Patient Education and Counseling 104 (2021) 2628–2634

Contents lists available at ScienceDirect

Patient Education and Counseling

journal homepage: www.elsevier.com/locate/pec

Patient-centered innovation

Ethics of uncertainty

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ARTICLE INFO

Article history:
Received 7 July 2021
Accepted 12 July 2021

Keywords:
Uncertainty
Ethics
Evidence
Inferences
Decision-making

ABSTRACT

Uncertainty is inherent in clinical medicine. However, just because absolute certainty is unachievable does not mean that rational and optimal decisions cannot be made. It is argued that we need to distinguish legitimate from illegitimate scientific uncertainties that are generated by manufacturing doubts aiming to create mis- and disinformation. The attempt to create doubts implies that actions under uncertainties are impossible. Such a belief ultimately harms public, which requires reasoned actions within a context of genuine scientific and medical uncertainties. The latter indicates that rational decisions, even in the absence of guaranteed absolute certainty, are not only possible but, on average, beneficial both for society and individuals.

1. Introduction

It has generally been accepted that one of the key defining features of clinical medicine relates to uncertainty in all aspects of clinical practice: from diagnostic, prognostic and treatment uncertainty to uncertainty about disease, and uncertainty about eliciting patients' values, preferences and communicating risk [1,2]. There are many of sources of uncertainties, but the most common uncertainty is related to lack of evidence, conflicting evidence, or "information overload" at the point of care i.e., at the time when information is needed most. Other common sources of uncertainties include uncertainty about the application of research data ("group averages") to individual patients and the effect of bias in generating, observing, disseminating, reporting, and interpreting clinical data, and uncertainty due to ambiguity and vagueness related to unclear meanings of terms or words and classification of borderline cases [e.g., is a person with body mass index (BMI) ≥30 obese, while one with BMI = 29.9 is not?] [1,2].

Despite the importance and omnipresence of uncertainties in medicine, physicians are not well trained to understand, tolerate and communicate uncertainties. Ludmerer [3] asserted that the failure to educate physicians about uncertainty was "the greatest deficiency of medical education throughout the twentieth century". Although increasingly introduced training in elementary statistics and evidence-based medicine (EBM) in the curricula of medical schools around the world has increased attention to the role of uncertainty, so far there have been no major improvements in the way lay people and physicians deal with uncertainties.

The COVID19 pandemic that started in early 2020 brought this issue to forefront more than any other preceding event: despite access to massive amounts of reliable information – a volume unprecedented in human history-never have so many citizens avoided sane public health advice [4]. These include ignoring advice to wear face masks and practice physical distancing due either to lack of complete certainty in advice proffered [5,6], or manipulation of legitimate scientific uncertainties [4] by sowing doubt to undermine rational decision-making that literally could have saved innumerable lives [7].

Unfortunately, because absolute certainty of scientific inference is theoretically impossible [8,9], distinguishing legitimate scientific from illegitimate, manipulated uncertainties, is often difficult. Manipulation is a way of creating illegitimate uncertainties - *an appearance of uncertainties that are designed to obfuscate instead of to articulate uncertainty as a clarifying strategy for problem-solving and decision-making* [10]. That is, from a pragmatic point of view, it is useful to distinguish legitimate from illegitimate uncertainties. Even though uncertainty exists on a continuum, the notion of legitimate vs illegitimate uncertainties can be represented as a decision problem where one chooses to emphasize certain aspects of uncertainties that can be categorized as legitimate vs illegitimate even though precise mathematical definition remains impossible. Namely, in a technical, mathematical sense all scientific uncertainties are theoretically "legitimate" and there is no clear-cut

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https://doi.org/10.1016/j.pec.2021.07.025
0738-3991/

technological solution that can help distinguish legitimate from illegitimate scientific uncertainties. However, this distinction becomes conceivable and very useful when we understand how exploitation of extreme uncertainties to accentuate possible but highly improbable events can distort bedside decision-making and public policy. Therefore, a failure to distinguish between legitimate and illegitimate uncertainties has dramatic ethical implications for our actions and their consequences [11].

