IN MEDICAL EVIDENCE AND PRACTICE, WHAT LEVEL OF UNCERTAINTY IS ACCEPTABLE?

by

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ABSTRACT

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This thesis addresses the level of uncertainty in medical evidence and practice and asks if this level is acceptable. Current medical standards consider randomized controlled trials (RCTs) as the best, and most certain, form of evidence. Similarly, medical practice largely relies on differential diagnosis and diagnostic testing to diagnose patients. I will argue that RCTs as well as differential diagnosis and diagnostic testing contribute to uncertainty in medical practice. In the former, uncertainty stems from lack of representation, elimination of confounding factors, among other issues; while in the latter, uncertainty originates from technological limitations, similarity or variability in presentation, and number of diagnostic possibilities. I will argue that uncertainty in medical evidence and practice can and should be reduced. This can be done by expanding RCT testing and improving it by adding required mechanistic evidence, and by furthering research into better diagnostic technology and training.

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Introduction

Uncertainty is inherent in modern medicine, from medical evidence to medical practice. Uncertainty also can have negative consequences on patient outcomes, as high uncertainty can lead to preventable worsening of symptoms, and even preventable death. The current medical paradigm is rooted in evidence-based medicine (EBM), and. according to EBM, the "best evidence" is a randomized controlled trial (RCT) because it is believed to be the best way to eliminate confounding factors, and thereby the best way to reduce uncertainty (Reiss and Ankeny, 2016). However, RCTs themselves have an inherent uncertainty, because although RCTs attempt to prove effectiveness, it is not necessary to understand the mechanism behind a treatment in order for an RCT to progress. Thus, it can be difficult to know if the treatment is truly effective, or if confounding factors have not been successfully accounted for. Attempts to reduce confounding factors are made, however, without knowing mechanisms of actions, so this can be difficult to achieve.

Problems with this paradigm also arise when applying it to patients in clinical and surgical practice. For example, comorbidity is a common issue that physicians must consider in practice, yet is commonly not represented in RCTs. Lack of representation in RCTs leads to situations in which it is unknown if comorbid patients will be at a higher risk of being harmed or a lower chance of being helped. Thus, comorbidity can result in unequal benefit from treatments, and negatively impacts health justice. Additionally, this could also be considered a disregard of due diligence by the medical community, violating the principle of non-maleficence. Similarly, uncertainty as to the effectiveness of vitamins and nutritional supplements exists because they are not considered drugs or treatments and thus are not evaluated by RCTs. Yet, they can greatly impact patient

health and are commonly recommended. In these situations, doctors do not have assurance that they are not doing more harm than good. Consequently, another result of this uncertainty is a negative impact on the patient-physician relationship. Patients consult doctors for medical help, and while it is true that doctors cannot be expected to have all the answers, relatively higher uncertainty in one area can make patients doubt other, relatively less uncertain knowledge and recommendations, thus affecting other areas of treatment.

Uncertainty is a major part of medical practice, particularly differential diagnosis. Similarity in the presentation of symptoms and signs, variability of presentations between people, as well as the sheer number of possibilities gives diagnosing a fair amount of uncertainty. This uncertainty has clear repercussions for patients, like harm resulting from delayed or incorrect treatments.

In this thesis I will argue that the current level of uncertainty in medical evidence and practice is not acceptable and must be rectified. The level of uncertainty in medical evidence may be ameliorated by insisting on a greater emphasis on understanding treatment mechanisms in conjunction with the current standard of RCTs. This should overall reduce confounding factors in RCTs, including RCTS that include comorbid conditions. RCTs should also be used to evaluate the efficacy and safeness of vitamins and other nutritional supplements. Uncertainty in medical practice may be reduced by investments into improved technology and tests, as well as by training physicians to better manage and communicate uncertainty.

Uncertainty in Medical Evidence

To discuss uncertainty in medical evidence and why we should care about it, first I will explain what I mean by medical evidence. Medical evidence is usually explained in relation to evidence-based medicine, one of the most current and prominent theories in western medicine

(Sackett, 1997). Evidence-based medicine expresses that not all evidence is on a par. Instead, there exist "hierarchies of evidence" in which randomized controlled trials (RCTs) are at the top (Reiss and Ankeny, 2016). Following RCTs are non-randomized controlled trials, observational trials, mechanistic knowledge, comparative and cohort studies, and expert opinion. What affects the designation of the quality of evidence is the potential bias and potential uncertainty in the evidence (Reiss and Ankeny, 2016). By bias I am referring to "any process at any stage of inference which tends to produce results or conclusions that differ systematically from the truth" (Sacket, 1979). In other words, bias exists when results are skewed in a direction. By uncertainty, I am referring to the width of possible outcomes. Randomized controlled trials are widely considered to be the best form of evidence because they are thought to minimize bias and uncertainty (Reiss and Ankeny, 2016). Accordingly, I will start my discussion of uncertainty in evidence with them.

