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SPECIAL ARTICLE

When a Diagnosis Has No Name: Uncertainty and Opportunity

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Diagnostic uncertainty, commonly encountered in rheumatology and other fields of medicine, is an opportunity: Stakeholders who understand uncertainty's causes and quantitate its effects can reduce uncertainty and can use uncertainty to improve medical practice, science, and administration. To articulate, bring attention to, and offer recommendations for diagnostic uncertainty, the Barbara Volcker Center at the Hospital for Special Surgery sponsored, in April 2021, a virtual international workshop, "When a Diagnosis Has No Name." This paper summarizes the opinions of 72 stakeholders from the fields of medical research, industry, federal regulatory agencies, insurers, hospital management, medical philosophy, public media, health care law, clinical rheumatology, other specialty areas of medicine, and patients. Speakers addressed the effects of diagnostic uncertainty in their fields. The workshop addressed the following six questions: What is a diagnosis? What are the purposes of diagnoses? How do doctors assign diagnoses? What is uncertainty? What are its causes? How does understanding uncertainty offer opportunities to improve all fields of medicine? The workshop's conveners systematically reviewed video recordings of formal presentations, video recordings of open discussion periods, manuscripts, and slide files submitted by the speakers to develop consensus take-home messages, which were as follows: Diagnostic uncertainty causes harm when patients lack access to laboratory test and treatments, do not participate in research studies, are not counted in administrative and public health documents, and suffer humiliation in their interactions with others. Uncertainty offers opportunities, such as quantifying uncertainty, using statistical technologies and automated intelligence to stratify patient groups by level of uncertainty, using a common vocabulary, and considering the effects of time.

INTRODUCTION

Diagnosis names anchor patient care, research, administration, communication, and public policies in all fields of medicine, medical records, and public discourse. Diagnosis names are imperfect binary (present or not) labels listed in a record. There is no standard policy regarding patients whose diagnoses are ambiguous, who may be excluded from consideration or who may be assigned incorrectly. Diagnostic error differs from uncertainty; the former is correctable, whereas the latter is not (1–4). Diagnostic uncertainty is a common problem as nearly half of patients seen in a rheumatologic autoimmune disease clinic have uncertain diagnoses (5).

A common reason for uncertainty is that patients fail to fulfill classification criteria, which are often wrongly used for diagnosis, because they have too few objective abnormalities (for example, "pre-lupus"), have overlapping diseases (coexisting systemic lupus erythematosus (SLE) and rheumatoid arthritis, known as "rhupus"), or have diagnoses that change over time (a patient diagnosed as having SLE decades later is reclassified as rheumatoid arthritis or scleroderma).

Clinical management protocols, scientific inquiry, and administration policies apply to patients with named diagnoses, not to those with uncertain diagnoses, who can be denied access to laboratory tests and treatments, are not counted in administrative and public health documents, are excluded from research studies, and suffer ignominious personal interactions.

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On April 27 and 28, 2021, the Barbara Volcker Center at the Hospital for Special Surgery convened a two-day virtual workshop, "When A Diagnosis Has No Name." The goals were to deconstruct the concepts of diagnosis and of uncertainty and to identify opportunities for improvement.

The workshop program (Supplement 1) invited 75 participants (Supplement 2) representing the fields of patient care, medical research, industry, federal regulatory agencies, insurers, hospital management, medical philosophy, public media, law, and patients to answer the following six questions: What is a diagnosis? What are the purposes for which diagnosis names are used? How do doctors assign diagnoses? What is uncertainty? What are uncertainty's causes? How is uncertainty an opportunity to improve all fields of medicine?

To present an overview and to identify take-home points, workshop organizers systematically videotaped the workshop and reviewed additional slides and manuscripts provided by the speakers. The following were consensus themes: diagnostic uncertainty, which hinders patient care and science, can be reduced, and it can be used.

To reduce uncertainty, stakeholders must distinguish between societal purposes of diagnosis names (record-keeping, clinical trials, administration) and biologic purposes (classifying diagnoses by mechanisms). They can adopt consensus vocabularies that qualify diagnosis names with measures of certainty (diagnosis certain, diagnosis uncertain, or diagnosis not present). New biological science can provide molecular explanations for disease mechanisms and discover new diagnoses. Criteria committees must include all stakeholders to standardize diagnosis names among medical specialties. New computer and statistical methods should assist in validating diagnosis names.

To use uncertainty, stakeholders should quantify uncertainty and stratify patients by probability of diagnoses. In all cases, the effects of time on patient phenotype and on scientific knowledge must be considered.

Summaries of the workshop's answers to the questions follow.

WHAT IS A DIAGNOSIS?

