Epidemiologic Evidence: Use at Your *Own* Risk?
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Abstract

What meaning does epidemiologic evidence have for the individual? In evidence-based medicine, epidemiologic evidence measures the patient's risk of the outcome or the change in their risk due to an intervention. The patient's risk is commonly understood as an individual probability. The problem of understanding epidemiologic evidence and risk thus becomes the challenge of interpreting individual patient probabilities. I argue that the patient's risk is interpreted ontically, as a propensity. After exploring formidable problems with this interpretation in the medical context, I propose an epistemic reinterpretation of individual patient probabilities as credences. On this view, epidemiologic evidence informs medical uncertainty.

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1. Problem of the Meaning of Population Evidence for the Individual

Patients are not statistics. This statement is trite but true, and often underappreciated in an era in which medical care is driven by evidence from epidemiologic studies. The puzzle of what bearing group data have on individual patients is not new. It was hotly debated by physicians, physiologists and statisticians in the Nineteenth Century at the dawn of medical statistics (Matthews 1995). In the Twentieth Century, clinical trials pioneer Bradford Hill reflected that clinical trial results present "a *group* reaction. They show that one group fared better than another, that given a certain treatment patients, *on the average*, get better more frequently or more rapidly, or both. We cannot necessarily, perhaps very rarely, pass from that to stating exactly what effect the treatment will have on a particular patient" (1952, 117).

This problem of understanding what meaning aggregate data have for individual patients has gone unresolved, despite the rise of evidence-based medicine (EBM) in recent decades. EBM provides principles and tools to assist in the evaluation and use of epidemiological evidence in *individual* patient care. Among these tools are evidence-based decision aids like the graphic provided by the Mayo Clinic to help physicians and patients understand the results of epidemiological evidence on statins and heart attacks (Figure 1). Decision aids are now available for all sorts of interventions and medical conditions, from screening for cancer to antidepressants for depression.

The decision aid in Figure 1 represents the risk of heart attack in a certain low-risk population, as well as the effect of a statin, a drug for treating cholesterol, on lowering risk. It is derived from clinical trials studying the effectiveness of statins. The bottom line: if a certain population took a statin for ten years, there would be one fewer heart attack per one hundred people compared to that same population if untreated (a counterfactual comparison).
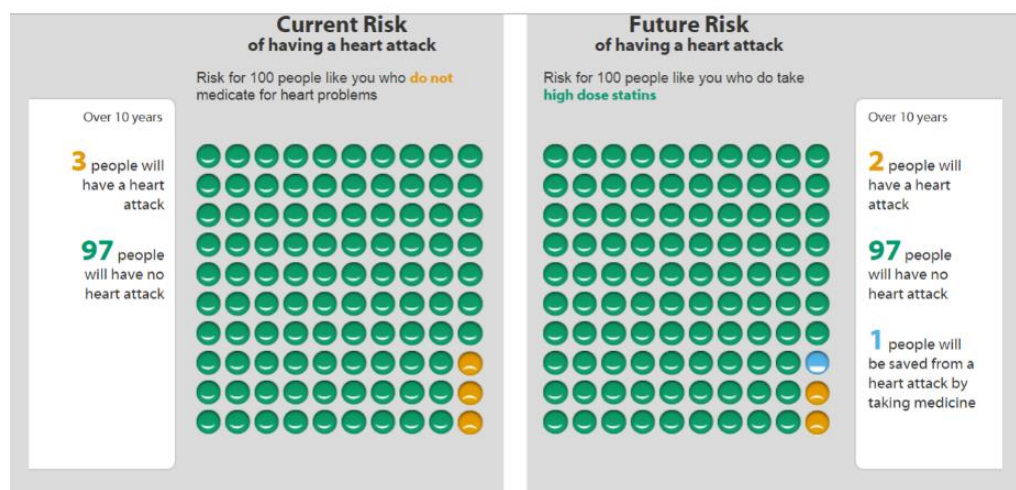

Figure 1. Decision aid representing the effect of a statin on risk of heart attack (Mayo Clinic 2017).

