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Mapping uncertainty in precision medicine: A systematic scoping review

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Abstract

Rationale: Although precision medicine is seen by many as one of the most promising advances in the field of medicine, it has also raised critical questions at various levels. Many of these concerns revolve around an observation described by Kimmelman and Tannock as the 'paradox of precision medicine': somewhat surprisingly, *uncertainty* seems to be a key characteristic of precision medicine in practice.

Aims and Objective: To better understand this concept and the underlying issues, a scoping review was undertaken to search for factors stated in the literature as contributing to or being aspects of uncertainty in precision medicine.

Methods: A systematic search of the literature was conducted in three databases (Pubmed, Web of Science, and Jstor) and complemented with a systematic hand-search. The initial search provided 1.252 items of which 51 articles for selected as eligible for further analysis. These articles were coded with MAXQDA and categorized into four main themes (a–d) of uncertainty. The main results were summarized and discussed with a view to the interrelations between different aspects and implications for precision medicine in practice.

Results: The mapping of different aspects and sources of uncertainty leads to the key result that 'uncertainty' should be understood as a cluster concept. Uncertainties are identified in many different respects and situated at different levels: Most complexity-related issues (theme a) can best be understood as *ontological* ('world-sided') aspects of the uncertainty paradox. Conceptual (theme b) and evidence-related uncertainties (theme c) are situated on an *epistemological or methodological* level, addressing foundational and normative challenges related to knowledge production in precision medicine. Finally, theme (d) targets issues on the level of material precision medicine *practices*. These levels are helpful to understand the different dimensions of the uncertainty paradox.

Conclusions: Uncertainty may not merely be a transient effect of the novelty of the precision medicine paradigm. Rather, it should be seen as a consequence of the ontological, epistemological and practical complexity of precision medicine, implying that uncertainty will not necessarily be reduced by more research. This finding

encourages further investigations to better understand the interactions among various factors and aspects of uncertainty in precision medicine and the resulting implications for research and medical practice.

KEYWORDS

evidence-based medicine, genomic medicine, individualized healthcare, omics technology, personalized medicine

1 | INTRODUCTION

Precision medicine is a novel, data-driven approach in biomedicine 'that takes into account individual differences in people's genes, environments, and lifestyles'[1] to develop treatments and preventive measures for diseases. This approach promises to achieve a more fine-grained and holistic understanding of the individual complexity of diseases and to develop innovative therapies that are precisely tailored to individual patient groups.* To achieve this goal, precision medicine critically relies on the analysis and amalgamation of complex forms of evidence using genomics, metabolomics and other omics technologies as well as e-health data sets and sophisticated IT infrastructure. In oncology, the pioneering and biggest subfield of precision medicine, patients can now be stratified and treated in subgroups based on genomic testing and the molecular profiling of tumours. In other areas of medicine, researchers and clinicians are currently investigating in what ways individualized treatments—for example, for chronic diseases—can and should take into account information regarding the metabolome, proteome, microbiome and lifestyle of patient subgroups. In these and other cases, precision medicine is hoped to lead to better-targeted and effective treatments. The main rationale behind this hope lies in the assumption that precision medicine tools will lead to a more exact, molecular and stratified understanding of diseases and, in a second step, will increase certainty regarding targeted development and choice of treatments for specific patient groups, replacing generalized disease classifications. On this basis, precision medicine aims to replace standardized group outcomes of clinical research, whose relevance for the individual patient is often unclear, with novel therapeutic principles that are tailor-made for the respective patient groups and thus effective with a higher degree of confidence.

Although precision medicine is seen by many as one of the most promising advances in the field of medicine, it has also raised critical questions at various levels. These include economic and political questions as well as ethical, legal and social issues (ELSI) that need to be considered and dealt with. For instance, economists have analysed questions revolving around the cost-effectiveness of precision medicine therapies for small subpopulations;[2] social scientists have scrutinized the political landscape in which precision medicine projects are embedded;[3] and bioethicists, biotechnology lawyers and social scientists have investigated ELSI of precision medicine. The latter includes work on incidental findings in genomic testing, issues in data privacy and regulation and discrimination in precision medicine, among other things.[4,5] In addition to these ethical and institutional issues, concerns have recently been raised about methodological and other epistemic aspects of precision medicine. Many of these concerns revolve around an observation described by Kimmelman and Tannock as the 'paradox of precision medicine'[6]: somewhat surprisingly, *uncertainty* seems to be a key characteristic of precision medicine in practice, in particular uncertainty regarding its evidential basis and in relation to clinical decision-making.† This observation is paradoxical because it is in tension with the main rationale of precision medicine just outlined, that is, the idea that precision medicine implies and *increases* certainty through a more exact understanding of and tailored therapies for diseases. It is precisely this tension that is the motivational starting point for this scoping review.

