right member of equation 7, and that a denominator has been introduced, the effect of which is to "temper" the result. This denominator comprises several terms, each of which refers to a diagnosis in the differential diagnosis list. Each comprises the PP value of the clinical datum present (*Mycobacterium tuberculosis*) and the S of the clinical datum absent (fever). These clinical data present and absent remain *unchanged for all terms*; but their respective PP values and S values change to values associated with each diagnosis. Equation 7 is then applied to these values in the numerator and each denominator term of equation 8.

Although equation 8 is related to Bayes formula, it does not violate clinical data *independence* condition because each of its terms refer to only one and the same clinical datum present, and to only one and the same clinical datum absent. The clinical datum present and the clinical datum absent are independent.

Referring to our example of *Mycobacterium tuberculosis* present in sputum and fever absent, we now apply equation 8 to calculate the probability of tuberculosis (P_{TB}):

$$P_{TB} = \frac{PP\ value_{TB}\ (1-S_{TB})}{PPvalue_{TB}(1-S_{TB})+PPvalue_{bronchiectasis}(1-S_{bronchiectasis})+PPvalue_{cancer}(1-S_{cancer})+PPvalue_{embolism}(1-S_{embolism})}$$

Substituting PP value and S with values from the clinical datum lists, we obtain:

$$P_{TB} = \frac{1.00\ (1-0.70)}{1.00\ (1-0.70) + 0.00\ (1-0.00) + 0.00\ (1-0.10) + 0.00\ (1-0.30)} =$$

$$= \frac{0.30}{0.30 + 0.00 + 0.00 + 0.00} = 1.00$$

Notice that equation 8 retains the correct value of P = 1.00 for confirmed tuberculosis, instead of P = 0.30, as was obtained with equation 7.

Equation 8 yields identical result if all PP values of the clinical datum *present* are substituted with the corresponding S′ of the same clinical datum, S otherwise typically used with clinical data *absent*:

$$P_i = \frac{PP\ value_i\ (1-S_i)}{PP\ value_1\ (1-S_1) + \ldots + PP\ value_i\ (1-S_i) + \ldots + PP\ value_n\ (1-S_n)} = \frac{S_i'\ (1-S_i)}{S_1'\ (1-S_1) + \ldots + S_i'\ (1-S_i) + \ldots + S_n'\ (1-S_n)}$$

Notice that the value of S′ (sensitivity of the clinical datum *present*) is *not* the same as the value of S (sensitivity of the clinical datum *absent*). Equation 8, with PP values, yields identical result as with S′ because PP value and S′ of a given clinical datum for a given diagnosis are directly proportional. When all PP values are substituted with the right member of equation 5, equation 8 can be simplified to its substituted form (right member) shown above. This simplification is possible because the sum $S_1+\ldots+S_i+\ldots+S_n$ in the numerator and denominator of equation 8 have identical values and cancel each other.

The denominator of equation 8—modified Bayes formula—can be seen as a *weighted average* of S′ of a clinical datum present for diverse diseases, weighted by S values of the clinical datum absent. Comparing the S′ of the clinical datum present for a specific disease with the average of S′ values for all diseases indicates the relative significance of the clinical datum for this specific disease.

For clarity and consistency, we will retain the original equation 8 (with PP values) for all further calculations, but the substituted form (with S′ values) might be useful for computer programming.

Equation 8 is then iterated to calculate the P that the clinical data pair *Mycobacterium tuberculosis*-fever confers to the remaining diagnoses in the differential diagnosis list. PP value and S value corresponding to each diagnosis must be substituted in the numerator; the denominator remains unchanged. Equation 8 *normalizes* the probabilities of the diagnoses, meaning that their sum ($P_{TB} + P_{bronchiectasis} + P_{cancer} + P_{embolism}$) now equals 1.

Referring to our example:

***Mycobacterium TB* - Fever**	**PP value**		**S**				**P**
Pulmonary tuberculosis	1.000 ×	(1-0.70)	= 0.300	(numerator)	÷ 0.300	(denominator)	= 1.000
Pulmonary embolism	0.000 ×	(1-0.30)	= 0.000	(numerator)	÷ 0.300	(denominator)	= 0.000
Bronchiectasis	0.000 ×	(1-0.00)	= 0.000	(numerator)	÷ 0.300	(denominator)	= 0.000
Lung cancer	0.000 ×	(1-0.10)	= 0.000	(numerator)	÷ 0.300	(denominator)	= 0.000
			Sum = 0.300 (denominator)			Sum	= 1.000

Step 3. Create clinical data pairs

As remarked above, each term of equation 8 comprises a clinical datum present and a clinical datum absent; we call this clinical data combination a *clinical data pair*. Each clinical data pair confers a *partial probability* to a diagnosis. To calculate the *total probability* of each diagnosis, the mini-max procedure must create *all possible clinical data pairs* with all thus-far investigated clinical data present and absent. The number of clinical data pairs created will equal the number of clinical data present multiplied by the number of clinical data absent.

