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CLINICAL REVIEWS

The Diagnostic Pursuit of Gastrointestinal Symptoms

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ABSTRACT

The present article attempts to model the reasoning underlying the process of diagnostic workup in a patient with GI symptoms. Diagnostic reasoning consists of two consecutive and repetitive steps. Test procedures help to contract a list of multiple competing diagnoses to one focal diagnosis. In a subsequent step, the focal diagnosis again becomes expanded to a second list of new diagnoses that are more precise than those on the first list. In the process of expansion, the focal diagnosis itself serves as a test with its own sensitivity values to generate the second list of associated diagnoses. The process of contraction and expansion repeats itself, until the focal diagnosis of the last contraction is no longer expansible or until diagnostic knowledge gained from further expansion loses therapeutic relevance. The process of contraction and expansion can be formalized by Bayes' formula. (Am J Gastroenterol 2001;96:298–302. © 2001 by Am. Coll. of Gastroenterology)

INTRODUCTION

Several models have been developed to describe the process of diagnostic reasoning by physicians (1–4). Feinstein, for instance, has suggested the use of algorithms to proceed from gross pathophysiological domains and disorders toward more specific pathoanatomic diseases (5–7). Others have used the decision tree to structure the contribution of a variety of differential diagnoses to an apparent medical problem and to classify them by their probability of occurrence and relevance to the problem under consideration (8, 9). To model a clinical problem as a decision tree, however, the variety and interaction of all relevant medical factors need to be fully understood beforehand. A decision tree is less suited to illustrate how physicians actually advance their understanding of a disease process when most of it is still unknown. How do gastroenterologists, for instance, advance from the description of a vague symptom to a well phrased diagnostic hypothesis? How do they select from a multitude of potential diagnoses the most likely one? When, in the diagnostic workup, do they decide in favor of endoscopy or other invasive procedures? The present analysis tries to understand the type of reasoning that underlies the diagnostic process and how, in this process, gastroenterologists advance from broad diagnostic ideas toward increasingly more refined diagnoses. Bayes' formula is used as the primary tool to formalize the process. The aim of this article is to describe the process of diagnostic reasoning as it occurs in the physician's head, but also as it could possibly be used in a computerized diagnostic decision support system.

A CASE SCENARIO

A 65-yr-old man presents to his physician with chief complaints of nausea and vomiting. Nausea and vomiting constitute rather unspecific symptoms that could relate to the GI tract or indicate a diagnosis affecting other organ systems. Upon questioning the patient also admits to suffering from epigastric pain. The physician now considers a disease involving the gastroduodenum *versus* the esophagus, pancreas, or hepatobiliary tract. Upon further questioning, the patient states that he noticed dark bowel movements and experienced weakness, as well as occasional spells of dizziness. Epigastric pain associated with possible GI bleeding could stem from gastric cancer or peptic ulcer. The patient describes a rather sudden onset of his symptoms and denies any recent weight loss. His father and brother both have been treated for duodenal ulcer disease. Except for signs of microcytic anemia, the laboratory panel does not reveal any other abnormality. Eventually a gastroduodenoscopy shows a duodenal ulcer.

SWITCHING BETWEEN CONSECUTIVE DIAGNOSTIC LEVELS

It seems that, in many instances, instead of choosing the correct diagnosis from a large set of potential final diagnoses, the workup is broken down into a repetitive sequence of consecutive choices among small sets of diagnostic options. As the workup progresses, the diagnostic options become more focused and narrowed down. Many of the decisions among various options are made during the initial history taking and physical examination. These decisions occur quickly and may be so ingrained that physicians do not even become fully aware of the mechanics underlying their medical reasoning. For instance, in the patient seen for the first time, the physician decides between "digestive" and "other" disease conditions. Such a decision is based on the presence of epigastric pain and the lack of other symptoms such as fever, headache, vertigo, etc. A subsequent decision differentiates between "gastroduodenal " and "other diges-