To approach this issue and to illustrate more clearly how uncertainty plays a role in the context of precision medicine, it is helpful to look at a few examples. In a much-noted commentary in the *New England Journal of Medicine*, Hunter[8] describes several aspects of uncertainty in precision medicine with an emphasis on uncertainty regarding testing procedures and the interpretation of complex data sets in view of their therapeutical implications. Other sources for epistemic uncertainty that have been highlighted in the biomedical literature include unclear evidence thresholds and opaque machine learning algorithms ('decision black boxes') for predicting therapeutic outcomes.[6,9] Uncertainty is also discussed as a feature of precision medicine in the philosophy of science and science studies literature. For example, the unclear causal status of genetic markers and the unreliability of genomic testing have been cited as contributing to uncertainty in precision medicine.[10,11]

In summary, uncertainty is highlighted as a *structural feature* of precision medicine. While uncertainty is a typical feature of many new developments, in particular in biomedical research, technology development and medicine, in precision medicine, more specific questions of uncertainty seem to become relevant too. In particular, there seems to be systematic link between uncertainty in precision medicine and other much-noticed aspects of this field—such as its complexity, its reliance on big data technologies, and its aim to reorganize disease taxonomies—that are in need of further exploration.

*The terms 'personalized medicine' and 'genomic medicine' are also used to express this idea. I will come back to associated terminological questions in the methods section.

†Also, see 'The precision paradox: How personalized medicine increases uncertainty',[7] which was published after I finished the main analysis of the scoping review.

To the extent that uncertainty is indeed a widespread issue in precision medicine, it points to an important epistemic dimension of this new approach in biomedicine, with potential implications for the theoretical and practical assessment of translational research and therapy. However, so far, there neither exists a broad overview of factors that may contribute to uncertainty in precision medicine nor a description of its main characteristics (or forms) in this context. For one thing, there is no integrated discourse of uncertainty in precision medicine. Rather, the discussion is scattered in different areas of biomedicine on the one hand and philosophy of science, science and technology studies and related metascience fields on the other. In addition, aspects and sources of uncertainty in precision medicine have only been discussed selectively and isolated in different areas of precision medicine. This is problematic as it is bound to only bring certain factors into focus, while neglecting others. Furthermore, there is an underlying concern that precision medicine may at times be ill-positioned to address crucial issues of uncertainty due to its strong focus on certainty and precision.

This article is meant to mitigate this situation by reporting the results of a systematic scoping review of uncertainty in precision medicine. More specifically, this review article aims to answer the following research question:

> *What factors are stated in the literature as contributing to or being aspects of uncertainty in precision medicine?*

This review of different aspects and sources of uncertainty in precision medicine is meant to serve three main purposes. (1) It will provide an integrated overview of factors that have, so far, been discussed in a fragmented way, thereby generating a more comprehensive picture of the facets of uncertainty in precision medicine. This will also shed light on the notoriously ambiguous concept of uncertainty and its use in this specific context. (2) The review shall enable a systematic discussion of forms and aspects as well as sources and effects of uncertainty in precision medicine. Such a discussion could then (a) explore the interplay of different uncertainty-inducing factors, (b) build connections to other uncertainty discourses and frameworks in theoretical medicine and healthcare,[12–14] and (c) enrich the metascientific discourse on uncertainty.[15,16] (3) The results of this review will also be useful for identifying normative implications of different aspects of uncertainty in precision medicine, thereby contributing to an integrated discussion of epistemic and ethical issues in precision medicine and, by implication, to socially responsible innovation and application in precision medicine.[17] In fact, this article takes initial steps in this direction, starting from an argument for the likely persistence of uncertainty in precision medicine that feeds into the existing discourse.

In addition to these main objectives, the scoping review is intended to prepare an empirical project that will investigate the handling of epistemic challenges in precision medicine of chronic diseases.[‡] The generated findings will be used for 'theoretical senitization' with regard to uncertainty-related topics that might be relevant, absent and/or different in this context.

2 | METHODS

Systematic scoping reviews are used to survey the literature in an area of interest, for example, to identify the available evidence or knowledge gaps in a specific field.[18] Moreover, they can be used as a tool 'to identify and explore characteristics or factors associated with a particular concept'[19] in a given body of literature or field. This is particularly useful in cases of complex concepts that include diverse elements (e.g., uncertainty can be understood as an ontological feature of the world or an epistemic state).[20] In this sense, this review aims to *explore and map the concept of uncertainty to better understand the types of epistemic challenges it actually targets in the field of precision medicine*. To achieve this aim and to adequately scope a fragmented body of literature, the approach deployed here is very broad and attempts to cover as much of the available literature as pragmatically feasible. This is reflected in the broad research question as well as the search strategy and the eligibility criteria deployed. Before I go into these in more detail, a few terminological remarks on the notion of 'precision medicine' are in order.

As stated above, 'precision medicine' is not the only term that is used to express the idea of this new type of medicine. Next to 'personalized medicine' and 'genomic medicine', the terms 'systems medicine', 'stratified medicine', 'individualized medicine' and 'P4 medicine'[§] are also in use; sometimes interchangeably, to express the same approach, sometimes to emphasize specific aspects of the basic idea as favoured by different stakeholders (e.g., 'P4 medicine' as a signature term of big data companies in healthcare).[21] However, the terms 'precision medicine', 'personalized medicine' and 'genomic medicine' used in this scoping review, are clearly the most prevalent terms in the current discussion and have sufficient overlap in their usage. They appear, for example, much more frequently in medical journals than the other terms and are dominating public and scientific debates.[¶] The focus on these terms was hence suitable to secure an inclusive search strategy.