Returning to our previous example, we had 5 clinical data present (cough, expectoration, hemoptysis, dyspnea, and *Mycobacterium tuberculosis*) and 2 clinical data absent (cavity and fever), creating a total of 10 clinical data pairs (cough-cavity, cough-fever, hemoptysis-cavity, hemoptysis-fever, dyspnea-cavity, dyspnea-fever, expectoration-cavity, expectoration-fever, *Mycobacterium tuberculosis*-cavity, and *Mycobacterium tuberculosis*-fever).

Because PP value and S value vary with each diagnosis, the total number of resulting *partial P values* equals the number of clinical data pairs created multiplied by the number of diagnoses in the differential diagnosis list. In our example, we had 10 clinical data pairs and 4 diagnoses (pulmonary tuberculosis, pulmonary embolism, bronchiectasis, and lung cancer), yielding a total of 40 partial P values.

Step 4. Create clinical data pair tables

We then organize the 40 partial P values as 10 *clinical data pair tables*, one table for each clinical data pair. Each table is headed by the clinical data pair; its first column lists the diagnoses in the differential diagnosis list; intermediate columns apply equation 8, and its last column lists the resultant partial P values. For our example:

Clinical data pair tables

Cough-Cavity	**PP value**		**S**				**Partial P**
Pulmonary tuberculosis	0.276 ×	(1-0.60)	= 0.110	÷	0.730	=	0.151
Pulmonary embolism	0.172 ×	(1-0.00)	= 0.172	÷	0.730	=	0.236
Brochiectasis	0.310 ×	(1-0.10)	= 0.279	÷	0.730	=	0.382
Lung cancer	0.241 ×	(1-0.30)	= 0.169	÷	0.730	=	0.231
			0.730				1.000

Cough-Fever

Pulmonary tuberculosis	0.276	× (1-0.70)	=	0.083	÷ 0.731	=	0.113
Pulmonary embolism	0.172	× (1-0.30)	=	0.121	÷ 0.731	=	0.165
Brochiectasis	0.310	× (1-0.00)	=	0.310	÷ 0.731	=	0.425
Lung cancer	0.241	× (1-0.10)	=	0.217	÷ 0.731	=	0.297
				0.731			1.000

Hemoptysis-Cavity

Pulmonary tuberculosis	0.222	× (1-0.60)	=	0.089	÷ 0.767	=	0.116
Pulmonary embolism	0.333	× (1-0.00)	=	0.333	÷ 0.767	=	0.435
Brochiectasis	0.167	× (1-0.10)	=	0.150	÷ 0.767	=	0.196
Lung cancer	0.278	× (1-0.30)	=	0.194	÷ 0.767	=	0.254
				0.767			1.000

Hemoptysis-Fever

Pulmonary tuberculosis	0.222	× (1-0.70)	=	0.067	÷ 0.717	=	0.093
Pulmonary embolism	0.333	× (1-0.30)	=	0.233	÷ 0.717	=	0.325
Brochiectasis	0.167	× (1-0.00)	=	0.167	÷ 0.717	=	0.233
Lung cancer	0.278	× (1-0.10)	=	0.250	÷ 0.717	=	0.349
				0.717			1.000

Dyspnea-Cavity

Pulmonary tuberculosis	0.148	× (1-0.60)	=	0.059	÷ 0.774	=	0.077
Pulmonary embolism	0.370	× (1-0.00)	=	0.370	÷ 0.774	=	0.478
Brochiectasis	0.037	× (1-0.10)	=	0.033	÷ 0.774	=	0.043
Lung cancer	0.444	× (1-0.30)	=	0.311	÷ 0.774	=	0.402
				0.774			1.000

Dyspnea-Fever

Pulmonary tuberculosis	0.148	× (1-0.70)	=	0.044	÷ 0.741	=	0.060
Pulmonary embolism	0.370	× (1-0.30)	=	0.259	÷ 0.741	=	0.350
Bronchiectasis	0.037	× (1-0.00)	=	0.037	÷ 0.741	=	0.050
Lung cancer	0.444	× (1-0.10)	=	0.400	÷ 0.741	=	0.540
				0.741			1.000

Expectoration-Cavity

Pulmonary tuberculosis	0.417	× (1-0.60)	=	0.167	÷ 0.672	=	0.248
Pulmonary embolism	0.010	× (1-0.00)	=	0.010	÷ 0.672	=	0.016
Bronchiectasis	0.469	× (1-0.10)	=	0.422	÷ 0.672	=	0.628
Lung cancer	0.104	× (1-0.30)	=	0.073	÷ 0.672	=	0.109
				0.672			1.000

Expectoration-Fever

Pulmonary tuberculosis	0.417	× (1-0.70)	=	0.125	÷ 0.695	=	0.180
Pulmonary embolism	0.010	× (1-0.30)	=	0.007	÷ 0.695	=	0.010
Bronchiectasis	0.469	× (1-0.00)	=	0.469	÷ 0.695	=	0.675
Lung cancer	0.104	× (1-0.10)	=	0.094	÷ 0.695	=	0.135
				0.695			1.000

