Mini Review

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Controversies in diagnosis: contemporary debates in the diagnostic safety literature

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Abstract: Since the 2015 publication of the National Academy of Medicine's (NAM) *Improving Diagnosis in Health Care* (Improving Diagnosis in Health Care. In: Balogh EP, Miller BT, Ball JR, editors. Improving Diagnosis in Health Care. Washington (DC): National Academies Press, 2015.), literature in diagnostic safety has grown rapidly. This update was presented at the annual international meeting of the Society to Improve Diagnosis in Medicine (SIDM). We focused our literature search on articles published between 2016 and 2018 using keywords in Pubmed and the Agency for Healthcare Research and Quality (AHRQ)'s Patient Safety Network's running bibliography of diagnostic error literature (Diagnostic Errors Patient Safety Network: Agency for Healthcare Research and Quality; Available from: https://psnet.ahrq.gov/search?topic=Diagnostic-Errors&f_topicIDs=407). Three key topics emerged from our review of recent abstracts in diagnostic safety. First, definitions of diagnostic error and related concepts are evolving since the NAM's report. Second, medical educators are grappling with new approaches to teaching clinical reasoning and diagnosis. Finally, the potential of artificial intelligence (AI) to advance diagnostic excellence is coming to fruition. Here we present contemporary debates around these three topics in a pro/con format.

Keywords: artificial intelligence; clinical reasoning; diagnostic error; machine learning; management reasoning; overdiagnosis; patient safety.

Position 1 – The 2015 National Academy of Medicine definition of diagnostic error [1] best serves clinicians and patients

PRO

In 2015, the National Academy of Medicine (NAM) defined diagnostic error as a “failure to (a) establish an accurate and timely explanation of the patient's health problem(s) or (b) communicate that explanation to the patient” [1]. In the process of developing this definition, the NAM substantially advanced our conception of “diagnostic errors” from the limited scope conveyed in *To Err is Human* [2] and the clinician-oriented definitions popularized in the early 21st century [3, 4]. While earlier definitions situated diagnostic error within healthcare systems [2, 4], the NAM advanced a definition that accounts for how teams and their ecosystems influence the diagnostic process (Figure 1). In addition, the NAM model seemingly reconciled debates about which diagnostic errors really matter [5] and whether processes of arriving at a diagnosis – i.e. the “workup” – or disease labels – i.e. what medical terms we use to codify the patient's symptoms and signs – are of higher importance [6]. The NAM definition also accounted for two increasingly appreciated aspects of the diagnostic process: uncertainty and patient-centeredness.

Moving away from narrow, black-and-white concepts like “delayed diagnosis” and “misdiagnosis”, the first clause of the NAM definition appreciates the nuance and challenge of diagnostic uncertainty [7, 8]. Often, an unconfirmed hypothesis is a clinician's most accurate *explanation* for a patient's symptoms. Under the NAM approach, these uncertainties do not represent

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Figure 1: The diagnostic process, adapted from the NAM model [1].

unsettling failures, but rather byproducts of the iterative nature of the diagnostic process (Figure 1) [1]. Prioritizing *explanations* over diagnostic certainties might not only improve diagnostic decision making but could also reduce provider burnout and engender higher trust with patients [7, 9, 10].

The NAM definition and model also reinforce the importance of teamwork in the diagnostic process, an imperative given the complexity of the healthcare system. More importantly, the NAM definition includes the patient on the diagnostic team [1]. Arguably, because of the NAM's model, diagnostic teamwork and patient-centeredness are gaining more attention than ever before [11]. The NAM definition calls us to move beyond the obvious benefits of interdisciplinary diagnosis, such as improved communication amongst clinicians [12, 13], and it aligns with larger trends in healthcare to incorporate the patient into team-based care [14].

CON

The NAM's definition falls short of the greater goal of improving diagnosis in healthcare. Because the definition of diagnostic error is not risk-adjusted, all errors are treated equally, whether or not they result in permanent morbidity or mortality. In addition, the NAM definition prioritizes eliminating underdiagnosis without recognizing the risks of overdiagnosis. Finally, the NAM's approach does not repudiate flawed diagnostic processes that eventually achieve accurate diagnostic labels despite inflicting

collateral damage, such as excessive testing or complications from inappropriate procedures.