If you are an individual patient (or their clinician), you ultimately want to know whether the statin will benefit *you* (or your patient). Are you a smiling green person, a frowning orange person, or a brimming blue person? This question is precisely *not* one that the evidence and the decision aid answers. A preferred measure of effect size in EBM is the number-needed-to-treat (Guyatt et al. 2015), the number of individuals a physician would need

to treat with the intervention to prevent one outcome. The number-needed-to-treat represents the same kind of information captured by decision aids like Figure 1.

EBM tries to bridge the divide between populations and individuals using a unique concept of medical risk, 'the patient's risk', an individual probability. The patient's risk has become an important target of prognostication and treatment in healthcare (Aronowitz 2015). Clinicians often speak of predicting and managing risk. Indeed, preventive interventions like statins are understood as 'lowing' or 'reducing' one's risk of some undesirable outcome. The field of risk communication sprang up to study empirically how people (especially patients and physicians) understand risk and to enhance discussions through tools like graphical aids – the psychology of risk. Yet, the meaning or interpretation of the patient's risk as a probability remains virtually unexplored. Goodman, an epidemiologist, writes: "The concept of risk has undoubtedly become an enormously useful and essential part of medical science, but evidence-based medicine must grapple with the fact that in the individual patient, one of its pillars—the concept of probability—is ambiguous and elusive" (1999, 606). Effective risk communication hinges on the problem of risk interpretation, with which philosophers can be of some help.

Here, I show how EBM's view of evidence and risk makes the problem of the meaning of population evidence difficult to resolve, and I propose an epistemic interpretation of individual patient probabilities as a corrective. In section 2, I illustrate EBM's view of epidemiologic evidence qua medical evidence as measuring the patient's risk or the change in

the patient's risk. I argue that the concept of the patient's risk is interpreted ontically as a propensity, and that it is problematic in several ways. In section 3, I contrast the ontic interpretation with an epistemic (re)interpretation of individual patient probabilities as credences, in which epidemiologic evidence is instead seen as informing medical uncertainty.

2. The Patient's Risk as an Ontic Probability

After evaluating the quality of epidemiologic evidence (e.g. the likelihood of bias), the next step in the EBM process is to ask, what are the results (Guyatt et al. 2015)? In prognosis, a measure called the absolute risk (AR), the relative frequency of the outcome, is regarded as perhaps the most important information a study can provide. In therapy, some measure of effect size like the absolute risk reduction (ARR), the difference in AR between study groups, is thought to be the most useful takeaway.

On their own, these measures do not tell us how justified we are in believing that an individual patient will have a certain outcome or that the treatment will prevent it. Think back to the left-hand side of Figure 1. Once we have summarized the AR – 3% of people will have a heart attack – what should we infer about the patient, about whether they will have a heart attack? In EBM, the fact we infer is about another kind of risk, *the patient's risk*. Prima facie, the patient's risk is meant to connect ARs and ARRs to the patient. Says the American College of Cardiology evidence-based guidelines for cardiovascular disease prediction: "It is important

to note that *risk* estimation is based on group averages, which are then applied to *individual*

patients in practice" (Goff et al. 2014, S53; my emphasis). According to their guidelines for

cholesterol treatment: "statin therapy is recommended for *individuals* at increased ASCVD

[cardiovascular disease] risk who are most likely to experience a net benefit in terms of the

potential for ASCVD *risk reduction*" (Stone et al. 2014, S7; my emphasis). Not all experts

always agreed with this approach (recall Hill's skepticism); nonetheless, it is the dominant

approach in healthcare today.

There is good reason to suspect that conceptually the patient's risk is different from the

absolute risk, the finite frequency in the population. For one, the patient's risk is about an

individual, not a population. Moreover, we can alter the patient's risk by providing the patient

(as opposed to the whole population) with a treatment like a statin drug. In fact, numerous

authorities in EBM and epidemiology understand the patient's risk as a probability (Goodman

1999; Dulbegovic et al. 2011; Guyatt et al. 2015). Probabilities are typically considered to be

closely linked to finite frequencies like the AR, yet distinct. The value of the patient's risk is

taken to equal the AR, and the value of the change in the patient's risk due to treatment is

taken to equal the ARR or some other AR-derived measure of the effect size. However, the

patient's risk is *inferred from* the AR, and the change in the patient's risk due to treatment is

inferred from the ARR.

