Risk, uncertainty and ignorance in medicine

Exploration of healthy patients' risk factors for disease has become a major medical activity. The rationale behind primary prevention through exploration and therapeutic risk reduction is not separated from the theoretical assumption that every form of uncertainty can be expressed as risk. This article presents taxonomy of uncertainty, something which is well known in the philosophy of science («risks» as quantitative probabilities in a known event space, «strict uncertainty» where the event space is known, but not quantified, and «ignorance» where the event space is unknown). This conceptual model has hitherto been little used in medicine. In this article we will show that an expansion of the concept of risk is useful for analysing a standard clinical situation (examination for cardiovascular disease). Strict uncertainty will invariably and ignorance will occasionally be a feature of such situations. This will cause the traditional decision-theory rationale for primary prevention to collapse, and instead we propose an alternative ideal model for exercising rationality under uncertainty and ignorance, focusing on the patient's well-considered reasons. This model has profound implications for the current understanding of medical professionalism as well as for the design of clinical guidelines.

Guri Rørtveit
guri.rortveit@isf.uib.no
Department of Global Public Health and Primary Care
University of Bergen
Ulriksdal 8c
5009 Bergen

Roger Strand
Centre for the Study of the Sciences and the Humanities
University of Bergen
Allégaten 32
5020 Bergen

Eva, 68 years, comes for a consultation with a general practitioner because she would like to have «a full check-up». She is mildly overweight, does not smoke and feels basically healthy. She goes out on a daily walk with her dog. When asked by the doctor, she explains that her father died suddenly at the age of 55; «it was something with his heart». A maternal uncle of hers «has angina», but there is otherwise no clustering of cardiovascular disease in her family. The doctor deems it natural to initially concentrate on the risk of cardiovascular disease and finds her blood pressure to be 140/90 mm Hg. The clinical examination, ECG and blood tests all come out normal, with the exception of her cholesterol level, which is 8.5 mmol/l. When checked three months later she has tried to change her diet somewhat and now has a cholesterol level of 8.3 mmol/l. Her HDL amounts to 1.3 mmol/l and her triglycerides 1.0 mmol/l. Should she be prescribed anti-cholesterol medication?

The disease panorama in Western countries has changed considerably over the last century. For various reasons, the emphasis has moved from acute disease, especially infections, to diseases of a more chronic nature, such as cardiovascular diseases, diabetes, chronic obstructive pulmonary disease etc. (1). This has caused a shift from primarily therapeutic to more preventive medical activity.

The aspiration to predict disease in individuals is closely linked to the idea of prevention. Epidemiologists are in demand, investigating risk factors for one disease after another (2). Not all risk factors are equally high, and not all diseases are equally frequent or serious. However, identification of risk factors evokes major interest in contemporary society, with an equivalent degree of media coverage.

Patients and doctors are therefore experiencing a bewildering array of risk factors, and one of their main problems is to separate the wheat from the chaff (3). There is a comprehensive literature available on the definition and calculation of risk, including in Norwegian (4–7). There is also widespread debate on how the complicated concept of risk can be made more understandable to patients (8, 9).

Such efforts are essential to enable the health services and patients to cope as well as possible with the new opportunities and tools that accompany the risk factors. At the same time, there is no reason to believe that we will solve all problems associated with the risk factors' appearance in medicine only by being sufficiently *skilled* at calculating risk. Like all other knowledge, risk information and epidemiology have their assumptions and limitations. How can we best combine qualitative clinical insights and considerations with the quantitative logic of risk estimates? What happens to professional identity, and how is society being affected by the intense attention devoted to risk factors? Medicine is entering a new phase, and we must be prepared that this may require new ways of thinking.

Nobody, the authors of this article included, can provide any definitive answers to this situation. One place to start, however, is to investigate what happens when the ubiquitous phenomenon of *uncertainty* is transformed into a quantified *risk*. Such analyses of the concept of risk and discussions of more comprehensive concepts of uncertainty are well known from the philosophy of science, but have yet been little applied to medicine (10). In this article we will show

how it may be beneficial to distinguish between risk, uncertainty and ignorance when common clinical situations are analysed (Table 1). Such an approach will not necessarily simplify decision-making. However, it could render the doctor and the patient better able to weigh up relevant considerations prior to making a decision.