The diagnostic error community has struggled with how to handle diagnostic errors that do not harm patients [15]. Misdiagnoses around benign, self-limited conditions, such as confusing viral bronchitis with bacterial sinusitis, do not substantially impact patient outcomes though they represent diagnostic errors. While these errors may expose other cognitive or procedural failures, they detract attention from the misdiagnoses that are most amenable to practical solutions and most injurious to patients, like a missed epidural abscess or bacterial meningitis [16]. Using the framework of “undesirable diagnostic events” [16], rather than the NAM definition, the diagnostic safety community would focus on readily diagnosable conditions that satisfy the following criteria: (1) The diagnosis has objective, valid reference standards; (2) The diagnosis is prone to error; (3) The diagnosis benefits from timely recognition; and (4) There are measurable, preferred pathways to achieve diagnosis [16]. Table 1 expands upon two commonly missed diagnoses that align with this approach.

Although mentioned in the NAM report, overdiagnosis is not incorporated into the definition of diagnostic error [1]. In its strictest sense, overdiagnosis refers to detection of a disease that would have never caused harm in a patient's lifetime; indolent cancers detected only through screening tests represent a classic example [17]. Related problems include (1) overdetection of irrelevant findings, such as thyroid nodules found on computed tomography (CT) scans ordered for suspected pulmonary

Table 1: Two examples of commonly missed diagnosis that may represent undesirable diagnostic events.

Presenting complaint	Diagnosis	Objective standard	Benefit(s) of early recognition	Preferred pathways to diagnosis
Incidental lung nodule	Lung cancer	Biopsy	Lower stage at diagnosis (if cancer), longer survival	– Dedicated lung imaging (CT) for suspicious nodules – Guidelines for evaluation based on nodule size – Multiple approaches to obtain tissue (biopsy)
Nausea and abdominal pain	MI	High-sensitivity troponin assays, consensus definitions of MI	Lower risk of death and complications including enlarging territory of infarcted myocardium, heart failure, apical thrombus, etc.	– 12-lead ECG – Troponin – ECG and/or cardiac MRI – Coronary angiography

CT, computed tomography; ECG, echocardiography; MI, myocardial infarction; MRI, magnetic resonance imaging.

embolism; (2) expanding disease definitions, such as decreasing thresholds of glycosylated hemoglobin to diagnose diabetes mellitus; and (3) overmedicalization of potentially normal variants, the so-called “disease mongering” that gave rise to entities like testosterone deficiency and restless legs syndrome [17]. Clinicians constantly face the tenuous balance of promptly recognizing and treating disease against the risks of harm from over-testing and overtreatment. Common conditions like sepsis exemplify the importance of maintaining over- and underdiagnosis in equilibrium [18]. When sepsis is under-recognized, more patients succumb to organ dysfunction and death. Yet if every hospitalized patient with hypotension were evaluated and treated for suspected sepsis, resource utilization would skyrocket. In addition, patients would suffer tangible consequences like antibiotic-related side effects and fluid overload. The NAM definition’s focus on reducing underdiagnosis oversimplifies the goals of diagnostic safety.

Highlighting undesirable diagnostic events and overdiagnosis align with larger goals of improving the diagnostic process, which includes cognitive steps by the clinician and clinical activities within the broader system [19]. As both are amenable to continuous process improvement and educational interventions [19], they may be even more relevant than NAM-defined diagnostic errors, even in the absence of overt misdiagnosis. Consider the example of pulmonary embolism. While routinely ordering CT pulmonary angiography for every patient suspected of having a pulmonary embolism would reduce rates of missed diagnosis, such an evaluation carries risks of radiation exposure, false-positives, incidental findings, and high cost. Improved diagnostic processes, such as integrating pulmonary embolism risk prediction calculators into decision support tools, could result in more efficient evaluations and greater cost-effectiveness, thereby promoting homeostasis between over- and underdiagnosis [19].

Position 2 – Medical education in clinical reasoning should address diagnostic and management reasoning as related albeit distinct concepts

PRO

Though an undeniably important part of the diagnostic process, clinical reasoning remains challenging to define [19]. One recent suggestion has been to distinguish between diagnostic reasoning and management reasoning in clinical reasoning pedagogy [20]. Management reasoning has been defined as “the process of making decisions about patient management, including choices about treatment, follow-up visits, further testing, and allocation of resources [20].” It differs from diagnostic reasoning in that management reasoning can have multiple correct answers, is influenced by clinician and patient preferences, requires shared decision-making, is intrinsically dynamic, and is dependent on context. On the contrary, diagnostic reasoning largely involves classifying clinical findings into useful labels, such as syndromes and diseases.

