

Opinion Paper

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The approach to a diagnostic dilemma

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Abstract: Diagnostic dilemmas refer to situations in which physicians face a challenging clinical scenario. The goal of our paper is to outline strategies which we have found to be most helpful in the approach to a diagnostic dilemma. We review each strategy and provide illustrative clinical examples. Among the most helpful strategies are performing a thorough history and physical examination (H&P) (including pertinent epidemiological factors and careful medication review), avoidance of non-specific testing and empiric treatment, judicious use of consultants, maintaining an open-mind and humility and ongoing, open communication with your patient.

Keywords: diagnostic dilemma; diagnostic error; diagnostic strategies; history and physical examination.

Introduction

Most physicians have faced diagnostic challenges in medicine, and many have faced very difficult ones. “Dilemma” is defined as “any difficult or persistent problem” [1]. In the practice of medicine, it refers to the clinical presentation of a particular patient during which the accurate and correct diagnosis is difficult to make.

Collectively, we have had the opportunity to be taught and mentored by several master teachers and clinicians, to practice general internal medicine for almost 60 years and to be involved in undergraduate medical education for over 35 years. We discuss the approach to a diagnostic dilemma that we have found to be the most effective.

When faced with a diagnostic dilemma, in addition to the strategies mentioned below, we did not hesitate to call one of our previous mentors for thoughts and guidance.

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One particular mentor would jokingly claim that most diagnostic dilemmas would lead to the diagnosis of vasculitis, and he was often correct.

Many of the diagnostic strategies discussed below should be followed routinely, including a thorough history and physical examination (H&P), creation of a problem list, review of all medications, open communication with patients and being open-minded and humble.

For each of the strategies listed in Table 1, we discuss the steps we recommend be followed when faced with a diagnostic dilemma.

Perform a complete history and physical examination (H&P)

A complete H&P is the first (and often most important) part of the evaluation of a patient presenting with any complaint. The components of a complete history include all aspects of the present illness, past medical history, social history (including smoking habits, alcohol use, drug use – past and present, occupation, sexual history), pertinent family history and complete review of systems. The latter involves multiple questions covering many body “systems” to be sure nothing is overlooked. A complete physical examination includes all parts of the body, including a thorough examination of the skin, neurological examination, examination of the breasts, thyroid, rectal exam and in women a pelvic (and rectal) examination. Why the emphasis on the term “complete?” Unfortunately, despite being taught to perform a complete H&P in medical school, as students move into residency and then independent practice, both the history and physical exam often become “victims” of time constraints, specialty bias and other factors leading to items not being covered. The social history is often not fully explored, missing a critical detail such as recent travel to an area of endemic illness, a recent fad diet or an occupational or recreational exposure. Schiff and his co-authors found that aspects of history taking and physical examination contribute to 20% of missed or delayed diagnoses [3]. Verghese et al. identified several commonly omitted aspects of the physical examination such as the rectal exam, examination of the skin,

Table 1: Recommended strategies to be followed when faced with a diagnostic dilemma.

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1. Perform a complete history and physical examination
 2. Create a comprehensive problem list
 3. Consider the epidemiologic clues [2]
 4. Carefully review all medications, including complementary and alternative medications
 5. Consider somatic manifestations of an underlying psychiatric disorder
 6. Focus on the patient's symptoms and signs rather than on incidental findings that may not be significant. "Keep your eye on the ball."
 7. Avoid over-testing and using non-specific tests (including tumor markers)
 8. Avoid empiric treatment
 9. Follow your patient closely and consider repeating portions of the history, physical exam, lab testing and imaging
 10. Judiciously use consultants, and directly communicate with your consultants. Be humble
 11. Openly communicate with your patient. Ask the patient what she thinks it may be
 12. Consider paraneoplastic syndromes, HIV, TB, lymphoma, renal cell carcinoma, atypical thyrotoxicosis, adrenal insufficiency, vasculitis and unusual infectious diseases
 13. Look for subtle clues
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evaluation for the presence of a hernia and genital exam [4]. Each of these components of the exam, if omitted, can lead to diagnostic problems. In our experience, additional parts of the exam often either not performed or performed incompletely include the neurological exam, fundoscopic exam, breast exam, pelvic exam and examination for lymphadenopathy. Barriers to performing parts of the physical examination include insufficient time, lack of an available chaperone, anticipated resistance on the part of the patient and lack of confidence on the part of the examiner. Strategies should be developed to overcome these barriers as it is clear that physical examination inadequacies are a preventable source of medical error, and adverse events can be caused by failure to perform the relevant examination [4].