2.1 | Eligibility criteria and search strategy

To operationalize the research question ('What factors are stated in the literature as contributing to or being aspects of uncertainty in precision medicine?') for the scoping review, inclusion and exclusion criteria were meant to be sufficiently broad so as not to run the risk of excluding too much potentially relevant literature. It was stipulated

[‡]Both scoping review and empirical research project are embedded in the cluster of excellence 'Precision Medicine in Chronic Inflammation' (https://www.precisionmedicine.de/en/about-the-cluster).

[§]P4 medicine stands for *p*redictive, *p*reventive, *p*ersonalized and *p*articipatory medicine.

[¶]For example, a PubMed search in May 2021 yielded 38.1 thousand hits for 'precision medicine', 21.5 thousand hits for 'personalized/personalised medicine', 15.7 thousand hits for 'genomic medicine', while it generated only 4.9 thousand hits for 'systems medicine', 2.1 thousand hits for 'individualized/individualised medicine', and under 1 thousand hits for 'P4 medicine' and 'stratified medicine'. Google's Ngram Viewer shows a similar trend.

that articles were to be *included* for further analysis if they (a) explicitly discussed some form of uncertainty and/or general evidential issue (e.g., lack of certainty regarding the clinical implications of genome analysis, unclear evidence thresholds) and (b) focused on precision medicine in the context of biomedical research and/or therapy and individual healthcare. Articles were to be *excluded* if (a) they did not discuss uncertainty or general evidential issues in precision medicine in the context of biomedical research and/or therapy and individual healthcare (e.g., articles that focused on public health), (b) their focus was solely on economic or institutional uncertainty associated with precision medicine applications (e.g., how to regulate precision medicine by law), or (c) their focus was on a specific case or study with no general implications for precision medicine (e.g., a study focussing solely on a specific biomarker or therapeutic agent).

A systematic search of the literature (up until July 2021) was conducted in three databases covering a wide spectrum of literature in the life sciences, medicine, the social sciences and the humanities for publications that were published between 2011 and 2021: PubMed, Web of Science and Jstor (see Figure 1 for details). The search was limited to English language articles with no limitations regarding article type. The following Boolean search was used in each database: Articles that have ['precision medicine' OR 'personalized medicine' OR 'personalised medicine' OR 'genomic medicine'] in the title AND [uncertain* OR certainty OR eviden*] in any field. The terms 'certainty' and 'eviden*' were added to the second-word group, as uncertainty is often phrased as a low degree/insufficient/lack of certainty or spelled out as (a consequence of) an evidential issue. For instance, in comments or systematic reviews on specific precision medicine approaches, uncertainty is frequently expressed in terms of unreliable, unclear or ambiguous evidence and so forth. An initial search with the terms of the second-word group restricted to title/abstract yielded unsatisfactory results, in part because many of the potentially relevant articles do not have abstracts, or the abstracts are not reliably stored in databases. For this reason, the final search procedure was not restricted in this way.

The scoping review was complemented with a systematic hand-search from journals in philosophy and social studies of science/medicine because many of the key journals in these fields are not reliably listed in databases. Even Jstor, one of the most comprehensive databases for these fields, is not a fully adequate humanities equivalent to PubMed, since not all journals, and especially not all current volumes, are listed here. As I expected many important discussions of uncertainty in precision medicine to take place in philosophy and social studies of science/medicine, hand-searching key journals in these fields was the best available option. The journals were selected based on background knowledge regarding their standing in the respective fields and the publication of important articles on precision medicine in some of them:

- *British Journal for the Philosophy of Science*;
- *BioSocieties*;
- *European Journal for Philosophy of Science*;
- *New Genetics and Society*;

