

## FEATURE

# Clinical Decision Making—A Functional Medicine Perspective

临床决策—功能医学前景观点

Toma de decisiones clínicas: Una perspectiva médica funcional

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As 21st century health care moves from a disease-based approach to a more patient-centric system that can address biochemical individuality to improve health and function, clinical decision making becomes more complex. Accentuating the problem is the lack of a clear standard for this more complex functional medicine approach. While there is relatively broad agreement in Western medicine for what constitutes competent assessment of disease and identification of related treatment approaches, the complex functional medicine model posits multiple and individualized diagnostic and therapeutic approaches, most or many of which have reasonable underlying science and principles, but which have not been rigorously tested in a research or clinical setting. This has led to non-rigorous thinking and sometimes to uncritical acceptance of both poorly documented diagnostic procedures and ineffective therapies, resulting in less than optimal clinical care.

In this discussion, we will address the challenges of clinical decision making in a functional medicine practice, looking at various models of human decision making and identifying strategies to improve their application in the healthcare setting.

## CHALLENGES FOR THE FUNCTIONAL MEDICINE CLINICIAN

The personalization of care achievable through the functional medicine approach is the only real solution to the crisis of chronic disease facing us today. However, to practice this form of medicine is difficult, complex, and requires higher standards of decision making by clinicians. The functional medicine approach to diagnosis demands not only that we determine what disease the patient is suffering from, which can be challenging, but also what the patient's underlying physiological dysfunctions are, and the underlying cause(s), which is a complex process.

### Sumatriptan or Magnesium?

Consider the clinician who wants to practice the best medicine and therefore reads not only standard medical journals but also the nutrition research. The clinician decides to compare sumatriptan to magnesium for a patient suffering migraine headache. Looking at a metaanalysis of various triptans in the treatment of migraine patients, the clinician would conclude that 100 mg of sumatriptan is likely effective in 59% of patients.<sup>1</sup> (Efficacy is defined as relief of

headache pain within 2 hours.) Being a responsible clinician, he/she would also consider adverse drug reactions and would see that the placebo-subtracted proportion for patients with at least 1 adverse drug reaction (ADR) is 13%; for at least one central nervous system symptom, 6% (3.0%-9.0%); and for at least one chest symptom, 1.9% (1.0%-2.7%). The clinician might compare these data with other triptans, and choose rizatriptan instead, since it shows somewhat better efficacy and consistency, and similar tolerability.

In contrast, looking at the research for magnesium, the clinician would find a response of 41.6% from oral magnesium. This reduction in attack frequency in the magnesium group compared to 15.8% in the placebo group might be compelling, but the incidence of ADRs of diarrhea (18.6%) and gastric irritation (4.7%) would likely preclude use.<sup>2</sup> Not surprisingly, the conventional practitioner would very likely make an evidence-based medicine (EBM) decision and choose rizatriptan over magnesium.

However, digging deeper would show a dramatic difference in response to magnesium based on serum ionized magnesium levels (IMg<sup>2+</sup>). Eighty-nine percent of those responding to intravenous magnesium showed low pretreatment serum magnesium levels, while only 37.5% of non-responders had a low IMg<sup>2+</sup> level.<sup>3</sup> Digging even deeper, the clinician would notice that magnesium is twice as effective if the patient also suffers a prodromal aura.<sup>4</sup>

Conventional diagnosis of migraine is pretty straightforward, although atypical presentations are probably more common than previously recognized.<sup>5</sup> The causes, however, are myriad. A research team at SaluGenecists, Inc, performed a comprehensive review of the research literature (over 10 000 research articles studied; 1000 cited) and identified at least 27 different physiological dysfunctions that can lead to the clinical presentation of migraine headache. Patients get to migraine via complex, individual pathways. Further, there are research reports to be studied concerning approximately 40 different "natural medicine" approaches to migraine (nutritional, herbal, and lifestyle therapies). And 20 environmental toxins may need to be evaluated in order to normalize physiological dysfunctions. The clinical decision-making process has now become far more complex than simply diagnosing migraine and prescribing a triptan! This 2 orders of magnitude increase in complexity dramatically increases the need for rigorous decision making.