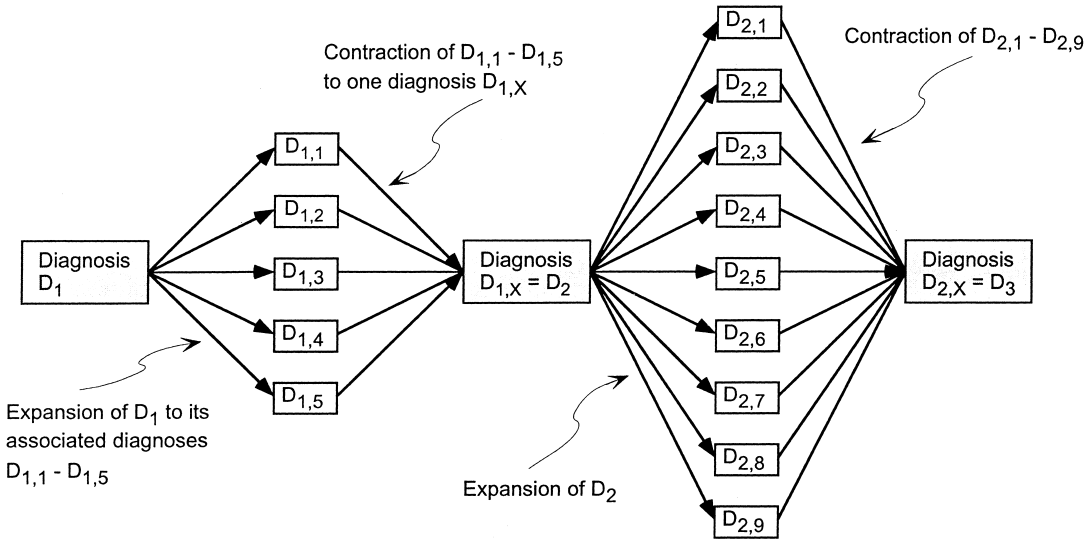

Figure 1. Scheme of the diagnostic process involving a consecutive sequence of expansions and contractions. In an expansion, the focal diagnosis of a previous contraction is expanded to a new list of associated diagnoses. As the diagnostic process progresses, the diagnoses of each new diagnostic level become more refined and focused toward the final diagnosis.

tive" conditions. Many of these initial decisions do not deal with diagnoses in the common sense and are often described by adjectives rather than technical terms. A physician may not always follow the same sequence of decision making. If the patient complains of dysphagia at the onset of the encounter, the physician would most likely skip the aforementioned sequence and start the diagnostic reasoning by deciding between "mild" *versus* "severe," "acute" *versus* "chronic," and then between pharynx, esophagus, and stomach. In case of food stuck in the mid-esophagus, a physician may continue wondering about problems originating "inside" or "outside" of the esophagus. At the initial stage, the tests advancing the decision between different diagnostic options relate to questions about the history or obvious physical findings. Only at later stages, as the workup advances through different levels of diagnostic decisions, do the tests become technically more involved. A diagnostic level comprising true clinical diagnoses such as gastric cancer, duodenal ulcer, or gastroenteritis is entertained relatively late in the workup process.

DIAGNOSTIC CONTRACTION AND EXPANSION

A diagnostic test is chosen to distinguish between two or more diagnostic alternatives. Sometimes several tests need to be applied consecutively to the same set of differential diagnoses, to raise the diagnostic probability of one particular diagnosis. A diagnosis becomes quickly validated or refuted even by a series of rather insensitive tests, if all test results return positive or negative, respectively. Diagnostic testing serves to contract a set of multiple competing diagnostic possibilities to one focal diagnosis. For instance, based on the presence of possible melena, the list of differential diagnoses (including gastroduodenal disease, esophageal disease, pancreatic disease and hapatobiliary disease) was narrowed down or became contracted to gastroduodenal disease as the most likely alternative. A diagnostic procedure, the presence of a symptom, or a clinical finding can all constitute a test; and frequently the distinction between test, symptom, and diagnosis becomes blurred. For instance, abdominal pain might be predictive of a digestive disease, and melena might be predictive of GI bleeding from peptic ulcer or gastric cancer. A "predictive value" or a posttest probability predicts the presence of a given diagnosis after a particular test result. In other words, it indicates the probability for a test result, clinical sign, or symptom to be associated with a second sign, symptom, or a diagnosis.