Uncertainty in the Design of Randomized Controlled Trials

Despite their status as the gold standard of evidence, RCTs are inherently uncertain. This inherent uncertainty in RCTs stems from several different factors. One such contributing factor is the inability of confounding factors to be totally removed from RCTs. Confounding factors are variables that "may mask an actual association or, more commonly, falsely demonstrate an apparent association between the treatment and outcome when no real association between them exists" (Skelly, Dettori, Brodt, 2012). It is difficult for confounding factors to be confidently removed from RCTs because RCTs do not necessitate the understanding of treatment or disease mechanisms; therefore, potential confounding factors are unknown. By mechanisms, I am referring to physiological or proximal physiological causes. In general, RCTs have at least one control group and treatment group into which participants are randomly placed (Reiss and Ankeny,

2016). In the ideal double-blind study, neither the researchers nor participants know what group any given participant is in. By random assignation to trial groups, RCTs attempt to evenly distribute and thus control for confounding factors; by double blinding the trials, RCTs attempt to control for bias. Although randomization is used to attempt to control for confounding factors, randomization is not always successful, especially in small sample sizes. It is possible for randomization to be successful and still not equally distribute confounding factors. Furthermore, without understanding the mechanisms of action, it is impossible to determine if all potential confounding factors have been accounted for, because not all potential confounding factors are known. However, RCTs do not call for mechanistic understanding of the treatment(s) they are testing. Although many RCTs do have at least partial or some mechanistic reasoning backing them, even this is not enough to confidently and entirely account for confounding factors. Without accounting for confounding factors, it is impossible to know for certain if it is truly the treatment that is causing the effect. Thus, in many cases results of RCTs may convey correlation but not causation. While the treatment may still work even when causation is not established, this is not always the case, especially when applying the results of the RCTs to the general population. Additionally, this setup can lead to pursuing supposed treatments or paths of research that actually have no bearing on the desired subject. This can lead to wasting of resources, inefficiency, and delayed treatment for those in need; all consequences of uncertainty that definitely cause harm to either individual patients, or society at large.

Another source of uncertainty in medical evidence that originates from RCTs is the question of whether RCTs have external validity. RCTs are often not reflective of the population for which the treatment is targeted. This has been an issue for class, race, ethnicity, gender, and other demographic dimensions (Melloni, Chiara et al., 2010) (Hoel et al., 2009). Although all of

these factors are still issues, recent studies have brought into focus the underrepresentation of women and ethnic minorities in RCTs, and as a result, there has been acknowledgement of the issues and movements to correct them (FDA, 2018). Comorbidity is another important factor that often can lead to exclusion from clinical trials. Less attention has been paid to the effects of such exclusion, and so I will focus my discussion here. People with comorbid conditions are often precluded from inclusion in RCTs in an attempt to remove more confounding factors (Fortin et al., 2006). As a result of such exclusion, relevant, applicable medical evidence often may not exist for people with comorbid conditions. When there is a lack of medical evidence, uncertainty is rampant. In these situations, it is unknown if patients with comorbid conditions will have different results from those included in the trial- if there is a greater risk to their health because of differing side effects or complications, or because the treatment just plain does not work. One example of such negative consequences is in the exclusion of comorbid patients from clinical trials regarding a potential treatment for MS, interferon-β. One study on MS patients taking interferon-β found that interferon-β increased the severity of headaches in the patients that were already prone to headaches (Patti et al, 2012). If these patients were not initially excluded from the clinical trials on interferon-β, perhaps they could have been assigned a different treatment, or further research could have been done to limit this side effect.

Overall, exclusion of comorbid patients from clinical trials negatively impacts the health justice of people with comorbid conditions. Health justice is the principle that "in the distribution of burdens and benefits the allocations should be equal" (Summers, 2009). Because people with comorbid conditions have unknown, but potentially unequal benefit from treatments, and greater risk from the results of clinical trials, health justice with respect to them is violated. As health justice is considered one of the fundamental principles of medical ethics, the frequency with which

this principle is violated with respect to patients with comorbidities, along with other underrepresented minorities in RCTS, should be of great concern. A violation of the principle of non-maleficence, another tenet of medical ethics, is also implicated. Non-maleficence is the principle that physicians and medical researchers should "[inflict] the least harm possible to reach a beneficial outcome" (Sundean and McGraff, 2013). If the medical community is aware that such a disparity in medical outcomes exists as a result of insufficient evidence from non-comprehensive representation in RCTs, and it is possible to fix the disparity, then failing to act to remediate the discrepancy is a failure to inflict the least harm possible. The results of uncertainty from the current medical evidence paradigm has now been shown to at best be inefficient or wasteful, and at worst cause violations of two of the main principles of medical ethics to which the medical community holds steadfast.

Uncertainty Resulting from Lack of Medical Evidence

Besides uncertainty from the design of RCTs, uncertainty in medical evidence also stems from when some treatments are not held to the standard of medical evidence, i.e. RCTs are not run on them. One prime example of this that I will discuss is vitamins and similar nutritional supplements. Vitamins are not considered to be medicine by the FDA (FDA, 2018). As a result of this, they are not required to be tested by RCTs. RCTs have been done on vitamins, but for some vitamins, like vitamin D, there is still no consensus as to how much vitamin D is necessary or appropriate (Jorde and Grimnes, 2015). Furthermore, even when RCTs are performed on vitamins, they are not performed on dosages that are purported to be on the market. For example, although some studies have been performed on the efficacy of vitamin C, the dosages given to the participants were not representative of current vitamin C supplement dosages sold. Most vitamin C supplements available for purchase are 500 mg or 100 mg. However, one study evaluated the

effectiveness of 50 mg versus 500 mg of vitamin C. The results of this study found that 500 mg was three times more effective at preventing contraction of the common cold than 50 mg (Sasazuki et al., 2006). Although knowledge was gained from this conclusion, ultimately the study design could have been improved by also testing higher dosages that may be more likely to be effective, such as 1000 mg or more (Hemila, 2017).