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Considering a human's approximately 4000 enzyme systems, 1,000 chemical mediators (these 2 numbers are my estimates; I could not find an actual count), 2,000,000 possible single nucleotide polymorphisms (SNPs), approximately 250 nutrients known to be important in human health, and several thousand endogenous and exogenous xenobiotics, the true size of the challenge becomes readily apparent.

## CLINICAL DECISION MAKING

### How Good Are We at Critical Thinking?

How do we expand upon the current disease-based diagnosis and treatment model to achieve a clinically effective understanding of the biochemical, physiological, and environmental uniqueness of our patients? What diagnostic challenges does this expanded model create for clinicians? One of the most important services a clinician provides his or her patients is decision making. Disease diagnosis, physiological function assessment, determining optimal treatment, limiting adverse drug reactions—all involve critical thinking skills.

How do clinicians make diagnostic and therapeutic decisions? What influences clinical decision making? What data contribute to accurate decisions? What induces errors into a clinician's decisions? How can we improve the accuracy and reliability of clinical thinking? What happens when the complexity becomes too great?

While we seldom think about the process of decision making, our ability to do it efficiently and accurately impacts our every interaction with patients. Unfortunately, research has shown that clinical critical thinking skills need more attention in order to avoid systematic logic errors and misinterpretation of the actual predictive value of various types of patient information.

Improving the reliability of the information clinicians use to make decisions is obviously critical. To that end, EBM has become a recurrent theme in the medical research and academic literature. A recent survey showed that virtually all (122 of 126) LCME-accredited (Liaison Committee on Medical Education) medical schools included EBM as a required course of at least 20 hours.<sup>6</sup> However, formal courses devoted specifically to critical thinking are rare. Utilizing the AAMC (American Association of Medical Schools) curriculum search tools found only 6 institutions with courses that included 1 of the terms "decision" or "critical" or "analytic," and the hour allocations were low. Obviously, critical thinking is informally taught in many courses and clinical rotations. Nonetheless, it seems to receive limited formal attention. A survey of 417 US internal medicine residency programs found formal clinical decision making training (critical appraisal, searching for evidence, posing a question, and applying it in decision making) in only 99 of 269 (37%) institutions that responded.<sup>7</sup>

A Cochrane review of the research evaluating the effect of teaching critical thinking skills to healthcare professionals already caring for patients found a

remarkable 25% improvement in clinical accuracy.<sup>8</sup> However, the Cochrane review also said there were too few properly designed and conducted studies to be confident in the size of the improvement or its actual clinical significance. Nonetheless, the well-documented evidence of frequent clinician error and its role in the incidence of suboptimal care and adverse clinical outcomes is compelling. One widely reported epidemiological study that reviewed published reports found that 4% to 18% of consecutive outpatient visits result in adverse effects, with one study asserting that up to 69% of the adverse events were preventable with better decision making.<sup>9</sup>

It appears undeniable that patients receive a lower quality of care than would be expected considering the high level of practitioner training and the huge body of research now available. The need for accurate decision making is even more critical when clinicians adopt the principles and practices of functional medicine.

### What Can We Learn From Artificial Intelligence (AI) Research?

One way to improve critical thinking skills is to better understand how humans make decisions. As computers became available with enough power to mimic human thinking processes, researchers had to rigorously dissect how humans make decisions. While most of the early research centered on the creation of chess programs that could match human masters, of particular relevance here is the effort to duplicate the thinking processes of healthcare professionals.