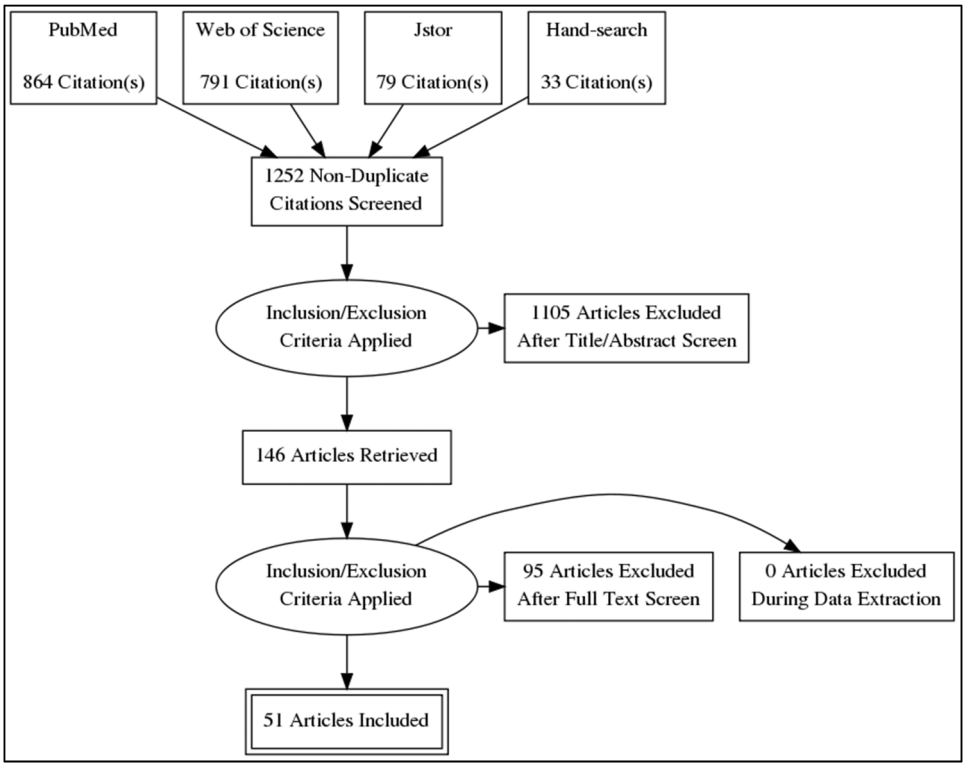

FIGURE 1 Flow diagram (generated with PRISMA, "Preferred Reporting Items for Systematic Reviews and Meta-Analyses", flow diagram generator)

- *Philosophy of Science*;
- *Science, Technology, & Human Values*;
- *Social Science & Medicine*;
- *Social Studies of Science*;
- *Studies in History and Philosophy of Science Part A and C*;
- *Synthese*;
- *The Journal of Medicine and Philosophy*; and
- *Theoretical Medicine and Bioethics*.

This selection was validated by experts in my network. All volumes from 2011 onwards were searched for relevant articles, excluding book reviews. In addition, articles that were recommended by colleagues and two articles from a well-known anthology[22] were added to the search results. These steps of the search strategy contribute to a robust review strategy by reducing selection bias due to database limitations.

2.2 | Screening and selection of articles

Details for all search results were downloaded into the reference manager Endnote and duplicates were removed, resulting in 1.252 items. All titles and abstracts were screened for relevance. In case, no abstract was available or the information provided in the abstract was insufficient for a decision, articles were kept. This procedure resulted in 146 items for full-text eligibility assessment—with one article not being retrievable.[23] Based on the predefined inclusion and exclusion criteria, 95 articles were excluded as not relevant, resulting in 51 articles for further analysis. At this stage, most articles were excluded based on exclusion criteria (a) and (c), that is, they only mentioned a very generic form of medical or scientific uncertainty and/or were solely concerned with specific biomarkers and so forth.

2.3 | Data extraction and analysis

All 51 articles were analysed with a software tool for content analysis. The computer-assisted data analysis programme MAXQDA was used to code key text passages that addressed some form of uncertainty and/or general evidential issue related to precision medicine, thereby identifying core themes relating to the research question. This was done in an iterative process along the lines of 'abductive qualitative research',[24] that is, an approach that does not start with a fixed coding framework but is open to the material while being informed by relevant background knowledge. In particular, the discussion of types and sources of uncertainty in Han et al.[25] provided relevant starting points for the coding process. Coded passages were clustered into main themes and refined according to the principles of qualitative content analyses.[26,27] This process resulted in four main themes of uncertainty in precision medicine. The main results are summarized and discussed with a view to the interrelations between different aspects and implications for precision medicine in practice.

3 | RESULTS

Thirty-eight of the analysed articles were published within the last 5 years. Only 13 of the articles were published before which may imply an increasing interest in uncertainty, but could also be a mere consequence of a general increase in publications on precision medicine. Although there are more applications for precision medicine now, there still is a strong focus on oncology in the analysed publications. Most articles (39) were publications in medical and applied life science journals (and one book chapter), such as *Genetics in Medicine* and *Journal of Clinical Oncology*. Nine articles were published in life science-oriented *Humanities* and *Social Science* journals, such as *Studies in History and Philosophy of Science* and *New Genetics & Society*. Only three of the analysed articles were published in broad interdisciplinary journals, for example, *Science* and *Nature*. The most common article type (22 articles) was commentary/brief analysis (including viewpoint pieces). Thirteen articles reported the results of medical research (including reviews), nine articles the results of social research (e.g., interview studies). In addition, there were three case studies in history and philosophy of science and four texts that were classified as introductory overviews. The analysis did not reveal any systematic correlations between aspects of uncertainty discussed and specific fields or publication formats. A numbered list with bibliographic information of all analysed articles is available in Supporting Information: Appendix I.

The analysis identified four main themes of uncertainty related to the research question: (a) complexity-related challenges, (b) conceptual issues, (c) uncertainty in evidence collection and synthesis and (d) practical challenges and infrastructure. For an overview of all themes and main MAXQDA codes see Table 1. In the following paragraphs, I present the findings on these themes, emphasizing important elements and aspects of each. Overlapping points are each assigned to one of these themes, highlighting some connections. Key points will be illustrated with quotes from the analysed articles. Bracketed numbers in the results section refer to the bibliography in Supporting Information: Appendix I.

