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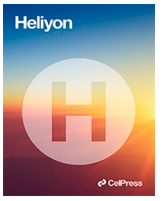

Research article

The interrelation of scientific, ethical, and translational challenges for precision medicine with multimodal biomarkers – A qualitative expert interview study in dermatology research

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ABSTRACT

This qualitative study examines the impact of scientific, ethical, and translational challenges of precision medicine for atopic dermatitis and psoriasis. The study explores how these challenges affect biomarker research for inflammatory skin diseases as identified by stakeholders, including patient board representatives, pharmaceutical industry partners, and postdoctoral and senior researchers from multiple disciplines in biomarker research. We recruited participating experts both within and associated with the international Biomarkers in Atopic Dermatitis and Psoriasis (BIOMAP) consortium to ensure representation of the different organizational units of the consortium. For the study, we followed the COREQ checklist. The interviews were conducted using GDPR-safe online platforms and the pseudonymized transcripts were analyzed using Atlas.ti. We analyzed the interviews from participants' personal experiences, topic-oriented, and group specific to identify the main themes presented in this article. The findings were presented to peers and to the wider BIOMAP audience, discussed, and a draft was circulated within the consortium for feedback. In this study, we identify and discuss the interrelation of challenges that are relevant to improving precision medicine with multimodal biomarkers. We show how scientific challenges can interrelate with ethical and translational issues, and explain these interdependencies and articulate epistemic and social factors of interdisciplinary collaboration. Based on our findings, we suggest that including patient representatives' perspectives is crucial for highly interrelated and widely diverse research. The proposed integrative perspective is beneficial for all involved stakeholders. Effective communication of science requires reflection on the tension between scientific uncertainty and the goals of precision medicine. Furthermore, we show how changing the perception of the diseases, atopic dermatitis, and psoriasis can benefit patients beyond medical practice.

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1. Introduction

More than 300 million people are affected worldwide by atopic dermatitis and psoriasis (AD/Pso), the two most common and widespread chronic inflammatory skin diseases [1–4]. However, the clinical heterogeneity of these two diseases and a variety of possible root causes, which remain yet to a large extent unidentified, pose an increasing need for targeted treatment [5] and no one cure fits all patients. This more targeted approach, which belongs to personalized medicine, takes into account factors like the patient's genetics, and socio-economic and environmental differences [6,7]. In dermatology, it also aims to identify better diagnostic, prognostic, predictive, and therapeutic biomarkers and targets to stratify patients into distinct subgroups. The goal is to identify multimodal biomarkers and develop better treatment options, either by rearranging existing treatment plans or by developing new targeted medicine and treatment options in the future [8–10]. Furthermore, by understanding what drives, triggers, or precedes the onset of the diseases, a better understanding of these very heterogeneous diseases can be gained [11,12].

To this end, the Biomarkers in Atopic Dermatitis and Psoriasis (BIOMAP) consortium was launched in 2019. BIOMAP is an international research consortium for chronic inflammatory skin diseases that brings together genetic, epidemiological, and clinical expertise as well as novel bioinformatics tools and molecular analytic techniques. With 33 partners from academic and pharmaceutical institutions as well as patient board representatives from 13 countries, this mulitidisciplinary team joins forces to enable precision medicine on an hitherto unknown scale. (https://www.biomap-imi.eu/overview, https://www.biomap-imi.eu/network). The consortium aims to bridge and fill the gaps between current problems and solutions for diagnostics and treatment of AD/Pso. It has established a glossary of clinical phenotypes and key outcomes by harmonizing available biosamples from 60 studies [13] and contributed reviews to identify potentially promising candidate biomarkers along with possible limitations [14,15].

Ethical and social implications of biomarker research have been widely considered in oncology [16] but are still mostly implicitly discussed in the literature on dermatological diseases and biomarker research [17]. Identifying ethical and translational issues in biomarker research is an important task of our working subgroup (Work Package 8/Ethics) within BIOMAP. Although ethical and legal considerations are an integrated part of most research endeavors in biomedicine, the exchange between research, ethical considerations, and specifically patient involvement in actual research practice is not yet regularly practiced, nor are these interdependencies regularly analyzed and reported. Some good examples of how this can be done are Rauter, Wohlke [18], who distinguish between four sub-classifications of patient organizations when deciding how and to what extent patients provide data for big-data research in precision medicine. Further, Parker, Fabbri [19], investigated how attitudes and relationships towards the pharmaceutical industry could be related to a variety of interactions with patient groups, and Kirby, Kenny [20] conducted qualitative interviews with health professionals, patients, and family carers in cancer research. Apart from ethical issues of precision medicine, how to address heterogeneity in cancer genetics was addressed by Bechtel [12], the actionability and trustworthiness of data-centered discovery in exploratory oncology research in its relation to clinical diagnostics by Tempini and Leonelli [21], and how precision medicine reshapes expectations when living (well) with cancer by Broom, Kenny [22] and Flore, Kokanović [23]. Nonetheless, we know little about how the perspectives of researchers and pharmaceutical representatives compare to those of patients' representatives when deliberating the perceived challenges in biomarker research for AD/Psodermatology research, where precision medicine is in its early stage. Thus, with this qualitative study, we take an inclusive stance. Our study gives equal weight to the deliberations of scientists, pharmaceutical representatives, and patient organizations to show how scientific challenges in heteronomous and complex research objectives interact with ethical and social aspects. In concrete, we ask how scientific, ethical, and translational challenges and their interrelations affect the aims of precision and personalized medicine and the perception of the two diseases. We explore how these aspects are relevant for how to communicate uncertainty in precision science and consider related translational efforts. In addition, we inform existing literature concerning the tension between different aspects of uncertainty in precision medicine empirically [24].

Scientific challenges are often regarded separately from ethical, social, and translational issues. Specifically, for interdependent research problems, which involve not only different stakeholders but exceed research interests to reach the pharmaceutical industry and the general public, a more holistic understanding is beneficial. In this article, we first compare different expectations, voiced by different stakeholders concerning the development of targeted treatment options and stratification into subgroups. Second, we identify relevant scientific, ethical, translational, and communication challenges and show how these challenges interrelate in actual research practice. Third, we discuss the implications of our results for performing and communicating precision medicine research and for achieving changes in disease perception and increasing awareness among the general public.

2. Methods

2.1. Study design

This article presents the results of an expert interview study conducted as part of the BIOMAP consortium by the work package "Ethics" (WP8). In this work package and together with the University of Vienna, as the main addressee for legal aspects, we focus on ethical, legal, and social issues and challenges in biomarker research and application for AD/Pso.