***Mycobacterium TB* -Cavity**

Pulmonary tuberculosis	1.000	×	(1-0.60)	=	0.400	÷	0.400	= 1.000
Pulmonary embolism	0.000	×	(1-0.00)	=	0.000	÷	0.400	= 0.000
Bronchiectasis	0.000	×	(1-0.10)	=	0.000	÷	0.400	= 0.000
Lung cancer	0.000	×	(1-0.30)	=	0.000	÷	0.400	= 0.000
					0.400			1.000

***Mycobacterium TB* -Fever**

Pulmonary tuberculosis	1.000	×	(1-0.70)	=	0.300	÷	0.300	= 1.000
Pulmonary embolism	0.000	×	(1-0.30)	=	0.000	÷	0.300	= 0.000
Bronchiectasis	0.000	×	(1-0.00)	=	0.000	÷	0.300	= 0.000
Lung cancer	0.000	×	(1-0.10)	=	0.000	÷	0.300	= 0.000
					0.300			1.000

Step 5. Calculate partial P that each clinical data pair confers to each diagnosis

To calculate the partial P that each clinical data pair confers to each diagnosis in the differential diagnosis list, equation 8 is applied to the PP value of the clinical datum present and the S of the clinical datum absent for each diagnosis (see clinical data pair tables above).

Notice that throughout these iterations of equation 8, the entire denominator remains unchanged for each clinical data pair and table. However, the numerator does change with each iteration; it assumes the value of the denominator term corresponding to the diagnosis being processed.

Step 6. Create mini-max tables

Now, we must determine the *total probability* that the partial probabilities mentioned in steps 3, 4, and 5 confer to each diagnosis in the differential diagnosis list. This is achieved by creating a *mini-max table* for each diagnosis (see next page).

The first column of each mini-max table lists each clinical datum present. The second column lists the PP value of each clinical datum present; its bottom cell repeats the greatest of these values, which is the total P of the diagnosis *before* clinical data absent are considered. The next several columns show the partial P values that each clinical data pair confers to the diagnosis; the number of these columns equals the number of clinical data absent. The heading of each column shows the clinical datum absent and its S for the diagnosis. Each partial P value is transferred from the clinical data pair table to the mini-max table cell where the clinical data present and absent converge. The bottom cell of each column repeats the greatest partial P value appearing in the column. The last column repeats the smallest value appearing in each row. The bottom cell of this column, which also is the last cell of the mini-max table, repeats the greatest value of the column; it equals the total P of the diagnosis, *after* clinical data absent have been considered.

Step 7. Determine total P of a diagnosis

In the mini-max table, the last column lists the smallest values of each row; the greatest value in this last column, repeated in the last cell of the table, equals the total P of the diagnosis. Therefore, the algorithm determines the total P of a diagnosis based on partial P values; it involves the following concepts:

1. A clinical data pair comprises a clinical datum present and a clinical datum absent.

Mini-max table for tuberculosis

TUBERCULOSIS	PP value = partial P before considering clinical data absent	Partial P with Cavity absent S = 0.6	Partial P with Fever absent S = 0.7	MINIMUM VALUE IN EACH ROW
Cough present	0.276	0.151	0.113	0.113
Hemoptysis present	0.222	0.116	0.093	0.093
Dyspnea present	0.148	0.077	0.060	0.060
Expectoration present	0.417	0.248	0.180	0.180
MTb present	1.000	1.000	*1.000*	1.000
MAXIMUM VALUE IN EACH COLUMN	1.000	1.000	1.000	**Total P = 1.000**

MTb, *Mycobacterium tuberculosis*. The total probability of **tuberculosis** at this diagnostic step is the maximum value (**1.000**) in the last column.

Mini-max table for pulmonary embolism

PULMONARY EMBOLISM	PP value = partial P before considering clinical data absent	Partial P with Cavity absent S = 0	Partial P with Fever absent S = 0.3	MINIMUM VALUE IN EACH ROW
Cough present	0.172	0.236	0.165	0.165
Hemoptysis present	0.333	0.435	0.325	0.325
Dyspnea present	0.370	0.478	*0.350*	0.350
Expectoration present	0.010	0.016	0.010	0.010
MTb present	0.000	0.000	0.000	0.000
MAXIMUM VALUE IN EACH COLUMN	0.370	0.478	0.350	**Total P = 0.350**

The total probability of **pulmonary embolism** at this diagnostic step is the maximum value (**0.350**) in the last column.

Mini-max table for bronchiectasis

BRONCHIECTASIS	PP value = partial P before considering clinical data absent	Partial P with Cavity absent S = 0.1	Partial P with Fever absent S = 0	MINIMUM VALUE IN EACH ROW
Cough present	0.310	0.382	0.425	0.310
Hemoptysis present	0.167	0.196	0.233	0.167
Dyspnea present	0.037	0.043	0.050	0.037
Expectoration present	*0.469*	*0.628*	0.675	0.469
MTb present	0.000	0.000	0.000	0.000
MAXIMUM VALUE IN EACH COLUMN	0.469	0.628	0.675	**Total P = 0.469**

The total probability of **bronchiectasis** at this diagnostic step is the maximum value (**0.469**) in the last column. Were the second column not included in the calculation, total P of this diagnosis would be 0.628; see property 5 B of mini-max procedure (explained later).