Create a comprehensive problem list

The problem list should be comprehensive and include both active and inactive problems. Active problems include the reason(s) a patient is seeking care, "positive" findings on the H&P and abnormal laboratory and radiologic findings and results from any other testing. Inactive problems may include things such as a previous history of smoking, previous history of drug use, previous surgery and previous medical problems (seemingly, but not always, unrelated to the current problem at hand).

Creation of a problem list as well as ongoing review and modification of the list (adding new problems as they arise, indicating that a problem is no longer active) is a crucial part of the approach to a diagnostic dilemma. In reviewing the list, physicians are often able to "cluster" a number of problems in forming a hypothesis of a possible/likely diagnosis. In 1968, Weed noted that a problem list

"is not static in its composition...and can be updated at any time. Separate problems all found to be part of the same entity or diagnosis may be combined" [5]. An example of this would be a patient with a problem list that includes palpitations, nervousness, weight loss, tremor and increased heart rate leading a physician to "cluster" these and consider hyperthyroidism. These problems would also fit an "illness script" which describes the thinking a physician has when encountering a patient with symptoms and signs typical of a particular clinical condition [6].

Diagnostic dilemmas may not fit a typical "illness script" and may not be apparent to a physician when attempting to "cluster". This could be due to a number of factors: an unusual disease, an unusual presentation of a common disease, a disease that a physician has never seen or not seen in the recent past, a physician's failure to recognize heuristics or an incomplete problem list. One of us had the experience of caring for a 91-year-old man with recurrent lower gastrointestinal (GI) bleeding. His eventual diagnosis of a bleeding Meckel Diverticulum was not made until surgery, a delay likely contributed to by the failure to consider this diagnosis in an elderly individual, thereby not fitting a typical "illness script" [7].

Consider the epidemiologic clues

Important clues to solving a diagnostic dilemma often come from a thorough evaluation of the epidemiology involved. This includes where the patient lives, whether the patient has traveled recently (or even travel that is not recent), time of year, age of the patient, pets at home or exposure to animals in other settings (petting zoos, ocean or freshwater swimming) and many more [2].

A patient presenting with fever, chills, headache and muscle aches may have influenza but if the same symptoms occur after a patient has had environmental exposure to an unusual organism, an alternative diagnosis should be considered. A highway patrol officer presented several years ago to our practice with fever, chills and headache. His initial evaluation did not lead to the diagnosis, but after further epidemiological information was uncovered (exposure to a canal where rodents are present), a diagnosis of leptospirosis was made. This is a potentially life-threatening infection, but treatable once diagnosed.

In the summer of 2003, there were a number of patients in South Florida diagnosed with malaria although none of them had traveled to regions of the world where malaria is prevalent. A combination of astute physicians and the skills of the public health department contributed to this discovery and the presumed epidemiologic factor was an infected mosquito (or mosquitos) that had survived a trip in luggage from outside the US, and subsequently bitten these individuals.

Carefully review all medications, including complementary and alternative medications

Medical students are taught to always take a careful history regarding all prescribed and over-the-counter (OTC) medications a patient is taking. Prescribed drugs may cause illness directly or may lead to expected clinical signs being absent (an example being the absence of tachycardia in a patient taking a β -blocker) [8]. However, students and physicians often fail to ask and patients frequently fail to mention medications that are considered complementary or alternative medications. The reason(s) for this is not always clear. Complementary or alternative medications frequently have many different components, many of which have the potential to cause illness.

A woman in her 60s was admitted to our service years ago with unexplained severe, acute liver disease. She did not drink alcohol or have evidence of viral hepatitis. Other potential causes of her condition were considered but not found until one of her grown daughters brought in all of the complementary medications her mother had been taking. Amongst them was Jamaican bush tea which contained a potential hepatotoxic herb. There was a delay in her diagnosis because this exposure was not initially considered.