In what follows, I first give a short summary of the key concepts of uncertainty, after which I provide a brief overview of how we scientifically and cognitively respond to given uncertainties. Throughout, I try to separate between different ways uncertainties have been expressed- scientifically legitimate vs. exploited- and attempt to resolve the tension by stressing that rational decision-making is possible. While this distinction may not always be possible at the level of inferences, rational decisions -at the bedside or policy level- that will result in favorable health outcomes for our patients and public is firmly within the realm of sound evidence-based decision-making [12]. Importantly, there are underlying processes at work that are sufficiently predictable to be generalized as an operating principle within the ethical framework of practice of medicine. Exploitation of illegitimate uncertainties has important ethical and moral implications for the well-being of individual patients and society at large.

2. Definitions, taxonomy and theory of uncertainty

There is no generally accepted definition of uncertainty-there are many meanings of uncertainty [1,2,13]. Nevertheless, most authors define uncertainty in epistemological or statistical terms [1,13]. Epistemic uncertainty refers to the relationship between the unknown and existing knowledge, while statistical uncertainty defines it via quantification of unpredictability and risk, using the language of probability (see Table 1A) [1,13]. Similarly, a number of taxonomy of uncertainties were proposed [1]. Han and colleagues proposed a taxonomy of uncertainty according to its sources (probability, ambiguity, complexity), issues (scientific, practical, personal, which ultimately can be construed as epistemic—related to the incompleteness of one's knowledge) and locus (e.g., patient vs clinician) [2].

In addition, there is no universally agreed-upon theory of uncertainty. Many theories have been proposed [1]. All theories rely on the probability calculus but differ with respect to the notion if the language of probability is sufficient to describe all uncertainties [14]. Here, it is important to note that most contemporary authors consider probability as a measure of "degree of belief" rather than the property of the world [1]. That is, probabilities are states of mind and not states of objects [1]: "The only relevant thing is uncertainty — the extent of our knowledge and ignorance. The actual fact of whether or not the events considered are in some sense *determined*, or known by other people, is of no consequence" wrote a statistician DeFinetti [15]. However, states of mind can be influenced by many factors including emotions and affect giving rise to the notion of understanding the probability as "risk as feeling" [16,17]. In turn, emotions and affect violate analytical rules of probability calculus in a rather predictable manner [18,19], although not necessary always in irrational ways [20,21]. Nevertheless, psychological research during the last several decades has generated a large body of evidence showing that people routinely violate the normative rules of probability calculus and do not (correctly) employ probabilities in their problem solving strategies under conditions of uncertainties [1]. Probability theory, with its modifications from the insights gained from psychological research, has been proposed as the dominant theory of uncertainty in clinical medicine today [1].

Table 1
Uncertainty vs Doubts*.

A) Definitions of Uncertainty*
Definitions of Uncertainty in Relation to Knowledge
1. "The state of being indefinite, indeterminate, unreliable, unknown beyond doubt. Not clearly identified or defined, and/or not constant."
2. "Cognitive state created when an event cannot be adequately defined or categorized due to lack of information."
3. "The inability to determine the meaning of illness-related events" resulting from the ambiguity, complexity, unpredictability of illness, deficiency of information about one's illness and its consequences.
4. "The difference of 'knowing' and the concept of 'being certain' is not of any great importance, except when 'I know' is meant to mean 'I cannot be wrong.'"
5. "The lack of information which quantitatively or qualitatively can describe, prescribe or predict deterministically and numerically a system, its behavior or other characteristics."
Statistical Definitions of Uncertainty
6. "A parameter, associated with the result of a measurement (e.g., calibration or test) that defines the range of values that could reasonably be attributed to the measured quantity. When uncertainty is evaluated and reported in a specified way, it indicates the level of confidence that the value actually lies within the range defined by the uncertainty interval."
7. "Standard deviation of the collection of data samples approximating the measurand, the quantity being measured."
8. "A parameter associated with measurement that characterizes the dispersion of the values that could reasonably be attributed to measurand. The parameter may be a standard deviation or the width of a confidence interval." "Uncertainty represents the range of all determination, while error refers to the difference between an individual result and the true value of measurand."
__*from ref #1 [Djulbegovic B, Hozo I, Greenland S. Uncertainty in Clinical Medicine. In: Gifford F, ed. *Philosophy of Medicine (Handbook of the Philosophy of Science)*. London: Elsevier; 2011:299–356.]
B) Definition of doubts*
To call into question the truth; a feeling of uncertainty about the truth, worry, concern about reality, or nature of something, inclination to create distrust, not to believe or accept research findings by referring to the possibility of events of happening or not happening that remain within a range of legitimate but highly improbable scientific estimates often with the goal to spread misinformation (i.e., false information, regardless of intent to mislead), or disinformation (i.e., to provide deliberately misleading or biased information; manipulated narrative or facts; propaganda.) These uncertainties can be called illegitimate uncertainties (best epitomized with so called "The Sunrise Problem" (see manuscript for details).
__*definition reflects the spirit of Michaels (33–35) "Doubt is Their Product", "Manufactured Uncertainty", and "Triumph of Doubt". That is, definition excludes self-doubt and, honest doubt, but refers to the attempt to generate doubt in others for the purposes of exploitation of uncertainties as discussed in the article. [see also https://www.dictionary.com/browse/disinformation.]