3.1 | Complexity-related issues

Precision medicine deals with highly complex systems that are a source of empirical uncertainty precisely because of their complexity. This aspect is addressed in publications that emphasize the challenge to take into account the vast number of factors and interactions influencing biological processes at different levels (25) or question the possibility to understand and predict complex systems in precision medicine (15). In particular, a focus on genomics is described as 'proliferating uncertainty' (29) and as a complication for generating reliable evidence for precision medicine applications (26), as it reveals layers after layers of complexity that can hardly be comprehensively accounted for. This complexity is also reflected in discussions of complex disease patterns and traits (20, 47, 48), which are seen as a major barrier to accurate diagnoses. In precision

TABLE 1 Coding system

Overview: Themes and main MAXQDA codes
Theme (a): Complexity-related issues
complexity simpliciter
complex patterns/disease traits
interventions
Theme (b): Conceptual issues
evidence frameworks
evidence standards
classification
misc
Theme (c): Uncertainty in evidence collection and synthesis
sampling
instability
validation
evidence integration
misc
(gen)omics
Theme (d): Practical challenges and infrastructure
knowledge bases
data processing
standardization practices
tissue sampling
misc

oncology, this issue is most prominently discussed in relation to tumour heterogeneity and misclassification (38, 51). An important reason for this assessment is 'inherent limitations of a single biopsy reflecting the genetic complexity of an advanced tumour and heterogeneity of the tumour microenvironment' (9), that is, limitations to a precise examination of tumour tissue (see also the discussion of tissue sampling below). Complex precision medicine *interventions* are considered to contribute to uncertainty too (17, 18), as they comprise 'complex ensembles of technologies, procedures, and the clinical characteristics of patients' (17). The rationale for this assumption is that each element in an intervention in precision medicine (e.g., genomic testing, interpretation of findings, idiosyncrasies of patients) is subject to specific types of vagueness that in combination generate even more severe forms of (complex) uncertainty in clinical contexts.

3.2 | Conceptual issues

Precision medicine does not only raise empirical but also conceptual questions. Most uncertainty-related conceptual issues that were discussed in the literature concern challenges to evidence standards and frameworks in precision medicine. First, there are discussions about conceptual uncertainties on what it means for a finding to be significant and regarding proper thresholds for deciding whether a finding should be considered actionable or not (6, 16, 51). Second, there is doubt regarding the use of existing evidence standards for clinical practice, for example, the clinical utility of genetic risk scores (9, 20). Third, there are foundational uncertainties regarding the conception and use of evidence frameworks in precision medicine (12, 14, 15, 32, 35). These are expressed in terms of precision medicine-induced challenges to established evidence frameworks, in particular, randomized controlled trial regimes in evidence-based medicine (EBM), and the unavailability of a widely shared and practical evidence framework that could replace EBM in supporting clinical decision-making. A related factor that is seen as contributing to conceptual uncertainty in precision medicine is the lack of shared criteria to compare results from different studies, which is considered to inhibit the development of reliable recommendations for clinical care (40).

A further conceptual issue concerns stratification attempts in precision medicine. As mentioned in the introduction, precision medicine aims at the stratification of patient groups as a basis for fine-grained treatment regimes. Two articles point out that there are difficulties in defining thresholds and criteria for distinguishing patient groups that will or won't benefit from a certain treatment due to inherent biological vagueness and blurred boundaries (31, 47). A related issue concerns decisions regarding disease stratification. In precision medicine, this is often attempted by using (gen)omics data as a basis for new disease subcategories. However, this approach may, according to Green et al., suffer from existing uncertainties in the reliable identification of clinical phenotypes and result in unstable disease subcategories as 'the interpretation of genomic data is inherently dependent on existing systems of classification' (15).

3.3 | Uncertainty in evidence collection and synthesis

Most discussions on aspects and sources of uncertainty in precision medicine in the analysed literature could be clustered under this theme (115/172 quotes coded in MAXQDA), with the majority relating to (gen)omics. This subsection first presents general aspects of uncertainty in evidence collection and synthesis, namely issues with sampling, evidence instability, validation and integration. Subsequentially, it will report evidential issues specific to (gen)omics.

Since precision medicine aims at patient stratification, it often needs to rely on small sample sizes to test new treatment options. Some authors see this with concern, since it may increase the risk of statistical bias and error. In terms of evidence collection in precision medicine, this is considered to result in uncertain and low-grade evidence on treatment choice (10, 31) and as overestimating the relevance of newly discovered biomarkers (15). In addition to these discussions, there are concerns regarding evidence stability in

precision medicine that may contribute to uncertainty at different levels. Fast developments and the increased scale of research in precision medicine do not only induce uncertainty related to knowledge infrastructure and standardization practices (see below). According to some articles, they generally generate instable and 'rapidly outdated' evidence (2, 14, 39). Instability may also be a consequence of measurement instability in trials overestimating different response rates to therapeutic agents (46). One article (45) emphasizes diagnostic uncertainty in precision oncology as a consequence of instable evidence that is frequently revised using 'a multitude of technologies and tests' and that 'calls into question the extent to which the much sought after "finality" in cancer diagnosis can be achieved' (45). In connection with the robustness of evidence in precision medicine, some articles highlight a lack of adequate validation processes as a source of uncertainty. This may be the case for the analytic and clinical validity of biomarkers (including genomics) (13, 18, 21, 28, 38), machine learning algorithms—that is, artificial intelligence (AI) approaches in precision medicine (49), and may also affect entire biomarker ensembles: 'for most approved targeted medicines, the complete intervention ensemble has not been fully tested, and it is not known whether the marker diagnostic is actually a necessary component of the therapeutic strategy' (17).