While diagnostic reasoning and management reasoning often occur in parallel, prioritizing the latter confers several advantages to improving trainees’ diagnostic acumen [21]. First, whereas the cognitive processes of arriving at a diagnosis are difficult to deconstruct and measure, the analytical and decision-oriented nature of management reasoning provides more discrete opportunities for education and assessment [20]. Second, management reasoning can play a role in navigating diagnostic uncertainty, a challenging topic to teach learners [7, 22]. When a diagnosis is unclear, educators can still assess

a learner's ability to create a management plan, including judicious ordering of tests, collaborating with other health care providers, and writing accurate documentation [20]. Third, management reasoning entails questions such as whether a diagnosis should even be pursued or what changes in management will come from diagnostic testing. Thus, it aligns with broader efforts to promote high-value care in medical education [23, 24].

Testing and treatment thresholds represent an underutilized approach to teaching management reasoning (Figure 2A) [25]. Though the concept was introduced

nearly 40 years ago, students still have only a “fair” understanding of thresholds, likely due to underemphasis of this concept in medical training [26]. While diagnostic probabilities are encapsulated in any threshold-based management decisions, this approach to management reasoning focuses on practical, situational decision-making that is largely independent of the diagnostic process. Providing a clear structure for management reasoning might include delineating the types of management (e.g. medications, laboratory studies) and parties involved (i.e. patient, clinician, and system). For

Figure 2: The test-treatment threshold approach to clinical decision-making (A) and factors and dimensions that modify thresholds (B) as adapted from Pauker and Kassirer [25].

In Panel A, diagnoses considered unlikely fall below the testing threshold (T_T) and do not merit additional diagnostic evaluation. Diagnoses considered likely enough that the benefits of treatment outweigh the risks of awaiting diagnostic testing are above the treatment threshold (T_{Tx}) and are empirically treated. As shown in Panel B, multiple factors and dimensions of a case may modify these thresholds.

example, deciding to prescribe antibiotics in a patient with an upper respiratory infection might depend on the acuity of illness, the patient preference to take antibiotics, the provider comfort with prescribing antibiotics, and the cost to the system from increasing antimicrobial resistance (Figure 2B).

CON

Although separating these processes may have philosophical underpinnings, the diagnostic process and patient management decisions are inextricably linked for practicing clinicians. Narrowly conceiving of diagnosis as a “means to an end” for proper management [20] or an exercise in disease labeling allows for this artificial separation. This simplistic approach, however, belies the complexity of the diagnosis process. Instead, clinicians often use the diagnostic process as part of a larger, more dynamic mental framework for making sense of clinical data [27]. Again, take the evaluation of a hypotensive patient with suspected sepsis as an example. On initial evaluation, the diagnostic hypothesis of sepsis is rarely certain. As the patient’s illness evolves, the probability of sepsis is refined through management, whether watchful waiting, evaluation for competing alternative diagnoses, or clinical responses to empiric treatments such as fluid loading and antibiotics. As clinicians observe this evolution, they re-evaluate treatment strategies and iteratively reprioritize diagnoses. Ergo, diagnosis and management are fluid, co-dependent processes; diagnostic reasoning is management reasoning.

Creating a false dichotomy threatens advances in both diagnostic excellence and management reasoning. Many prioritized areas in diagnostic safety, such as overdiagnosis, handling uncertainty, and diagnostic stewardship, reflect the codependence of diagnosis and management. For example, overdiagnosis occurs when a legitimate medical condition that would have not caused symptoms or harm is discovered through aggressive case finding [28]. As discussed, overdiagnosis takes many forms, but all examples cited earlier, such as early cancer detection or shifting glycated hemoglobin thresholds, reflect the tension of impacting the disease course by diagnosing it earlier against the harms of early detection – i.e. management reasoning. Similarly, the decision to even label a newly discovered disease inherently includes value judgments about potential management. For example, as genome and exome sequencing become commonplace, we will continually face questions about whether variants represent true disease and how to act upon such results [29]. Finally, as diagnostic stewards, clinicians can only justify testing when they understand the therapeutic implications, and therapy is defensible

only when we understand how diagnostic testing informs disease probability. Using the contemporary prototype of diagnostic stewardship *Clostridioides difficile* (*C. diff.*) testing, clinicians should not only consider whether a patient’s clinical syndrome likely represents true colitis before testing but also whether a positive test result would prompt treatment [30].

In other words, clinicians constantly face test-treatment thresholds. Accordingly, clinicians must weigh the reliability of diagnostic tests, the risks of overtesting, and implications of treatment [25]. The false divide between diagnostic reasoning and management reasoning detracts from the broader goals of improving critical thinking. Promising pedagogical approaches, such as teaching relational reasoning, can potentially unify these related topics [31]. Relational reasoning prompts learners to seek meaningful patterns in clinical data, a skillset suited for both diagnosis and treatment. Failing to recognize and teach the inter-related nature of diagnosis and treatment, however, is a threat to both fields.