3. Exploitation of scientific uncertainties and its cognitive responses

It is testability that distinguishes pseudo-scientific claims from scientific ones - only propositions that are testable are accepted seriously; others are disregarded [22,23]. (And, eventually only those propositions that pass severe scientific tests are accepted as potentially truthful [22,23]). However, those individuals who put forth pseudo-scientific claims do not necessarily negate the need for testability (and methodological requirements for verification, corroboration, or ideally falsification of the proposed hypotheses). Rather, they imply or claim that because the findings cannot be 100% certain, their alternative propositions are equally valid, or at least remain within a realm of scientific possibilities, regardless of how far-fetched they can be.

The ultimate basis for these claims are rooted in the way we cognitively process information expressed as probabilities, often described with a range of our best estimates of "truth", such as confidence, "cones of uncertainty", or credibility intervals [24]. Many cognitive biases have been described to explain how emotions and the experiential cognitive apparatus affect interpretation of probability [25,26]. Elsewhere, I described how our responses to uncertainties employ analytical, deliberative mechanisms to calibrate risk as required by the probability calculus axioms, but are often distorted when we employ experiential, affect-based cognitive processes [11,19]. For the purposes of this paper, two are particularly relevant:- the so called "possibility effect" and the "certainty effect". The *possibility effect* reflects humans' difficulties in distinguishing cause from the coincidence [27], and inclination to over-weigh small probabilities and under-weigh moderate and large probabilities [28,29]. Thus, a change from impossible to possible has stronger impact than an equal change from mere possible to more possible. The *certainty effect* refers to people's inclination to value a change from a possible to a certain effect much more than an equal change from a merely possible to a more likely one [28–30]. These psychological mechanisms are the basis for our quest for therapeutic and diagnostic certainty [6,31]. They are also at the heart of exploiting legitimate uncertainties, best captured in the *"Sunrise Problem"*: even though, by scientific estimation, the probability that we will see the Sun tomorrow is close to 1, there is no absolute certainty that the sun will rise tomorrow morning [32]. However, just because it is scientifically possible that the sun will not rise tomorrow (i.e., the probability is not 0), it seems irrational that one should doubt the pragmatic scientific estimates that the sun will indeed rise tomorrow with near absolute certainty [32]. Most of us would go on with our lives under assumption that the world will remain as certain tomorrow as it is today. The "Sunrise Problem" vividly illustrates how exploitation of legitimate scientific uncertainties can be used to create illegitimate ones that are for all practical purposes irrelevant to a decision at hand. The fact that scientifically the event is *possible even if highly unlikely* -the probability that Sun will rise tomorrow is less than 1 (it is estimated to be at 0.99990002 [32])–is at the heart of using extreme legitimate uncertainties to generate illegitimate ones.