Another case proves the importance of a very careful investigation of a patient's medications. A patient with a history of coronary artery disease and hypothyroidism

presented with a pattern of unstable angina. He was admitted to the hospital and after stabilization, underwent coronary catheterization (a procedure he had also had several years prior). The results looked identical to the prior catheterization and the reason for his chest pain remained unclear. Prior to his discharge from the hospital, a careful review of his medications revealed that about 1 month prior to his admission, he had refilled his thyroid medication and had been inadvertently given a much stronger (higher) dose. The patient was in his 70s with impaired vision and had not noticed the color difference of the pills. Once the correct dosage was restarted, his symptoms resolved.

Patients at times take medication that was not prescribed for them with the hope of a potential beneficial effect such as weight loss or increased energy. These medications may include L-thyroxine, diuretics or laxatives. Many patients do not disclose this to the physician, and both the existence of these syndromes and clues to their presence must be sought. Clues may include an abnormally increased heart rate (when taking thyroid medication) or unexplained hypokalemia when taking a diuretic or laxative. Appropriate lab studies should be undertaken if one is suspicious of a factitious syndrome. Measurement of thyroid-stimulating hormone (TSH), free thyroxine (T-4) and free triiodothyronine (T-3) (in the case of factitious thyrotoxicosis), urinary potassium (in surreptitious use of diuretics) and evaluation for the actual drug (in urine or blood) in cases of diuretic or laxative use should be performed.

Physicians should also consider recently stopped medications with long half-lives that may continue to exhibit adverse effects such as amiodarone [8].

Consider somatic manifestations of an underlying psychiatric disorder

Psychiatric disorders are frequently accompanied by somatic symptoms. Not infrequently, these symptoms are the reason a patient seeks attention from a physician. Common complaints in this situation include excessive fatigue, difficulty sleeping, headache, generalized aching and abdominal pain. However, other symptoms may predominate including itching, chest pain, dizziness, diarrhea or constipation and many others. Physicians must consider an underlying psychiatric condition as the etiology of a patient's complaint(s), whether the condition is already known to exist or not.

In general, it is not a good idea to assume that a patient's complaint is as a result of a psychiatric condition.

Physicians have the responsibility to be both thorough in every patient encounter and also to not “jump too quickly” to assume a relationship exists. Every patient with a psychiatric or psychological condition may (and usually does) at some point have a co-existing non-psychiatric illness. It is often helpful to obtain non-specific laboratory tests such as an erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) to help distinguish between somatic or functional complaints (these tests would typically be normal) and complaints that are part of a systemic disease (these tests are frequently abnormal).

Physicians’ self-awareness of their emotional response to a patient may help prevent diagnostic errors [9]. Many physicians have seen patients who were thought to be “drug-seekers”, and a physician’s initial emotional response to such a patient may be negative. However, even if there may be a component of drug-seeking behavior, the same patient may have a clinical condition that requires immediate recognition and treatment. Being in the moment with both one’s own initial response as a physician and the patient’s symptoms helps to maintain the objectivity that every patient deserves.

A case that highlights the importance of this was a young woman who was seen in the emergency room with abdominal pain. She had been diagnosed with Crohn Disease several years prior and had been coming to the emergency room on an almost weekly basis with abdominal pain. Each time, her evaluation had not shown evidence of any exacerbation of her disease or other pathology. She was felt to be displaying drug-seeking behavior and on a return visit to the emergency room, the physician did not fully evaluate her and decided to simply admit her to the floor team. She was not examined for several hours until a nurse found her unresponsive, and she was ultimately found to have suffered a bowel perforation.

Focus on the patient’s symptoms and signs rather than on incidental findings that may not be significant. “Keep your eye on the ball.”

With increasingly advanced technology accompanied by highly sensitive laboratory and radiologic testing, it is easy for physicians to take their “eye off the ball”. In clinical medicine, this refers to taking the focus off of a patient’s chief complaint(s) and instead focusing on a finding (often unexpected) from a diagnostic test performed. In radiologic terms, these “incidentalomas” are very frequently

unrelated to a patient’s current presentation, and most often of little to no consequence. However, when such incidental findings are reported, the treating physician may feel the need to address them at that time instead of maintaining the focus on the patient’s complaint.