Table 1 Wynne's taxonomy of uncertainty (10). Wynne's concept of «indeterminacy» has been excluded.

Risk	Uncertainty in the form of quantified probabilities of well-defined outcomes
Strict uncertainty	The outcomes are well-defined, but their probabilities cannot be meaningfully quantified.
Ignorance	Not all possible outcomes are known («we do not know what we do not know»)

Risk assessment of Eva

Quite naïvely we could argue thus: Eva has (among her other conditions) an elevated cholesterol level. An elevated cholesterol level is a causal factor in cardiovascular disease, and she therefore needs anti-cholesterol medication. This reasoning avoids any consideration of risk and uncertainty, but it is poor medical practice. Use of medication involves a risk of adverse effects, and not least in primary prevention the doctor needs to be familiar with the patient's baseline risk of disease (11). The doctor needs to identify the level of Eva's known risk factors.

Already here the problems start occurring. The doctor in our narrative has several tools for calculation of risk at her disposal. She starts with WHO's action programme for hypertension (12). According to this, the patient is mildly hypertensive, and with her age, elevated cholesterol level and likely hereditary component she can be placed in the group that has a high ten-year risk (20–30 %) of cardiovascular disease. In addition, the doctor uses her computer program for calculation of risk, based on the Framingham study and which she has received free of charge from a pharmaceutical company. The program returns a ten-year risk of ischaemic heart disease of 17 %, while the risk of stroke is estimated at 4.6 %.

However, our doctor also uses her clinical discretion and notes that despite her high cholesterol level, Eva has lived for a long time without any kind of symptoms. Moreover, she is uncertain whether a treatment of some of Eva's risk factors will in fact help reduce her risk. For example, lowering the cholesterol level has no purpose unless this will also help lower the risk of cardiovascular disease and early death. The doctor consults the comprehensive medical literature in this field and finds that no relevant treatment studies have been undertaken on Eva's category of patients, i.e. healthy women with elevated cholesterol levels who are approaching 70 years.

Uncertainty in calculation of medical risk

The doctor now has several options, but plans to start by using the calculated risk value and pursue an action programme in the hope of reducing the patient's risk. She is feeling, however, somewhat uneasy about this. She is uncertain of how she should rank the patient's family-related risk. She cannot know for sure whether the father died from heart disease, and exactly what amount of risk could be caused by a relevant disease in a maternal uncle? From her searches in the literature she knows that the treatment effects in this case have been extrapolated from studies of healthy *men* (13) and studies of patients of both genders *with* established cardiovascular disease (14). Not to mention all the known and unknown risk factors that are not measured and included in the estimate. All these factors introduce into the risk estimate an uncertainty which is not quantifiable in any meaningful way. We are thus dealing with *strict uncertainty* (Table 1).

Drawing up a calculation of the risk of disease versus the risk of adverse effects presupposes that all uncertainty can be quantified (15). When strict uncertainty is present, the calculation breaks down, unless we are to start guessing a figure for «residual uncertainty». We can set it to zero and pretend that Eva is a man, for example. But how robust is such guesswork?

Uncertainty in inferences from groups to individuals

Epidemiological risk factors do not in fact refer to individuals, but rather to investigated populations. From the paragraph above we can apparently deduce that the situation would be simpler if Eva were a man, since there are studies available on the treatment effect of anti-cholesterol drugs in healthy men (13). In this section we will clarify why epidemiological data cannot directly help reduce strict uncertainty to calculated risk in individual clinical decisions.

Making inferences from groups to individuals is simple when the groups are homogenous, for example black or white balls. People are extremely heterogeneous. Epidemiological studies therefore need to be large to statistically even out all individual idiosyncrasies. To be able to infer the risk for one individual from the risk for a certain group of men, we need to assume that he is representative of the group. He must not possess any medically relevant idiosyncrasies.

But such idiosyncrasies exist. Some of them may be included in the next study, with a finer resolution in the information on physiological and genetic parameters. Other idiosyncrasies are too subtle for statistical epidemiology. One could imagine an overweight, but heavily grief-stricken pastry chef who quit smoking six months ago. He deals with grief by eating his own elaborate patisseries. If he stops comfort-eating there is a high risk that he will start smoking again. In this case, dietary advice will increase his risk of cardiovascular disease, in spite of all convincing epidemiological data stating that overweight is an independent risk factor. After all, smoking entails an even higher risk.

