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How precision medicine changes medical epistemology: A formative case from Norway

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Abstract

Rationale and Aims: Precision medicine (PM) raises a key question: How do we know what works when the number of people with a health problem becomes small or one ($n = 1$)? We here present a formative case from Norway. The Norwegian Board of Health Supervision was faced with a cancer patient, who had improved after treatment with a drug in the private health sector but was refused continued treatment in the public health service due to lack of clinical trial evidence. The Board overturned this decision, arguing that the drug had been unambiguously documented to work in the individual case. We aim to provide an in-depth analysis of this case and The Board's decision and thereby to illustrate and elucidate key epistemological and ethical issues and developments in PM.

Method: We provide our analysis and discussion using tools of critical thinking and concepts from philosophy of science and medicine, such as uncertainty, evidence, forms of inference and causation. We also examine the case in light of the history of evidence-based medicine (EBM).

Results and Discussion: The case reflects an epistemological shift in medicine where PM puts greater emphasis on evidence that arises in individual patients after the treatment is provided over pre-existing population-based evidence. PM may rely more heavily on abduction to decide what works and qualitative, rather than quantitative judgements. The case also illustrates a possible shift in the concept of causation from regularity accounts to mechanistic and process accounts. We discuss the ethical implications of a shift from more 'traditional' to 'personalised EBM'.

Conclusion: A framework that is more based on abductions and evidence arising in the individual case has problems in creating quantifiable, reliable and generalisable evidence, and in promoting transparency and accountability. PM currently lacks clear criteria for deciding what works in an individual, posing ethical challenges.

KEYWORDS

causality, epistemology, evidence-based medicine, medical ethics, philosophy of medicine, practical reasoning

1 | INTRODUCTION

How do we know if something works, or causes an effect, in a particular case? This key epistemological problem was discussed explicitly already 2400 years ago in the Hippocratic text 'On the Art of medicine' (*Peri techné*).[1] Today, precision medicine (or personalised medicine [PM]), which promises treatments tailored to individuals, is bringing this problem back to the forefront.[2] As the number of people who share a specific diagnosis approaches one ($n = 1$), statistically based strategies, such as randomised controlled trials (RCTs), become hard or impossible to conduct.[3] In this situation, several authors have argued that PM spurs an epistemological shift, creating uncertainty about what should be regarded as evidence, and that evidence-based medicine (EBM) needs an update.[2,4–7]

In this study, we describe a special case illustrating how medicine is brought out of epistemological balance. This case is not unique, but from it, specific challenges come out clear; it had clear consequences, creating a precedent in Norway, and, as relevant documents are here publicly available, we can perform in-depth analysis.

In 2019, the Norwegian Board of Health Supervision (hereafter 'The Board'), which examines cases where someone claims health services have been deficient, made a decision in the case of a cancer patient.[8] The patient had experienced improvement with an experimental immune therapy drug provided by a private hospital and paid out of pocket. Conflict arose when a hospital as part of the public health system declined to pay for the continued treatment due to a lack of evidence for the treatment from clinical trials. The Board overturned this decision stating that it had been unambiguously documented to work in this case. This created fierce ethical debate. If people of economical means can gain exclusive access to publicly funded treatment because they can try them out privately first, this undermines the key principle of equal access to care in the public healthcare system. The focus of this study, however, is the epistemological issues underlying The Board's decision: How could The Board know that the treatment worked? This question is of generic, international interest as PM progresses.

The aim of this study is to provide a detailed, in-depth analysis of the case and The Board's decision and thereby to illustrate and elucidate key epistemological and ethical issues and developments in PM. We will begin by presenting our method and The Board's decision in detail.

2 | MATERIAL AND METHODS

The main material for this study is The Board's written and publicly available decision containing its argument, hereafter 'The Decision'.[8] We will describe it *as the Board itself presents it*. This main material is supplemented with information via email from Halfdan Sørbye, the leader of the Norwegian Expert Panel for Secondary Care Services (hereafter 'The Expert Panel') (Sørbye, personal communication). This is an advisory body assessing treatment options when established treatments were exhausted in patients with serious, life-shortening disease, which provided critical considerations in underlying The Decision.

In our analysis and discussion of this material, we apply tools and concepts of critical thinking and philosophy of science and medicine, specifically uncertainty, evidence, generalisability, causation and forms of inference and argument. We also examine the case in light of EBM history.