Despite not being considered medicine, vitamins play a large role in the health of patients. Vitamins are essential amino acids that cannot be synthesized by the human body, but are necessary to live; they must be obtained from outside sources. Because vitamins are so important, physicians will often recommend that patients take vitamins if they are not consuming the recommended amounts of vitamins. Consequences of not getting enough vitamins can vary, but are often severe. Vitamin D deficiency, for example, can cause bone to become weak, brittle, or misshapen (Mayo Clinic, 2018). In a similar vein, vitamin B deficiency can cause anemia and neurological damage, among many other symptoms (Mayo Clinic, 2018). In addition to having vitamin deficiencies, people can also have vitamin inadequacies. While vitamin deficiencies are more common in the developing world, vitamin inadequacies are more common in the developed world. Vitamin inadequacies are cases in which "intake is above the level associated with deficiency but below dietary intake recommendations…[and] may cause covert symptoms only that are difficult to detect clinically," such as fatigue, lowered immune system response, and impaired focus, memory, or mood (Drake, 2017). In the United States, 94.3% of the US population in 2010 did not meet the daily required vitamin D intake (Drake, 2017). Vitamin D inadequacies were highest among black and Latino people (Forrest and Stuhldreher, 2011).

Despite the importance of vitamins, uncertainty may prevent many physicians from prescribing vitamins to their patients. One reason physicians may hesitate to prescribe vitamins is

that there is uncertainty as to the adequate and necessary dosage. Because the treatment level dosage is still unknown for many supplements, physicians may be unsure what amount of vitamins to recommend. There is also uncertainty beyond dosage, but as to whether vitamins work at all. More often than not, there is no RCT evidence supporting vitamin supplement usage. Therefore, physicians may not feel comfortable recommending something that may or may not help, and even more importantly, may or may not harm their patients. Some doctors take an even stronger stance and will refuse to recommend vitamin supplements because they believe that if there is no evidence, then the vitamins do not work. The physicians in the latter situation are incorrect in assuming that because there is no evidence, vitamins must not work. On the contrary, because there is no evidence, it is uncertain if vitamin supplementation works. In both of the former and latter scenarios, uncertainty affects the way in which physicians recommend vitamins. This effect on prescription behavior should not be dismissed lightly. When patients are vitamin deficient and physicians cannot prescribe vitamins, patients go without help that they need. As outlined earlier, vitamin deficiencies or inadequacies that could result from this can have serious health consequences. Moreover, physicians fail in their duty to provide medical aid.

Another reason physicians may hesitate to recommend vitamin supplementation is because of uncertainty in the products. As a result of not being considered medicine, vitamins are not regulated the same way that medicine is regulated, and seemingly the same vitamins can vary between brands (LeBlanc, Perrin, Johnson, Ballatore, Hillier, 2013). One study of vitamin D found that the amount of vitamin D in the supplements tested ranged from 9 percent to 146 percent of the amount listed on the label (LeBlanc, Perrin, Johnson, Ballatore, Hillier, 2013). Variation was found not only among different brands and manufacturers, but also among different pills from the same bottle (LeBlanc, Perrin, Johnson, Ballatore, Hillier, 2013). Thus, the dosage of vitamins in

supposedly standard products is unknown. Different dosages will have different effects and efficacies, and people who unknowingly take the vitamins that are under treatment level dosage may suffer from untreated vitamin deficiency, despite taking vitamin supplementation.

Finally, different enantiomers of vitamins exist and may affect efficacy. Enantiomers are two molecules that are nonsuperimposable mirror images of each other. They are also known as optical isomers. Any molecule that has at least one chiral center, barring meso compounds and other more specific types of isomers, will have an enantiomer. A chiral center is an atom, usually carbon, that has four different substituents. Although enantiomers are thought to have identical physical and chemical properties besides their abilities to rotate plane-polarized light in equal but opposite directions, enantiomers do not always react identically in chemical reactions, particularly reactions in the body. This is because reactions in the body are often highly stereospecific, meaning only the enantiomer with the correct orientation will be able to react correctly. Specifically, most vitamins and other amino acids used in the human body are L-enantiomers (Smith and Silas, 2009). Thus, the vitamin product sold must also be the correct enantiomer in order for them to be effective. Although it is known that only one enantiomer works, it is uncertain if this is the enantiomer that is being consumed in supplements. As vitamins are regulated as nutritional supplements and not medicine, it is only taken in good faith that the product is the correct enantiomer. However, as I discussed earlier, it has already been shown that current vitamins on the market are not always compositionally what they advertise themselves to be; caution and further investigation into the identity of the enantiomer being sold would not be unwarranted. Thus, knowledge of stereospecificity is another issue that can contribute uncertainty to the usage and prescription of vitamins and similar chiral products.