The diagnostic test narrows down or contracts a multitude of differential diagnoses to one particular diagnosis that seems to be the most probable. Subsequently, the contraction within the first diagnostic level and the selection of one focal diagnosis from a multitude of possible differential diagnoses are followed by an expansion of this particular diagnosis to a second set of more precise diagnoses. Their entirety forms the next diagnostic level. Each focal diagnosis of a previous contraction serves as a focal point for a subsequent expansion (Fig. 1). For instance, the symptoms of nausea and vomiting were first expanded to GI *versus* other types of disease. Subsequently, GI disease was expanded to a longer list of differential diagnoses involving the gastroduodenum, esophagus, pancreases, or hepatobiliary tract. Finally, gastroduodenal disease became expanded to gastric cancer *versus* peptic ulcer (Fig. 2). Frequently, a lengthy diagnostic workup seems to constitute a sequence of contractions and expansions of increasingly more precise diagnostic levels.

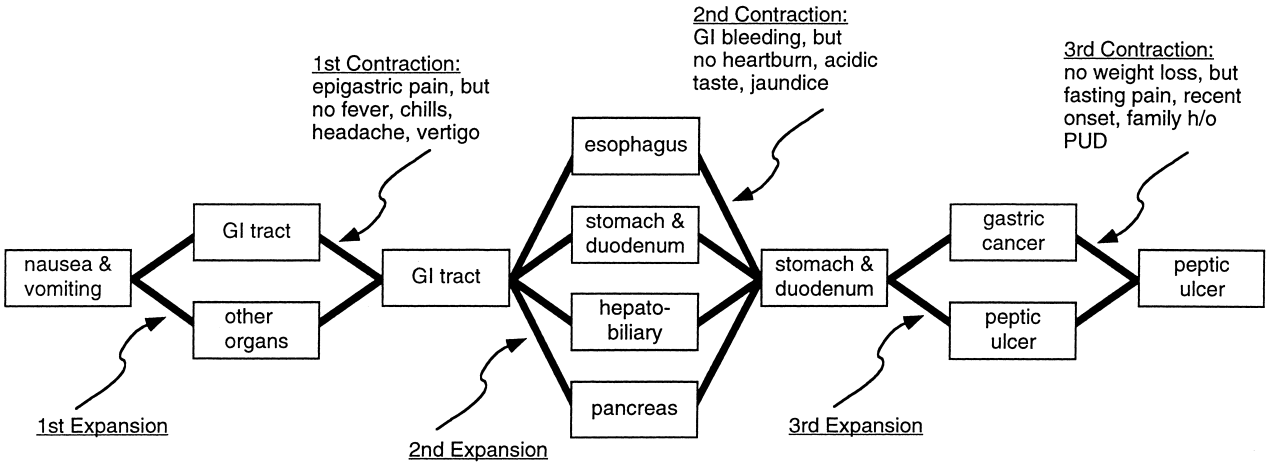

Figure 2. Three consecutive steps of expansion and contraction in the workup of a hypothetical patient with initial symptoms of nausea and vomiting.