In Fuller and Flores (2015), we call the standard model used in EBM to make these

inferences the Risk Generalization-Particularization (Risk GP) Model. We argue that the

inferences rely on nontrivial and sometimes problematic assumptions. One of these assumptions is that the target population is a chance setup, like a lottery. We can then model the population using a hypothetical urn containing coloured balls. Imagine that the treated and untreated diagrams in Figure 1 represent two such urns. When a patient presents for risk assessment and treatment, it is analogous to choosing one of the two urns, randomly drawing a ball from it and then waiting ten years to find out what its identity will be: green (smiling) or orange (frowning). The single case probability that the drawn ball (patient) will be orange (have a heart attack) is given by the finite frequency of balls – in Figure 1, the counterfactual probabilities are 3% (untreated) and 2% (treated). In the next section, I will argue that we should interpret these probabilities epistemically. But how *does* EBM interpret 'the patient's risk', which is usually equated with the probability provided by our urn model?

How do we interpret any probability? There are several ways of distinguishing the kinds of interpretations on offer, including subjective vs. objective interpretations (Gillies 2000) and belief-type vs. frequency-type interpretations (Hacking 2001). Both these dichotomies separate epistemic conceptions of probability (where probability refers to an epistemic notion like degrees of belief or the bearing of evidence on a hypothesis) from ontic conceptions of probability (where probability refers to something independent of our beliefs or evidence like frequencies or propensities).

I will first consider whether EBM's concept of the patient's risk is interpreted epistemically in medicine. On this view, the patient's risk might be a certain degree of belief

the physician has (or should have) that the patient will develop the outcome. Or it might be the logical support that the proposition 'the patient will develop the outcome' receives. However, a problem arises when we try to understand what it means to say that a statin lowers the patient's risk of heart attack. Seemingly, it means that the treatment causes their risk to be lower. On any realist theory of causation, causes exert a real effect in the world outside our minds. Sure, my belief that you will have a heart attack might be diminished if you take the medication, but the effect to which we are referring when we say that the intervention lowers your risk is not the effect the intervention has on my beliefs.

The patient's risk is more likely an ontic concept, locating probabilities in the world. One such interpretation to consider is frequentism, in which probabilities are either finite or 'long-run' frequencies. Yet the finite frequency *just is* the AR, so interpreted this way the patient's risk would fail to make population data any more meaningful for the individual. Meanwhile, the long-run or limiting frequency would be the proportion of orange (frowning) balls drawn from the urn if we drew a ball randomly and then replaced it ad infinitum. That interpretation would only expand the population and our problem. Either variety of frequentism is prone to the notorious difficulty (if not outright futility) of making sense of a frequentist probability for a single case, and thus is not a good candidate for EBM's singularist concept of the patient's risk.

The most plausible classic ontic interpretation of the patient's risk is as a propensity, a physical property of the single case that tends towards the outcome. Consistent with the way

guidelines and clinicians speak about the patient's risk, it is best conceived as their individual propensity towards some clinical outcome, and a lowering of the patient's risk risk due to an intervention is best conceived as a change in that propensity. The value of the patient's risk would then represent the strength of that propensity or the frequency of the outcome that the propensity manifests. Many philosophers are quite comfortable ascribing propensities to radioactive atoms or coin-tossings, but are clinical outcomes genuinely chancy in this way?

Clinical outcomes result from biomedical mechanisms. For example, heart attacks result from coronary atherosclerosis, the buildup of a fatty plaque in the innermost layer of the coronary arteries supplying the heart due to the accumulation of LDL-cholesterol. A heart attack usually results from plaque rupture, leading to a blood clot that cuts off blood flow to heart muscle and deprives it of oxygen. A statin is thought to work by lowering LDL-cholesterol (among other potential effects). To say that outcomes like heart attack and statin prevention are chancy is to suggest that pathogenic mechanisms like these are chancy, which is far from accepted or obvious. Thus, the first difficulty for the propensity interpretation is that the existence of propensities for clinical outcomes (never mind macro-level outcomes generally) is not a given.