Mini-max table for lung cancer

LUNG CANCER	PP value = partial P before considering clinical data absent	Partial P with Cavity absent S = 0.3	Partial P with Fever absent S = 0.1	MINIMUM VALUE IN EACH ROW
Cough present	0.241	0.231	0.297	0.231
Hemoptysis present	0.278	0.254	0.349	0.254
Dyspnea present	0.444	*0.402*	0.540	0.402
Expectoration present	0.104	0.109	0.135	0.104
MTb present	0.000	0.000	0.000	0.000
MAXIMUM VALUE IN EACH COLUMN	0.444	0.402	0.540	**Total P = 0.402**

The total probability of **lung cancer** at this diagnostic step is the maximum value (**0.402**) in the last column.

2. A specific clinical data pair, that we call *determining clinical data pair*, determines the total P of a specific diagnosis.
3. Applying equation 8 to the PP value of the clinical datum present and the S of the clinical datum absent in the determining clinical data pair, yields a specific partial P that we call *determining partial P* because it determines and equals the total P of the specific diagnosis.
4. A *specific cell* for this *determining partial P* exists in the mini-max table of this specific diagnosis.
   - In this specific cell, the mentioned clinical datum present converges with the mentioned clinical datum absent.
   - In this specific cell, the value (italicized) of the determining partial P was transferred from its clinical data pair table to the corresponding mini-max table.
   - In this specific cell, the value of the determining partial P is at once the smallest in its row and the greatest in its column.

To find the determining clinical data pair responsible for the current total P of a diagnosis, we must backtrack the steps that led from that pair to the total P. Start at the last cell (total P) of the mini-max table and ascend (following the arrows shown in the tables above) to any cell with the same value, then go left on that row until any cell with the same value (the determining partial P) is encountered. The clinical datum present and the clinical datum absent that converge to this cell comprise the requisite determining clinical data pair; the respective PP value and S are shown in the mini-max table.

Example: In the mini-max table of Lung Cancer (see above) the last cell shows the current total P (0.402) of this diagnosis. Following the arrows takes us to another cell with the italicized value 0.402, which is the determining partial P. To this cell converge PP value (0.444) of dyspnea present and S (0.3) of pulmonary cavity absent. The determining clinical data pair dyspnea-cavity is responsible for the current determining partial P and total P (0.402).

Mini-max tables are not based on Bayes formula and therefore circumvent the problem of clinical data independence and disease incompatibility.

Broken monotony

Typically, the partial P values in the rows of the mini-max table present a monotone relation; this means that when in one row the partial P value increases or decreases from one cell to the next, in the other rows the changes occur in the same direction. However, sometimes

this monotone relation is broken. This is due to the especial interrelation among the diverse S and PP values in the clinical data pair tables. Broken monotony has several consequences:

- A single determining partial P that is at the same time the greatest partial P of its column and the smallest partial P of its row may no longer exist.
- The *maximum partial P* in the last column and the *minimum partial P* value in the last row do no longer yield the same value, equal to *total P* of the diagnosis, as it occurs when monotony is not broken.
- A clinical datum of smaller PP value is able to increase the total P more than a clinical datum with greater PP value, violating the rule that the greatest PP value of clinical data supporting a diagnosis equals the total P of this diagnosis (equation 6).
- A clinical datum of smaller S is able to decrease the total P more than a clinical datum with greater S, which does not occur when monotony is preserved.

The interested reader will find more details on this subject in our previous book [6]. Our new diagnostic program ignores broken monotony, selecting one (greatest value of last column in mini-max table) of the two different resultant total P values for the same diagnosis, because their difference in magnitudes is insignificant, and our program proved to remain accurate and efficient.

Step 8. Update the differential diagnosis list

Next, we again sort all diagnoses in the differential diagnosis list, according to decreasing total P values:

Differential Diagnosis List	**Total P**
Tuberculosis	1.000
Bronchiectasis	0.469
Lung cancer	0.402
Pulmonary embolism	0.350

Notice that the total P values of the diagnoses have changed and are more widely dispersed, but they still do not satisfy, except for tuberculosis, our threshold requirements for confirming as final or ruling out each of the other diagnoses. Accordingly, additional clinical data must be investigated. Then the mini-max procedure must be iterated with each additional clinical datum, and the total P of all diagnoses recalculated, until requirements for conclusion of the diagnostic quest are satisfied.

The previous example creating mini-max tables is didactic but oversimplified, because it assumed that each clinical datum list included a similar number of only four existing diagnoses. In reality, clinical datum lists include diverse number of diagnoses, from only one (when the clinical datum is exclusive—pathognomonic—for this diagnosis) to numerous (when the clinical datum, *e.g.*, fever, can be manifested by many diagnoses). Our program integrates the differential diagnosis list including all diagnoses listed in all clinical datum lists (selected by clinical data present). Consequently, the number of diagnoses in the differential diagnosis list will equal the number of diagnoses in the longest clinical datum list plus other diagnoses, not included in this longest clinical datum list, but listed in other clinical datum lists.