Phenotype/biotype. A diagnosis is a binary, time-specific name used to describe health abnormalities. Diagnoses can be defined by phenotype (consistent patterns of symptoms, physical findings, and laboratory tests) or by biotype (specific genotype, biomarker, and other inflammatory profiles). Phenotypic and biotypic definitions rest on different overlapping bases. All stakeholders use diagnosis names; few specify whether the definition of the name is phenotypic or is biotypic, and miscommunication ensues.

Those who favor the phenotypic definition are patients, physicians, clinical researchers, administrators, and policy makers. These stakeholders classify groups of patients in medical records, public policy, and communication; they use phenotypic

diagnoses to justify physicians' and society's responses. Medical philosophers consider diagnoses to represent health care rituals that confer "credibility on the patient's complaints and (justify) health care eligibility, sick role, and a preliminary route to treatments and clinical research" (6). They qualify diagnoses with analyses of societal impact and note disparities in health care delivery.

Stakeholders who favor the biotypic definition are practicing physicians and clinical researchers. The biotypic definitions provide individual patients access to "off label" uses of tests and medications. Biotypic definitions allow consideration of "precision medicine" mechanisms and suggest imaginative intervention options.

Objective/subjective data. Symptoms, clinical signs, laboratory or imaging tests, and environmental exposures all justify the use of a diagnosis name. These elements use subjective/objective data and quantitative/qualitative measures. Depending on the subjective/objective and quantitative/qualitative balance, some diagnoses have high certainty; others have low certainty. Common discourse about diagnoses does not distinguish diagnosis names by levels of certainty.

Classification criteria-based definitions. Clinical researchers, public policy makers, and administrators use classification criteria created by expert committees (sometimes self-appointed, sometimes convened by professional organizations) to define diagnoses.* Most criteria-setting committees use standard consensus-conference measures such as Delphi or 1000 Minds (www.1000minds.com) to select criteria that are evidence based and quality assured for sensitivity and specificity (7). No overview administrative group approves criteria for common use across all fields of medicine. Different medical specialties and national organizations offer criteria that sometimes disagree.

Classification criteria specify clinical and laboratory data, allot quantitative and qualitative points for these data, sum the points, and establish threshold levels that must be met. Classification criteria deny the use of a diagnosis name for patients who do not meet the threshold; they do not suggest alternative diagnoses.

Patients do not meet classification criteria thresholds for the following four reasons: quantification (abnormalities exist but fall below thresholds), qualification (a required element is absent or an exclusionary element is present), concatenation (the sequence and pace of illness presentation falls outside criteria guidelines) (8), and times of onsets that stakeholders choose to apply a diagnosis name.

Regarding times of onset, basic scientists may choose the moment of first noted susceptibility or trigger, for instance, a genetic flaw or an environmental exposure. Clinical investigators may choose the time of the first clinical or laboratory abnormality,

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*The difference between diagnostic criteria and classification criteria is well understood, but in clinical practice, the latter are often considered equivalent to the former.

such as an incidentally found abnormal blood test, clinicians may choose the first symptoms that led to a medical consultation, administrators may choose the first physician visit, and clinical researchers may choose the point at which a patient first meets classification criteria. Each of these times can be biased by a patient's education, geography, access to care, and personal viewpoints about when the illness began (9,10).

The time of onset chosen by stakeholders differs. Stakeholders use the same diagnosis name but describe different populations. Stakeholders who choose a late time, for instance, when the patient first meets criteria, ignore opportunities to understand the origins and possible prevention of an illness.

WHAT ARE THE PURPOSES FOR WHICH DIAGNOSIS NAMES ARE USED?

Societal. The societal purpose for diagnosis names uses exclusionary data to carry out clinical studies and trials, basic mechanism studies, population data acquisition, and communications. It groups patients for research, administration, and public health policies. The societal purpose allows administrators to provide clear protocols and guidelines, lawyers to litigate disputes (11), and payers to restrict access to treatments and reduce fraud.

Biological. The biological purpose for diagnoses uses inclusive definitions. It accepts patients with uncertain diagnoses in studies of illness mechanisms in individuals and allows physicians to intervene, prognosticate, and communicate (12–14). The biological purpose stratifies patients according to environmental, socioeconomic, comorbidities, genetic, and phenotypic contributors to outcome (15–18).

In practice, conversation, and communication—but not in medical records—physicians discuss "pre-diagnosis"; they use biological definitions to access tests, seek "precision medicine" explanations, use medications "off label," and recruit for basic science studies (19,20). No overview committee decides who writes the rules and for what purposes individual stakeholders apply them.

HOW DO DOCTORS ASSIGN DIAGNOSES?

The processes. In medical records, a diagnosis is a retrospectively seen binary event in an illness journey (21). It becomes part of a medical record in the following four steps: A physician evaluates clinical and biomarker phenotypes, hypothesizes a diagnosis, tests the hypothesis by acquiring new information (laboratory test, occurrence of new symptoms), and records a diagnosis name in a medical chart. In the United States, the diagnosis is usually recorded as an International Classification of Diseases (ICD) code.