All quotations are translated from Norwegian by us. Of ethical note, the patient has already identified himself publicly in the media.[9]

2.1 | The case

The case concerns a man who, as a 41-year-old in 2013, was diagnosed with cancer at the juncture between the oesophagus and ventricle. By 2017, all established treatments had been tried. An immune therapy drug, *nivolumab*, was offered to the patient, who paid out of pocket, at a private hospital. Nivolumab was not approved in Norway at the time and was not offered for this cancer type in the public health service as it was considered experimental. The patient, however, experienced a sudden, substantial improvement after starting the treatment, and then sought to have it continued in a public hospital (hereafter 'The Hospital').

According to The Decision, The Hospital declined to continue the treatment (4). In its argument, it first referred to lack of evidence from randomised clinical trials for this drug relating to this condition, stating that there were no "aspects about the tumour's properties or other aspects of the disease" that separated this patient from the general patient group, and that it 'could not [later] provide a treatment that they had not found reason to give in the first place'.[8]

The patient then contacted ***The Expert Panel***. According to The Decision, it stated the following:

(1) That the patient 'belongs to a subgroup of 11% that seems to benefit from the treatment'. This creates the impression that there was empirical evidence for the benefit of *nivolumab* after all. However, The Expert Panel here refers to two open-label, single arm, phase 2 studies on another immune therapy drug, *pembrolizumab*,[10,11] assuming a group effect from immune therapy drugs (Sørbye, personal communication).

(2) Radiological findings documented a 'striking' response to the treatment.

(3) That, on these grounds, further positive development of the disease was more likely if one continued the treatment, and

(4) That continuing the treatment was therefore advisable.

After the Expert panel assessment, the case was returned to The Hospital, which reiterated its 'no', this time referring to the principle of equal access to care, that is, that providing treatment to this patient and not to other patients who could not afford initial private treatment would create unwarranted differences.

In the end, the case proceeded to The Board. The Board then judged that, if the treatment is not continued in the public system, the patient has not been granted lawful, responsible health care (footnote[1]). In its argument, The Board cites two categories of evidence:

(1) with reference to the Expert Panel, it states that 'the patient belongs to a subgroup of 11% that seems to have good benefit from the treatment.'

(2) the Board cites The Expert Panel stating that the patient had 'a clear objective response' or a 'striking radiological response'.[12]

Based on the above, The Board assumed a documented, 'very good response to the treatment and that this response is also sustained after one year's treatment'. Then, addressing the patient directly, The Board writes: 'You have provided documentation that you belong to a small group of patients who stand out, and who have a large effect from the treatment'.

The Board calls the documentation 'comprehensive and unambiguous.' It also states that it thinks the treatment will be cost-effective if continued.

3 | RESULTS AND DISCUSSION

3.1 | Evidence before and after the intervention

In performing this analysis, we find it useful to separate the evidence behind The Decision into two categories: First, the evidence that was available *before* the intervention was provided, and, second, what became available only *after* the intervention.

In the present case, the only evidence in the first of these two categories that The Decision explicitly refers to come from the trials of another immune therapy drug, *pembrolizumab*.

Additionally, the experts involved—and The Board, which leans on them—may tacitly have relied on mechanistic knowledge (about the tumour and drug effects) that was also available before the intervention.

Then, *after* the provision of the treatment, new information becomes available that pertains to this patient. This is the 'striking', radiologically confirmed improvement.[8]

The way we read The Decision, the category of information that weighs most heavily for The Board is the evidence arising *after* the treatment is given. Had the doctors seen no or negative development in the patient, it would likely not have 'unambiguously' judged it to work. The Board refers to previous evidence from clinical trials as 'limited', and it relates to a different drug, but calls the observed changes in the case 'striking'. As mechanistic knowledge will likely form a larger part of the rationale for trying drugs in patients in PM, nivolumab may have been tried in this patient even with *no* existing clinical trial evidence beforehand.[6,13,14]

[1]The concept of responsible conduct is central in the Norwegian Health Personnel Act, §4. https://www.regjeringen.no/no/dokumenter/act-of-2-july-1999-no-64-relating-to-hea/id107079/

3.2 | An argument based on strong evidence and inferences?

How can The Board conclude that it has been 'unambiguously documented' that it was the treatment that caused the observed changes in this case? In this section, we will examine the types of inference that underlie The Decision and their ability to support the same. As we will see, deduction, induction and analogical inference are here all applied to evidence that was there *before* the treatment was given, while abduction stands out as also being applied to evidence that arises only *thereafter* in this individual patient.