Viewing epidemiologic evidence as measuring propensities invites further problems. Firstly, the aggregate propensity or the change in aggregate propensity in an epidemiologic population may be an unreliable estimate of individual propensities or changes in propensity, respectively. As a measure of propensity, the AR would first and foremost be a measure of

aggregate or average propensity in a population. A propensity theory for medicine would have to assume that different patients have different propensities because ARs generally vary by clinical subpopulation according to risk factors. The question is whether the aggregate propensity is a good estimate of the individual propensity for most individuals. Similarly, the ARR would be a measure of the aggregate reduction in propensity in a population. As the individual treatment effect can vary among members of the population (Kravitz et al. 2004), we should wonder whether the aggregate change in propensity is a good estimate for most individuals.

Whether or not an aggregate propensity (or change in propensity) is a good estimate for most individuals depends on the distribution of individual propensities (or changes in propensity) in the population. If the distribution is narrow and unimodal, then the true value for most individuals will cluster around the mean, so that the aggregate will usually be a pretty good estimate for the individual. If the distribution is not narrow or not unimodal, then many individuals will cluster away from the mean, and the aggregate will often be a poor estimate for the individual. As an illustration, if the clinical outcome is fully determined rather than governed by propensities, then individual probabilities and reductions in probability will only have two values, 0 or 100%, which means that the AR or ARR is aggregating an extreme bimodal distribution. What kind of distribution typically occurs in medicine?

It is difficult to know because virtually the only information we have about risks comes from aggregate studies. We do know (for instance) that the AR of heart attack or stroke will

vary widely from less than 1% to over 50% in common subgroups of patients (Goff et al. 2014), which suggests a large spread of cardiovascular propensities in the population. We have tools to further stratify patient risk, but not down to the level of the individual. In general, we should worry that any AR and ARR might be a poor estimate for the individual unless we have evidence to suggest otherwise.

One reason to treat this possibility as worrisome is that assuming that the aggregate is a good estimate for all individuals has two alarming consequences if we are mistaken. First, we ascribe a definite non-zero individual risk to everyone. Because individual risks are increasingly treated as diseases in their own right (Aronowitz 2015), this ascription turns everyone into a patient (e.g. a 'cardiovascular risk patient') with an individual risk that might need monitoring and intervention. Moreover, we assign a non-zero potential individual risk reduction to everyone, which makes it appear as though the intervention is universally effective – everyone stands to benefit by having their own risk lowered. The assumption of an equal distribution of individual risk and risk reduction could lead to high healthcare anxiety, high healthcare utilization and costs, and overtreatment.

The final problem with EBM's view of epidemiologic evidence as measuring individual risks-as-propensities is that individual propensities are just not what epidemiologic studies directly measure, even if it turns out that some of the time an epidemiologic study's results accidentally provide a good approximation of individual propensities. A 3% individual propensity towards heart attack is a property of the individual, analogous to a 100-faced die

that has a 3% propensity towards rolling orange because three of its hundred faces are orange. We infer that there is a 3% probability of rolling orange by studying the die's properties (number of faces, weighting, symmetry). In contrast, we modeled our epidemiologic study results as an urn containing balls. We infer that there is a 3% probability that the ball we have drawn is orange not from facts about this ball but from the frequency of orange balls in the urn. How then should we interpret this individual probability?

In summary, the patient's risk is interpreted ontically in EBM, as a propensity. I am not denying that there might be clinical propensities, and the alternative I will now propose is agnostic to their existence. However, EBM's concept of the patient's risk faces serious problems: the existence of clinical propensities is not a given, aggregate epidemiologic outcomes might be a poor estimate of them (which could lead to overdiagnosis of individual risk and overtreatment), and they are not what epidemiologic evidence directly measures. Rather than individual propensities ('the patient's risk'), EBM should reconceive of the role of epidemiologic evidence as supplying *epistemic* patient probabilities.

3. An Epistemic Reinterpretation

To provide a head-to-head comparison between EBM's interpretation of individual patient probabilities and the interpretation I endorse, I will follow EBM in assuming that epidemiologic studies measure ARs and effect size statistics derived from the AR like the

ARR. I will further follow EBM in inferring individual patient probabilities that are equal in value to the AR. I am not necessarily advocating this approach, but I will provide a better interpretation of these probabilities if we do choose to infer them.