The Mathematics of Diagnostic Contraction and Expansion

Bayes' formula helps in deciding between the presence and absence of a particular diagnosis or between two different diagnoses D_1 and D_2. A positive test result (T+) changes the pretest probabilities of the two competing diagnoses from $P(D_1)$ and $P(D_2)$ to the posttest or positive predictive probabilities $P(D_1|T+)$ and $P(D_2|T+)$, respectively:

$$P(D_1 \mid T+) = \frac{P(D_1) \cdot P(T+ \mid D_1)}{P(D_1) \cdot P(T+ \mid D_1) + P(D_2) \cdot P(T+ \mid D_2)}$$

$$P(D_2 \mid T+) = \frac{P(D_2) \cdot P(T+ \mid D_2)}{P(D_1) \cdot P(T+ \mid D_1) + P(D_2) \cdot P(T+ \mid D_2)}. \quad (1)$$

$P(T+|D_1)$ and $P(T+|D_2)$ are the test sensitivity with respect to the first and second diagnosis, respectively. The equations can be changed easily to apply to more than two differential diagnoses. As discussed above, the presence of a diagnostic symptom or clinical sign (D+) could also be regarded as a positive test, and T+ would become replaced by D+ in the formulas from above. Diagnostic expansion can be conceptualized as a process that reverses Bayes' contraction. In general, Bayes' formula serves to contract a multitude of diagnostic options to one single diagnosis. It can also be used to expand one primary diagnosis D_1 to two or more secondary diagnoses $D_{1,1}$, $D_{1,2}$ ... $D_{1,i}$ associated with the positive presence of a primary diagnosis D_1. Using Bayes' formula to expand the primary diagnosis D_1 into two secondary diagnoses $D_{1,1}$ and $D_{1,2}$ yields:

$$P(D_{1,1} \mid D_1+) = \frac{P(D_{1,1}) \cdot P(D_1+ \mid D_{1,1})}{P(D_{1,1}) \cdot P(D_1+ \mid D_{1,1})) + P(D_{1,2}) \cdot P(D_1+ \mid D_{1,2})}$$

$$P(D_{1,2} \mid D_1+) = \frac{P(D_{1,2}) \cdot P(D_1+ \mid D_{1,2})}{P(D_{1,1}) \cdot P(D_1+ \mid D_{1,1}) + P(D_{1,2}) \cdot P(D_1+ \mid D_{1,2})}. \quad (2)$$

The structure of equations [2] is identical to that of equations [1] from above. Instead of the two primary diagnoses D_1 and D_2, the new equations are concerned with the two secondary diagnoses $D_{1,1}$ and $D_{1,2}$. Instead of the positive T+, the presence of a positive diagnosis D_1+ now serves to decide in favor of the two secondary diagnoses. The positive predictive probabilities of the two new secondary diagnoses, that is, $P(D_{1,1}|D_1+)$ and $P(D_{1,2}|D_1+)$, depend on their general prevalence $P(D_{1,1})$ and $P(D_{1,2})$ in the patient population, as well as on the sensitivity of their relationship with the primary diagnosis, that is $P(D_1+|D_{1,1})$ and $P(D_1+|D_{1,2})$. The sensitivity $P(D_1+|D_{1,1})$ describes the fraction of $D_{1,1}$-positive patients who also present with D_1+. In the present example, this fraction corresponds to the sensitivity of nausea and vomiting regarding any disease affecting the GI tract as opposed to other organs. The sensitivity values could be considered the driving force of the expansion. The primary diagnosis becomes expanded dependent on its sensitivity for the subsequent more precise secondary diagnoses. The predictive value bridges the gap between the two diagnoses from different levels. It should also be mentioned that, in the present context, the term "diagnosis" is used in a rather loose fashion. As already indicated in the preceding section, during the early stages of a workup, the focal diagnosis of expansion may represent little more than a sign, symptom, or broad diagnostic category.