The number of diagnoses in the differential diagnosis list equals the number of terms in the denominator of equation 8 and the number of mini-max tables. New clinical data present or absent will add new rows or columns respectively to the existing mini-max tables. Only when a clinical datum present, creating a new clinical datum list that includes a new diagnosis, such diagnosis is added to the differential diagnosis list, the corresponding term is added to the denominator of equation 8, and a corresponding new mini-max table is generated. This diagnosis, if confirmed final, will be concurrent to the previous ones because it does not share any of previously obtained clinical data; otherwise it would be listed in their clinical datum lists.

The set of mini-max tables can be seen a three-dimensional deck, in which x-axis comprises clinical data absent, y-axis comprises clinical data present, and z-axis comprises the diverse mini-max tables (diverse diagnoses). Such a set is cubic. Always remember that normalization is done in the direction of z-axis. Each cell of each

table contains a partial P that is normalized and competes with partial P values of similarly located cells in all the other mini-max tables (summating 1), except cells in last column and last row, which contain respectively minimum and maximum partial P values. Conversely, partial P of cells in each *single* table are not normalized with partial P of other cells in this table; they are compared and minimums and maximums are computed in x-axis and y-axis directions respectively, determining total P of the corresponding diagnosis with this non-Bayesian procedure.

***

Properties of the mini-max procedure

1. Each additional clinical datum present generates a new *row* in an existing mini-max table.

2. Each additional clinical datum absent generates a new *column* in an existing mini-max table.

3. Each new diagnosis in the differential diagnosis list generates a new *mini-max table*.

4. A mini-max table, when monotony is not broken, has only one determining partial P cell, the value of which (italicized in the table) is *the smallest of its row and the greatest of its column*. The clinical datum present and the clinical datum absent that converge to this cell constitute the determining clinical data pair that originated this determining partial P, which equals the *total P* of the diagnosis.

5. When an additional clinical datum *present* is processed with the mini-max procedure, typically the total P of the diagnosis may increase, if its PP value is greater than the current total P before considering clinical data absent (last cell of second column). When an additional clinical datum *absent* is processed with the mini-max procedure, typically the greater its S, the more it decreases the P of the diagnosis. However, exceptions to this rule result from the effect this S has on the partial P of the other diagnoses that share its clinical data pair table, and from the interaction of the resulting partial P values in the mini-max table. The total P of the diagnosis will either decrease, increase, or remain unchanged:

   A. *Total P decreases*. Let's concentrate on a clinical data pair table. For a specific diagnosis, the S value of the clinical datum absent is *inversely* related to the partial P resulting after applying equation 8 to *this* diagnosis, and *directly* related to the partial P values resulting after applying equation 8 to the *other* diagnoses. An additional clinical datum absent typically reduces the total P of a diagnosis if its S is greater than the S of the absent clinical datum in the *determining clinical data pair*, in turn responsible for the current *determining partial P* of the diagnosis. If this condition is fulfilled, this new partial P will be smaller than the current determining partial P and become the new determining partial P that equals total P in the mini-max table.

   B. *Total P increases*. The mini-max procedure is not intended to increase the total P of a diagnosis based on clinical data absent. Nevertheless, this occasionally occurs, but only when a *first* clinical datum absent is processed; because at this point only one clinical datum absent column is generated, smaller values do not exist in the rows. The greatest partial P value in this column becomes the determining partial P and if it exceeds the current total P, it will replace the latter. Any subsequent clinical datum absent that is processed—regardless of its S value and resulting partial P—can only decrease the total P, because only the smallest partial P in a row can become a determining partial P. If we do not want a first clinical datum absent to increase the current total P of a diagnosis, then the second column of the mini-max table must be included in the calculation. In this way, we avoid violating the general rule that a clinical datum absent must never increase the total P. An example is the mini-max table for

bronchiectasis (see above), where the total P of this diagnosis would have been 0.628 (italicized) instead of 0.469, were the second column not included in the calculation.

C. *Total P does not change*, when a clinical datum absent does not fulfill any of the conditions for decreasing or increasing total P. This occurs frequently; furthermore, the total P of a diagnosis is quite resistant to change, especially for diagnoses with a great total P. This is an important advantage of the mini-max procedure, because it precludes ruling out a confirmed diagnosis (strongly supported by clinical data present) by some relatively unimportant clinical datum absent (as seen in the previous example of tuberculosis).

6. The order in which clinical data are processed is irrelevant; it will change only the relative position of the generated new row or column without affecting the total probability of the diagnosis. This commutative property is intuitive and consistent with physician's experience.