3.2.1 | Analogy

When The Board—by accepting the judgement of the expert panel—tacitly accepts two studies on *pembrolizumab* as evidence for a similar effect of *nivolumab*, this is an analogy.[15] The weakness of analogical inferences is that small or unknown differences in the compared entities may render the analogy invalid and they are therefore usually considered unreliable for decision-making alone.

The application of analogy, in this case, may have broader relevance to PM: In situations where there is little evidence for a particular drug or doctors lack access to a certain drug, one may turn to treatments that are analogous to drugs that have more evidence.

3.2.2 | Deduction and induction

While deductions move from general knowledge or laws to particular instances, inductive inferences move from particular observations to general knowledge.[16] When the Board states that the patient belongs to a subgroup of 11% who have an effect of nivolumab, this is a deduction from general, population-based knowledge to this patient. This knowledge is in turn generated through induction from the data on individual patients in clinical trials.

The kind of deduction The Board performs here is common in EBM. The problem, in this case, is that the evidence generated from two phase 2, open-label, non-randomised, single arm trials is very weak by EBM standards. Additionally, the observed change can only be found in 11% of the population using *pembrolizumab*. In the language of uncertainty, the deduction The Board makes contains considerable uncertainty in applying class probability to case probability.[17] It is false to infer—as The Board does—that a change in this particular patient must necessarily be because he belongs to a subgroup that has an effect. This could still be due to some other cause.

By leaning on the experts who inferred from mechanistic, physiological knowledge that *nivolumab* had a chance of working, The Board may have relied on a second, different, deduction. The experts and The Board cannot, however, know all the interacting parts of the patient as a system and thus predict the outcome in a lawful manner. In other words, there is considerable *model uncertainty* in such cases,

relating to the difference between the simplified model of a phenomenon and the reality.[17] This has broader relevance for precision medicine where deductive reasoning from mechanistic knowledge is proposed to take on a greater role—as is presently the case in molecular tumour boards.[6,13,14,18] This means that model uncertainty becomes more important. Medical history, however, is full of examples where such deductions have led to ineffective or dangerous interventions.[19] On the other hand, biological knowledge can support inferences, which is also appreciated in the Bradford-Hill criterion of biological plausibility.[20]

In sum, our take-home message here is that, although these analogical, deductive and inductive inferences, and the evidence they rely on, can strengthen the argument that nivolumab worked and will continue to work in this case, they are quite weak especially by EBM standards, involving considerable uncertainty when predicting an effect in an individual—or deciding if the drug was the cause of a change in this patient. This has broader relevance for PM, where evidence can often be expected to be weak *before* the treatment is given.[3,5,6] Judgements may thus need support from other types of evidence and inference, which we turn to now.

3.2.3 | Abduction

Also called *inference to the best explanation*, abduction refers 'to the place of explanatory reasoning in justifying hypotheses',[21] implying 'that the hypothesis that best explains the evidence at hand should be embraced'.[22] In abductions one finds the best explanation for a phenomenon by combining observations about it with background knowledge about other factors, and by comparing the strength of different candidate explanations. The aim of an abduction is to persuade the audience that something is the actual cause of an event.[16] (p. 167).

In this case, the abductive argument runs something like this:

In a patient in whom other treatments are not working, who belongs to a group of patients who rarely improve spontaneously, in whom the biology in the case makes an effect plausible, in which there is some weak epidemiological evidence to support an effect, and in whom one sees a striking improvement just after an intervention with no better explanation (including placebo effects), the best explanation is that the treatment is the cause of the improvement.

The weakness of abductions is that there may always be some other better, unknown explanation for an effect. The patient may for example belong to a special subgroup that spontaneously improves, or the change may be a placebo effect. This does not mean, however, that abductive inferences cannot be strong or *forceful*, in the sense that they can make a conclusion *probable*.[16,21]

The abduction is supported in the present case by the radiologically verified change in the patient, which is supported by mechanistic knowledge, and by it being 'striking', occurring just after the treatment is given. These elements correspond to the Bradford-Hill criteria for causal relations in epidemiology (biological plausibility, effect size and temporality).[20] Importantly, this case illustrates that one can in many instances follow and document the change in the patient in relation to the treatment step by step.

On the other hand, while the abduction may make the explanation *probable*, this probability cannot be precisely quantified. This is a critical point: As discussed further below, abductions like this are hard to quantify and instead involve a qualitative judgement that contributes to a qualitative reduction in uncertainty. Moreover, while it may explain what has happened (improvement) it has in principle no bearing on what will happen in the future.