Physicians must be both mindful of this tendency yet also carefully document the finding so it may be addressed at the appropriate time. Discuss this with the patient and carefully explain the reason for maintaining one’s focus on the current symptoms in order to make an accurate and timely diagnosis. At the same time, do not underestimate a patient’s likely concern about a new, incidental finding, and communicate openly about the option to evaluate this in the future. An incidental finding may at times be very significant and require immediate attention. An example may be the radiologic finding of a previously undetected abdominal aortic aneurysm of a size requiring urgent intervention. In this context, it is important to be mindful of hindsight bias. Dhaliwal describes hindsight bias as “...to judge the quality of the decision-making process by the result rather than the logic” [10]. For example, if a physician orders a test based on a few clues, she may be considered an expert diagnostician. If her diagnosis is wrong, she may be considered to have fallen prey to the cognitive error of “premature closure” [10].

Avoid over-testing and using non-specific tests (including tumor markers)

In the clinical evaluation of a patient with a diagnostic dilemma, a physician has at his or her disposal numerous choices, including laboratory tests, radiologic tests and even interventional procedures. Depending on the situation and the acuity of the illness, many of these tests may be appropriate. However, it is advisable for physicians to seek to utilize those tests and procedures that have the highest sensitivity and specificity for the diagnosis considered and are most likely to affect one’s management of the patient. Very non-specific tests, if “positive”, frequently lead to confusion, an incorrect diagnosis and associated anxiety on the part of the patient [e.g. a positive antinuclear antibody (ANA)].

When considering the possibility of an underlying malignancy as the cause of a patient’s complaint(s), the ordering of non-focused tumor markers and non-focused radiologic procedures, although sometimes helpful, is often non-diagnostic and confusing. Typically, serologic tumor markers have their highest utility when used to

follow a patient's clinical course after a specific diagnosis of malignancy is made, rather than as a potential clue to the presence of a yet to be diagnosed malignancy. A patient's anxiety caused by an abnormal test should never be underestimated, and despite reassurance, may never be assuaged. The radiologic analogy to the unfocused use of tumor markers is the "pan-computed tomography (CT)" approach of ordering extensive imaging for a patient in the search for a diagnosis. Sometimes this is helpful, but often it leads to "incidentalomas" being identified with the associated anxiety and need for further testing to help clarify.

Avoid empiric treatment

Empiric treatment is utilized appropriately in many clinical conditions. If a patient is suspected of being bacteremic or having another serious or potentially life-threatening infection, empiric antibiotics are indicated. Non-infectious clinical conditions may also justify empiric treatment. An example of the latter is a patient presenting with visual symptoms suspected of having giant cell arteritis, a condition for which corticosteroids should be promptly administered before a definitive diagnosis is established.

However, in non-life-threatening situations when the diagnosis is not established, empiric treatment is usually best avoided. Empiric treatment may lead to adverse effects, including symptoms and signs that may interfere with the ability to make an accurate diagnosis. Empiric treatment may mask symptoms or signs of the underlying disease, and may delay a definitive diagnosis. Dealing with uncertainty is difficult for both the patient and the physician, but is very common in the practice of medicine. Open, honest communication with the patient is very important throughout the process of dealing with a diagnostic dilemma, including the reasons why empiric treatment may be inadvisable.

Follow your patient closely and consider repeating portions of the history, physical exam, lab testing and imaging

Whether the patient is an inpatient or outpatient, a diagnostic dilemma is associated with numerous encounters between patient and physician. This may be daily (or more frequently) visits in the hospital, or frequent office visits.

On each occasion, previous findings from the H&P should be reviewed and certain aspects should be repeated. It is critical to ask the patient if previous symptoms are still present and if so whether they have changed in any way. New symptoms should be sought and if present, discussed at length. At a minimum, portions of the physical examination should be repeated, based on the clinical situation. Examples of the latter include careful re-examination of the skin for rashes or lesions in a patient with a febrile illness and re-auscultation of the heart in a patient at risk for infective endocarditis.

Close follow-up allows for the discussion of options for additional (or repeat) laboratory or other diagnostic studies. Non-specific laboratory tests, including ESR and/or CRP may be useful in the diagnostic evaluation. If any of these had already been performed, a repeat test could be valuable in a number of ways. If the result had initially been normal and is still normal, it could be reassuring. If initially normal, and now elevated, it could be a clue to an active process (inflammatory, infectious or other). If initially elevated, and now lower (improved), it could be evidence of a resolving process. Every physician has had experiences when patients improve without a specific diagnosis having been made, and although this may be intellectually difficult to accept, what matters most is the patient's illness has improved or resolved.