Methodologically, we draw from Döringer [25] for conducting problem-centered expert interviews to investigate implicit expert knowledge, specifically, we focus on participants' perspectives to learn about possible social and ethical implications of their research practice. We used computer-assisted qualitative data analysis software (CAQDAS) for an updated application of the grounded theory approach (Charmaz [26] as supported by Yin [27] and Bryman [28]. The methods are reported following the COREQ (Consolidated Criteria for Reporting Qualitative Research) reporting guidelines [29]. The interviewers discussed saturation early on since the main challenges presented here were apparent after about 10 interviews, but we continued interviewing to reach an in-depth understanding

of similarities and differences as explicated in the different stakeholder groups. Concerning triangulation: The researchers are organizationally part of the investigated field, the BIOMAP consortium WP 8: Ethics (see Fig. 1). As such, we participated in joint consortium meetings before, throughout, and after the interview phase. During the COVID-19 pandemic, notes were taken for participant "observation" in online meetings. These helped us to better understand the organizational interdependencies within the consortium. To obtain an in-depth understanding of the different contexts and increase the validity of our interpretation, the authors actively took part in joint consortium activities and meetings. This included participation in analysis meeting of different work packages/task forces, engagement in the communication group, patient involvement and meetings with presentations and discussions of research findings from the consortium involving patient representatives and stakeholders from all work packages. Additionally, there were meetings aimed at the harmonization of concepts and variables as a prerequisite for interdisciplinary use of all available datasets [13]. Moreover, an article on severity biomarkers was composed, highlighting the need for further exploration of the ethial implications associated with severity biomarkers and policy development in this domain [30]. All authors contributed to two-round Delphi survey conducted for the consortium by Ziehfreund [31]. We analyzed the interviews focusing on participants' experiences, topic relevance, and group specificity to identify the main themes as presented in this article. To assure the accuracy of our interpretations, we solicited and received feedback in an exchange meeting open to all consortium members and in annual meetings. All these activities contributed to the understanding of the field and assessing the context for interpreting the interviews.

2.2. Recruitment and sample strategy

Our participative approach allowed us to identify experts through purposeful sampling who represented the different organizational units of the BIOMAP consortium. Of the 35 participants contacted via E-mail, 28 agreed to be interviewed. Our sample includes researchers with and without direct contact with patients from a wide range of disciplines: dermatologists, immunologists, microbiologists, molecular biologists, epidemiologists, bioinformaticians, and statisticians; as well as from a range of career stages, from early postdocs to senior-level researchers. Special care was taken that participants were selected to equally represent each of the consortiums' working groups with different group responsibilities, career-levels, and depicting a wide range of involved institutions from more than 10 countries for achieving a broad range of perspectives. At the time of interviewing the 28 participants comprised about 20 % of the actively involved people in BIOMAP (see Table 1).

We provided the study information while confirming the date and time for each interview; however, none of the participants withdrew at this stage. Besides the scientific members of the consortium, we recruited organizational stakeholders, pharmaceutical and patient board representatives to ensure a diverse range of perspectives. To be clear, the interviewed group of patient representatives is part of the BIOMAP consortium. They have organizational responsibilities for their respective patient organizations. There is no patient group in our participant sample, although some of our interview partners across all groups mentioned being personally

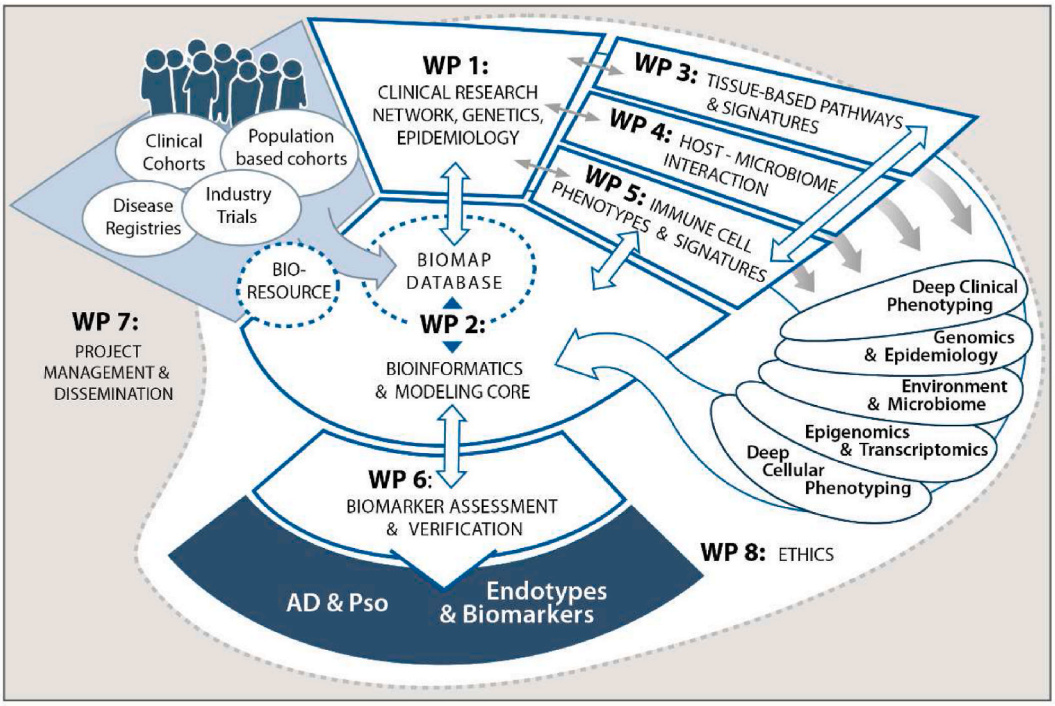

Fig. 1. Setup and workflow of the consortium. The graphic depicts the tight interaction between the individual work packages and relates to the major aims. ©Biomap consortium.

Table 1
Study participant characteristics.