7. When an additional clinical datum present or absent is incorporated into a mini-max table, the previously calculated partial P values of the diagnosis in the table remain unchanged and need not be recalculated. Such P values are retained in case a need arises to determine which clinical datum pair generated a partial probability in a cell. The algorithm need remember the values in the last column only. Whenever an additional clinical datum is processed, new clinical data pairs are generated and new partial P values are calculated. The algorithm then compares these new partial P values with the existing partial P values in the last column and calculates the new total P of the diagnosis. Although unchanged values in mini-max table cells do not need to be recalculated, our algorithm and program iterates the entire mini-max procedure from start, recalculating the total P values of the diagnoses, simultaneously processing all present and absent clinical data each time an additional clinical datum becomes available. If a future database, including all known diseases and clinical data, creates computer time problems, then the property 7 may be enforced.

8. An interesting property of the mini-max procedure is revealed when the sum of the total P of all diagnoses in the differential diagnosis list is substantially greater than 1; it suggests that not all such diagnoses are competing, but that some represent concurrent diseases. The degree of support that a clinical datum gives to a diagnosis is directly proportional to its corresponding PP value. This value can be found in the clinical datum list associated with the diagnosis or in the second column of the mini-max table. If all clinical data predominantly support the same diagnosis, the remaining diagnoses tend to compete and the sum of the probabilities of all diagnoses in the differential diagnosis list is close to 1. When some clinical data predominantly favor one diagnosis and other clinical data predominantly favor another diagnosis, these diagnoses tend to be concurrent; the sum of their probabilities will be considerably greater than 1; each concurrent diagnosis can by itself attain a probability up to 1. The greater the sum of the probabilities, the greater the number of concurrent diseases.

9. When a clinical datum present *with* a PP value that approaches or equals 1 strongly supports or confirms a diagnosis, a clinical datum absent—regardless of its S value—*cannot* reduce the great P that such a clinical datum present confers to the diagnosis. This property also is true for concurrent diagnoses with great probability in the differential diagnosis list. This important advantage precludes a confirmed diagnosis from being ruled out by a relatively unimportant clinical datum absent, as mentioned earlier. However, the P of a diagnosis *without* a confirming clinical datum present *may* be reduced by the S of such a clinical datum absent. Retaining diagnoses with great P, while simultaneously ruling out diagnoses with a small P, enables concurrent diagnoses to be distinguished from competing diagnoses.

What happens when a diagnosis with a great P, based on a clinical datum present with a PP value = 1, is confronted with an additional clinical datum absent with an S = 1? Would the clinical datum present or the clinical datum absent win the rule in/rule out contest? In an actual case, this confrontation would be impossible

to occur because S = 1 means that this clinical datum is always present, contradicting its absence. Furthermore, the mini-max procedure precludes the discredit of a diagnosis with a great total P by a clinical datum absent (property 9 of mini-max procedure).

Total P of each diagnosis is calculated by its corresponding mini-max table, based on PP value of clinical data present, S of clinical data absent, and resulting partial P values, all of which are specific for this diagnosis, allowing a certain independence among diverse diagnoses. This enables that each diagnosis, which P reaches the confirmation threshold, is declared final or confirmed diagnosis, irrelevant of how many other diagnoses also reach this threshold; all of such diagnoses are considered concurrent. Competing diagnoses are ruled out, by reaching the deletion threshold.

COMMENTS

Clinical data—symptoms, physical signs, diagnostic test results, and diagnostic procedure results—are collected from a patient and matched with diseases models in the database, selecting all diseases that present a match as potential diagnoses. This typically creates a pretty large differential diagnosis list. The next problem is to determine which of these diagnoses are the one or more than one that actually afflict the patient, which requires to calculate the probability of each such diagnoses. Diagnoses that reach a probability of certain empirically determined confirmation threshold are considered final and representing the diseases that afflict the patient, whereas diagnoses that yield a probability below an empirically determined deletion threshold are ruled out. Bayes formula and other mathematical instruments used in previous existing programs do not address satisfactorily this problem; for this reason they are presented as training tools or educational tools rather than efficient diagnostic aids. Most of these programs are not capable to diagnose several diseases afflicting simultaneously a single patient (concurrent diseases), a situation that occurs frequently in complex clinical presentations. A computer program executing our mini-max procedure provided us with a prototype that proved to diagnose accurately and efficiently when challenged with real clinical cases, including concurrent diseases.

Our complete diagnostic program includes several other important functions that are expected to be published in coming papers, and currently described in our book *Computerized Medical Diagnosis: A Novel Solution to an Old Problem* [6] that stresses theoretical and historical issues, and in our recent and more practical book *A Practical Computer Program that Diagnoses Diseases in Actual Patients* [8]. Some of these functions, not discussed in the present paper are:

- Best cost-benefit clinical data next to investigate in a patient, which recommends at each diagnostic step the clinical data to investigate next, that will most efficiently and at lowest overall cost (price, risk, and discomfort) reach end of diagnostic quest, also based on mini-max procedure.

- Adjustable empirical parameters and diverse abridged output lists of recommended clinical data that enable to reduce the sometimes great number of recommended clinical data to investigate, without compromising the accuracy of the diagnosis.