The usage of vitamins and other nutritional supplements that are important to the health of patients are ridden with high levels of uncertainty from multiple sources. These different uncertainties all culminate and prevent patients from receiving the medical help that they need in order to be healthy. Similar levels of uncertainty and their consequences exist for other treatments that did not benefit from RCTs.

Uncertainty in Medical Practice

Now that I have discussed uncertainty in medical evidence, I will progress my discussion into uncertainty in medical practice. Uncertainty in medical practice is just as prevalent, if not more so, than uncertainty in medical evidence. One of the most uncertain practices in medicine is the process of differential diagnosis. Differential diagnosis is a technique by which physicians generate a list of possible diagnoses following a patient history and physical examination, and then systematically rule them out via further examination and testing until only one diagnosis is left. The expectation is that the remaining diagnosis is the one that fits best and will be acted upon. The goal of this process is to be as certain as possible that this is the correct diagnosis. However, it is possible that the differential diagnosis does not produce the correct diagnosis and thus correct treatment. Uncertainty greatly contributes to the production of incorrect diagnoses from differential diagnoses.

Uncertainty in the Process of Differential Diagnosis

Uncertainty in differential diagnosis stems from several factors. First, there is often significant similarity between the presentations of symptoms and signs of multiple diseases. This similarity is noted in the list of possible diagnoses generated in the differential diagnosis. Symptoms may be common to many diseases and create a differential diagnosis with an enormous number of possible diagnoses that must then be filtered through. At first glance, it may be difficult

to distinguish between identical symptoms and signs caused by different diseases. Although further testing can often discriminate between different pathological causes, the sheer volume of potential diagnoses may make it difficult to effectively eliminate incorrect diagnoses in a timely and cost-effective manner. Physicians often will choose a starting point on the list based on the statistical likelihood of the diagnosis occurring. Thus, diagnoses that are more statistically likely, or more easily come to mind, will be addressed first. This type of heuristic can lead to what is known as availability bias. This is an issue because inferences about diagnosis shouldn't be based solely on the likelihood of the disease, but also on the consequentiality of it: what are the consequences of the disease, how severe the disease is, and what, if anything, can be done to treat it. Additional diagnostic biases can also impact diagnostic decision making and thus the accuracy of outcomes. One such bias is anchoring bias, which occurs when an earlier diagnosis is stuck to despite new and relevant information gained. Confirmation bias, another common bias, is "assigning preference to findings that confirm a diagnosis or strategy" (Wellbery, 2011). Similar to confirmation bias is framing bias, which is configuring elements that support a particular diagnosis. Finally, premature closing is failing to consider new information after an initial diagnosis has been settled upon. These biases can make differential diagnosis an uncertain process.

Furthermore, although uncertainty is generated by similarity in presentation of symptoms and signs among diseases, uncertainty also can come from variability of presentation of symptoms and signs among people suffering from the same disease. For example, it is now known that signs of heart disease often present differently in men than in women. This then-unknown difference led to the increased misdiagnosis of heart disease in women, which inevitably led to increased suffering and preventable deaths. However, even individuals in the demographic group can vary

in their disease presentation, just based on differences between individual systems and functioning. Variability in disease presentation occurs more often in cases when not much is known about the disease mechanisms in question, like glomerular diseases (Mariani and Kretzler, 2015). Subsequently, diagnostic tools and tests do not adequately reflect biomarkers of the molecular mechanisms, leading to variable diagnosis and treatment. While variable presentation is different from unreliable diagnostic tools, it is a lack of information on what presentations- signs, symptoms, markers- to use to diagnose that leads to this uncertainty in diagnosis. Thus, in cases where patients do not fit the paradigm of disease presentation, "patient and clinician experience is marked by delays in diagnosis and uncertainty regarding prognostic and therapeutic decisions" (Mariani and Kretzler, 2015).

Specificity, Sensitivity, and Uncertainty in Diagnostic Tests

I will now discuss the role and outcomes of uncertainty in diagnostic tests. Sensitivity and specificity are properties of diagnostic tests. The sensitivity of a test is the proportion of true cases that result in a positive test result (Coulthard, 2007). Similarly, the specificity of a test is the proportion of unaffected individuals that result in a negative test result (Coulthard, 2007). Using sensitivity and specificity, a positive predictive value (PPV) and negative predictive value (NPV) can be calculated. The PPV is the proportion of cases out of all positive test results that are true positives, while the NPV is the proportion of cases out of all negative test results that are true negatives (Coulthard, 2007).