It is this recognition that scientific methods are fallible and that absolute certainty is impossible [8,9,22] that has led to a manipulation of uncertainties to promote the interests of various parties to create doubt about veracity of scientific claims [33,34]. The strategy which Michaels aptly calls "doubt is their product" [33,35] refers to the inclination to create ambiguity. This, in turn, leads to distrust, fostering lack of willingness to believe or accept research findings, by referring to the possibility of events happening or not happening within a range of legitimate but highly improbable scientific estimates. Michaels seemed to have identified an operating principle at work here- illegitimate uncertainties will be promoted by those who stand to benefit from creating them [33,35]. Table 1B presents a definition of "doubt" as the mechanism of generation of illegitimate uncertainties. The recent examples of sowing doubts about effectiveness of public health measures such as wearing face masks and physical distancing to minimize spread of COVID-19 infections [4,36], as well as the classic example of manipulation of uncertainties raised with respect to harmful effects of tobacco [33,34], are clear examples of the deadly effect of failure to distinguish legitimate scientific uncertainties (summarized with the intent to describe the status of underlying knowledge) from promotion of doubt (to create illegitimate uncertainties with the intent to misinform and disinform the public). The lack of "definitive" scientific proof that masks are effective in prevention of spread of SARS-CoV2 virus or that smoking is harmful to people's health has resulted in the failure to enact the mask-wearing mandates and the postponement of tobacco legislation for decades, with the unfortunate consequences of much avoidable disease and death [33,37,38]. The practice has been increasingly adopted by some pharmaceutical companies as well as the manufacturers of substances that are potentially toxic to our environment and to our health [34,35]. The approach has resulted in the rise of so called "product defense" industry [35], which -by generating doubts in scientific estimates- has successfully squashed the time-honored practice of relying on the "precautionary principle" [39,40] when it comes to regulation of potentially toxic substances in our environment. This questioning of the certainty of our estimates about industry pollutants, or the effects of wearing masks during COVID-19 pandemic, is an example of the so-called "litigation support" specialty [35], or "troll epistemology" - a brazen systematic attack of disinformation designed to confuse people about truths vs falsehood [4] - which, astonishingly, has sometimes even emanated from the very highest level of the former US government [41,42].

4. Optimal outcomes can be achieved without requiring absolute certainties to act: A brief overview of rational decision-making and problem-solving under uncertainty

It has been argued that reasoning in complex environments is essentially probabilistic, fraught with uncertainties [19]. Thus, adaptive evolutionary mechanisms have evolved to effectively deal with ambiguities and uncertainties that surround us both in daily life and clinical medicine. As mentioned earlier, our response to uncertainties is a reflection of both intuitive, affect-based and deliberative, analytically driven cognitive processes [43,44]. However, from the perspective of clinical medicine, we are mostly concerned about our *actions and decisions* that will yield best possible outcomes for our patients. Such outcomes are best guaranteed if our reasoning and decision-making adhere to the principle of *rational decision-making* [20].

But, what exactly constitutes rational decision-making? When offered health interventions, say, vaccines against COVID-19, how should participants rationally respond to the uncertainties about the effects of hoped-for benefits and unknown harms in the clinical setting that relies on trust, but which is potentially exploitive? Table 2 lists core ingredients of rationality commonly identified across theoretical models published in the contemporary literature [20]. A fundamental idea that emerges from these considerations is that life requires problem solving, and even though evidence exists on the continuum of credibility (from impossibility to certainty), decision-making is always a categorical exercise- we decide and act, or we don't [45]. Therefore, it is important that we distinguish inferences or conclusions from decisions [9,46]. Inferences refer to the truthfulness of scientific findings under formalized theoretical assumptions, whereas decisions refers to the consequences of specific actions in specific circumstances [9,47]. It is latter that we are

Table 2
Core ingredients ("Principles") of rationality commonly identified across theoretical models.

- P1: Most major theories of choice agree that rational decision-making requires integrations of
  - Benefits (gains)
  - Harms (losses)

in order to fulfill our *goals* (e.g., better health)
- P2: It typically occurs under conditions of *uncertainty*
  - rational approach requires reliable evidence to deal with the inherent uncertainties
  - relies on cognitive processes that allow integration of probabilities/uncertainties
- P3: Rational thinking should be informed by *human cognitive architecture*
  - composed of type 1 reasoning processes, which characterizes "old mind" (affect-based, intuitive, fast, resource-frugal) and type 2 processes (analytic and deliberative, consequential driven, and effortful) of "new mind"
- P4: Rationality depends on the context and should respect epistemological, environmental and computational constraints of human brains
- P5: Rationality (in medicine) is closely linked to *ethics and morality* of our actions
  - Requires consideration of *utilitarian* (society-oriented), *duty-bound* (individual-oriented) and *right-based* (autonomy, "no decision about me, without me") ethics

From ref #20 [Djulbegovic B, Elqayam S. Many faces of rationality: Implications of the great rationality debate for clinical-decision-making. *J Eval Clin Pract.* 2017;23(5):915–922.]

concerned here, and that can give us a way out of uncomfortable insights that although the world is ultimately unknowable it is very much knowable in the pragmatic sense of how to live our lives [48].