The implicit interpretation of these probabilities in EBM is ontic: the patient's risk as something mind-independent, most likely a propensity. Assuming you are a member of the untreated population represented in Figure 1, your individual risk or propensity of having a heart attack in the next ten years is 3%. The virtue of a statin is that it lowers your propensity of heart attack from 3% to 2%. In comparison, an epistemic interpretation of these probabilities sees them as the probability of a hypothesis about you. The relevant prognostic hypothesis is H: you will have a heart attack in the next ten years if untreated. The epidemiologic evidence represented in Figure 1 can be viewed as providing probabilistic support for this hypothesis: 3% represents the probability of H conditional on the evidence E ($p(H|E) = $ AR).

There are various epistemic interpretations on the menu, including classical, logical and credence varieties (Gillies 2000). I will endorse interpreting patient probabilities as (rational) credences or degrees of belief over other epistemic interpretations for several reasons. First, credence is currently the leading contender among epistemic interpretations in philosophy, statistics and medicine. Thinking about credences in prognosis and therapy might not be a huge conceptual leap for EBM, as Bayesian inference is commonplace in evidence-based diagnosis (Guyatt et al. 2015). Moreover, uncertainty is widely recognized in medicine

as an important feature of clinical reasoning and decision-making (Djulbegovic et al. 2011; Tonelli & Upshur 2018). Medical evidence is often seen as having some bearing on medical uncertainty, hopefully reducing it by providing new information, but sometimes increasing it by challenging existing thinking. Credences are a ready and useful way of representing uncertainty. Epidemiological evidence informs uncertainty by grounding our credences in frequencies.

Lastly, a credence interpretation is well suited to our probability model: an urn containing coloured balls. We have drawn a ball randomly from the untreated urn in Figure 1. The probability that we have drawn an orange (frowning) ball is 3%, which can be interpreted as our credence that the ball is orange given evidence of the frequency of orange balls in the urn. I do not mean that this credence is the one that a particular physician will have, descriptively speaking. I mean that it is the rational credence we ought to adopt if the epidemiologic evidence is our evidence. Asserting E as our evidence makes several assumptions beyond the important one that we have no independent evidence[1] (these

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[1] If we do have 'independent evidence' (evidence not bearing on E itself), our epidemiologic credence could still be regarded as rational if we treat it as our prior probability that we can then update using the independent evidence. We might also have 'non-independent evidence' (bearing on E itself), supporting the assumptions upon which E relies, for instance the assumption that the clinical trial population is representative of the target population.

assumptions are explored in Fuller & Flores 2015). It amounts to claiming that our probability model represents our patient and our patient population well enough. If we grant these assumptions, the justification for setting our credence to the AR can be provided by one of several rational principles, including the Principal Principle (Lewis 1980) or the Principle of Direct Probability (Hacking 2001). I do not have space to discuss these principles here.

In section 2, I raised the concern that because their populations are heterogeneous, epidemiologic studies might provide an inaccurate estimate of the patient's true individual propensity. Our rational credence cannot be inaccurate in the same way as the propensity estimate because it is not intended as some ideal credence equal to the patient's propensity. It rather represents our uncertainty given variability in the outcome in the population, captured by the aggregate outcome. Some of this variability may be due to stochasticity: the outcome might actually be governed by propensities. However, some of the variability also results from causal heterogeneity. The study's aggregate outcome packages together any genuine stochasticity with causal heterogeneity. Its weakness in estimating an individual propensity is simultaneously its strength in serving to represent the physician's uncertainty to the extent that the physician does not know where in the propensity distribution the particular patient is located.

In section 2, I rejected an epistemic interpretation of the patient's risk because it is unfaithful to how the concept is used in practice. Physicians speak of lowering the patient's risk with an intervention, which is best understood as a causal effect of the intervention on the

patient rather than its effect on our beliefs. Similarly, the ARR and other measures of effect

size present a challenge for my epistemic alternative to the patient's risk. How can our

credences reflect the causal import of the ARR, which measures not just a difference in

frequencies but a difference caused by the intervention?