Interest in this area increased dramatically with the publication of MYCIN (1980), an "expert system" that came out of research at Stanford University in the late 1970s. What caught the imagination of the AI and healthcare communities was that, for blood-borne infections, MYCIN outperformed not only medical students and residents, but also infectious disease fellows and medical school faculty (see Table). How did it do this? By having logicians and programmers work with a group of infectious disease experts to exhaustively determine all the "rules" they used to determine which bacterial species caused a blood-borne infection and the optimal intervention for its eradication. Converting their knowledge into software logic required that the clinicians exhaustively think through how they make decisions. This level of rigor resulted in

**Table MYCIN vs Students and Clinicians (1980)**

Healthcare expert	Score
Perfect score	80
Medical student	24
Resident	36
Actual hospital outcome	46
Infectious disease fellow	48
Medical school faculty	34-50
MYCIN	52

better decision making, not only because the model was able to incorporate the best thinking of many experts, but also because it applied those rules consistently with every patient.

According to Enrico Coiera (Foundation Chair in Medical Informatics, Faculty of Medicine, University of New South Wales, Australia), “If physiology literally means ‘the logic of life,’ and pathology is ‘the logic of disease,’ then health informatics is the ‘logic of healthcare.’”<sup>10</sup>

There are now over 70 AI tools in use in conventional medicine to improve diagnosis (actually outperforming clinicians in some areas), avoid drug interactions, interpret x-rays and laboratory tests, teach medical students, and perform other tasks (see Judith Federhofer’s excellent review at [www.computer.privateweb.at/judith](http://www.computer.privateweb.at/judith)). We can continue to learn much about the mechanics of medical decision making and areas of potential error by formally coding our decision making processes into computer programs. These programs consistently reproduce our thinking processes so that they can be subjected to evaluation. By identifying where our decisions lead to correct or incorrect outcomes, we can refine our thinking and improve our use of evidence and patient data.

#### ARTIFICIAL INTELLIGENCE—MANY WAYS OF THINKING

Studying the types and diversity of AI systems (called expert systems when they are used to duplicate experts in a field of study) that have been developed to mimic human thinking is very informative.

In general, 5 types have been used in medicine (there are actually many more types of AI, but these are the most common in healthcare):

- Rules-based systems
- Case-based reasoning (CBR)
- Neural networks
- Fuzzy logic
- Bayesian networks

This discussion may appear daunting, but we will draw from it some straightforward guidance. Busy clinicians can’t be expected to calculate all the probabilities before making recommendations for each patient, but their critical thinking skills can be improved by understanding better how decisions are made.

#### Rules-based Systems

Rules-based systems are fairly straightforward. They look like flowcharts with “If . . . then” statements. Many clinical guidelines are based on this model. Figure 1 shows a diagram modified from a flowchart developed by Herb Joiner-Bey, ND, for an article by Nancy Sudak, MD, on a functional medicine approach to migraine headache, published in Volume 2, No. 6 of *Integrative Medicine: A Clinician’s Journal*. Each branch point is simply an “If . . . then” logic statement. This

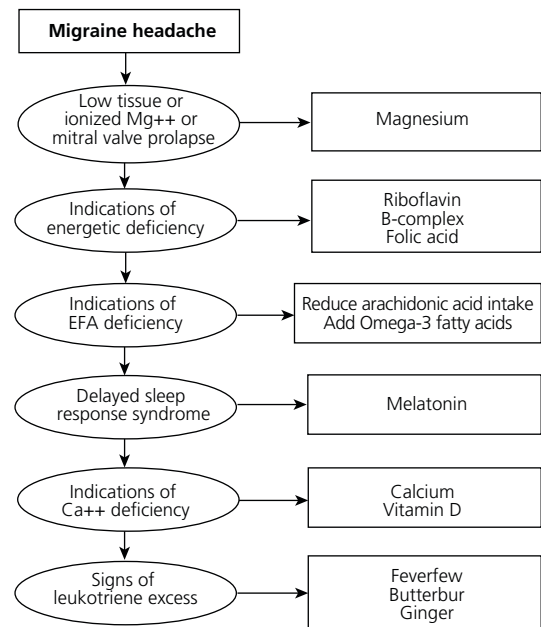


Figure 1 Migraine flowchart.

matches human reasoning well in simple cases, especially when pathognomonic decision points are available (like Koplik’s spots in measles).