Precision medicine needs to integrate large amounts of genomic, clinical and other types of information to succeed. This demand generates challenges that may in turn induce uncertainties, for example, regarding the integration of diverse types of data from different sources and on different levels (30, 49)—in particular when there is 'a lack of alignment between genomic and clinical parameters' (2), and regarding ways to synthesize data with contradictory information (4). Additional issues that were emphasized are that it may be unclear how to handle situations where data sources differ in data quality and reliability (13) and how to interpret the results of automated evidence integration and interpretation tools (31).

As stated above, most issues in evidence collection and synthesis are related to the use of omics technology with genomics as its main approach. Several articles highlight the enormous volume of information in genomic testing as a major cause of uncertainty, suggesting that the amount of big data exceeds our ability to analyse the information in a meaningful and precise way (1, 37, 38, 39 49). But the most discussed (and partially overlapping) aspects of uncertainty in omics relate to unclear and erroneous results next to predictive limitations and insufficient knowledge of genomics: Many articles point out that there is much ambiguity in the interpretation of (gen)omic results in the context of precision medicine, in particular regarding biological significance, diagnostic value for individual patients and treatment choice (e.g., 4, 11, 22, 34, 37, 38, 45). Variants of uncertain significance (VUS) are considered to be among the most important epistemic challenges in precision medicine, that is, it seems unclear how to interpret and how to deal with genomic variants with unknown biological/clinical implications (e.g., 16, 27, 40, 42). One article highlights that this problem is exacerbated by the increasing use of whole-genome sequencing technologies, which often generate high numbers of VUS (26). Furthermore, a qualitative case study in personalized medicine (11) suggests that interpretative omics technologies that are supposed to provide decision support (in this case: risk scoring in transcriptomics) are not always well understood by health practitioners, leading to the 'black-boxing' of results as another source of uncertainty in precision medicine.

An additional issue discussed in the analysed articles is the diagnostic accuracy of genomic testing which is sometimes considered unreliable due to inherent limitations (e.g., 8, 33, 34), (possibly) in particular in the case of commercially available tests (24). According to several articles (37, 38, 40), testing limitations frequently lead to erroneous results, most importantly to false positive and false negative results, with corresponding uncertainties for diagnosis and therapy in precision medicine. Moreover, uncertainty in relation to (gen)omics is often expressed in terms of predictive limitations at different levels—this factor is often associated with testing and VUS (20, 25, 32, 48). However, James (25) mentions another relevant factor, namely that the 'cause-effect relationships at the individual level exhibit substantial stochastic (i.e., random or chance) variability that undermines individual and subgroup predictive validity'.

Finally, an issue discussed in several articles relates to general limitations in our medical understanding of (post)genomics, which is often expressed in knowledge gaps concerning the relationship between the level of genomics and biological/pathological macrocharacteristics (1, 21, 37, 44), where 'our' can also refer to the limited understanding of nongeneticists in precision medicine (33, 44). In one article (2), rapid change in genomic knowledge is considered a factor that contributes to this type of uncertainty in precision medicine.

3.4 | Practical challenges and infrastructure

Precision medicine is big data-intensive. Hence, it requires a sophisticated data infrastructure. Several of the analysed articles discuss challenges in establishing and using such a knowledge infrastructure for precision medicine in relation to epistemic uncertainties. One basic source of practical uncertainty is (big) data quality, especially in terms of data completeness, adequate metadata or sample quality in biobanks. These problems are seen as a consequence of inadequate data infrastructures, curation, and/or management (13, 15). Additional issues are considered an effect of the fast turnover of evidence in the field of precision medicine, since databases 'cannot rely on the existence of stable, standardized forms of knowledge and practices and thus contain uncertain and sometimes contradictory information' (2). Data *processing* can also be a source of uncertainty in precision medicine. This includes issues where the amount of noise in different types of big data—collected from different sources—leads to difficulties in data interpretation and to uncertainties in data integration processes (16).

There are two more key practical aspects that were identified in the analysis. Both are interwoven with data infrastructure and processing. The first aspect concerns standardization practices that contribute to uncertainty in precision medicine. For one thing, a lack

of *shared* standards for some laboratory services may contribute to data-related uncertainties in precision medicine (1). Also, standardizations for treatment options may be difficult to keep current in light of the fast-evolving evidence landscape in genomics and related fields (9). The second aspect concerns tissue sampling that may lead to an uncertain basis for diagnosis and therapy choice. Issues addressed in the analysed literature include poor sample quality in the context of precision medicine (51) and challenges in collecting adequate DNA samples, for example, due to contaminations (26). An interview study with scientists and clinicians in precision medicine (29) also emphasizes tissue sampling practices in a clinical setting as a source of uncertainty. The authors describe, among other things, how it can be very difficult to collect (sometimes multiple) samples when patients are very unwell, which can lead to quality trade-offs and ambiguous biopsy results (see above).