Participant characteristics		Number (N = 28)	Percentage
Gender	Female	13	46 %
	Male	15	54 %
Stakeholder	Researcher postdoc	7	25 %
	Researcher senior	8	29 %
	Pharmaceutical representatives	7	25 %
	Patient board representatives	6	21 %

affected by AD/Pso in one way or another. However, any of these personal disclosures were either excluded from the analysis or fully anonymized to protect our participants. A semi-structured topic guide was developed collaboratively by the author team (and checked with a bigger peer audience). We conducted two pilot interviews to test and revise the topic guide. These pilots were excluded from the analysis. Questions anticipated best and worse outcomes of biomarker research, anticipation of potential harms of stratification into subgroups and access to treatment, the role of socio-environmental factors, and reflections about possible change of the perception of the diseases, among others. The open-ended questions encouraged the interviewees to add anything they thought to be interesting. Interviews were conducted by the first and third authors between May and July and one in September 2021 by using GDPR-compliant online tools either in the office or home office. Informed consent was obtained verbally before the interview was conducted. Only audios were recorded on external audio recorders without internet connection to ensure privacy. All interviews were in English, except for one which was in German. Most interviews took approximately 50 min, with a range from 17 to 115 min. Transcribed interviews were pseudonymized and checked for accuracy by both interviewers.

2.3. Data analysis

The interviewers initially analyzed two interviews separately to identify the main codes and then compared these two interviews and refined the codes before three coders (two interviewers and one student assistant) coded all interviews. To ensure interrater reliability, all interviews were coded iteratively at least twice, by up to three people with different disciplinary background (philosophy, cultural studies, medicine, sociology, business studies). Core analytic categories and codes emerged from both the pre-conceptualized interview guide (content-analysis) and from a constant-comparison (GT) analysis approach. We continually extended the codes in a discursive manner and revisited the interviews to remain grounded in the data. Through this iterative analysis of the complete interviews, we identified the main themes: aims and goals of biomarker research, ethical challenges, research specific challenges, challenges related to communication, patient related themes, and further organizational themes. We checked the findings with an iterative group-based analysis, which presented additional perspectives on the main themes. Thus, dominant themes emerged

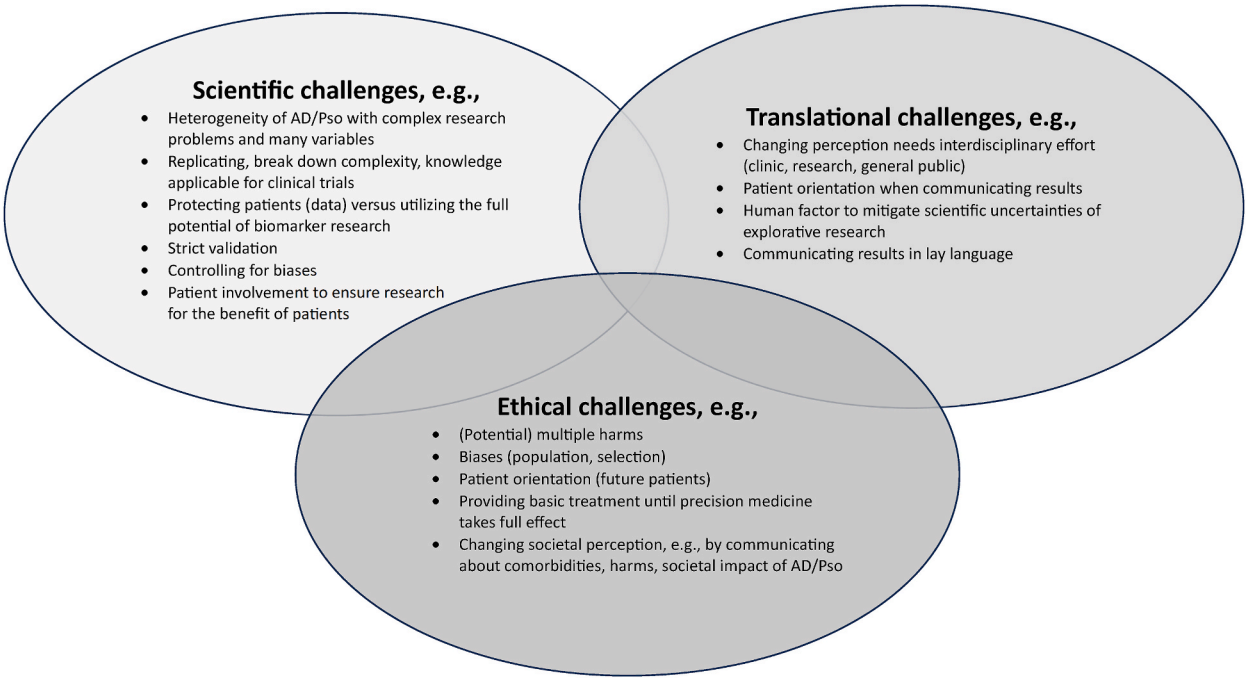

Fig. 2. Interrelations of scientific, ethical and translational challenges in biomarker research/application for AD/Pso.

from deductive, thematic, and inductive analysis as well as in-depth cross-sectional analysis on selected aspects. The interviewers accompanied the analysis process with written memos, which were reviewed by each of them. Our reflections about the re-occurring minor and major themes build the framing for this article. The findings were first presented in an open exchange meeting to the BIOMAP consortium, feedback was reflected within an internal peer audience with the involved stakeholders, including patient board representatives. Then an earlier version of the draft was distributed within the consortium and comments were integrated with the learnings from the open exchange meeting (see Fig. 2).

2.4. Research questions

A major research focus of our study addresses the following questions: "How do scientific, ethical, and translational challenges relate to each other in biomarker research for AD/Pso? How do the identified issues and their interrelations affect the aims of precision medicine and the perception of the diseases?"

3. Findings

3.1. Overall goals for AD/Pso research about the different stakeholder groups

Many of our participants, regardless of their characteristics, location, or affiliation, mentioned variations on the precision medicine slogan of finding the "right treatment for the right patient at the right time" (P1). They used and agreed to this slogan from precision medicine [32], e.g., Ref. [33], independently of their different perspectives as researchers, internal and external advisors, pharmaceutical or patient board representatives. Although all participants ascribed to the aim to find better treatment options for clearly identified subgroups of AD/Pso and in all groups participants expressed the goal to better understand what triggers its onset, the patient board also hoped to be able to get rid of the diseases altogether. While researchers and pharmaceutical representatives were more cautious, limiting their statements to better understanding the diseases to find out what triggers their onset for preventing AD/Pso in the future. There was broad consensus between clinicians and patient groups that an important goal is to change the perception of the diseases in the general public but also throughout involved disciplines to raise awareness for the implications of the diseases, which are associated with sometimes life-threatening comorbidities, which put patients in need of additional treatment.