Keeping in mind the lack of sensitivity and specificity of an elevated ESR or CRP is very important, however. An elevated ESR does not always mean active disease, and a normal or improving ESR does not always indicate the absence of active disease.

Judiciously use consultants, and directly communicate with your consultants. Be humble

Consultants may be invaluable in the evaluation of a patient with a diagnostic dilemma, but how consultants are used and the communication with the consultants deserve further elucidation. One should carefully consider each clinical situation and decide which area of consultation (specialty) is most important and likely to be most helpful. Ideally, the referring physician should communicate directly with the consultant both to provide pertinent information and to specifically request what the consultant is being asked to address. The referring physician should ask each consultant to contact him to discuss his findings, thoughts and recommendations. It is critical that one individual (most often the patient's primary care

physician) coordinates the overall care of the patient and to be aware of all recommended tests and results.

Consultation could involve a physician of the same specialty or a different specialty. Resources to consider include online diagnostic platforms that are freely accessible to physicians to crowdsource the thoughts of an online physician community (<https://www.humandx.org/>).

Patients could also be referred to centers that deal specifically with rare, undiagnosed diseases such as the Undiagnosed Disease Network funded by the National Institutes of Health (<https://undiagnosed.hms.harvard.edu/about-us/>).

Maintaining one's humility as a physician is critical. Discuss with your patient that no single physician will always be right or able to make a correct diagnosis in every circumstance, and that seeking a second opinion or consultation will potentially benefit both the patient (most importantly) and the physician. If the suggestion for a consultation or second opinion originates with the patient, the physician should endorse it and assist the patient in successfully achieving it. The physician should make it clear to the patient that he or she will provide all relevant information to whomever the patient is going to see, and will continue to see the patient going forward. Working together as a team (the patient, family and all physicians involved in a patient's care) improves the likelihood of both an accurate diagnosis and shared-decision making regarding the options of treatment.

Openly communicate with your patient. Ask the patient what (s)he thinks it may be

As mentioned above, open, honest and ongoing communication with your patient is very important. A diagnostic dilemma is not only difficult for a physician, but very stressful for the patient. Anxiety about diagnostic possibilities can be extremely high, often including malignant causes. It is not easy for patients or physicians to deal with uncertainty and the often lengthy time it takes to make an accurate diagnosis, but ongoing and open communication helps immeasurably. Having the humility to admit one's uncertainty yet still demonstrating one's commitment to the patient are strong aspects of the patient-physician relationship in such situations.

A strategy that may prove helpful, often unexpectedly, is to ask the patient what he or she thinks may be responsible for their illness [11]. The patient may turn

out to be right or, at the least, may provide clues that had been previously overlooked. Opportunities to consider or re-consider stressful life events, complementary/alternative medications, adverse effects from prescribed medications and other factors should be sought during these conversations.

Consider paraneoplastic syndromes, HIV, TB, lymphoma, renal cell carcinoma, atypical thyrotoxicosis, adrenal insufficiency, vasculitis and unusual infectious diseases

Early in our training, one of our attending physicians told us that when dealing with a diagnostic dilemma, always consider one of three diagnoses (if not already considered). At that time, these three diagnoses were tuberculosis (TB), syphilis and lymphoma. Over the ensuing years, HIV and its associated opportunistic infections replaced syphilis. The reason for this sage advice is that these diseases may clinically present in many different, and at times, confusing or atypical ways. However, there are many other conditions that can do the same thing.