We live by our decisions. We decide to act or not act. The more choices we have, the higher uncertainty we face. When a physician is equally undecided between choosing among competing management alternatives, entropy- the measure of uncertainty about choice – is at its maximum [1]. Paradoxically, however, the minute we decide to choose one option out of many, entropy drops to zero resulting in alleviation of discomfort associated with facing uncertainty. This probably explains why it is so rare that physicians do not make a diagnostic or treatment decisions- acting and deciding whether to act result in resolution of uncertainty, however, temporary that may be. However, a decision to choose- even though it may help resolve uncertainty- does not in and of itself guarantee that the choice is the right one.

The entire branches of sciences such as decision theory [14] have evolved to optimally structure our response to thus defined uncertainties. Here, a leading contender for the optimal decision approaches is based on expected utility theory (EUT), the only theory of choice that satisfies all mathematical axioms of rational decision making [20]. According to EUT, rational decision-making is associated with selection of the alternative with higher expected utility such as, for example, treatments that result in higher quality-adjusted life years. A particularly popular extension of EUT is the so called *threshold model of rational action,* which proposes that the most rational decision is to prescribe treatment or order a diagnostic test when the expected treatment benefit outweighs its expected harms at a given probability of disease or clinical outcome [45]. At the very threshold, we are maximally uncertain [49,50]. Consequently, the threshold model requires that we carefully contrast the balance between benefits and harms at the uncertainty threshold. Following this process, choosing one management option over another (rational action) should follow [45,51–56]. Importantly, the approach help us resolve underlying uncertainty while enabling achieving optimal health outcomes even though absolute guarantee in favorable outcomes cannot be secured. But, this is the best we can do- outside of being clairvoyant- over time, this approach has provided the best possible adaptative mechanisms to the complex world that surrounds us [14].

The threshold and other similar mathematical models allow rational action even when perfect knowledge of all input variables is not known. For example, even though we cannot be absolutely certain that masks reduce risk of falling sick due to COVID-19, reasonable estimates indicate that in the absolute terms they do decrease risk of getting infected by SARS-Cov2 virus by fewer than 1 in 500 people who are at risk of contracting the disease [57]. Should such an intervention with seemingly small effect be accepted? Because it is well known that people pay attention to what others do, one strategy to decide whether we should act is to compare the use of a proposed health intervention against the effects of some commonly accepted benchmarks. For example, we can compare the effects of face masks against use of statins for primary heart disease prevention. Millions of people use statins even though their beneficial effects are very small (about 1 in 500 people will have his/her heart disease prevented). When compared to using statins -i.e., widely acceptable behavior-, formal calculation of effects of masks indicate that more than 95% of the US public would have reasonably accepted masks as one of the key protective measures in the fight against COVID-19 [57].

As powerful as the formal EUT models are they characteristically do not take *context* in the account [58,59]. In addition, they typically deal with *risks* (when probabilities of events are known/knowable), which should be distinguished from true *uncertainty* (when probabilities of events are either not known or not available) [1,60]. It is under these circumstances that humans resort to intuition, heuristic and emotions as guide to judgments and decision-making [16,17,20,21,61]. In fact, human brains can be thought as an instrument with capacity for unparalleled data reduction strategies – capable of narrowing the range of possible explanations from several hundreds, or even thousands, to perhaps 3 or 4 at most [10,62]. That is, under these context-rich circumstances, relying on human cognitive architecture driven by intuition and emotions such as the aim to minimize regret, may provide optimal solutions to the problem at hand. One effective strategy for resolution of uncertainties is to employ the cognitive emotion of regret, which links affect with analytical, counterfactual deliberations of human cognitive systems [20]. It can be also thought as the cognitive mechanism of the “precautionary principle” [39,40]. For example, under context and emotion-free calculus, EUT theory indicates that we should administer long, 6–8 month treatment against tuberculosis when we suspect that the probability that a patient has tuberculosis barely exceeds 2–6% [63,64]. This means that a small probability that some patients may have serious, life-threatening disease requires that we should be willing to unnecessary treat over 94–98% patients who do not have tuberculosis [65]. However, when taking regret of a patient’s holistic situation and unnecessary treatment into consideration, most physicians require that the probability of tuberculosis exceed 20–50% in order to act.[63,64] Often, asking a decision-maker if h/she would regret less by acting on the best possible information vs awaiting for absolute certainty represents the most optimal decision strategy [20]. In fact, threshold models [58,59] have been reformulated within regret [45,53,66,67] as well as dual processing theories [68] frameworks and have demonstrated to be superior to the EUT threshold models [52].