Knowing the percentage of false positives and negatives is important in regards to uncertainty in diagnostic tests because acknowledging uncertainty allows for some of it to be mitigated. For example, a test with a high sensitivity but low specificity, means that there is less uncertainty in the predictive value of a positive test result, but more uncertainty in the predictive

value of a negative test result. On the other hand, a test with lower sensitivity but higher specificity means that there is more uncertainty in the predictive value of a positive test result, as there is a higher chance of a false positive, whereas there is less uncertainty in the predictive value of a negative test result. In cases like the latter scenario, where there is higher specificity and lower sensitivity and thus more uncertainty in a positive test result, it is important to acknowledge that while the value of a negative test result may have a strong predictive value, the value of a positive test result is limited. As such, a positive test result may warrant further investigation. Without knowledge of such limitations, the uncertainty could not be moderated, and there would likely be an increase in incorrect diagnoses. For example, if a diseased person goes undetected by the diagnostic test, the patient would not get the treatment they need, and thus the condition would likely worsen, could potentially become harder to treat, and could also lead to preventable death. On the other hand, if a person without a disease is declared as diseased by the diagnostic test, the resulting treatment could actually harm them, in addition to wasting time, money, and resources. A more specific example can be seen with strep throat. The fast-acting strep test, or rapid antigen detecting test, has a sensitivity and specificity of 64.6% and 96.79%, respectively (Gural et al., 2010) This means that 35.4% of patients who actually have strep will falsely receive a negative result. While strep is a disease that usually can be treated easily, if it is left undetected, it can develop into rheumatic fever, which can cause inflammation of the heart and heart valve stenosis. Because of this, a negative result to the rapid antigen detecting test is usually followed up by a throat culture, which has a higher sensitivity of according to one study, 81% (Tanz, et al., 2009). However, even 81% still has room for improvement. Thus, specificity, sensitivity, and the resulting NPV and PPV values play important roles in acknowledging and moderating uncertainty in diagnostic tests.

However, even tests with high sensitivity and high specificity can give uncertain results. This can occur when the test cannot identify the result as either positive or negative; this result is regardless of correct or incorrect positives or negatives, but instead is just uncertain. According to one paper, an uncertain result from a diagnostic test, such as an ultrasound, would be the absence of any images, or the presence of inconclusive images (Garcia-Romero, Garcia-Barrios, Ramos-Gutierrez, 1996). Diagnostic fields like radiology, and laboratory testing, especially tests involving flocculation, fluorescence, or immunoassays are more vulnerable to this kind of uncertainty (Garcia-Romero, Garcia-Barrios, Ramos-Gutierrez, 1996). These results often require interpretation and may not necessarily have simple yes or no conclusions. Furthermore, even the act of interpretation itself is ultimately subjective, and depends on the knowledge and experience of the interpreter. It is also subject to biases, like those discussed earlier.

Just as uncertainty that results from medical evidence, uncertainty that results from medical practice can also lead to incorrect treatments and diagnoses or delays in treatment and diagnoses, both of which can cause an increase in harm to patients. Furthermore, because medical practice, such as differential diagnosis, relies on medical evidence but is still subject to its own unique uncertainties, uncertainty in medical practice is compounded by uncertainty in medical evidence.

Uncertainty and the Patient-Physician Relationship

Besides leading to delayed or incorrect diagnoses and treatments, uncertainty can also harm the patient-physician relationship. There are many different positions on and models of the ideal physician-patient relationship. In their paper, *Four Models of the Physician-Patient Relationship*, Ezekiel Emanuel and Linda Emanuel discuss four main models known as the paternalistic, informative, interpretative, and deliberative models (Emanuel and Emanuel, 1992). Some patients may want a physician who acts as a friend or confidante, such as in the deliberative framework,

someone who will listen to them and will help them make a choice that is in line with their values. Others may think the ideal physician is one who solely relays information and allows the patient to do with that information what they will, such as in the informative model. However, a common denominator throughout all four of these models is that patients seek out physicians for medical help, and important underpinnings of all physician-patient relationships are trust, respect, autonomy, and values. Whether the physician acts as a paternalistic figure, or as a technical advisor, patients want help. For this to occur, there must be mutual respect and trust. Although uncertainty is inherent in medicine, excess uncertainty can threaten trust and respect in the physician-patient relationship. This inherent uncertainty stems from uncertainty in medical evidence and practice, as discussed earlier. Physicians may make educated assertions, and disprove other assertions, but due to limitations in evidence and diagnosis, cannot ever entirely remove uncertainty. This level of uncertainty is not negligible but is currently *acceptable* due to our definitions of and amount of evidence, and our limitations in technology. It exists when there is enough knowledge for physicians to make educated assertions, and advanced-enough testing technology and differential diagnosis to disprove a significant amount of incorrect diagnoses. However, when uncertainty beyond this baseline level exists, perhaps caused by inadequate evidence, inadequate knowledge of the condition, or inadequately advanced testing technology, the patient may doubt the knowledge of the physician, and distrust recommendations made by them even in cases when uncertainty is relatively lower. Thus, trust and respect of the patient-physician relationship is eroded, and the patient is not able to sufficiently receive the help they need.

Reducing Uncertainty in Medicine

Now that I have discussed the existence of uncertainty in medicine from evidence and practice, as well as its consequences, I will argue that this uncertainty, the width of possible outcomes can and should be reduced. Along with the width of possible outcomes, so should any biases or shifting of results one way or the other be reduced.