Position 3 – Artificial intelligence is a distraction, not a panacea. The future of diagnostic medicine rests in human hands

PRO

In recent years, artificial intelligence (AI) has shown promise in automating steps in the diagnostic process. For example, using machine learning, algorithms can flag potential cases of intracranial hemorrhage on CT [32] or identify patients at risk of clinical heart failure based on echocardiographic computations [33]. These advances could expedite care and prioritize cases requiring expert clinician review, thereby revolutionizing how we arrive at diagnoses.

Before debating the utility of AI in diagnostic safety, however, one must understand how the machines actually learn. Generally, two approaches predominate: supervised and unsupervised learning [34]. With supervised learning of diagnoses, the computer is provided with a set of variables which include a clinician’s determination of the diagnosis. Using the example of intracranial hemorrhage, the machine reviews a large number of CT images and links imaging patterns to the diagnoses provided by radiologists. In unsupervised learning, the computer infers groups of similar patients simply by associations of patient variables.

Thus, to participate in the diagnostic process, the computer requires human oversight and quantifiable, discreet variables. Supervised learning excels with a human-derived reference, i.e. the gold standard of an expert clinician's diagnosis. The output of unsupervised learning requires humans to contextualize and interpret associations. Either way, the entire premise of using AI to advance diagnostic excellence hinges on the availability of expert human judgment [34]. Variables used in current machine learning algorithms are based on numerical data or discreet text inputs found in electronic data sets. Thus, algorithms can handle imaging studies, which can be distilled into pixels, voxels, and other discreet quanta, but may not process nuances or irregularities.

Reliance on AI could have other undesirable effects in diagnostic safety. Most saliently, progressive dependence on diagnostic technology can perpetuate “de-skilling”, or the attrition in human skills [35]. Given that AI requires human inputs for optimization, this de-skilling presents an enormous threat to diagnostic accuracy. Arguably, our collective love affair with technology has already created an environment in which we neglect the basic steps in the diagnostic process, such as history-taking or physical examination. These basic failures account for many diagnostic errors in contemporary medicine [36, 37]. Moreover, AI is prone to bias; it lacks the insight to recognize anomalies or to grasp the importance of the non-randomness of missing data [38]. The latter problem can magnify health disparities and could leave out groups who traditionally have poor access to care. An abundance of data from majority ethnic groups or high socioeconomic status patients further risks biasing AI as the computer will learn diagnostic patterns from these over-represented groups.

CON

Homo sapiens have progressed as a species by innovating and adapting to change. We are fortunate to live in an era of immense technological capacity; we have access to large clinical data sets and can use advanced computational methods, namely AI and machine learning, to optimize the diagnostic process. Ignoring these tools in healthcare risks stagnation and would be a disservice to our patients.

AI and human cognition have different strengths, and few believe AI to be a panacea for diagnostic safety. With proper oversight, however, AI can overcome the limitations of human cognition that have become abundantly clear in the information age. A single person or group of persons cannot efficiently collate, internalize, and analyze large – let alone massive – data sets. Using

incredible computing power, machine learning can identify patterns among these data, integrate seemingly disparate data points, and even make sense of healthcare data in novel ways [39]. In other words, machine learning will not only expedite clinicians' abilities to recognize patterns in data for individual patients, but it will likely uncover and define entirely new diagnoses.

The computational power of AI will enhance diagnostic safety in other novel ways. The connectivity and updatability of computer networks give them another edge on human decision-makers who have difficulty keeping current and assimilating new knowledge [40]. As such, AI can rapidly integrate new scientific discoveries in diagnostic algorithms. In addition, AI will advance our understanding of diagnostic errors [41]. Harnessing big data will allow us to view interconnected data points, such as patterns of patient visits or symptom-disease associations [42], which may signal potential delays in diagnosis. In this way, AI will provide another avenue for investigating the magnitude and causes of such errors.

AI itself is a product of human knowledge, and machine learning is a “natural extension [of] traditional statistical approaches” [39]. Similarly, we must view AI in our clinical work and research as expected evolutions in science. As we humans continue to expand our understanding of health and disease, we will work closely alongside AI-guided computers. We will program them, refining their algorithms, and accept or reject their suggestions, giving them the necessary feedback to improve. We must embrace this synergy.

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