4 | DISCUSSION

The results of the scoping review clearly show that the discussion of uncertainty in precision medicine is indeed scattered over different academic fields and that the concept in use is quite diverse.

Hence, mapping and synthesizing different sources and aspects of uncertainty in precision medicine is a useful contribution to an improved understanding of the many facets of this concept in precision medicine and can serve as a starting point for further analysis. The next paragraphs will (4.1) discuss salient aspects of the findings, (4.2) highlight uncertainty-related challenges and implications that seem most relevant for further exploration and (4.3) point out the limitations of this review.

4.1 | Main results

Since uncertainty in precision medicine is addressed in biomedical, social scientific and philosophical fields, it is important to pay attention to the interdisciplinary nature of the discussion—which is reflected in the systematic integration of hand-searched social science/humanities journals. Notably, much of the discussion of uncertainty in precision medicine takes place in commentaries and short theoretical analyses in science journals. This points to an important function of these publication types. They serve as spaces of inner-scientific reflection and timely critical explorations of new scientific/medical developments and associated challenges that merit further analyses.

The mapping of different aspects and sources of uncertainty leads to the key result that 'uncertainty' in precision medicine cannot be sharply defined. Rather it should be understood as a *cluster concept* where the different instances are connected via 'a complicated network of similarities overlapping and criss-crossing'.[28], § 66 This result is not only consistent with the broader discussion of uncertainty in medicine but is further confirmation of the prevalent understanding of this concept in the philosophy of medicine.[13]

Uncertainties in precision medicine are identified in many different respects and situated at different levels—representing different perspectives: Most complexity-related issues (a) can best be understood as *ontological* ('world-sided') aspects of the uncertainty paradox. Conceptual (b) and evidence-related uncertainties (c) are situated on an *epistemological or methodological* level, addressing foundational and normative challenges related to knowledge production in precision medicine. Finally, theme (d) targets issues on the level of material precision medicine *practices*. These levels are helpful to understand the different dimensions of the uncertainty paradox. Naturally, there are many intersections between these ideal-typic levels and some aspects of uncertainty in precision medicine extend across several levels.

For instance, the uncertainty resulting from the multilevel complexity of biological systems (i.e., humans) and disease traits seems to translate into uncertainty in the handling of information in precision medicine approaches aiming to represent the various features of a patient/disease as comprehensively as possible. The generated amount of (big) data on possible biomarkers is massive and extremely heterogeneous and, because of that, may elude straightforward analysis, unambiguous synthesis and clinical interpretation. In this sense, it can be seen as the epistemic reflection of ontological uncertainty. Evidence-related and conceptual uncertainties also seem to go hand in hand. Ambiguities and difficulties in the meaningful interpretation of new biomarkers in clinical settings, in particular in relation to their actionability, will in many cases be intimately linked to unclear evidence thresholds and barely existing evidence frameworks to support clinical decision-making. In addition, methodological and practical challenges may be entangled in such a way that they mutually amplify uncertainty in precision medicine. This is most evident in situations where testing errors and low-grade evidence are in part a results of small subgroups and statistical bias and in part a results of uncertainty generated in untrustworthy data processing. Finally, consider the reported challenges in finding reliable ways to stratify diseases. These challenges will not only be intensified by the rapid change in our (still limited) understanding of (post)genomics and the evolution of clinical evidence over time. To the extent that the validation of biomarkers is indeed realized in unreliable practices, it will further contribute to this aspect of uncertainty in precision medicine. An implication of the sketched interactions is that research results and clinical decisions in precision medicine can be uncertain not only in different degrees but also in various respects at the same time.[††]

While some of the findings of this scoping review were to be expected in light of well-known debates on general obstacles of precision medicine—uncertainty as a consequence of complexity, massive data and issues in omics, such as the interpretation of new biomarkers and VUS—there are also two unexpected gaps in the analysed literature. First, the analysis revealed only little discussion of AI as a decision black box which is unexpected given the prominence of discussions on the need for explainable AI in medical contexts.[29,30] Second, the review did not identify any specific discussions on

[††]Thanks to Robert Meunier for making me aware of this.

uncertainty in identifying and measuring social biomarkers or 'socio-makers'.[31] This is unexpected given that (a) precision medicine is often explicitly promoted as paying attention to lifestyle and other socioeconomic information and (b) that measuring socioeconomic aspects of health/disease is widely considered a challenging task. This lacuna could indicate that there still is a strong emphasis on (gen) omics and on the biological aspects of disease in precision medicine. (See, however, the remarks on limitations of the scoping review.)