Reducing Uncertainty in Medical Evidence

Uncertainty from RCTs can be reduced in multiple ways. One way would be to run RCTs that include comorbid patients. Although this would appear to introduce more confounding factors, and defeat the purpose of the RCTs, this increase in confounding factors would be accounted for by implementing further stages of testing. Currently, most research trials have a preclinical phase followed by phases 0-IV. Phases 0-I, as well as the preclinical phase, involve establishing the safety, efficacy, and pharmacokinetics of the treatment. During phase II, the treatment is given in a therapeutic dosage to patients to establish efficacy. Up until the treatment passes phase 2, the treatment is assumed to not have any efficacy. Phase II of the trial does not include a placebo group. In phase III, the efficacy of the treatment is compared to other, (if there are any) current treatments. This phase has multiple arms. Once a treatment has passed phase II, it is approved by the FDA and can be sold. Finally, phase IV is surveillance on the population taking the treatment for long-term side effects.

I propose that there be an additional stage or substage implemented between stages III and IV. In the third stage, comorbid patients would still be excluded to minimize confounding factors. In the stage immediately following this, comorbid patients would be included to maximize evidence and generalizability for more patients, and to reduce uncertainty. This stage could be called stage 3B, or the new stage IV and the old stage IV renamed stage V. If comorbid patients were included in RCTs, RCTs would produce evidence that would be relevant to people with

comorbid conditions. Thus, the higher uncertainty regarding their outcomes with the treatment in question would be reduced. This reduces health care discrepancies and increases health justice between those with comorbid conditions, and those without. The stages of testing can also be expanded to differentiate between different comorbid conditions as necessary. Although the addition of another stage of testing might initially be more expensive, I argue that this is worth the cost. First, this would generate more evidence, which would reduce uncertainty and help more people. Second, ultimately this would reduce long term health costs of unknown side effects from comorbidity.

Another change that can be implemented in order to reduce uncertainty in medical evidence is an increased emphasis on understanding underlying mechanisms, in other words, an increased emphasis on mechanistic reasoning. As defined earlier, mechanisms refer to physiological or proximal physiological causes. If treatment and disease mechanisms are better understood, the consequences of comorbidity and treatment interactions could be predicted better. Additionally, a better understanding of mechanisms will potentially lead to better knowledge of confounding factors. This would help to eliminate uncertainty because if confounding factors are known, they can be better controlled for than if they are unknown. Finally, more mechanistic knowledge will help to reduce incorrect diagnoses in patients that have atypical disease presentation. Physicians may be able to look for underlying signs or symptoms that are universal to the condition, as opposed to common, as they would be able to utilize the mechanism by which the condition acts. Similarly, better mechanistic knowledge would also lead to improved diagnostic testing. Ultimately, patients who may not outwardly show typical disease presentation, may be better identified. Thus, the uncertainty in diagnosis for these patients is greatly reduced.

More specifically, a change to the preclinical phase of research should be implemented. During this preclinical phase, research is done on toxicity, efficacy, and relevant chemical makeup of the treatment. Phase 0 is the phase in which pharmacokinetics is observed. This includes observations as to how the treatment is metabolized. Accordingly, a natural addition to these phases would be to include research about the mechanisms by which the treatment is proposed to act. Thus, I propose that researchers be required to include mechanistic research as part of their preclinical phase and phase 0. The details of the mechanism do not have to be fully developed, but a basic idea as to how the treatment functions, with supporting evidence, should be provided. Additionally, while all RCTs should at minimum have a mechanistic outline by phase I, mechanistic research can be continued throughout the duration of the clinical trial. RCTs with additional mechanistic evidence should be considered to be superior evidence to RCTs that only have the minimum of mechanistic evidence; and therefore, would be higher on the evidence pyramid.

However, it is important to take into consideration that mechanistic knowledge may be difficult to attain. Waiting for sufficient mechanistic knowledge may delay much needed RCT data beyond a reasonable amount of time. Furthermore, mechanisms may have their own uncertainty, as proposed mechanisms may not be correct. To address this, I acknowledge that while there may be initial uncertainty, proposed mechanisms can be tested and corroborated. Research into mechanistic knowledge will ultimately reveal more information and evidence about mechanisms, and help to decrease uncertainty overall. Difficulty in attaining mechanistic knowledge is tempered by the fact that the proposed amount of mechanistic evidence is minimal. Only a basic outline of how the proposed treatment works, with corresponding evidence would be necessary. Additional mechanistic evidence beyond this basis would be unnecessary, but would

accordingly give the RCT more evidence, and thus yield better results. Attempts should be made to elucidate all mechanistic knowledge as a new paradigm, but it is understood that attaining such evidence is an ideal to work toward. Particular effort towards uncovering mechanistic evidence should be put forth for treatments in which there is little to no current understanding of disease or treatment mechanisms. This is because in these situations, there is little foundational evidence to guide treatment development, and thus uncertainty is greater compared to those that use mechanisms as guides.

An argument could be made that such a focus on mechanistic reasoning is irrelevant because what is most important is reduction in human suffering, i.e. the only thing that matters is that it works. While it is true that ultimately what is important is to reduce human suffering, with treatments in which the mechanism of action is not understood, it is unknown if the treatment will work for everyone with the disease because the treatment may not be targeting the issue at its source. This mentality is less effective at overall reducing human suffering, because it fails to take into account when treatments may not work on individuals, as presentation of symptoms can vary between individuals. Thus, by focusing instead on understanding the mechanism, treatments will be more generalizable and apply to more people because it targets the true source or cause.