3.2.4 | Counterfactual inference

It may also be that the above-described abduction was supported by *counterfactual inference*. The Board—and the experts it relies on—may have asked: What would have happened to the patient if the treatment had *never* been given? In this and many other cases studies and/or clinical experience provide prognostic knowledge about what usually happens in the absence of treatment of a condition. This constitutes a form of control group. In this case, we know that the 5-year survival rate for this type of cancer without treatment is poor.[23] One case of spontaneous full regression has been reported for this type of cancer, and 19 in gastric cancers worldwide.[24] If these are seen as exceptions, the Board may reason counterfactually that the treatment is the likely difference-maker in this case. However, it is not possible to definitely say that this particular case improved due to the treatment and not some other unknown factor.[24]

In sum, the Decision is based on abduction, which is supported by several premises and seemingly also counterfactual reasoning, but this inference does not provide a necessary conclusion.

3.3 | Inference from past to future effect

A critical aspect of The Board's decision is, that it does not only draw a conclusion about the treatment having worked in the patient, but also predicts that it will work in the future.

This inference seems based on the premise that it was the drug that caused the improvement and that the patient's condition had not changed significantly. Against this premise, one might object that the effect of many cancer treatments dissipate after some time,[25,26] and that no long-term data exist for this drug, making it difficult to assess future development. Hence, if it were the drug that resulted in the observed improvement, it appears plausible that it will do so in the future. However, this is not well supported by empirical information about other cases.

3.4 | Epistemological shift: Towards 'personalised EBM'?

We will now relate the present case to current debates about PM representing an epistemological shift in EBM.[5–7]

EBM emerged in part as a reaction to problems by using expert judgement based on case histories and predictions from physiological knowledge, such as arbitrariness and lack of accountability.[27] The epistemology of EBM with its emphasis on RCTs, meta-analyses, systematic reviews and evidence-based guidelines has become dominant in medicine. As a telling example, The Board itself has previously explicitly stated that, 'If practice substantially deviates from professional guidelines, the risk that the service borders on the irresponsible increases'.[28] In the current case, The Board shifts its position: Responsibility is strongly tied to an abduction based on events in one individual case. Also, while in the previous EBM, evidence production and application have usually been held separate, the evidence is here created and applied in the same case. This reflects a drastic change that may take place with PM.[29] In these ways, The Board appears to shift from what we can call a 'traditional' EBM-based judgement to a 'personalised' EBM judgement.

This shift is evident in the contrast between the epistemology of The Hospital and The Board. The Hospital emphasised the evidence *before*, referring to the lack of RCTs. In fact, when it states that no evidence exists that suggests that the patient may belong to a subgroup that benefits and that it 'could not [later] provide a treatment that they had not found reason to give in the first place',[8] it in fact argues as if no new information has arisen after the treatment was given at all. The Board, by contrast, emphasised the evidence arising *after* the treatment in the individual patient.

Here, we should note that different study designs, such as basket and umbrella trials, have been proposed as alternatives when study populations become too small for 'traditional' RCTs.[30] However, there will still be many situations where no trial evidence exists for a certain tumour and treatment option.[3] One proposed alternative in this situation is *n*-of-1 trials where patients serve as their own controls, and which precisely utilise the evidence arising from the individual case *after* the treatment.[4] *N*-of-1 trials constitute a well-described, rigorous method.[31] However, these trials may often not be feasible, either for ethical (e.g., problem of giving periods of placebo to critically or acutely ill patients) and practical reasons (they are cumbersome in everyday practice). As a consequence, *n*-of-1 strategies that do not follow the same rigorous procedures, but are more like case histories consisting of detailed biomedical information that may be compared to other case histories and analysed with artificial intelligence, are proposed as an alternative.[32] Biologist and PM pioneer Leroy Hood, for example, when asked about why his team's Hundred Person Well Project did not have an RCT design, stated: 'We hope to develop a whole series of stories about how actionable opportunities have changed the wellness of individuals'.[32] In such stories, abductions would play an important role in inferring that certain actions caused the observed changes, and the stories would then be compiled as evidence for further practice. In sum, PM poses epistemic challenges to evidence production in medicine.

3.5 | Philosophy of causation—a shift?

To determine if something works is to determine if it has caused an (intended) effect. As part of an epistemological shift, The Board's decision thus also illustrates a shift in how one establishes causation in medicine.