Although equations [2] are similar to equations [1], there are several important distinctions to keep in mind that are not obvious from a superficial inspection of the formula. First, in the conventional Bayes' formula, the sensitivities describe the characteristics of a test procedure. The test is physically and conceptually detached from the diagnoses and works completely independently of the list of differential diagnoses. In the formula for expansion, on the other hand, the primary diagnosis itself is the test; it serves as a test procedure to predict the probability of finding any of the secondary diagnoses of the next diagnostic level. The sen-

Table 1. Example of Three Consecutive Steps of Expansion and Contraction in a Hypothetical Patient With Nausea and Vomiting

Focal Diagnosis D+	Nausea and vomiting		Digestive Tract, Nausea, and Vomiting				Stomach/Duodenum	
Expansion Diagnoses	Digestive Tract	Other Origin	Esophagus	Stomach or Duodenum	Pancreas	Hepatobiliary	Gastric Cancer	Peptic Ulcer
Pretest probability	50	50	25	25	25	25	50	50
Sensitivity of D+	70	20	40	70	50	60	50	30
Expansion probability	78	22	18	32	23	27	63	38
Test	Episgastric pain		Melena present				No weight loss	
Sensitivity of test	70	20	30	70	10	10	70	30
Contraction probability	92	8	17	68	7	8	80	20

All numbers in the table represent percentages. Sensitivity of D+ corresponds to the sensitivity of the focal diagnosis with respect to the expansion diagnosis. The expansion and the contraction probability both correspond to positive predictive probabilites calculated with Bayes' formula.

sitivity describes the relationship between the primary and secondary diagnoses. Second, in the conventional Bayes' formula, the pre- and posttest probabilities concern one identical diagnosis. Bayes' formula helps in selecting between the diagnoses of the same diagnostic level by raising or lowering the pretest probability of one particular diagnosis $P(D_1)$ to a posttest probability $P(D_1|T+)$. The formula for expansion, in contradistinction, establishes a connection between two separate diagnoses from two different diagnostic levels, for instance, D_1 and $D_{1,1}$.

A Detailed Example

The following section provides a simple example of the calculations used in the scenario of a patient who presents with chief complaints of nausea and vomiting. The workup with its sequence of three expansions and contractions is shown in Figure 2. The calculations are presented in Table 1. The top part of Table 1 shows the focal (*i.e.*, primary) diagnoses (D+) at each of the three steps and the list of potential expansion (*i.e.*, secondary) diagnoses. The middle part contains the pretest probability (*i.e.*, prevalence) and sensitivity used in the calculation of the expansion (*i.e.*, positive predictive) probability. Without prior knowledge of the true prevalence rates of the individual secondary diagnoses in a given patient population, the probabilities were equally split between the various diagnostic options. The sensitivity of D+ defines the sensitivity of the focal diagnosis with respect to the expansion diagnosis. For instance, the sensitivity of nausea and vomiting for disorders affecting the digestive tract or other organs were considered to be 70% and 20%, respectively. The expansion probabilities were calculated according to equation [2] as:

$$P(D_{1,1} \mid D_1+) = \frac{50\% \cdot 70\%}{50\% \cdot 70\% + 50\% \cdot 20\%} = 78\%,$$

$$P(D_{1,2} \mid D_1+) = \frac{50\% \cdot 20\%}{50\% \cdot 70\% + 50\% \cdot 20\%} = 22\%.$$

The bottom part of Table 1 lists the types of test and their respective sensitivities used to calculate the contraction probability—again, applying Bayes' formula as shown by equations [1]. It should be noted that the pretest probabilities, as well as the positive predictive probabilities after expansion and contraction, always add up to 100%. The diagnosis with the highest contraction probability is then used as the focal diagnosis in the next round of expansion. For instance, because a disease of the digestive tract seems more likely, it becomes the focus of the subsequent second diagnostic expansion. In the second expansion, a disease of the digestive tract associated with nausea and vomiting becomes expanded into four potential differential diagnoses.