Reducing Uncertainty in Usage of Vitamins

Now I will discuss the future of RCTs and vitamins. Although there is currently some evidence regarding vitamins, I argue that this evidence is not sufficient. The level of uncertainty surrounding usage of vitamins and other nutritional supplements is unacceptable. Vitamins are not held to the same standards of evidence other treatments are held to. For many vitamins, it is unknown what are the necessary and sufficient dosages. Furthermore, the concentrations of vitamins available for patient usage are unknown and vary within singular bottles. Given these

current conditions, vitamins and other nutritional supplements should be considered medicines and regulated as such. One component of this is that RCTs should be run on vitamins and other nutritional supplements. Additionally, the standard of mechanistic evidence should be met. This will reduce uncertainty on not only the efficacy of the vitamins themselves, but on the efficacy of different dosages. Running RCTs on vitamins would generate evidence that is sufficient and up to the standard to which all other treatments are held. Appropriate dosages would be learned, and then standardized as the appropriate treatment. Accordingly, because there is an increase in evidence and decrease in uncertainty, physicians would have less hesitation in prescribing vitamins. Regarding vitamins and nutritional supplements as medicine also means that vitamin manufactures would be forced to standardize and regulate the composition of their products. Concentrations of their product would no longer vary per bottle and not match what the label says, nor would there be any question as to which enantiomer was present in the product. Thus, uncertainty in the usage of vitamins and the like would be greatly reduced. The reduction of uncertainty would allow physicians to feel more confident in prescribing vitamins, and patients would obtain the treatment that they need.

Reducing Uncertainty in Medical Practice

Uncertainty from diagnostic practices can and should be reduced as well. One way this can be done is by increasing investments, research, and development into improved diagnostic technology and diagnostic tests. Improved diagnostic testing will have better sensitivity, specificity, and faster than current diagnostic tests. Better sensitivity and specificity will directly increase the rate of true positives as well as true negatives, and decrease the rate of false positives and false negatives. This leads to an increase in certainty of the value of the test results.

While it may be impossible to improve the sensitivity and specificity of every diagnostic test, overall, more resources should be allocated to the production of better diagnostic tests. Accordingly, any increase in research has an increase in funds necessary. Although there will be an increase in funding needed, I argue that this action is worth the cost. With better diagnostic technology, patients will be correctly diagnosed faster and more efficiently, and with less uncertainty. The sooner the correct diagnosis is given, the sooner the appropriate treatments can be delivered. Not only does the patient receive faster treatment, but also fewer resources are wasted. Additionally, as I touched upon earlier, improvement in diagnostic technology would also decrease uncertainty for patients that have atypical disease presentation. This is because better diagnostic technology would use more universal or underlying markers for the diseased condition, as opposed to just common markers.

It is also important to address the accuracy of the tests themselves. Currently, the accuracy of diagnostic tests is assessed using specificity and sensitivity, and is most commonly evaluated using cohort studies (Rodger, Ramsay, Fergusson, 2012). However, a question that is worth answering is that of whether the results of the sensitivity and specificity need to be evaluated with RCTs as well. I argue that the accuracy of diagnostic tests does need to be evaluated using a trial configured specifically for adjudicating diagnostic tests. This would involve performing the new diagnostic test that is under evaluation, and an existing diagnostic test on the same group of patients, and comparing the results of both of the tests against a reference standard (Kennedy, 2016). Although there would not be randomization, implementing this standard would allow the diagnostic tests to be directly compared to each other. Additionally, although this may not increase the accuracy of the test, this would increase the certainty and value of the test results themselves. For example, it would increase the certainty that a true positive is indeed a true positive.

Considering the importance of correctly diagnosing patients, and the consequences of incorrectly diagnosing patients, increasing the standard of evidence for the accuracy of diagnostic testing is a straightforward solution to a problem that could have major, negative impacts on the health of patients.

Specific diagnostic and treatment tools like Watson and other supercomputer programs also have the potential to decrease uncertainty in medicine with further research invested in them. Watson and other supercomputer programs have the potential to have the capabilities to access databases, review data, and make treatment recommendations based on the most up to date evidence, data, and guidelines in real time. Thus, Watson ideally would contribute to both diagnosis and treatment. However, current implementation of the Watson supercomputer for cancer treatment shows that the programming of Watson is still too rudimentary to improve outcomes of patients or improve diagnosis of cancer (Peck, 2018). Once Watson's programming has been improved so that it can achieve its diagnostic potential, it will be a tool that will help to reduce uncertainty in diagnosis. Specifically, the supercomputer may be able to not only help physicians keep up with the influx of new data regarding treatments, but it may also help reduce biases, such as availability bias, from individual physicians. Reduction in biases will accordingly improve diagnostic accuracy and decrease diagnostic uncertainty. It must also be acknowledged that Watson itself was created by human programmers, and thus their biases were imbued in its programming. Both the algorithm that drives the AI and the data that is put into the AI come from human sources. For example, a study by the American Economic Review found that interviewers preferred applicants with "whiter-sounding" names than applicants with "blacker-sounding names" (Eder, 2018). Recruiting and hiring software are trained using that biased data, and then perpetuate the bias themselves. A similar situation could easily happen with medical software, in

which a certain disease is underdiagnosed in a certain population due to bias, this biased data is fed to Watson, and Watson becomes biased in turn. So, Watson will not be free of biases either. However, Watson may still be able to help physicians overcome their individual biases that may be hindering development of the diagnostic and treatment process by adding a different, although still imperfect perspective.