The overall goal of the interviewed researchers, independent of disciplines, clinical involvement, or career stage, was to use stratification into subgroups to optimize treatment outcomes for patients either by using current therapies in a more targeted way or by matching the right patients or groups of patients for better treatment response.

Many participants but particularly patient representatives emphasized their hope in stratifying patients into subgroups toward developing a more targeted treatment, to get rid of the trial-and-error approach. This is currently a common practice of trying several treatments successively, until hopefully finding the one that works best.

In addition to the psychological, social, and societal impact of the diseases, patient board representatives and clinical researchers called for a change of perception within the general public, also by raising awareness of the multiple implications within the scientific community. One pharmaceutical representative (P2) mentioned that in comparison with the "invisible killer" cancer, there is higher public awareness but the "visible killer" AD is still underestimated.

Participants from the pharmaceutical representative group are in itself a diverse group, some have educational backgrounds as clinical research scientists, experienced biomarker researchers, or data analysts. Although all of them work for one of the pharmaceutical companies that collaborate with the BIOMAP consortium, they have no active scientific research role in BIOMAP. These participants described their roles as advisory and/or supporting the management. Apart from stratification into different subgroups in the expectation to have "better classification of responders and non-responders to current therapies" (P3, pharmaceutical representative), "the clear goal [is] to improve patient's lives by providing perhaps, better treatment or disease management paradigms for the patients." (P1, pharmaceutical representative)

They shared this goal mostly with the group of researchers to "… better understand what is underlying the cause of the symptoms" (P2) and explain that:

> "… biomarkers are these really characteristic … pointers … who will get which diseases. Those can then be tested in new clinical trials and they will help provide really new insights that will help even further facilitate early diagnosis … we know that everybody needs to know very early what is the actual cause of this disease and how [it] will progress."(P2, pharmaceutical representative)

However, pharmaceutical representatives emphasized the necessity for testing research results in clinical trials, in line with what patient representatives did, and in contrast to researchers. Along with the goal of precision medicine, this participant transparently described the trajectory toward this goal.

> "… we are currently describing diseases by the way a physician sees it, like psoriasis or like atopic dermatitis but not by the different root causes which link to the disease. So, there's … a disconnect, but that's a gap we need to fill between how a disease manifests itself and there might be different root causes or at least different subgroup[s] of patients who develop that disease. And if we understand and can fill this gap, this allows us to have better-. Actually, the word which is sometimes used, precision medicine approaches, for that. And that means you have the right treatment for the right patient at the right time." (P1, pharmaceutical representative)

In the following, we describe the main overarching themes of scientific, ethical, translational, and communication challenges with a view to their interrelations.

3.2. Scientific challenges for different stakeholders

Our participants identified uncertainty stemming from the high number of variables as one of the most important challenges of interdisciplinary collaborative research. In this regard, the main issues were scientific uncertainties, introduced through the many variables, which complicate meaningful analysis for multimodal biomarkers to stratify patients into subgroups. The many variables in biomarker research are due to the diverse ontological heterogeneity of the diseases, and they lead to complicated analysis tasks on many levels, (e.g., cellular, molecular, genetic, endogenetic, socio-economic). The analysis is further complicated by population and selection bias, among other things. The latter refers mainly to *what* data, although available, is analyzed. Thus inclusions or exclusions for meaningful analysis depend on the quality of the data and these decisions can impact the scope and the outcome of the analysis and results.

Scientific challenges were predominantly discussed by the interdisciplinary group of researchers and a few pharmaceutical representatives with a scientific background as data analysts. Reoccurring themes were how to guarantee the quality of data for meaningful analysis and the heterogeneity of the research field with its many variables and scientific uncertainties. Since biomarker research applies to a widely diverse and heterogeneous research field, where different disciplines address research objectives on their specific level while also collaborating across disciplines to connect the learnings from these different fields, they face interdisciplinary challenges on the conceptual, theoretical, and practical level. To solve the complicated riddle of biomarker research for AD/Pso, all involved research fields have to develop ways how to communicate their contribution to others. The harmonization of the available, mostly historic, data to enable meaningful research across disciplines (see [13]) was repeatedly mentioned as a first milestone throughout the interviews. Here, we start with topics related to scientific trust in terms of patient orientation in exploratory research for asking the right research questions, which is related to how to deal with scientific uncertainty and validation procedures. This also concerns the question of to what extent newly developed scientific knowledge is expected to be reliable or still in the process of validation.

The next quote depicts the different levels of data analysis and deliberates about scientific uncertainties:

> "just to be clear there are molecular … level information, which means you measure molecules in cells. And then there are cellular level information in which you measure … the abundance of cells and cell types. And then you have … phenotypic analysis and then you have symptomatology and then you'll have … kind of broader high-level epidemiological analysis in which you check the diet, you check the demographics, you're checking part of certain heart rates, et cetera. When you think about molecular analysis [it] is not only genetics, molecular analysis starts from DNA, which … is not too predictive in these complex conditions, but then entailed also RNA with transcription analysis protein, and then it could be epigenetics. So, level of methylation of DNA, and can entail proteomics, can entail metabolomics, can entail most recently meta-genomics, …checking the lab measuring the molecules through further the level of the presence of microbiota. So, this is all about molecules. And then there are the cellular analysis in which we can measure cells: So, how many synovitis you have in a blood count of [an] atopic patient or a psoriasis patient? How many granulocytes you have? I mean, what is the phenotype of T and B cells and the K cells, et cetera. And then you have all this additional, more kind of classical epidemiological analysis. *So, how all of these are analyzed that's the question of the questions. This is really the core of the science here. And there is no recipe*." (P4, pharmaceutical data analyst, *our emphasis*)

Expressed in lay language, the metaphor of the needle in the haystack can be useful: This research is searching for a couple of needles [multimodal biomarkers] on different levels of a haystack [patient]. In addition, the researchers have to develop the tools to identify the needles, the tools to classify them as a useful and reliable needle and to classify the specificity to evaluate how to benefit patients or groups of patients.