To the extent that the doctor is aware of such idiosyncrasies, she will have to assess their importance. The question will be whether the pastry chef's representativity is so small that discarding the standard estimates of risk will be reasonable. The answer to this question will often be uncertain. Quantifying this uncertainty in the form of risk is nearly hopeless, since there is no epidemiological knowledge on grief-stricken pastry chefs. The doctor is therefore facing a situation characterised by strict uncertainty.

On other occasions, such issues objectively exist without the doctor being aware of them. From a bird's eye view, we are apparently observing a paradoxical situation: it seems less problematic to use the risk estimate *when we have less information on the patient*. Could a lack of knowledge help us avoid the problem of strict uncertainty?

The paradox can be solved by realising that before a decision on medical procedures is made, we are making a choice of methodology. It is always *possible* to choose to handle strict uncertainty as risk (possibly adjusted with the aid of some medical discretionary judgment). The question is whether this is *wise*. The doctor who receives the pastry chef as his patient discerns this choice of methodology and will in this case have ample reason to discard the risk estimate. However, an implicit choice of methodology is invariably made.

How large is the medical effect of using risk estimates instead of de-emphasising them and instead spending more time and effort on looking for relevant idiosyncrasies in the patient's history, life situation and

self-concept? Is the effect positive? Can we know anything in general about this at all?

In our opinion, it is self-evident that establishing mathematical control over clinical uncertainty with the aid of risk estimation is an illusion.

Uncertainty in biomedical theory

A possible conclusion to be drawn from the above is to remind ourselves that epidemiology is uncertain and hope that biomedicine may eliminate strict uncertainty.

The mechanisms of cardiovascular disease are not known in detail, but it appears evident that an elevated cholesterol level contributes to thrombosation of the blood vessels and is thus a causal factor.

Experimental biomedical research is undertaken under controlled and thereby often artificial conditions, such as in animals, isolated tissue or cell cultures. However, extrapolating from certain knowledge obtained *in vitro* to the clinical situation *in vivo* introduces strict uncertainty (16). This problem is potentially important in multifactorial diseases. In the experimental disciplines, «cause» means that A brings about B under otherwise identical conditions. *In vivo*, however, we cannot assume «otherwise identical conditions». Patients with an elevated cholesterol level may equally well remain healthy because of subtle interaction between factors that are unknown to us – an opaque causal complex is involved. We can ascertain that an elevated cholesterol level is a necessary factor in many of the causal complexes that are sufficient to trigger cardiovascular disease (17). These causal complexes, however, are not necessary, since there are other causal complexes that may also lead to cardiovascular disease. Biomedical knowledge can only describe the composition or frequency of such causal complexes to a limited extent, and has barely any predictive function in individual clinical situations. As of today, biomedicine cannot eliminate strict uncertainty from the consultation with Eva.

Complex diseases

This leads to the next question: Will biomedicine in the future be able to reduce or remove this strict uncertainty? Is this only a matter of doing enough research?

If it is possible to analyse and predict the various causal complexes of a disease on the basis of general mechanisms as long as sufficient knowledge is available, we can speak of a *complicated* disease. Although it will be difficult to establish an overview of the causes of the disease in each case, it will nevertheless be possible. However, if the individual variation and the number of synergies, homeostases and other regulatory systems of a somatic and/or mental nature are so great as to render the course of the disease essentially unpredictable, we can speak of a *complex* disease. The key issue in the distinction between a complicated and a complex condition is thus that a complex condition is essentially unpredictable, while the entire field of medical risk analysis is based on the view that we need to be able to predict disease to the greatest possible extent.

Is it appropriate to regard cardiovascular diseases as complex diseases? Or are they merely complicated? A relevant question in the philosophy of science is the extent to which the world is complex, essentially unpredictable, and thus hardly permitting the same degree of scientific success that the objects of science have permitted so far.