Besides just reducing uncertainty in medicine, uncertainty can also be managed and communicated better in order to limit its effects. Physicians should be taught how to recognize diagnostic uncertainty, how to manage diagnostic uncertainty and how to effectively communicate it to patients (Kennedy, 2015). It is important to be able to identify uncertainty because before it can be managed, physicians must understand where the uncertainty comes from. One review study, *Managing diagnostic uncertainty in primary care: a systematic critical review*, analyzed ten studies on diagnostic uncertainty in order to assess the ways in which physicians manage uncertainty. Because of its small sample size, it was not able to identify the most effective ways to manage uncertainty. Thus, more research, with larger sample sizes is still needed in order to assess these techniques. However, the review was able to divide the techniques (adaptive and maladaptive) used by physicians to manage uncertainty into three categories: cognitive, emotional, and ethical. Then, it offered ways in which to improve the reactions in each domain. In the ethical domain, physicians may often feel inclined to limit communication of uncertainty with the patient. However, the study suggested they should focus on increasing communication of uncertainties to patients in order to abide by the principle of informed consent and to improve medical outcomes. In the emotional domain, physicians may react to uncertainty by becoming stressed or anxious; physicians can counter this by becoming aware of their emotional responses. Additionally, increased mental health services and support should be implemented starting in medical school in

order to help physicians cope with uncertainty and stress. Finally, in the cognitive domain, the review discusses that physicians often use heuristics, which can be buffeted by use of diagnostic aids, thorough examinations, and acceptance of uncertainty (Alam et al., 2017).

The three domains in which diagnostic uncertainty can be managed could be taught to physicians or medical students in order to help them better identify and manage diagnostic uncertainty affecting them. Furthermore, there should be an increase in focus on identifying and managing uncertainty in medical school curricula. One study reported that while the majority (75%) of internal medicine residency directors surveyed thought clinical reasoning needed to be taught in all four years of medical school, 57% of medical schools surveyed did not have dedicated curricula to clinical reasoning. Additionally, respondents indicated that the majority of medical students entered their residencies with only poor to fair knowledge of diagnostic and clinical reasoning (Rencic, Trowbridge, Fagan, Szauter, Durning, 2017). Thus, there is a demonstrated need for medical students to be taught diagnostic reasoning, and, by default, diagnostic uncertainty as well. If this change was implemented, medical students would be given the resources to build all the skills they need to be successful physicians in the future. This includes directly teaching medical students techniques on how to communicate uncertainty to patients. It is important to recognize that communicating uncertainty may be difficult. Different patients may want different levels of details, and some may react negatively to uncertainty. Communication of uncertainty requires tact, sensitivity, and depends on many factors. However, this difficulty further shows the importance of physicians being trained to properly communicate uncertainty.

Finally, physicians must be sure to communicate diagnostic uncertainty with fellow physicians as well. As collaboration between physicians is becoming more common, communication of diagnostic uncertainty between relevant physicians is important to ensure that

the physicians are on the same page. Any miscommunication of diagnostic uncertainty could directly result in harm to patients.

Conclusion

Uncertainty in medical evidence and practice comes from multiple sources, but overall can and should be reduced. Although there have not been many studies done on the results of reducing uncertainty in clinical trials, several studies have been performed on training physicians to better handle and communicate uncertainty, and the results have found that this training does significantly improve physician awareness and communication of uncertainty (Alam et al., 2017). Minimizing uncertainty is important to achieve the best patient outcomes, reduce preventable worsening of symptoms, and reduce preventable death. By improving the design of randomized controlled trials first with the addition of a research phase specifically dedicated to diagnostic mechanisms, uncertainty from randomized controlled trials can be reduced. Second, by adding another testing phase in which people with comorbid conditions can participate in the trial, the medical uncertainty of whether the intervention in question is effective in those people is reduced and health justice is improved. Randomized controlled trials should also be run on vitamins and other health supplements; this will reduce uncertainty in the usage of vitamins, specifically by allowing physicians to be more certain of efficacy and dosage when prescribing them. Uncertainty can also be reduced by investing in better diagnostic tests and technology, and by implementing a standardized way to evaluate the diagnostic tests themselves. Starting in medical school, physicians should be trained in diagnostic reasoning, trained to be able to recognize and manage diagnostic uncertainty, and trained to communicate the uncertainty to both their patients, and their peers. Medical schools and medical workplaces should also implement formal support systems to help physicians deal with uncertainty, stress, and mental health. Thus, it is important that these

changes be implemented and that medical uncertainty from all of these sources is reduced in order to improve medical outcomes for patients.

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