Among our participants, most data analysts confidently proposed their trust in how to deal with the many variables including variables of the natural sciences and other factors such as socio-economic variables in a methodologically reliable way:

> "I think … if they (variables) do matter, they will be significant enough to … become apparent. I think we can't close our eyes to them. And I think … researchers do need to … question whether we're actually looking at a very narrow perspective or not, whether we actually have a big enough-, our eyes are open wide enough to really take in what's happening. … I think that if [variables] they're significant enough, they will show up as an anomaly. There'll be a … subgrouping that doesn't make sense. That will be an observation that just can't be connected to something that we are measuring, and therefore we'll have to speculate that it comes from somewhere outside and that might lead us to kind of look broader and wider." (P5, pharmaceutical data analyst)

In this exploratory phase of research, it is important to stay open-minded. Even if researchers start with one set of variables, the key is to think broadly to include possibly significant variables, which only become apparent at a later stage of research for an encompassing and meaningful result. The following researcher expressed yet another way how to tackle the many variable challenge.

> "… for some cohorts thousands of variables [are] of clinical interest and we have in the best-case hundreds of cohorts and with 10.000s of patients, for which we have up to a thousand of variables, it's quite tough to combine those variables …. So, in the end on every level of the data, may it be wet-lab data, clinical data or environmental data, we have huge variations which we

somehow … have to handle, either by homogenizing or to make it, so to say, accessible for correction when analyzing the data." (P6, researcher)

We identified a tension between the inherent scientific uncertainty in innovative and explorative research at this stage of development, and the forward-looking proposed goals of precision medicine to reduce uncertainties for groups of patients and find effective treatment options for them. For researchers as well as pharmaceutical representatives, it was important to transparently discuss the gaps and needs to make sure to arrive at reproducible and reliable results. Only when mastering these challenges do they express confidence in starting to identify targeted treatment options for patients, the aim of precision medicine. The tension is rooted in the high expectations and promises towards precision medicine and the gap facing the current challenges, as this data analyst expressed:

"So, the idea … is that we will define them [biomarkers] based on additional data and then we will have to make sure that they are kind of reproducible, no artifacts. And if they are really kind of reproducible, then we should try to use those as strata in kind of prognosis-related analysis. This is the final goal of precision medicine that you can define some new disease, let's say, endotypes, which are more homogeneous with the idea that they have maybe some particular pathway which is destroyed. And then ideally, there is some treatment option which will then work in this particular group of patients. If this is kind of coming up and reproducible, then one has to look at trying to personalize or at least stratify therapy options." (P7, data analyst, researcher)

Awareness was expressed in all participant groups that at this stage of research, with its multiple scientific uncertainties, the bigger picture, including the human factor, needs to be better kept in focus. Nevertheless, none of these participants challenged the belief that precision medicine is the way to go with heterogeneous complex diseases, such as AD/Pso. Although many acknowledged that social and environmental aspects may play an equally important part than the genetic, cellular, and molecular data.

"And I think, it's an inherent hand risk of wanting to define and define and define that we do not take into consideration that the patients are patients and therefore, also there's physical, personal, and environmental aspect to disease stratification that we might miss because we're so inclined to look at that data that we can sample. So, that'll be interesting, at least, to see how personalized medicine will make sure to keep at least an eye on the patients as well. As well as not being able to just take a home test and then you are this kind of disease. So, there's a social aspect to it, I think, in terms of looking at patients as patients and not as collection of data sets, data points that you can solve and put into a box." (P8, pharmaceutical representative)

In addition to the implications of scientific uncertainty, the worry of having a truly representative dataset as basis for the analysis of multimodal biomarkers for AD/Pso was repeatedly mentioned. Biased data are to be avoided in research because they distort research results and thus affect the representativeness and effectiveness of these results. Population bias concerns a selective and in the worst case not representative selection of the diversity of patients as part of the investigated population as basis for the analysis. Whereas selection bias, as we use it here, concerns the selection procedure of the available data, through data quality or data cleaning. Both, population and selection bias relate to each other, they threaten proper randomization and both have a scientific as well as ethical aspect to them. We start with the scientific aspects.

Concerning selection bias, we found that both, researchers and pharmaceutical representatives when asked conceded that socio-economic and socio-environmental factors matter for the quality of data because analyzing data from different and diverse sources generally increase representation of the data. However, since there already are so many biological variables on many investigative levels, the challenges apparent in complicated analysis tasks make it sensible to start with variables easier to control for, e.g., genetic information. Whereas socio-environmental variables are thought to be included later in the process. This pharmaceutical representative described scientific practice pragmatically. Research, specifically exploratory research in an early phase, has to evolve in many steps and needs to be perceived as an ongoing process until a satisfactory outcome will be reached:

"I think we're in the very early stages of this [research] and I think the genetic information is easy to obtain and analyze, and the other ones are difficult to obtain and harmonize. So, BIOMAP and all of the big data initiatives have a risk of a bias towards, trying to find a genetic marker for disease or a biomarker for a disease where it might be just as important what environment you grew up in. So, I think everybody is conscious of that. But I do also have to say that … we're looking at this with specific eyes on genetic and biomarker data and therefore, the outcome will be reflecting of that. … And I think the other ones [e.g., non-genetic] will have to catch up at some point, but it's very difficult to measure." (P8, pharmaceutical representative)

However, one of the advantages of asking the same interview questions to different stakeholders and researchers from different disciplines suggests the benefit of interdisciplinary research efforts especially for highly complex research problems like those addressed above, when a data analyst working for the pharmaceutical industry is confident that "… if [variables] they're significant enough, they will show up as an anomaly. There'll be a … subgrouping that doesn't make sense. That will be an observation that just can't be connected to something that we are measuring …" (P5, pharmaceutical data analyst)

To redeem the promise of precision medicine, this research has to address the clinical heterogeneity of the diseases, the interdependent research objectives as well as the complexity arising from the various interdisciplinary fields which have to work together to achieve the goals set for biomarker research in AD/Pso. Scientific challenges named by the participants related to the high heterogeneity of the research objectives and the many variables in explorative research which contribute to scientific uncertainty. On the other side, participants name trust in scientific modeling and data analysis practice and to include the "human factor" "to look at patients as patiens", not as data points to mitigate what is not yet known. The analysis is complicated by population and selection biases affecting the quality of the data as a basis for the analysis. However, the biases need to be considered not only scientifically but also ethically, which will be discussed in the following section.

3.3. Ethical challenges for different stakeholders

As indicated above, important ethical challenges identified by participants were various biases, the tension between protecting the privacy of patient data and facilitating the full potential of the data for research purposes, as well as multi-facets of harm.