Similarly, use of heuristics - powerful rule-of-thumb decision-making strategies - can surprisingly be more accurate than formal models relying on the probability calculus, or strategies requiring absolute certainty for action [69,70]. Heuristic approach to decision making is the mechanism of implementation of so called theory of bounded rationality [71–73], which rely on a satisficing process (finding a good enough solution) instead of maximizing approach (finding best possible solution) under uncertainty. Often these simple strategies can outperform complex statistical models, in a phenomenon known as “less-is-more” [69].

Thus, accumulated scientific knowledge during the last two centuries convincingly point that optimal outcomes can be achieved without requiring absolute certainties to act. Importantly, however, different problems will require different approaches to finding the best solution under uncertainty: sometimes we should rely on EUT, sometimes on cognitive emotions such as regret, and sometimes we should employ heuristics, or other problem-solving strategies.

5. Rational response to “irreducible uncertainty, inevitable errors, unavoidable injustice” [74]

The main point I am trying to make here is that despite the impossibility of inferential and decision certainty [1,8], a formidable scientific apparatus has been developed during last couple of centuries to allow rather accurate problem-solving strategies. While this is best evidenced by ever continuing progress of scientific methods and society at large, it is important not to forget that because uncertainties are irreducible, and cannot be eliminated, inevitable errors both in inferences and decision-making will occur [74,75]. The errors can be of two kinds: false negatives and false positives, and they can relate to either benefits or harms. For example, we can fail to administer treatment to patients who have disease (false negatives), or unnecessary treat those without disease (false positives) [8,56,75]. Evolutionary, we have evolved to ascertain signal related to harms vs benefits differently. It seems that this is because harms, particularly, scary vivid events are typically associated with intense emotions, which, in turn, amplify signal that is easier encoded in individual and collective memory [76]. Therefore, in order to avoid potential harms, we are more willing to act even if the signal is likely false positive [9,77]. This can explain the vaccine hesitancy in wake of rare [78], possibly false-positive coincidental blood clots reported with the COVID-19 vaccines [77,79]. As a result, many people decided not to receive the vaccine based on the reports of adverse events that may be false positives even though benefits of receiving COVID-19 vaccine outweigh risks by large margin [77,79,80]. That is, when it comes to benefits, we are more conservative – we would like more assurance before we act even if the signal is possibly false negative. This attitude toward false positives vs false negatives has been long enshrined in practice of medical research where it is typically accepted to set false negative error (β) at 0.2 and false positive error (α) rate at 0.05, i.e., we are routinely willing to miss true signal at 4 time higher rate than accept one false positive finding.

These attitudes are, of course, context dependent, and we may modify our tolerance toward magnitude of false positive vs false negative errors depending on the consequences of potentially wrong actions. This is often seen when we consider the consequences of our errors at individual vs societal level. These attitudes- giving more weight to potential errors that can effect health individuals vs population – have continued to plague decision-making of the regulators as they struggle with decision whether to halt the roll out of vaccine against COVID-19 in wake of rare adverse events, or speed up the vaccine campaign to control disease faster at the population level [77,81]. How to make this decision under uncertainty while calibrating the consequences of our errors can be further memorably illustrated using a classic trolley ethical dilemma: [82,83]

A trolley is speeding up toward 10 people. You can divert the trolley by pulling a railway switch. If you do nothing, a trolley will kill all 10 people. But, if you pull the lever to divert the trolley to another track, it will kill one person. Which option is more ethically acceptable: intentionally killing one individual or passively allowing 10 to die?

