In praise of “Our stubborn quest for diagnostic certainty”

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This year marks the 30th anniversary of the publication of the paper “Our stubborn quest for diagnostic certainty. A case of excessive testing” written by Jerome Kassirer, who was at that time director of the New England Journal of Medicine. It’s been over thirty years since the publication, but its contents are still actual. This is because Kassirer was a pioneer or because our way of facing uncertainty and of coping with it did not change?

The article starts with an unquestionable sentence: “Absolut certainty in diagnosis is unattainable, no matter how much information we gather, how many observations we make, or how many tests we perform”. This is still true nowadays and it will be true even in the future when the so-called precision medicine will become a reality. Big data, personalized medicine, telemedicine, artificial intelligence, and medical apps will have the potential to increase information available without nullifying the probability of false test results or of treatments’ efficacy. Dealing with patients, symptoms, diseases and treatments, the question of uncertainty will always remain present. Referring to the classic clinical methodology we perform a test to enhance our confidence in the diagnostic hypothesis, but as Kassirer highlighted, “more tests do not necessarily produce more certainty”. Furthermore, he warned that “the more tests we perform, the higher the risk for the patient”, concluding that we excessively test to reduce our discomfort in uncertainty.

There are several other causes contributing to overtesting: notably, pressure from patients and relatives, dilution of responsibility, the “do-something” bias, expectation bias, easiness of prescribing, defensive medicine, financial incentives, ignorance of test characteristics, desire to feel updated, but also our uneasiness - as human beings - to deal with uncertainty. To cope with our Achilles’ heel, we often overprescribe tests and treatments with the risk of increasing false positive results and iatrogenic harms.

Physicians are rationally aware of uncertainty because the practice of medicine involves “inherent variability in outcomes and unpredictability of patient response (aleatoric uncertainty) and the limitations and imperfection of our knowledge and complexity of risk information reliability, accuracy, and generalizability (epistemic uncertainty)”\(^2\). However, physicians are accustomed to think categorically and they are thus uncomfortable of using probabilistic reasoning. It is well known that risk probabilities have limited applicability at the individual level because each patient either will or will not be affected\(^3\) (the so called “paradox...
of single-event probability”). The acceptance of diagnostic uncertainty is a function of the available therapy and the combination of efficacy and risk. We can tolerate a level of uncertainty for a highly effective treatment with a low side effect occurrence rate, but we need to be more attentive when facing the possibility of a therapy with high risk of side effects. However, the biomedical field entails a culture that reveals an innate unwillingness to acknowledge these issues. We know that individuals often do not decide in a fully reasonable way but using cognitive strategies (simplified cognitive shortcuts, called heuristics), allowing them to overcome the limitations imposed by their imperfect rationality and the difficulties derived from uncertainty.

**Uncertainty in the EBM era**

After 30 years of EBM and thousands of well-conducted clinical trials we are still treading on wide gray areas where the state of evidence is not sufficient to either confirm or refute the benefits of a course of action. For example, we do not know whether to prescribe statins to low risk patients, the efficacy of the screening of hepatocellular carcinoma in chronic liver disease, the effects of adult weight change on mortality, or whether to suggest direct-to-consumer genetic testing. According to the Clinical Evidence handbook, only half of our daily practice have evidence-based support and most recommendations of international clinical practice guidelines are based on low level evidence or expert opinions. This is due to several problems:

- across the many types of clinical investigations, the randomized controlled trial is the key scientific tool used to measure the efficacy and adverse effects of a diagnostic or therapeutic approach but the strength of scientific evidence is affected by the study protocols: issues with recruitment of patients, sample size, dosage, length of treatment and follow-up, the choice of the comparative, appropriateness of the outcome measures used, controlling of confounders increasing uncertainty and making it more prone to bias or to chance events (internal validity);

- the validity of the study's results are furthermore jeopardized by the high rate of “medical reversals”, when a RCT is overturned by a following RCT or by a comprehensive meta-analysis. According to the study of Prasad of the 363 articles testing standard care 40.2% reversed that practice;

- interpretation of trial result increases the level of uncertainty. For example, a study examining congruence among different meta-analyses found differences among reported findings to be relatively small in comparison to substantial disagreement in the authors' interpretations with regard to clinical applications of the findings;

- generalizability of the data obtained by the RCT is also problematic. Costantino evaluated the characteristics of patients referred to the heart failure outpatient clinic compared with those of patients enrolled in clinical trials on heart failure pharmacological treatment. On average, only 34% of the outpatients would have been included in at least one of the 16 trials published during a 10 year period (external validity). “Extrapolating risks derived from studies examining one duration of treatment to another, from one formulation to another, from a composite endpoint to its components, or from one population to another also introduce ambiguity, as do differences in how the same studies are interpreted.”

Even in the era of EBM, in most clinical cases, we still must decide and prescribe in conditions of uncertainty.

**Uncertainty in the clinical scenario**

Uncertainty is often ignored or suppressed in the physician/patient encounter because physicians feel more confident to assertively propose the utility of a test and the efficacy of a treatment. On the other hand, patients feel less distressed accepting that the prescribed test will solve diagnostic ambiguities and that the prescribed therapy will remove all symptoms. Physicians are conditioned by the expectation bias (when a physician tend to trust in data that are in accord with their own expectation for the outcome and minimize data that appear to be in conflict with those expectations, unconsciously manipulating the information to obtain the acceptance of the treatment by the patient) and by the “do-something” bias (when...
a physician feels uncomfortable in not prescribing anything to a patient complaining of a symptom).