Population biases concern the fair representation of the relevant patient groups, including patients from socially disadvantaged backgrounds. Those can be underrepresented in research although they would benefit most from biomarker research for AD/Pso and are considered crucial for the quality of the dataset. Problems concerning population diversity in the available datasets as a basis for a meaningful analysis were most mentioned in connection with population bias and selection bias throughout all participant groups. Researchers and pharmaceutical representatives worried most about the lack of population diversity in the available datasets as a basis to analyze potential biomarkers. Statements like "[t]hey collect a lot of tissue, but it's a predominantly Caucasian population" (P9, see also P5) and a young men overrepresentation but also "underrepresented groups are not part of population samples although they would benefit most from treatment" (P10, P11) "being a research participant can be quite a middle-class thing to do" (P10, researcher). These worries were mentioned repeatedly throughout the researcher group.

> "In the UK … ethnic minorities have been less willing to take part in research. I strongly suspect that they are therefore underrepresented in the samples that we are analyzing, although they may well represent a very important patient group where certain treatments might work less well or better. And if we don't have samples from those patients, obviously, we can't answer that question." (P11, researcher)

Very few of the researchers interviewed expressed confidence, rather than concern, that the overall population was well represented in the BIOMAP data [P13, researcher, expressed this belief]. Population bias extends to translational challenges when clinical trials, to test the results from biomarker research for AD/Pso are limited to Northern American and European studies for financial reasons. Some of these analysts expressed the tension between legal and ethical obstacles, which they perceived as artificial or unscientific barriers to do research for the benefit of patients (see P5, P12, P13).

> "That would be the blockades of the use of the real power of BIOMAP. So, I would say that it would be extremely pity[ful] if these GDPR or ethical issues would prevent to promote ethical issues. […] I really want to say that I have tried so hard to make this data to be available [.] for the benefit of the BIOMAP, but also the benefit of the patients, the patient organizations and science. And still it has not been possible to do that and deliver that data properly." (P13, researcher)

Not being able to progress science for the benefit of patients just because of unscientific legal obstacles was expressed as unethical by data analysts from the group of researchers and also some pharma representatives.

> "… because of, […], various governance reasons will not-, or cannot release those data to be reused for these purposes. Sometimes that's against the wishes or the principles of these study participants. But because of the way that the data was collected, or because of the prior ethical approval, […] everybody's hands are tied, and I think that's a frustrating negative outcome. If patients want to help researchers understand these disease settings, and they cannot do that because we cannot access their data because of historical regulation[s]. So, I think there are some negatives and those negatives are just that we do not move the research forward. And we fail our objectives just because we cannot get hold of the data in a sufficient timeframe." (P5, pharmaceutical data analyst)

However, after persisting effort, this issue could be resolved by the legal department of the consortium later during the time of the project. Other biases of concern were disease severity and selection bias. Others flagged possible negative consequences of misusing data or inappropriately selling it (see P14, patient representative). Among our participants, clinically oriented researchers worried more about population-relevant biases whereas data-analysts tended to worry more about ensuring data protection and enabling complex data analysis with many variables at the same time. Analogous to the group of researchers, pharmaceutical representatives discussed data-security issues in terms of how to enable meaningful research without compromising the privacy of patients. Although for some fields in dermatology it is already common practice to take photos while protecting individuals' privacy, unfortunately, especially highly complex research and the heterogeneity of the diseases seem to increase the need for specific photos and perceived tension and ambivalence to protect patients. This example about diagnostic practice and challenges highlights the problem which emphasizes the importance of where they are taken to render important information:

> … within atopic dermatitis, there are subtypes of disease that … lack real description. And often, the best way to describe it is to see a photograph. … Depending on where the biopsy is actually taken from, is it taken from the centre? Is there an ulcer present? Is it taken from the edge of the lesion? How close is that non-lesional to a lesion? This information isn't ever given. And also … it's rarely given [if] it [is] taken from the elbow, the knee, the belly, the leg? And these all have different features, even if you look at healthy skin. …" (P9, researcher)

Overall, data security, data protection, and privacy were mentioned in multiple dimensions throughout interviews by the different groups. Ethical challenges concern many levels of harm AD/Pso and biomarker research for AD/Pso can propose. However, to do these issues justice and give an encompassing picture of topics related to data issues and harm exceeds the scope of this paper and will be addressed along with other topics in separate in-depth articles. For the present article, we just note the tension between having to rely on encompassing, meaningful datasets for the full benefit to deliver the best possible research for patients, protecting patients' privacy, and prevent future harm at the same time. We now focus on the field's heterogeneity and how the multifaceted scientific challenges in generating reliable knowledge intersect with ethical, social, societal, and legal issues. This leads us to the third topic: addressing the

challenges of translation and communication in precision medicine. How can we accurately report and communicate scientific goals and results to peers with a focus on patient-relevant outcome measures, despite the inherent uncertainties in explorative, innovative research?

3.4. Translation and communication challenges for different stakeholders

The main issues identified with translational challenges were the inclusion of patients, patient orientation, e.g., concerning outcome measures and communicating results, and the human factor when translating basic research into clinical care in innovative research fields. Changing the perception of the diseases was yet another reoccurring theme.

When communicating results only on the research paper level to peers, participants from patient organizations worried they and the general public would be missing out. Some offered their help in formulating scientific results in lay language, even if this meant, finding out what does not work (e.g., P15, patient representative). Patient-oriented outcome measures were mainly mentioned by patient representatives, who expressed the hope that this orientation was guiding researchers when doing research and communicating results. They expressed this by stating that researchers, should not get lost in the rabbit hole for the sake of research – and findings should be relevant to the project objectives (see P14). On the other hand, patient orientation was repeated mentioned by all groups.

> "… even if there was progress and we did discover something very interesting about the mechanics of those two diseases, it would be terrible if nothing was done about it in terms of progressing treatments on the back of it. If it just stays at the scientific paper level where nobody actually translates these scientific results into interventions to help sufferers of those skin diseases, that would be really terrible." (P16, researcher)

However, communicating results and scientific knowledge to all relevant stakeholders can be described as another multi-layered challenge. For researchers from all disciplines communicating results, limitations, scope, and the consequences of the results to peers, are the bread and butter of their day-to-day practice. Some stated they would want to transparently report if they found something to be harmful to patients, while others emphasized the importance to report the reliability or uncertainty of findings in general. However, when we directly asked them to divulge information about negative results, none of these interviewees wanted to share explicit information, even if it concerned previous studies not connected to BIOMAP. This suggests publication bias, to only report publishable successes, progress, and what works, might also affect communication of relevant outcomes, especially if it concerns what did not work, or counts as tacit knowledge.