Medical science succeeds with simple diseases where only a single condition needs to be present, and where this condition can often be effectively removed or rendered harmless. Bacterial infections provide a good example. Achieving success with complex diseases is also possible, for example by using therapies that reduce the complexity that the symptoms reflect. Such an interpretation is especially evident in the psychiatric practices of the recent past. Lobotomy and psychotropic drugs clearly solved medical problems by reducing the patient's mental complexity. Drugs that have the ability to regulate genetic factors are another candidate for this discussion.

Treating complex diseases by reducing biological/psychological complexity is fraught with problems, both because of an essentially low predictability of the treatment effect, and because it may reduce the patient's quality of life. Therapies that primarily reduce individual complexity are more problematic than therapies that primarily remove the cause of a disease. When the patient is very ill, however, doctors are willing to go to great lengths. In primary prevention efforts, the patients are healthy during the consultation and we cannot tell whether they will ever be ill, and the effects of preventive treatment are marginal in many cases. The doctor in this narrative considers lowering the cholesterol level with the aid of statins, but the mechanism involved in the preventive effect of statins is not unequivocally clarified (18). We need to remain open to the possibility that this drug acts in other ways than only counteracting a single, plausible biological factor, i.e. the cholesterol level. Perhaps it involves a reduction of individual complexity? If so, the biomedical basis for treatment has been weakened.

Ignorance in clinical decisions

Ignorance is defined by the existence of relevant, but unknown outcomes (Table 1). Ignorance can be suspected beforehand, but determined only after the fact. A classic example is the surprising discovery of a high prevalence of vaginal cancer in adolescent *daughters* of women who had taken diethylstilboestrol during pregnancy (19). After the fact, we can ascertain that the decision to administer diethylstilboestrol was taken under a degree of ignorance that rendered all estimates of risk useless.

Ignorance of possible outcomes can be associated with all types of situations. The outcomes may be consequential for individuals, various groups of people and for diseases. Development of resistance from the use of antibiotics is an example of the latter.

With this in mind we will continue our fictitious patient narrative. The doctor recognises that the risk estimate must be supplemented with a conversation with the patient. She tries to explain the risk with the aid of the concept of NNT (number needed to treat) (9), but she senses that the patient fails to grasp this. Eva on her part feels that the doctor evokes trust, and she will therefore try to take these pills since the doctor suggests them.

Could this clinical situation involve any degree of ignorance, with a drug that is so well tested? When Eva returns for a check-up, she explains the following:

She is not affected by any known adverse effects. She has told her children about her elevated cholesterol level and encouraged them to have their own levels measured. A son has a normal cholesterol level, a daughter refuses to have hers measured and reproaches her mother for dwelling too much on these heart matters. Eva also says that this medication is excellent, because it relieves her of thinking so much about her diet. She has been feeling a little sluggish lately and assumes that it is because of the new pills. She has therefore let her husband take the dog out and prefers to watch the Discovery Channel. Surely it cannot matter that she has gained two kilos since her cholesterol level has turned out so well?

With the benefit of hindsight, the doctor now sees that her decision to propose anti-cholesterol medication to this patient was in fact inadequately analysed by failing to take the likelihood of disease, treatment effect or adverse effects into account. The treatment has *de facto* produced a number of unforeseen and potentially irreversible effects, including on family life, and it is by no means certain that the risk of cardiovascular disease has been reduced.

One could object that any absent medical effect in this patient is a calculated risk. We know beforehand that two-thirds of those who receive the drug will not have their risk reduced; this has been documented in randomised studies of anti-cholesterol drugs. This notwithstanding, the decision to prescribe

the drug was taken under strict uncertainty, as explained above. Added to this are all the changes in the patient's life which were not categorised as desired effects, nor specified as adverse effects, but which nevertheless take us far into the realm of ignorance.

Rational decision-making under uncertainty and ignorance: an ideal model

When all uncertainty can be quantified as risks it will be rational to use a risk estimate as the basis for decisions (15). When strict uncertainty or ignorance prevail it is *not rational* to rely on risk estimates alone, because the bottom has fallen out of the calculations. In this situation, rationality should rather be perceived as a general assessment of all available information, good reasons and subjective preferences. Of course, the risk estimate could be one of the good reasons to take into consideration.