- Safeguard function that precludes overlooking associated diagnoses with diseases confirmed by our program. Based on complex clinical presentation models that include diagnoses related by pathophysiologic mechanisms or statistical correlations, the program assures that all these associated diseases are processed for presence or absence in the patient.

- Safeguard function that precludes missing a diagnosis (*e.g.*, myocardial infarction), when an important clinical datum (chest pain) is masked by interaction with a concurrent disease (diabetes) or drug (potent analgesic).

The database of our current diagnostic prototype is integrated with 50 diseases models. Our diagnostic system, once implemented with all known diseases and clinical data, is expected to provide invaluable diagnostic benefits to patients, physicians, nurses, health insurance companies, malpractice lawyers, and the entire medical establishment.

CONCLUSIONS

Our algorithm, although somewhat complex, is straightforward, especially when compared to other attempts in this field. It emulates a clinician's diagnostic reasoning. It is logical and mathematically simple. Bayes formula is used with modifications, because it is unable to process properly interdependent clinical data (as are most symptoms) and concurrent diseases. To facilitate implementation and updating of the algorithm, we tend to avoid complicated tools of artificial intelligence, such as causal, hierarchical, and probabilistic trees and networks. The algorithm freely uses heuristic procedures, so as to preclude excessive proliferation of clinical data and diagnoses. It promises to be user friendly because it is expressed in natural language, is rational, and readily understandable. Determination of accurate sensitivity of clinical data and integration of clinical entities into complex clinical presentation models will be labor-intensive. A complete database with all known diseases, clinical data, clinical presentations, and other information should be created; this major task will require a dedicated team of medical specialists.

REFERENCES

[1] LEDLEY RS and LUSTED LB. Reasoning Foundations of Medical Diagnosis. Science, 130 (9): 9-21, July 3, 1959

[2] HENRION M, PRADHAN M, DEL FAVERO B, HUANG K, and O'RORKE P: Why is diagnosis using belief networks insensitive to imprecision in probabilities? Twelfth Conference on Uncertainty in Artificial Intelligence, Portland, OR, 446-454. 1996. SMI-96-0637

[3] MYERS JD, POPLE HE, and MILLER RA. INTERNIST: Can Artificial Intelligence Help? In: Connelly, Benson, Burke, Fenderson, eds. Clinical Decisions and Laboratory Use. Minneapolis: University of Minnesota Press, 1982: 251-269

[4] LUSTED LB. Introduction to Medical Decision Making. Springfield, Illinois, Charles C Thomas, 1968

[5] LUSTED LB. Twenty Years of Medical Decision Making Studies. CH1480-3/79/0000-0004$00.75. 1979 IEEE

[6] FEDER C. Computerized Medical Diagnosis: A Novel Solution to an Old Problem. Infinity Publishing, West Conshohocken, Pennsylvania, 2006

[7] POPLE HE. Heuristic Methods for Imposing Structure on Ill-structured Problems: The Structuring of Medical Diagnosis. In: Szolovits P, ed. Artificial Intelligence in Medicine, AAAS Symposium Series, Boulder, Colorado: West-view Press, 1982: 119-185

[8] FEDER C, and FEDER T. A Practical Computer Program that Diagnoses Diseases in Actual Patients. Infinity Publishing, West Conshohocken, Pennsylvania, 2008

MARTIN J: Computer Data-Base Organization. Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1977

CHAKRAVARTY S and SHAHAR Y. A Constraint-Based Specification of Periodic Patterns in Time-Oriented Data. Sixth International Workshop on Temporal Representation and Reasoning (TIME-99), Orlando, FL, 29-40. 1999. SMI-1999-0766

ALTMAN RB. AI in Medicine: The Spectrum of Challenges from Managed Care to Molecular Medicine. AI Magazine 20(3):67-77, 1999. SMI-1999-0770

BLEICH HL. Computer-Based Consultation: Electrolyte and Acid-Base Disorders. The American Journal of Medicine 53: 285-291, November 1972

BLOIS MS, TUTTLE MS, and SHERERTZ DD. RECONSIDER: A Program for Generating Differential Diagnoses. IEEE: 263-268, 1981

CHAKRAVARTY S and SHAHAR Y. Acquisition and Analysis of Periodic Patterns in Time-Oriented Clinical Data. 2000. SMI-2000-0822

DE DOMBAL FT, LEAPER DJ, STANILAND JR, McCANN AP, and HORROCKS JC. Computer-Aided Diagnosis of Acute Abdominal Pain. British Medical Journal 2: 9-13, 1972

ESHELMAN L, EHRET D, McDERMOTT JP, and TAN M (1987.) MOLE: A Tenacious Knowledge Acquisition Tool. International Journal of Man-Machine Studies, 26: 41-54

GENNARI J, MUSEN MA, FERGERSON RW, GROSSO WE, CRUBEZY M, ERIKSSON H, NOY NF, TU SW: The Evolution of Protégé: An Environment for Knowledge-Based Systems Development. 2002. SMI-2002-0943