Ambiguity that may have been present when the record was created is not visible in ICD codes. Instead, ICD-10-CM Official Guidelines for Coding and Reporting FY 2020 confusingly instructs users to use a series of Reporting Options, yes, no, unknown, and clinically undetermined (22). ICD codes may be dishonest when clinicians assign unambiguous codes to improve a patient's access to tests or treatments or when they record unimportant diagnoses to enhance reimbursement.

Computational technologies. New computational technologies—the electronic medical record, artificial intelligence (AI), natural language processing (NLP), phenome-wide association studies, and "precision medicine"—permit after-the-fact revision of charted diagnoses (23,24). "Precision medicine" allows investigators and clinicians to integrate clinical, biological, epidemiological, socioeconomic, geographic, and linguistic data to reassign binary names to diagnoses, even though in real time the diagnoses are analogue, incomplete, inaccurate, or evolving. AI and NLP can quantify uncertainty (25) and stratify patients by probability, sensitivity, and specificity of proposed diagnoses (26–30). Other fields inform the use of AI in health care (31), including the evaluation of inherent biases (32,33).

The number of diagnoses. The number of diagnoses grows exponentially. The first International Classification of Diseases (ICD-1, 1893) listed 44 diagnoses; today's ICD-11 lists 19,000 (34).

UNCERTAINTY AND ITS CAUSES

Ill persons have uncertain diagnoses for five reasons: Patients do not meet qualitative criteria, they do not meet quantitative criteria, they do so too slowly to meet concatenation rules, they are clinically heterogeneous, and stakeholders disagree on the times of onset that permit the use of a diagnosis name.

In the process of assigning diagnosis names, physicians evaluate the following nine domains: symptoms, signs, nonspecific laboratory tests, specific laboratory tests, response to therapy, prevention, biomarkers, biologic mechanisms, and molecular signatures. Some nosologic groups of diagnoses, for instance, trauma, infection, and neoplasm, which are based mostly on objective criteria (biopsy, blood culture), have high certainty. Objective data (positive tissue biopsies) point to diagnoses of high certainty, whereas subjective data (pain) yield diagnoses of low certainty. The nosologic classes of trauma, infection, and genetic abnormalities have high certainty; nosologic classes of dietary deficiencies, neoplastic, and exogenous illnesses have mid-level certainty; and degenerative, immunologic, and psychiatric illnesses have low certainty. Binary ICD-coded diagnoses do not distinguish among diagnoses with high, moderate, or low certainty.

OPPORTUNITIES

Societal definitions of diagnoses ignore patients with pre-, atypical, or evolving phases of illness. Biological definitions consider illness mechanisms and the timeline of the disease.

Conversations that prioritize societal and those that prioritize biological definitions take place in overlapping languages. A Rosetta stone that translates between societal and biological context is required.

Deconstruction of the concept of uncertainty is an opportunity to improve patient care, science, and administration. Table 1 summarizes workshop participants' recommendations, which are as follows.

To reduce uncertainty, stakeholders must agree on vocabularies that indicate the purpose for using a diagnosis name. Policy-setting committees must include all stakeholders. Stakeholders should use new biological and language-processing technologies to modify, at frequent intervals, the priorities of phenotypic and biotypic diagnosis definitions. They should indicate whether the name is binary or analogue and whether or not it is time restricted.

Stakeholders can use uncertainty to stratify patient groups, incorporate measures of time, and change strategies as new information (patients' clinical presentations and/or new scientific facts) accrues.

Deconstructing the concept of uncertainty is an opportunity to include—in private and public discourse, in science, clinical care, policy, and administration—patients who are ignored by binary diagnosis names today.

With inclusive definitions of their diagnoses, all patients may be eligible to enroll in informative studies. Quantifying uncertainty, conceptualizing diagnoses as analogue rather than binary, and using uncertainty to stratify patients will promote more imaginative exploration of the unknown. Clinicians who use broad definitions for diagnoses for patient care and narrow ones for recruitment

for studies, and who understand and communicate the different definitions, can lead the way. Cross-fertilization of all areas of science will then suggest paradigm-shifting possibilities that can improve all aspects of medical care.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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Table 1. Workshop participants offer these consensus recommendations to reduce, and use uncertainty to benefit all fields of medicine

Goal	Consensus recommendations
To reduce uncertainty	• Establish a consensus vocabulary • Distinguish biologic from societal uses of diagnosis names • Use new biologic science to provide molecular explanations for disease mechanisms • Engage all stakeholders in criteria committees • Use new computer and statistical methods to reassign diagnosis names
To use uncertainty	• Include and quantify uncertainty when making decisions • Stratify *individual* patients by probability of diagnoses • Stratify *groups* of patients by probability of diagnoses • Always consider the effects of time in individuals' illness journeys • Always consider the effects of time on changing science

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