Several Caveats

In assessing the above example, several caveats need to be appreciated. A rather simple and straightforward diagnostic process was evaluated. In reality, more intermediate steps of contraction and expansion may take place between the initial presentation of the patient and before a final diagnosis is made. For the sake of simplicity, only one diagnostic test was considered in deciding among various differential diagnoses. To simplify the calculations of Table 1, the new focal diagnosis D+ of each contraction was expanded, as if it had been confirmed with 100% certainty. A lengthy process of consecutive expansions without prior confirmation of the focal diagnoses would soon result in meaningless low probability values for all differential diagnoses. However, the use of multiple independent tests and the repetitive application of Bayes' formula allows one to achieve contraction probabilities that are close to 100%. For instance, in deciding between gastric cancer and peptic ulcer, the positive family history, recent onset of the symptoms, and a fasting pain might be additional "test results" that would point toward peptic ulcer. In the above example, the majority of tests relate to simple history taking and pointed questions. Because few or no costs are involved with such tests, the physician can easily afford to expand a focal diagnosis with a probability well below certainty. The pursuit of a wrong diagnostic hypothesis, even over several consecutive expansions and contractions, occurs at little expense to the patient or the physician. If the subsequent diagnostic search involves costly or risky procedures, however, most physicians will strive to narrow down the list of potential differential diagnoses as much as possible before advancing the workup.

One may argue that the possibility of knowing the sensitivity values of all conditions in an expansion process is very remote. This is one reason why, in clinical practice, most expansions rarely consider more than two to three simultaneous differential diagnoses. Because it may involve a cumbersome and lengthy process to extract from the literature the exact sensitivity and specificity values associated with each condition, outside the confinements of scientific pursuits, one could resort to estimating the values based on one's own clinical experience. Incomplete knowledge of all sensitivity or specificity values is not a particular problem of the present formalism, but relates to any medical use of Bayes' formula as well. The second expansion into disease of the esophagus, gastroduodenum, pancreas, or hepatobiliary tract also serves to illustrate that individual diagnoses need not represent exact medical terminology and could be grouped in any fashion that seems most convenient or operational to the physician.

Although the physician always pursues the most likely alternative of each contraction and advances the diagnostic pursuit through several consecutive levels of differential diagnoses, occasionally no diagnostic headway is made. As none of the diagnostic possibilities bears up, the physician needs to backtrack and to re-explore some or all of the previous diagnostic alternatives. Starting again at a previous focal diagnosis, a new expansion would consider previously ignored differential diagnoses and would try to contract the enlarged list by a new set of tests such as physical examination, laboratory work, or other diagnostic procedures.

CONCLUDING COMMENTS

The present article tries to show how the search for a GI diagnosis could be modeled as a repetitive sequence of expansions and contractions. In the processes of expansion, a clinical sign or primary diagnosis is expanded into a set of more refined secondary diagnoses. Mathematically, both processes of expansion and contraction rely on Bayes' formula. Bayes' formula is usually thought to mediate between the pre- and posttest probability of the same diagnosis, the post-test probability also being referred to as predictive value. A diagnostic procedure, the presence of a symptom, or a clinical finding may all constitute a test. In these instances, the sensitivity can be interpreted to represent the strength of the association between two symptoms or between a primary and a secondary diagnosis. This interpretation of sensitivity establishes a connection between two clinical findings that is potentially independent of any test procedure and that opens the possibility of using Bayes' equation to formalize the process of diagnostic expansion. Contraction underlies the conventional use of Bayes' formula when it helps in selecting the most probable diagnosis from a list of two or many more. The terms diagnostic contraction and expansion are newly introduced in the present context. They refer to the process by which symptoms or a clinical findings are used to develop a list of potential differential diagnoses.

Not every differential diagnosis uses Bayesian contraction, and not every diagnostic workup can (or needs to be) based on a sequence of contractions and expansions (10–12). A physician may recognize a particular pattern at first sight and may seek confirmation of the initial suspicion by some focused questions and very few tests. In other instances, the physician may use script-based models to pursue a diagnosis (10). In contradistinction to previous concepts of diagnostic reasoning, however, the simple mathematics that underlie the present model could render it easy to formalize and to incorporate in decision support systems. Even without applying the mathematical formulas, the concepts developed here may provide a useful framework to understand and conceptualize the process that underlies some forms of medical diagnosis.

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