#### Case-based Reasoning

Case-based reasoning starts by accumulating and evaluating a large number of “solved” cases to determine the characteristics of the successfully treated patients. It then tries to match new patients with patients in the database. This method duplicates human pattern matching pretty well, ie, once you’ve seen a patient with classic migraine, others are easy to recognize.

#### Neural Networks

Neural networks make no effort at understanding how humans think nor do they develop algorithms. Rather, they look at human decision making as a “black box.” By using a large number of examples of desired behaviors, they attempt to match input (signs and symptoms) to outputs (diagnoses or therapies). The computer software is set up to be similar to the parallel processing architecture of the brain. This process may match human thinking at a very early age, but does not help us much when trying to understand adult reasoning processes.

#### Fuzzy Logic

The concept of fuzzy logic puts me in awe of human creativity. The idea here is to look at particular information and attempt to determine the level of uncertainty. It could be described simply as a rules system with probabilities or uncertainties added.

#### Bayes Inference

An expert system used frequently in medical diagnostic systems is Bayesian inference, based on the probability

theory of the Rev Thomas Bayes, an 18th century mathematician. This heuristic reasoning system makes inferences based on the rigorous mathematics of the predictive value of information. His formula for determining the predictive value of information can be simply stated as:

$$P(D|F) = P(F|D) * P(D) / P(F)$$

where:

- D = Decision (eg, disease)
- F = Finding (eg, symptom)
- P(D) = The a priori probability of the decision (eg, the incidence of a disease in the general population)
- P(F) = The a priori probability of the finding (eg, the incidence of a symptom in the general population)
- P(D|F) = Probability of the decision given the finding
- P(F|D) = Probability of the finding, given the presence of the decision

The Bayes formula can be restated in terms of sensitivity and specificity:

$$P(D|F) = \frac{P(D) * TP}{(P(D) * TP + (1 - P(D)) * FP)}$$

Or

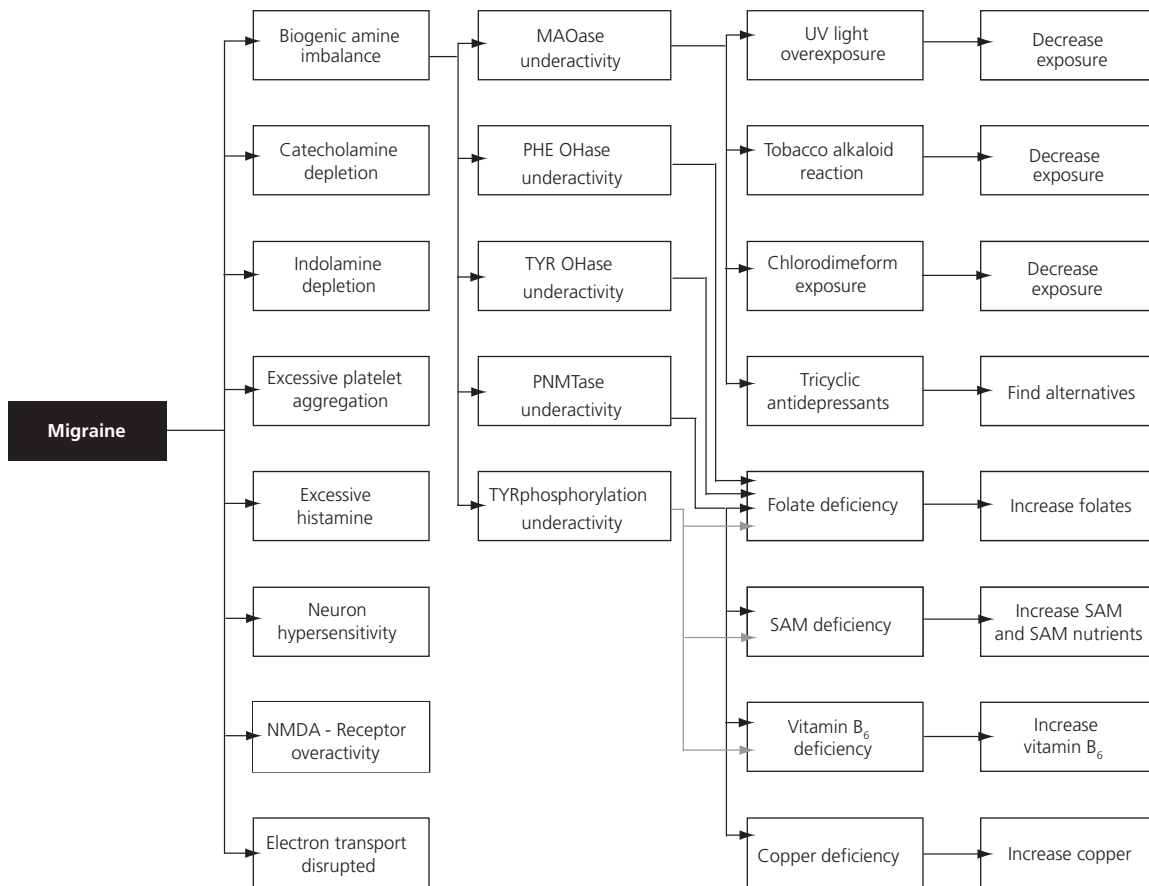
$$P(D|F) = \frac{P(D) * TP}{P(F)}$$

That looks pretty complicated, but the main take-away is that the probability of the decision's accuracy is inversely proportional to the a priori probability of the finding. In other words, the more prevalent a piece of information (a finding or symptom) is in the population, the less predictive it is in a specific patient.

Intuitively, this makes sense.

As you may recall from your study of statistics long ago, the issues of sensitivity and specificity are extremely important. They are frequently used in laboratory medicine where they provide us guidance on the usefulness of specific tests. For example, a lab test may be very sensitive, ie, is abnormal very frequently when the disease is present. However, if it has a high false positive (low specificity, where  $FP = 1 - \text{specificity}$ ), meaning the result is frequently abnormal even when the disease is not present, it is not very useful.

The value of this kind of an inference-based expert system is that it mimics human thinking well (human brains are remarkably effective inference engines). If the mathematically rigorous Bayes thinking is used, decisions can be more accurate, and long chains of logic can be used (see Figure 2). This is the method used by casinos to calculate odds and by the Mars Lander to pick a site and land on it safely. Equally important, this system can



**Figure 2** Bayesian inference network.  
 Note: Each arrow indicates a Bayesian inference.

be used to map human biochemistry, and we can learn a lot from it about the strengths and weaknesses of human thinking processes.

### THE ROLE OF UNCERTAINTY IN MEDICAL ERROR

A strong case can be made that underappreciation of uncertainty is a major cause of error in medicine.<sup>11</sup> McNeil has argued that the major hidden barriers to better healthcare result from a lack of discussion about the impact of uncertainty in medicine.<sup>12</sup> She enumerates 3 sources of uncertainty that cloud decision making:

1. uncertainty as a result of lack of convincing evidence,
2. uncertainty about the applicability of research evidence to clinical care, and
3. uncertainty about interpretation of data.

Others have asserted that the failure to learn how to make decisions under uncertainty is the leading cause of excessive diagnostic testing and inappropriate treatments.<sup>13</sup> Obviously, reliable evidence is critical for effective decision making. However, too often evidence is confused with decision making. The quality of evidence is now evaluated (several EBM scales exist, typically ranking evidence from 1 for meta-analysis to 5 for anecdotal evidence), which may be helpful, but clinical decision making is not only about the ranking of evidence; it is also about making choices in the face of uncertainty. The failure to train doctors about clinical uncertainty has been called “the greatest deficiency of medical education throughout the twentieth century.”<sup>14</sup>

### Lessons From Reverend Bayes

Rigorously dealing with uncertainty is exactly the problem addressed by the Bayes probability formulas. Consciously utilizing the false positive to balance the true positive in order to accurately portray the true level of uncertainty significantly improves the reliability of decision making. It does this by removing our overestimation of the certainty of decisions, pointing to the need for more information to improve accuracy.