Translating results into concrete interventions and implementation into clinical care was repeatedly mentioned by patient and pharmaceutical representatives. Whereas, clinicians and patient representatives emphasize the clinician-patient relationship as crucial to handle the many individual judgments which seem necessary from the patients' side. The clinician is presented in the interviews as the information and security addressee concerning scientific, psychological, and personal uncertainties. Despite strong belief in science and what stratification and personalized treatment might be able to accomplish for groups of patients, this patient representative states: "I just wouldn't want us to lose the human aspect of treating patients." (P14, patient representative) The impact of this aspect becomes apparent when treatment, especially if it's not straightforward as with the AD/Pso, needs good communication. Communicating about treatment matters for the compliance of patients, to keep them caring for themselves despite the sometimes frustrating perspective of no best cure available:

> "… you can have the best medicine that is guaranteed to treat … to improve your skin. But if a patient is wary of that treatment, or if they don't feel that they can take it or use it, then it won't work, because … they're not able to use it appropriately. So understanding and communication is important. And I think if a patient doesn't feel motivated to treat their skin, then they probably won't get the full benefit of any treatment, whether it's a cream, …a topical treatment, through tablets and injections. So, it's of huge importance that the psychological aspects of a patient are understood and why they may not take a medication because it could be something really quite simple that-, that's preventing them from using something and if that was just explained a bit better, it could make a huge difference. … Mood and motivation to improve or to treat one's skin is of huge benefit, of huge importance." (P14, patient representative)

It would be interesting to further investigate whether there is a relation between the motivation for compliance to use treatment efficiently and frustrations resulting from the trial-and-error approach, mentioned above. Translational challenges related to patient stratifications and access to affordable treatment were discussed by researchers and pharmaceutical representatives in terms of both scientific or technical issues as well as cost-effectiveness. In addition, this quote shows that translation and communication challenges appear in research but also impact the clinicians and others.

Pharmaceutical and patient representatives were the ones who emphasized the translation of scientific findings into clinical studies most when they state, biomarkers need to be implemented into clinical practice to be effective, otherwise, it's a "waste of time. In contrast, if public money was used for the expensive clinical validation process there is additional need for good justification why so much money is spent," [e.g. oncology].

> "… I do often think there is a disconnect between the biomarker scientists and the clinicians and the patients, because I've been working in biomarker research for […], ten years or so. […] especially exploratory biomarkers [can be used effectively] in clinical trials. You can do as much research as you like, but how readily are they actually used by the clinicians? […] But I also think that, […] in atopic dermatitis […] certainly, there's no validated biomarkers from a regulatory perspective. […] So, who's going to carry the burden of getting regulatory approval of biomarker? […] And if it's using public money, well, what's the

social justification for spending the money on that rather than something else? And so, as a researcher, you can identify as many biomarkers as you want. But will they be implemented? And ultimately, is all just a waste of time, […] if they're not. (P9, researcher)

This links back to the importance of how a disease is perceived by the general public. Both translational challenges and communicating science come together when facing the need to change the perception of the diseases AD/Pso. When we discussed these findings in an open exchange meeting with the internal BIOMAP audience, one patient representative told us they have been working towards this aim for decades and it was "a hard nut to crack".

Translational and communication challenges further complicate patient-orientated communication of results. The stratification into subgroups concerns translational challenges in clinical care, especially when discussing treatment costs and availability. Finally, we suggest the proposed integrative perspective is beneficial for all involved stakeholders in two ways: First to address the manyfold uncertainties in precision medicine and second to change the perception of the diseases. Both relate to all three identified challenges although the latter is mainly perceived as a communication issue.

4. Discussion

Important scientific issues in biomarker research for AD/Pso involve the tension between numerous scientific uncertainties and the goals of precision medicine. The many variables are due to the domain-specific ontological ('world-sided') heterogeneity of the two diseases and they lead to complicated analysis tasks on many levels, (e.g., cellular, molecular, genetic, endogenetic, socio-economic) with their methodological challenges. Scientific uncertainties on the ontological level arise from the numerous variables encountered when identifying multimodal biomarkers. This in turn makes it difficult to conduct meaningful analysis for multimodal biomarkers to stratify patients into subgroups with distinct endotypes and clinical phenotypes based on these biomarkers, presenting a methodological challenge in addition to the ontological one. Bechtel [12] discussed how heterogeneity is addressed in cancer research by combining pathway and network heuristics as strategies to identify mechanisms. These "discovery strategies" are suitable to highly heterogeneous fields in explorative research where the aim is rather to formulate reasonable hypotheses than to test them and by addressing heterogeneity "by turning to mechanisms" to "acquire a way of understanding how multiple different alterations all produce the same cancer hallmarks" [12]. Some of our participants actively referred to cancer research as a model for biomarker research in dermatology. More research to compare these fields needs to be done to find out whether the ontological and methodological heterogeneity in dermatology research poses an even more complicated task.

As we have shown in our findings, the analysis is further complicated by population and selection bias affecting the quality of the data as a basis for the analysis, an epistemological and methodological challenge. However, in scientific practice and with a view to patients the biases need ethical, in addition to scientific, attention. Ethical issues mentioned by stakeholders include privacy and data protection. This in turn links back to the scientific and epistemic challenge to assess the full potential of the data to enable meaningful research. Last but not least, translational and communication challenges deepen the issue of patient orientation when communicating results including how to communicate the scope of scientific progress in a way that does not give rise to unwarranted hopes but helps to improve therapy decisions for each patient. Rather it might be helpful to adapt the view to include "hope-with-uncertainty" in their lives with the diseases as research progresses [23]. This impacts clinical decision-making as much as the patient-physician relationships and interactions.

Our findings confirm both the interrelation of uncertainty aspects concerning precision medicine and the insights from researchers contributing to precision medicine as well as involved stakeholders by further confirming the "cluster concept" of uncertainties as pointed out by Lohse [24]. This implies the research but also beyond when communicating the goals and challenges of precision medicine, how to identify biomarkers to optimize treatment options for people living with chronic diseases with multiple dependent variables.

The main identified implication from the patient side is that the human factor (e.g., patient-clinician relationship) plays an even more important role, specifically, as long as the many scientific uncertainties take precedence over the clear benefit for patients in innovative, explorative research. Besides its scientific challenges, stratification into subgroups is concerned with translational challenges in clinical care specifically, when treatment costs and availability were discussed. Yet, it remains an open question why widespread diseases such as AD and Pso with high impacts on personal lives, social relationships, and society with their severe comorbidities [15] receive less attention than for example cancer research [21,23,24,34].