GINI RA and FEDER C. Informatica Clinica: Presente y Futuro. La Semana Medica (Argentina) 157: 113-128, 1980

GORRY GA, KASSIRER JP, ESSIG A, and SCHWARTZ WB. Decision Analysis as the Basis for Computer-Aided Management of Acute Renal Failure. The American Journal of Medicine 55: 473-484, 1973

GORRY GA, PAUKER SG, and SCHWARTZ WB. The Diagnostic Importance of the Normal Finding. The New England Journal of Medicine 486-489, March 2, 1978

GREENS RA, PELEG M, BOSWALA AA, TU S, PATEL VL, and SHORTLIFFE EH. Sharable Computer-Based Clinical Practice Guidelines: Rationale, Obstacles, Approaches, and Prospects. Medinfo, London, UK, 2001. SMI-2001-0860

HUANG K, HENRION M: Efficient Search-Based Inference for Noisy-OR Belief Networks: Top Epsilon. Proceedings of the Twelfth Conference of Uncertainty in Artificial Intelligence, 325-331. Aug 1996, Portland, OR. SMI-96-0640

ILIAD® 4.5 Diagnostic and Reference Tool for Physicians and Medical Professionals. User Guide. 1998

JAAKKOLA TS, JORDAN MI: Variational Probabilistic Inference and the QMR-DT Network. Sun May 9, 16:22:01 PDT 1999

LUDWIG DW. INFERNET – A Computer-Based System for Modeling Medical Knowledge and Clinical Inference. Proceedings of the Fifth Annual Symposium on Computer Applications in Medical Care: 243-249, November 1981

MIDDLETON B, SHWE M, HECKERMAN D, HENRION M, HORVITZ E, LEHMANN H, & COOPER G: Probabilistic Diagnosis using a reformulation of the INTERNIST-1/QMR Knowledge Base II. Evaluation of Diagnostic Performance. Section on Medical Informatics Technical report SMI-90-0329, Stanford University, 1990

MILLER RA, POPLE HE, and MYERS JD. INTERNIST-I, An Experimental Computer-Based Diagnostic Consultant for General Internal Medicine. The New England Journal of Medicine, 1982: 468-476

MUSSEN MA, GENNARI JH, and WONG WW: A Rational Reconstruction of INTERNIST-I Using PROTÉGÉ-II. Nineteenth Annual Symposium on Computer Applications in Medial Care. New Orleans, LA, 289-293. 1995. SMI-95-0574

MUSEN MA: Modeling for Decision Support. Section on Medical Informatics. Stanford University School of Medicine. Stanford, CA 94305-5479. SMI-98-0739

NOY NF and MUSEN MA. Ontology Versioning as an Element of an Ontology-Management Framework. Stanford Medical Informatics, Stanford University, 251 Campus Drive, Stanford, CA 94305, USA. SMI-2003-0961. March 31, 2003

PATRICK EA: Decision Analysis in Medicine: Methods and Applications. CRC Press, West Palm Beach, FL, 1979

PERLROTH MG, and WEILAND DJ. Fifty Diseases: Fifty Diagnoses. Year Book Medical Publishers, 1981

POPLE HE, MYERS JD, and MILLER RA: Dialog: A Model of Diagnostic Logic for Internal Medicine. Fourth International Joint Conference on Artificial Intelligence. Tbilisi, Georgia, URRS, 3-8 September 1975, Volume Two. 1975: 848-855

PRADHAN M, DAGUM P: Optimal Monte Carlo Estimation of Belief Network Inference. Proceedings of the Twelfth Conference of Uncertainty in Artificial Intelligence, 446-453. Aug 1996, Portland, OR. SMI-96-0638

SHORTLIFE EH. Computer-Based Medical Consultations: MYCIN. American Elsevier Publishing Company, 1976

SHORTLIFFE EH. The Next Generation Internet and Health Care: A Civics Lesson for the Informatics Community. In C.G. Chute, Ed., 1998 AMIA Annual Symposium, Orlando, FL, 8-14. 1998. SMI-98-0730

SHWE M, MIDDLETON B, HECKERMAN D, HENRION M, HORVITZ E, LEHMANN H, & COOPER G. Probabilistic Diagnosis Using a Reformulation of the INTERNIST-1/QMR Knowledge Base I. The Probabilistic Model and Inference Algorithms. Methods of Information in Medicine, 30(4):241-255, 1991. SMI-90-0296

SZOLOVITS P and PAUKER SG. Categorical and Probabilistic Reasoning in Medical Diagnosis. Artificial Intelligence. 11: 115-144, 1978

TU SW et al: Modeling Guidelines for Integration into Clinical Workflow. Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA. SMI-2003-0970

VAN BEMMEL JH, MUSSEN MA (eds): Medical Informatics. Springer, 1997

WEINSTEIN MC and FINEBERG HV: Clinical Decision Analysis. W. B. Saunders Company, 1980

WEISS S, KULIKOWSKI CA, and SAFIR A. Glaucoma Consultation by Computer. Comput. Biol. Med. 8: 25-40, 1978