Through the use of the true positive (sensitivity) and false positive (1-specificity), the mathematically correct strength of an inference can be determined—that is, the clinician can better understand the true predictive value of evidence.

The Bayes formula may look daunting, but its use can be surprisingly easy. In fact, there are available on the Internet simple Bayes calculators (I have one that runs in Excel that I am happy to share; contact me at drpizzorno@salugencists.com). However, the clinician does not need to make the calculation every time. After using the formula a few times, the needed modifications to decision making become more intuitive.

Let’s look again at that migraine patient. It appears that 41.6% of migraine patients respond to oral magnesium. How do you determine which ones will respond? What evidence is most predictive?

Muscle cramps are a common sign of magnesium

deficiency. The true positive (TP) is 48%. If the patient is experiencing muscle cramps with the migraine, the clinician might then assume that magnesium is very likely to work. However, muscle cramps are common in the general population (27.5%<sup>15</sup>) so the false positive (FP) is actually quite high, 25%. Therefore, the predictive value using the Bayes formula is that we’ve only increased the true confidence in magnesium being useful for the patient from 41.6% to 62%. This is still not very good, considering the potential for side effects.

Consider, instead, mitral valve prolapse as an indication of magnesium deficiency. Its TP is only 14%, which on the surface seems less compelling than muscle cramps. However, its prevalence in the population is low (4%<sup>16</sup>) so its FP is also low, only 3%. Therefore its predictive value is significantly higher—using the Bayes calculation, our confidence is now 80%—much more compelling! In addition, the incidence of an adverse reaction is now much less because we are now unlikely to be giving magnesium to a patient who does not need it.

This comparison is useful because we can see clearly that 1 piece of evidence appears on the surface to be more useful since it has high sensitivity, but it is actually much less useful than lower sensitivity evidence that has a much lower false positive.

The simple rule: If the prevalence in the general population of a piece of evidence (a symptom or other finding) is high, even though it may be highly associated, its predictive value is actually weak. Therefore, before the clinician can confidently make a recommendation, the right kind of evidence, i.e., that with a high ratio of TP to FP, needs to be gathered (eg, discovering whether the patient suffers a prodromal aura, measuring magnesium levels, and so forth).

The Bayesian calculations required for accurate inferential information highlight a vulnerability in the human thinking process that is relevant to functional medicine: using only the true positive and ignoring the false positive when making complex decisions in an area of high uncertainty skews the decision making. Stated differently, failing to consider the population prevalence of the evidence and the intervention leads to false confidence on the part of the clinician.

### SUMMARY

Uncertainty is a fact of life in health care. It arises from many sources: incomplete or inaccurate patient data; evidence that is not as good as we would like; and making inaccurate inferences from the evidence and data. Lack of awareness about this uncertainty principle leads to excessive confidence in our conclusions. Erroneously believing we have made a good decision results in stopping the evidence-gathering process prematurely. The clinical impact, then, is greater frequency of ineffective therapies and increased risk of ADRs.

What can clinicians do? There are 3 relatively straightforward steps that all healthcare practitioners can take:

1. Improve the quality of the evidence we use (the

evidence to be considered ranges from more accurate eliciting of patient data to better understanding of underlying physiology and biochemistry, the influence of environment on gene expression, and the effectiveness of assessment tools and therapeutic strategies).

2. Understand the true predictive value of evidence by considering not only the true positive but also the critical false positive, ie, become more aware of the population prevalence of the evidence and data we use and learn how to calculate their effect upon certainty.
3. Continue evidence gathering (especially evidence with a high true-positive to false-positive ratio) until the level of certainty supports a reasonable level of confidence in the efficacy and safety of the intervention. Removing overassessment of accuracy from clinical decision making helps us prioritize where additional information has to be gathered so that we can provide the best possible care for our patients.

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