In the European version of the trolley dilemma, the regulators in Germany identified seven cases of a rare cerebral blood clot, three of them fatal, out of 1.6 million who had received the AstraZeneca COVID-19 vaccine [83]. There is no evidence of the cause-effect relationship at the time of this writing. Nevertheless, and despite overwhelming evidence to indicate that benefits of vaccine outweigh its harms, small lingering uncertainty may mean that the continuing vaccinations might make regulators responsible for intentionally placing few people in harm's way — analogous to pulling the lever on the trolley tracks [83]. One can easily see how these legitimate ethical dilemmas may lead to exploitation of uncertainty to serve the interest of anti-vaxxers.

Importantly, the errors are intricately linked: if we want to decrease false negatives, we have to tolerate more false positives and vice versa [74,75]. Although balancing the trade-offs between false positives and false negatives is complicated even when data on errors are available and well articulated, such problems can still successfully be tackled using various decision and mathematical modeling approaches [8].

However, different issues emerge in case of so called complex ("wicked") problems that are ill-structured, and typically involve human values too complex to allow technical solutions [84]. Because the consequences of false positive vs false negative actions may affect different individuals in different ways, this can lead to what Hammond called "unavoidable injustice" [75]. For example, at individual level, patients facing terminal disease would accept referral to hospice only if there is 97–99% certainty that such a decision is accurate [85]. However, the request for such a high level of certainty results in thousands of patients not benefiting from hospice care as physicians typically wait until 3–7 days before the death i.e., until being as absolute certain as possible about the patients' imminenat death to refer the patient for hospice care [86]. As a result, the patients do not die at place of their choice with many unnecessary admissions to intensive care in the last few days of life [86].

Dealing with uncertainties like these requires considerations that escape easy technical solutions. It requires different attitudes towards the consequences of false positives vs. false negatives in search of finding a common ground among utilitarian, duty-oriented and right-based approaches to ethical decision-making [10]. The philosopher John Rawls recognized that *the quantitative approach to many problems that include ethical values* is often not feasible but require fair and just solutions. He advocated the use of so called *reflective equilibrium* to arrive at difficult moral decisions. It is *reflective* since it still takes into account the key precepts of moral philosophy (principle P5 in Table 2) ultimately linking it with the theory of rational choice (P1 in Table 2) [87]. Judgments are said to be *deliberative and considered* (P1 & P2) because they are derived systematically with the least likelihood of distortion [87], in an intertwined relationship between irreducible uncertainty, inevitable errors, and unavoidable injustice (P2, P3 and P4). This approach to decisions under uncertainty is known as *Rawlsian principle of reflective equilibrium/considered judgment* [87] and is effective antidote to "product defense" /"litigation support" industry [35], and "troll epistemology" manufactured uncertainties for the purpose of mis- and disinformation [41,42].

6. Conclusions

Although a precise theoretical distinction between legitimate vs illegitimate uncertainties is not possible, in practice the difference is often clear and can frequently be expressed as "I know it when I see it" – similar to a colloquial epistemological test employed by the US Supreme Court related to ruling what constitutes obscenity [88].

Elsewhere, we argued that uncertainties should also be embraced as the life without uncertainty, a future that is totally predictable and deterministic, would leave us with no choice to be made, no trade-offs to consider, and nothing to hope for -the life without meaning, which no human would want [1,89]. In this article, I focused on the darker side of uncertainties- the unwarranted calls for achieving absolute certainty, often for the purposes of creating mis- and disinformation and not for honest representation of the "truth" /legitimate scientific uncertainties[33–35]. These calls should be resisted as we do have the armamentarium at our disposable to make rational and optimal decisions under uncertainty both at policy and bedside level.

CRediT authorship contribution statement

I am sole author of this paper.

Competing interest

I have no competing interest in relation to this manuscript

Acknowledgment

I want to thank the editors and anonymous reviewers for constructive and helpful critique. In particular, I wish to thank an anonymous reviewer for the notion of "illegitimate uncertainties", which I subsequently adopted in this article. I also accepted his/her comments about definition of doubt and a notion that doubt can be honest (see Table 1).

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