It follows that any *rational* decisions must be made by the patient herself, since it is only she who is able to know her preferences as parts of herself and choose between values such as prolonging life as far as possible, the ability to function on long strenuous mountain hikes or to enjoy fatty cream sauces.

From this model of rationality it follows that the doctor's tasks include being an informant and an interlocutor. The doctor possesses a wealth of relevant technical knowledge. Insights into uncertainty in a wide sense are also relevant. For example, the doctor can explain that it is assumed that the pills can help some women without any established cardiovascular disease because they help some men, but we do not know for certain. Unpredictable issues may also appear, such as when some patients feel slightly lethargic and ascribe it to the treatment, and there is a risk that the gains will be outweighed by the losses.

In evidence-based medicine, much effort has been devoted to finding ways of presenting risk figures to patients in an understandable manner. The concept of NNT is an example (9). NNT, however, is based exclusively on risk estimates. It is a problem that when a risk message is presented in this way it conveys the impression that NNT describes hard facts. The truth is that some uncertainties go beyond what can be expressed by NNT. The patient needs to recognise that medical treatment is a double-edged sword, especially for those who are at a low risk. This is a matter of scientific literacy (20).

The doctor may also help the patient clarify her preferences through dialogue. However, preferences are strictly subjective and thus neither rational, nor irrational in themselves. Recognising this requires doctors to accept lifestyles that differ from their own.

In practice, it will by no means invariably be possible to adhere to the model for rational decision-making under uncertainty and ignorance. For example, some patients will appear unable to make an informed decision or are unwilling to do so, instead wanting «the doctor to fix it». Here, we will not enter into the debate on autonomy, but only point out that primary prevention most often applies to healthy people. They are thus better equipped to make autonomous decisions than patients who are ill and weary.

The role of the doctor in preventive medicine

We do not wish to support a proposal for doing away with risk assessments. They are appropriate for identifying high-risk individuals. We also believe that risk estimates are necessary, for example to identify cases for which a treatment proposal would be professionally *indefensible*. Through evidence-based medicine we have succeeded in setting the spotlight on the reprehensible practice of initiating forms of treatment that have no documented effect.

The patient (and the doctor) needs, however, to possess sufficient scientific literacy to be able to relate critically to her own wish to explore risk factors. There are no simple ways to achieve this. First, we need health information and debate of a kind that calls into question the medicalisation that goes on in society (21). Second, it is essential that in a consultation, the doctor calls into question the consequences of risk assessments before these are initiated. The benefits of this can be realised in the short as well as the long term. Third, we believe that general social development will produce a higher level of knowledge and awareness with regard to risk in general, not only in medicine (22). Eva's daughter may possibly represent a new generation in thinking that her mother is overly anxious about her heart. The more doctors can help promote a reflective attitude to the focus on risk, the better (23).

Conclusion: Uncertainty and ignorance should be included in the guidelines

In the grey zone of low risk, choices of concepts of uncertainty (in a wide sense) are of major importance. We have shown that characteristics of uncertainty and occasional ignorance are typical of primary prevention of cardiovascular diseases. We rapidly end up in situations where we cannot tell whether we are influencing the health of individuals in the right direction, and where the patient's reasons for her choices may be just as rational as hyper-specific risk assessments.

Before or during the risk analysis, the doctor may learn about the patient's clinical history, life situation or notions that all cause the traditional basis for primary prevention to dissolve. In this situation, should the doctor disregard this specific knowledge about an individual patient and choose to base her decision on statistical correlations in a population? In other respects we never tend to disregard knowledge. Instead, the doctor must rely on another type of rationality. The solution to this is not to do away with the guidelines and leave everything to clinical discretion. There is no reason to assume that such a change would have any other implications than even more examinations and defensive medicine (24).

However, all guidelines that we know of presuppose a decision-theory model that incorporates uncertainty only in the form of risk. We believe that guidelines should be of help to doctors, for example by elucidating uncertainty in decision making and allowing for completely individual issues that change the basis for examination and treatment. They need to function as a counterweight to defensive medical activity, for example by specifying situations in which abstaining from further examination and treatment is professionally sound. Such a change would constitute a step in the right direction of protecting the patient against overtreatment, protecting the doctor against the legal and moral pressure to perform defensive medicine and protecting society against excessive medicalisation.

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