Patients, on the other hand, are conditioned by the "cognitive dissonance" (when someone is psychologically uncomfortable and unable to uphold a contradictory stance between their own beliefs and behaviors). For example, in case of stable angina pectoris, we have several data demonstrating that the highly majority of patients overestimates the impact of coronary angioplasty in reducing mortality and myocardial infarction and have an unrealistic expectation of side effects\textsuperscript{18,19,20,21}. Seventy-five per cent of patients interviewed by Holmboe et al.\textsuperscript{22} believed angioplasty would prevent a future myocardial infarction and 71% would prolong their lives. In the Rothberg et al. investigation\textsuperscript{23} cardiologists beliefs were in accordance with trial results, while 88% of patients believed that angioplasty would reduce the myocardial infarction rate. Why do we observe such judgment discrepancy between patients and physicians regarding to the efficacy of a procedure? Empirical evidence suggests that clinicians rarely communicate uncertainty about evidence to patients: the analysis of 1057 clinical encounters by primary care physicians found that only 1% of time the benefit, compared to the reduction of symptoms, would be canceled after 5 years. The authors observe that, without an explicit statement that the benefits are limited to symptom reduction, patients feel justified to conclude that the opening of a stenotic coronary artery can avoid a heart attack. Furthermore, patients feel obliged to express an even more positive opinion of the treatment, for a kind of gratification towards the doctor\textsuperscript{26} and they fear that asking questions or expressing an antagonistic judgment can label them as ‘difficult’ patients\textsuperscript{27}, that it may irritate the doctor and that it may result in a less valid treatment\textsuperscript{28,29}.

**Communicating uncertainty**

In an era of shared medical decisions, physicians usually think to solve the uneasiness of their own uncertainty in making decisions by informing patients on all the data available from literature and from guidelines with the illusion of helping them to decide in an 'informed' condition. However, the more data they present, the more they charge patients with the responsibility to decide their own destiny. In most circumstance, patients are not able to process data\textsuperscript{30} because they do not have specific conceptual skills, they do not know how to evaluate alternative solutions in probabilistic terms, they are directly and emotionally involved in the consequences of the decisions, and are influenced by their personality traits from their perception of uncertainty. For example, those who are averse to medications might perceive uncertainty about medication risks more negatively than those who are comfortable with prescription medications\textsuperscript{31}. We transfer to patients complex information that have the potential to overwhelm and puzzle them and to paradoxically impair their capability to make truly informed decisions. As a result, in some conditions they might decide not to take the medication because of risk uncertainty (ambiguity aversion) and they feel unsatisfied with their decision\textsuperscript{32}. These conclusions raise ethical concerns because communicating uncertainty may reduce patient well-being and promote refusal of potentially beneficial interventions\textsuperscript{33}. Both patients’ and physicians’ interpretation of and responses to uncertainty may depend on their personal characteristics. Because of patients’ complex cognitive, emotional, and behavioral responses to uncertainty, the focus of risk communication should be on helping them to tolerate and cope with uncertainty rather than simply helping them understand it\textsuperscript{34}.

Communicating scientific uncertainty requires both simplifying and complicating normal scientific discussion but the manner in which uncertainty is communicated can affect how it is perceived and responded to, but little is known about the mechanisms of these framing effects. It is unclear whether the risks and benefits of treatments tradeoffs are best presented verbally, numerically, graphically, or using multiple formats. In the last few years, several decision aids and infographic frames to share predictions with patients and facilitate comparison between treatments have been developed but there
are limited experiences on how different types of visualizations are processed and understood, on how patients feel helped to manage uncertainty, keeping in mind that numeracy of each patient can affect comprehensibility and which is the best method to share comprehensible information. According to Schwarze, “these strategies fail to illuminate logical connections between the patient’s current condition, downstream outcomes, and events experienced along the way”35. Recently, Gigerenzer and Kolpatzik36 discussed the use of smart “fact boxes”, developed by Lisa Schwartz and Steve Woloshin37, that communicate evidence-based information on the benefits and harms of drugs and health screening. The fact box puts patients and physicians in a better position to make informed decisions with information that is easy to read, visualize, and share. “In general, fact boxes report the results from a randomized trial or, if available, a systematic review; provide quantitative, evidence-based information about benefits and harms; use absolute numbers rather than relative risk reductions or other formats that are known to confuse patients and physicians; and may use icon arrays or other graphic displays to help people who have difficulties understanding numbers”.

Conclusions

Thirty years after the pivotal paper written by Kassirer, even after the increasing number of RCTs, we are going to act without knowing the outcome of a diagnostic process or of a therapy given to a specific person. What changed is our awareness of the risks of overprescription. The Choosing Wisely movement38,39,40 launched in 2012 by a medical society (American Board of Internal Medicine Foundation) and a consumer association (Consumer Reports) was aimed to invite scientific societies to identify procedures at risk of inappropriateness and it was intended to encourage conversations with patients about whether a test or treatment would be necessary. Nowadays, the movement expanded to more than 20 countries with the recommendation of not using low value procedures nor to disseminate them among peers.

The admission of uncertainty forms the starting point for a more open conversation between patient and clinician41 because we are likely to raise patients’ confidence in our ability to manage their condition, because they will understand our difficulties to cope with it and we’ll be able to share the consequences of the decision with them. One of the biggest challenges is the authentic disclosure and communication of uncertainty in a meaningful way that enhances trust in the patient-provider relationship and improves decision-making and healthcare outcomes. As Simpkin states: “We believe that a shift toward the acknowledgment and acceptance of uncertainty is essential — for us as physicians, for our patients, and for our health care system as a whole”42.

Competing interests

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

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