Previously, in medicine and EBM, establishing causation has been tied strongly to the idea that one needs to identify regularities among not one, but many events, and to compare groups in which the treatment is present or absent.[33,34] Establishing causation is here strongly tied to statistics and quantification, and to establish cause in the individual case, one must be able to deduce an event in an individual from law-like, general knowledge about such cases.[34] This view goes back to early empiricism, and is congruent with a *regularity* view of causation and the related *probabilistic* view, and may also be called *empiricist* or *positivist*.[33–36]

In the present case, by contrast, causation seems primarily to be established by following and documenting the development in a single patient through time, in temporal relation to the treatment, step by step and by comparing the situation before and after the treatment. This is more in line with a *mechanistic* and *process* accounts of causation and a *realist* view (as opposed to empiricist view) where causation is understood not as consisting of regularities, 'but of real (and in principle observable) causal mechanisms and processes, which may or may not produce regularities'.[34] (p. 247). This kind of causal thinking may be better suited for establishing causal connections in a single context-dependent case, than for creating generalisable laws.[34] Such establishment of cause is less amenable to statistical analyses and can also utilise qualitative evidence for a qualitative reduction in uncertainty, which is also what happens in the present case.[34]

The Decision may thus be seen as an example of a shift in medicine's philosophy of causation from relying strongly on a regularity view of causation to more emphasis on a process and mechanistic view, but not a full departure neither from regularity views nor from counterfactual inference and interventionist accounts.[36]

In sum, the present case illustrates how PM fuels an epistemological shift and alternative types of evidence-production and causality, and we now ask whether this can provide an adequate basis for evidence-based practice.

3.6 | An adequate epistemology for evidence-based PM?

Above, we argued that The Board's argument in it this case found support particularly in analogy and abduction, potentially supported by counterfactual reasoning. In the era of PM, cases like this are far from unique. However, that does not mean that this kind of argumentation and inference will serve as a reliable basis for evidence production more generally in the future. The problem is not that such arguments cannot be forceful, it is that the challenges with arbitrariness and lack of accountability, which EBM tried to avoid, re-enter. EBM, with its GRADE system, has provided a framework for evaluating the strength of evidence that may not be perfect, but that provides a standardised system that everyone can relate to and that provides some predictability.[37] If one disrupts the rules for judging what works in medicine, this introduces an element of chaos.

Abduction relies strongly on human expert judgement and intuition. In this regard, it is akin to narrative reasoning (chapter 6).[38] This means that it is hard to quantify how likely an outcome is and how often such decisions will be correct. Such qualitative judgement may be better for giving crude estimates of probability, such as 'highly likely' or 'highly unlikely', 'not impossible', 'mostly' or 'quite possible' than providing a specific statistical likelihood.[16] Such estimates do not provide information about risk, understood as uncertainty that may be quantified, but it can reduce what has been called *strict* uncertainty.[39] This is uncertainty where the outcomes are well-defined, but where uncertainty cannot be quantified. Abductions thus represent a qualitative form of uncertainty reduction. However, the problem of quantifying uncertainties and reductions in uncertainties make such inferences less precise than judgements based on statistically based evidence (but not necessarily false or weak).

Of critical importance, without experiments with control groups, the risk of side effects will also be similarly hard to detect or quantify as positive effects.

Hence, the introduction of reasoning like the Board's brings back some problems EBM tried to overcome: Overreliance on physiological models, clinical experience and abductive reasoning that seems to suggest that the drug has worked, but that does not control for unknown, confounding factors and are hard to quantify and therefore often less reliable.[40]

3.7 | Generalisability

Importantly, an epistemological framework should provide generalisable knowledge that may be predictive in other cases. It should be pointed out, first, that one *can* make important generalisations from case histories and even single cases, depending on the context and question one has in mind.

If one wonders, for example, whether there is *any* chance of improvement in a specific condition, outcomes from only one or a few well-documented cases can make an important difference between no hope and some hope of improvement. This is the problem of induction turned upside down: Only one black swan disproves the generalisation that not all swans are white.[41] However, this does not establish a quantifiable, general connection between an intervention and the observed improvement.

More generally, medical generalisations were for a long time based on a series of case histories and physiological knowledge, and not all these generalisations were wrong. At the same time, such evidence suffers from a lack of validation through randomisation and a control group, a problem that EBM sought to remedy.[42]

Generalisations from case histories remain problematic. Tellingly, the Norwegian Health Ministry saw it as necessary to issue a formal statement in response to The Board's decision to underscore that it should *not* be regarded as generalisable to other patients or changing the knowledge base for future treatment: 'Experimental treatment is considered experimental even if the treatment has been tried and there has been a beneficial effect for concrete patients'.[43] What The Board did, however, was to generalise the idea that decisions like The Decision can be not only acceptable but the responsible way of determining what works.