This discussion provides starting points for an interdisciplinary research programme that systematically explores and assesses the interplay of uncertainty-inducing factors in precision medicine. Such a programme could build upon and enrich discussions in theoretical medicine and neighboring metascience fields, in particular empirical philosophy of science and science and technology studies (STS). This includes debates on the best taxonomy of sources of uncertainty in medicine[25,32,33] and decision-making in clinical contexts[13] and may also enrich more general discussions on scientific uncertainty with examples of ambiguous evidence thresholds and frameworks that do not seem to fit neatly within established ways of distinguishing different types of uncertainty.[34] Another line of discussion to build upon revolves around the fundamental question whether more evidence will necessarily lead to better medicine, starting with scepticism regarding the medicalisation of society[35,36] and critical voices on the capability of the problem-oriented record and EBM in providing us with useful data and a 'serviceable taxonomy for classifying the "problems"'.[37] Finally, recent work at the junction of empirical philosophy of science and STS is highly relevant for exploring uncertainty in precision medicine from a research-oriented viewpoint. In particular, work that investigates challenges in big data-driven life science (including data curation and processing) and the entanglement of theoretical assumptions, material practices and infrastructure will hold theoretical tools for further analysis of the uncertainty paradox in precision medicine.[38–41]

4.2 | Implications for precision medicine

One of the purposes of this article is to provide a broad overview of uncertainty in precision medicine to identify normative implications for socially responsible research, innovation and health care. Although the results of the scoping review should be considered as tentative in nature and an in-depth discussion of the ELSI of precision medicine is beyond the scope of this article, it will be useful to draw out initial points for further consideration. This seems warranted since the analysis so far corroborates the view that uncertainty may not merely be a transient effect of the novelty of the precision medicine paradigm. Rather, it should be seen—at least to some extent—as an (ultimately expectable) consequence of the ontological, epistemological and practical complexity of precision medicine, implying that uncertainty will not necessarily be reduced by more research. This point echoes authors who, based on more theoretical considerations, question the extent to which precision medicine is and can be more than a promise or vision.[7,42]

For one thing, there are normative questions regarding the right approach to deal with uncertainty in precision medicine research, given that research questions that can fruitfully be asked depend on conceptual, methodological and technological limitations. If uncertainty is indeed realized on so many levels of precision medicine, what kind of evidence framework is best equipped to deal with this challenge (cf. the critical discussion of an alternative epistemology for precision medicine in Vogt & Hofmann[43])? How can the omnipresence of uncertainty be integrated into such a framework, assuming that the collection of more evidence will *not* be the solution for all of the discussed issues? Are we currently in a position where the envisioned revision of disease taxonomies to improve our understanding of medical conditions through the identification of robust biopatterns is likely to succeed? It seems that the uncertainty paradox poses serious challenges to this aspiration and should give us some pause.

There also are potential normative implications for the clinic. These include ethical and legal concerns regarding negative consequences of uncertainty for diagnosis and therapy, for instance, due to overdiagnosis and intensified uncertainties regarding treatment choice in light of ambiguous test results and unclear evidence thresholds.[44] Although, some of these issues will need to be addressed on a case-by-case basis, the uncertainty paradox seems to imply a greater role for professional uncertainty management in the clinic and the health care system more broadly (see the related discussion in Green and Vogt[10]). How can healthcare professionals frame uncertainty as a somewhat unavoidable part of precision medicine? How should clinicians communicate different aspects of uncertainty to patients? How can uncertainty management become an integral element of shared decision-making without overwhelming the patient—and the clinician? To what extent can and should healthcare professionals consider patients preferences regarding uncertainty and take their 'uncertainty tolerance' into account when discussing alternative treatment options in light of several potentially actionable (and as the case may be: diverging) results? Although these issues are not completely new in medical ethics and law, precision medicine seems to take the associated challenges to a new level, implying the need to address epistemic, ethical and legal questions in an integrated way.

4.3 | Limitations

This scoping review has several limitations. First, the search strategy operationalised the nontechnical cluster concept of uncertainty by using only a small number of key terms thereby potentially reducing the number of resulting articles and in turn of (potentially) relevant aspects for further assessment. This was decided to ensure the feasibility of the review with limited resources and within a limited time frame. Second, screening, selection and coding of the articles were performed by only one researcher. This excludes the possibility to apply intercoder reliability practices to improve the intersubjective reproducibility of the analysis. To mitigate the risk of excluding potentially relevant literature, the screening of articles was conducted

in such a way that articles were retained rather than screened out when in doubt. A third limitation concerns the content level of the analysis. This scoping review provides no quality assessment but *reports* arguments, concerns and uncertainty-related issues as stated in the analysed literature. The reported issues do not necessarily represent true facts about the current state of affairs in precision medicine, but an overview of perceptions and arguments made by clinicians, metascience scholars (including humanities and social science scholars) and other experts on precision medicine. Accordingly, the results are indeed best understood as useful *starting points* for further investigation and critical discussion.

5 | CONCLUSION

This scoping review generates a rich (although not entirely comprehensive) overview of the uncertainty paradox and shows that uncertainty seems to be a prevalent feature of precision medicine at different levels. Mapping out uncertainty—as it is used and relevant in precision medicine—shows that it is a concept with many faces that does not lend itself to straightforward characterizations. Rather, it encourages further investigations to better understand the interactions among various factors and aspects of uncertainty in precision medicine and the resulting implications for research and medical practice. This will enable us to better understand which elements of uncertainty are transient and which should be considered inevitable elements of precision medicine, that is, to what extent uncertainty should be considered a signature of precision medicine. Such an understanding will enable a realistic assessment of precision medicine that does not buy into false 'hype vs. hoax' dichotomies.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in Supporting Information: Appendix I.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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