One tantalizing possibility is suggested by the depiction of the brimming blue person

in Figure 1. The decision aid assumes that the ARR of 1% reveals the frequency of individuals

for whom the statin prevented a heart attack. We might then infer that the probability that this

patient –presenting randomly from the population – will have their heart attack prevented by a

statin is 1%. This probability could be interpreted as our credence in the hypothesis that a

statin will prevent a heart attack for the patient.

Unfortunately, the decision aid goes beyond the trial evidence in ways that might not

be justified. The trials simply determined that a statin reduced the frequency of heart attack by

1% on net. It could be that the statin prevented a heart attack in 1%, but it could instead be (for

instance) that a statin caused a heart attack in 2% while preventing one in 3%. These sorts of

opposite or 'paradoxical' effects sometimes occur in medicine, like when an anticoagulant

prevents death in one person by preventing stroke but causes death in another by producing a

major gastrointestinal bleed, or when an antibiotic prevents death in one by treating a life-

threatening infection but causes death in another by triggering anaphylaxis. Furthermore, there

may be *nobody* in the trial for whom the statin prevented a heart attack in the deterministic

counterfactual sense of causing the absence of a heart attack when one otherwise would have

occurred. It could be that a statin lowered the chance of a heart attack in one or more individuals who otherwise would have had a chance of heart attack less than one. If we do not wish to rule out the possibility of paradoxical effects or chancy causation, we must depart from the decision aid's belief in the one blue person.

Thankfully, we do not need this additional assumption to make clinical trial evidence meaningful on an epistemic interpretation. Our urn model provides the answer. The two urns in Figure 1 generate two epistemic probabilities: $cr(H|E\&\text{untreated})$ and $cr(H|E\&\text{treated})$. Some of the epidemiologic evidence in E comes from cohort studies that followed populations of patients over time and measured the untreated AR: these studies are evidence for the frequency in the untreated urn. However, some of the evidence in E comes from clinical trials that measured the effect size (e.g. the ARR). The effect size allows us to predict the frequency in the treated urn from the frequency in the untreated urn because it quantifies the difference that the intervention makes in the population. Thus, our credences reflect relevant causal facts because they are conditional partly on causal evidence (from clinical trials). We can thus make a rational decision about whether to use the intervention partly by comparing our treated and untreated credences.

An epistemic interpretation provides at least a partial solution to the problem of the meaning of population evidence for the individual. It does so by providing a meaning or interpretation of the individual probabilities that epidemiologic evidence supplies: they represent our rational credence conditional on the evidence (and on several assumptions).

Rather than measuring individual propensities (the patient's risk), the role of epidemiologic evidence qua medical evidence is to inform medical uncertainty. The greatest benefit of the epistemic interpretation may be that it avoids the problems of the propensity interpretation discussed in section 2.

The epistemic interpretation has the additional benefit of restoring the importance of clinical judgment and expertise as well as the epistemic function of evidence to our understanding of epidemiologic evidence in medicine. In its quest for objectivity, EBM has divorced epidemiologic evidence from clinical expertise and from epistemic warrant: epidemiologic evidence measures facts about individuals rather than providing epistemic support for hypotheses. Yet, patients go their physician in part for the physician's medical opinion, their expert probability assignment. This epistemic probability need not be baseless; it should be grounded in objective facts supplied by evidence to allow for rational decision-making. Similarly, we need not dispense with decision-aids, which are often a helpful way of representing the evidence on which our credence is based. However, the evidence and the decision aids require interpretation to make them meaningful for the individual, and here the language of uncertainty should replace talk of the patient's risk.

On the other hand, part of the problem of the meaning of population evidence for the individual remains unresolved. Our evidence-based credence is set to the AR – a fact about the population – rather than reflecting facts particular to the person. The more relevant facts the population shares with a particular person, the more relevant the population evidence will be

for that person. However, regardless of how relevant some population evidence is, my

epistemic proposal at least makes this evidence interpretable for "a science of uncertainty and

an art of probability"[2].

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[2] This expression, describing medicine, is attributed to the physician William Osler.

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