3.8 | Ethical implications of an epistemological change

The epistemological change that the present case illustrates has several ethical implications:

On the positive side, one can envision that more people get a better personalised judgement, and access to helpful treatments that previously would not have been rejected with a blunt reference to lack of clinical studies. PM challenges the previous EBM and can also inspire it to reform and refine.

But some consequences may also be negative.

First, a lack of a clear, rule-based framework for assessing what is strong evidence, means that the epistemological shift poses problems of accountability, transparency, credibility and relevance, and may open the floodgates for poorly founded medicine. An important ethical consequence would be an increased difficulty in setting limits for what is considered the documented treatment and for who gets treatment. The weakening of limits will necessitate the drawing of new ones, a challenging task that is far from completed in PM.

Second, the lack of statistically based evidence on side effects is a significant problem for ensuring safety. Because the patients have little hope, eagerness to try new treatments could become excessive. Moreover, if one accepts that causal effects can be clearly demonstrated in single cases, then the same must be true for harms. Here too, what is formally taken to be 'documented' may be greatly expanded. This may change the responsibility of healthcare providers. Any unlikely event can be attributed to a treatment, for example, to vaccines.

Third, it may undermine thorough evaluation and research: If treatments are covered by insurers even if no clinical studies support them, the incentive for conducting such expensive research is compromised.

Fourth, the epistemological shift would generate large amounts of information pertaining to individuals, which is not necessarily generalisable to others. This means that patients may be subject to more decisions without high-quality, generalisable evidence.

As a fifth point, such an epistemological change can undermine fairness: When the likelihood of a treatment working is hard to quantify, it also becomes hard to estimate efficiency, for example, to make cost–benefit analyses that are used for prioritisation.

4 | CONCLUSION

In this study, we have applied a single case from Norway to highlight general epistemological challenges and developments in PM. We have shown how the Board's decision—and the difference between

the Board's thinking and the argument of the Hospital—illustrates a broader change in medical epistemology with great ethical implications: From more 'traditional' EBM to a 'personalised' evidence-based medicine (PEBM) that has yet to be clearly defined.

In our analysis, we have made a distinction between evidence that is present before the treatment is given and evidence that arises from the treatment in the individual case. The epistemological shift involves more emphasis on the latter.

Analysing the evidence and inference underlying The Board's decision, we find that the deductive, inductive and analogical inferences applied to evidence that was there before the treatment was given, are weak by EBM standard, illustrating a kind of situations that PM will often face. In seeking to verify that the treatment worked, The Board instead relied on analogy and abduction that relies heavily on evidence that arose in the individual case *after* the treatment. The case also illustrates a possible shift in causal thinking from a regularity view towards a process-oriented, mechanistic view, towards a new reliance on piecing together *n*-of-1 causal processes.

This illustrates how PM can provide important correctives and additions to EBM, but also comes with serious problems in producing quantifiable, reliable and generalisable evidence and promoting transparency and accountability that have yet to be resolved. Moreover, this epistemic shift poses several ethical challenges.

What the case primarily demonstrates, we have argued, is that there is no formalised and agreed upon criteria for assessing what works in the individual case when there is weak quantitative evidence from clinical trials and one relies more on physiological reasoning, case histories, analogies and abductive inferences. Importantly, the case illustrates how PM decisions based on analogies and abductions involve a qualitative judgement and reduction in uncertainty rather than quantitative. There is thus a need for more formalised criteria for judging when such inferences should be regarded as strong in PM.

Finally, there is no quick fix for these problems. The problem of deciding what works has been with medicine from the beginning.[1] The American physician William Osler is noted that, 'if it were not for the great variability among individuals, medicine might as well be a science and not an art' (cited in,[44] p. 1721). The present case illustrates that, while PM is the attempt of science to solve the problem of personalisation, Osler's point is still valid.

DECLARATION

I, the Submitting Author, Henrik Vogt, hereby declare that this study has not been published and is not being considered for publication elsewhere.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available at the Norwegian Board of Health Supervision Website, see https://www.helsetilsynet.no/publikasjoner/brev-og-horingsuttalelser-fra-statens-helsetilsyn/2019/statens-helsetilsyn-omgjoer-fylkesmannen-i-vedtak-gir-rett-til-noedvendig-helsehjelp/

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