Paraneoplastic syndromes are disorders that accompany benign or malignant tumors but are not directly related to mass effect or invasion of structures. The clinical manifestations are typically the result of the secretion by the tumor of cytokines or other products. This often leads to a diagnostic dilemma because the clinical manifestations exhibited by the patient are not from the direct effects of the tumor. A common example of this is renal cell carcinoma, commonly referred to as "the internist's tumor". The latter phrase is relevant because it is not uncommon for a patient with previously undiagnosed renal cell carcinoma to present with symptoms or findings that do not seem related to the tumor. These include the finding of an elevated serum calcium level (or symptoms secondary to hypercalcemia), fever of unknown origin or the finding of an elevated hemoglobin level. The typical presentation of flank pain, hematuria and a palpable mass may not be present. Renal cell carcinoma is not the only malignancy that may present with paraneoplastic manifestations. Others in this category include hepatocellular carcinoma (hypercalcemia), lung cancer [hypercalcemia, ectopic adrenocorticotrophic hormone (ACTH) syndrome, the syndrome of inappropriate secretion of

anti-diuretic hormone (SIADH), Lambert-Eaton syndrome], GI tract malignancies (nephrotic syndrome secondary to membranous glomerular disease) and lymphoma (hypercalcemia, fever of unknown origin). An unprovoked documented venous or arterial thrombosis (as part of an acquired hypercoagulable state) may be a clue to an underlying malignancy, especially in patients over the age of 50. A heightened awareness of possible underlying malignancy is an important strategy for a physician dealing with a diagnostic dilemma.

As mentioned earlier, infectious diseases may be very difficult to accurately diagnose. Careful attention to potential risk factors for unusual infections, including opportunistic infections, should apply. The acute retroviral syndrome may mimic many other common viral infections, and should not be overlooked. Careful history of possible exposure to HIV is an important clue. Known HIV infection should lead to an assessment of a patient's degree of immunosuppression in order to help determine to which opportunistic infections a patient is most susceptible. Infective endocarditis may be difficult to diagnose with certainty, especially if either a patient has received antibiotics prior to appropriate cultures having been performed or the infection is caused by an unusual and difficult to isolate in culture type of organism.

Certain endocrine diseases may be responsible for a diagnostic dilemma. Adrenal insufficiency may present with vague, non-specific symptoms including fever, fatigue and weight loss, and may not initially be considered by a physician. Hyperthyroidism, especially in the elderly population, may present in an atypical manner. "Apathetic thyrotoxicosis" refers to the presentation of excess thyroid hormone in an older patient who clinically demonstrates findings that may appear opposite of what one may see in a younger patient. The elderly may look "apathetic", be excessively fatigued and not have the more common symptoms or signs of hyperthyroidism. Almost invariably, however, such patients will have either sinus tachycardia or atrial fibrillation as consistent findings. Adrenal insufficiency and hyperthyroidism are both relatively straightforward to accurately diagnose once considered, and both are treatable with often very gratifying outcomes for both patient and physician.

Vasculitis may be very difficult to accurately diagnose. Traditional teaching is that when a patient presents with symptoms and signs that indicate involvement of more than one organ system, systemic vasculitis should be considered. Important in this category is the presence of a skin rash that may indicate the presence of a syndrome associated with small-vessel vasculitis.

Look for subtle clues

Physicians benefit their patients by being very attentive to all details of their case. Subtle clues may be present in a diagnostic dilemma, the significance of which may not be initially apparent. The value of an active and constantly updated problem list cannot be overstated. Findings that may at first seem unrelated and possibly unimportant in the approach to an accurate diagnosis may in fact be relevant clues. Examples of this include the finding of microscopic hematuria on a routine urinalysis, a mildly elevated alkaline phosphatase or creatine kinase on testing or the finding of otherwise unexplained thrombocytosis. Any of these abnormalities, in isolation, may not be clinically significant but, at the very least, deserve to be repeated. If persistent, appropriate further evaluation is usually indicated.

Whenever possible, obtaining a patient's previous records should be undertaken. This allows the physician to compare current laboratory and radiologic findings with previous ones, and may also provide other valuable information. The latter could include prescribed medications of which the physician was not aware and details of any previous hospitalizations and consultations.

Summary

Diagnostic dilemmas can be among the most challenging situations facing practicing physicians. Being thorough, being attentive to details and clues, maintaining an open mind, providing ongoing open, honest communication with your patient and maintaining one's humility are critical strategies in the approach to a patient with a diagnostic dilemma. In addition, we have hopefully provided an organized outline in this article for physicians to utilize. Dealing with uncertainty, although difficult, is a reality in clinical medicine. By considering the strategies outlined above, physicians may approach these challenging situations in a thoughtful and hopefully, successful manner.

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