From what we learned from analyzing the interdependencies mentioned in the expert interviews, many aspects mentioned in the ethical, scientific, and translational challenges have to be considered from different sides: E.g., integrating scientific findings into clinical care is mentioned as a challenge that requires special attention, particularly from clinical researchers. They emphasize that the expert-clinician-patient relationship is not a one-way communication, but rather, each step necessitates individual consideration. They point to an iterative process of updating practitioners with the new means and possibilities provided by precision medicine, which will take time, resources, and effort while establishing ways to incorporate feedback and experiences from patients. For good communication of science, it is relevant to reflect on how to proactively communicate the tension between scientific uncertainties and the aims of precision medicine.

In the literature, for instance, the attitudes and interests of key stakeholders in genomic medicine have been explored for implementation of pharmacogenetics and genomics medicine in one country [35]. In contrast, we delineate the interrelations of scientific, ethical, and translational challenges in biomarker research and clinical application for AD/Pso, as described by stakeholders across various European countries. This not only adds significant value to the future implementation process of biomarkers in clinical settings

for these diseases but also enriches the literature, establishing a base for future exploration of interrelated challenges in precision medicine in other fields.

With this qualitative study, we assessed our participants' views, who were experts in the field of biomarker research for Ad/Pso as well as patient representatives, beyond their field-specific expertise to anticipate social and ethical implications of their research practice that could be relevant to science and patients. Using this "problem-centered" view [25] we could highlight areas of interest within and beyond medical research where accompanying qualitative research helps to better understand what themes to consider for good decision-making in high-quality future-oriented research. As researchers, we hope to contribute to improving actual research practice affecting health care for AD/Pso by emphasizing how integrating all affected stakeholders can benefit both research and patient orientation. On the other side, our analysis takes up central concepts and methods discussed in the scholarly literature on precision medicine raised in oncology. We identified similarities and name possible differences in dermatology research. The high expectations surrounding the promises of precision medicine as described in the section about the overall goals (Section 3.1.), should be considered in the context of our participants' general endorsement of precision medicine. However, even among those openly supporting precision medicine, the gap between its promises and the actual challenges encountered in achieving the shared objective becomes apparent. We thereby contribute to a nuanced discussion about feasible expectations and how to communicate them.

Another strength of qualitative analysis in biomedical contexts is that it can highlight how social factors are connected to scientific problem-solving on many levels.

We hope to contribute to a better understanding of the concept of multiple uncertainties in precision medicine and offer some concrete recommendations on how changing the perception of the diseases can benefit patients beyond medical practice for researchers, pharmaceutical representatives, patient representatives, and the general public alike. Disease awareness could be raised through further accompanying qualitative research including targeted surveys, which would enable all stakeholders involved to respond to the findings and develop and implement structural organizational units to address issues raised in the identified challenges. Involving actors affected by and involved in research (e.g., as participants or donors) but not actively conducting research can offer additional advantages: Trust in science can be increased, through participation even if the targeted solutions may need to be extended for the benefit of future generations. The second advantage is that working scientists profit from the trust in science from outside science and can be sure that science as science benefits together with patients along the patient orientation.

4.1. Limitations

The focus of this article was to increase the general understanding of the challenges of innovative biomarker research in a highly heterogeneous field with interrelated scientific, ethical, and translational challenges. The challenges discussed here to give an overview warrant further in-depth analyses which will give a more comprehensive picture of the study and a better in-depth understanding of singular aspects of this study. Also exceeding the scope of this paper are legal challenges and policy recommendations.

As the interview questions were asked in a way to evocate language understandable for a lay audience, in-depth medical details and scientific knowledge might be better assessed through scientific articles from the different fields of biomarker research. As expressed in the introduction and in the study design, all the participants came from an international research consortium with the aim to identify biomarker for AD/Pso, with more than 30 partners from academic and pharmaceutical institutions and patient boards, from more than 10 countries. Within the (at the time of conducting interviews) 120 active consortium members we strove for a broad variety of participants and we are confident our analysis is an accurate representation of our in-depth understanding of the interviews generated in this study. However, as in any qualitative study, the findings depict our research context at a certain time and are not generalizable in a quantitative or longitudinal understanding of inflammatory biomarker research in general.

Although with this qualitative analysis, we aimed to identify areas where patient involvement makes the most difference and integrate reasons for patient representatives' aims, challenges, and worries with other stakeholders. We acknowledge as a limitation that there might be more relevant factors that we did not cover for this important question because they were not included in our interview guide.

5. Conclusion

The human factor (e.g., patient-clinician relationship) plays a particularly important role in biomarker research and application for AD/Pso, as long as the many scientific uncertainties identified within the development of precision medicine are intertwined with ethical and translational challenges, all of which together take precedence over the clear benefit for patients in the explorative biomarker research for AD/Pso, at least at the stage of rather explorative research described here. In the face of the repeatedly mentioned tension to utilize the full potential of biomarker research for the benefit of patients while at the same time protecting patients (data), the human factor translates into different concrete actions: e.g., the evaluation of patient-orientated outcome measures for researchers and the agenda of patient orientation throughout the mentioned ethical and translational challenges from basic research into clinical care (from bench to bedside). We suggest considering the proposed integrative perspective is beneficial for all involved stakeholders. Reflecting on the tension between scientific uncertainty and the aims of precision medicine is relevant for the communication within and of science to different stakeholders. In addition, we addressed in what way changing the perception of the diseases benefits patients beyond medical practice: The need to change the perception of the diseases relates to all three identified challenges and their interrelations. It is as much a communication and translational issue as it is connected to ethical and scientific challenges. Thus, changing the perception of the diseases has to address the tension between scientific uncertainties and promoting precision medicine in a responsible way.

Ethical approval

Ethics approval from the Technical University of Munich (TUM) Ethics Committee was granted for this study in December 2020, Nr. 792/20 S-SR.

Data availability statement

The data that has been used for this study is confidential. The raw data (audio and full transcripts) and personal information have been stored on a GDPR-compliant secure university server until deletion at the project end. The whole pseudonymized transcripts cannot be shared without compromising the protected identity of the participants. Participant keys have been further anonymized after acceptance of this article.

CRediT authorship contribution statement

Nora Hangel: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Alena Buyx:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – review & editing. **Marie-Christine Fritzsche:** Conceptualization, Data curation, Formal analysis, Software, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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