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What is Precision Psychotherapy?

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Abstract: Precision medicine impacts virtually all medical specializations, including psychiatry. Though precision psychiatry, in general, is a flourishing area of research and debate, psychotherapy as one pillar of psychiatry has received little attention. Theoretical discussions about precision psychotherapy are rare; research on precision in psychotherapy is just evolving. In this paper we provide a conceptualization of precision psychotherapy providing a common idea of what should be understood as precision in the context of psychotherapy and what kind of psychotherapy research can be considered to contribute to the aims of precision psychotherapy.

Keyword: Precision Medicine; Precision Psychiatry; Precision Psychotherapy

1.INTRODUCTION

Ten years after the decade of the brain, Thomas R. Insel, then head of the National Institute of Mental Health, reflected on the enduring impact those years had on the field of psychiatry. According to Insel, the primary progress during the 'decade of the brain' did not lie in specific research achievements but rather in the methodological advancements in biomedical research, the full potential of which would manifest in the subsequent

years.[1] Indeed, the emergence of precision psychiatry, capitalizing on these methodological advances, seems to validate his foresight (Walter 2013). In contrast, other medical domains, particularly pharmacogenomics for rare diseases and cancer, were quicker to harness technological advancements to enhance the prediction, prevention, diagnostics, and treatment of illnesses in an individualized manner (Spear et al. 2001; Collins et al. 2001; Hamburger et al. 2010; Jones 2013; Carrasco-Ramiro 2017; Lemoine 2017).[2] However, precision psychiatry gained momentum a few years later with the initiation of the RDoC Project (Insel, 2014). It is within this context that we encounter the initial mentions of the idea of 'precision medicine for psychiatry' and 'precision psychiatry' (Vieta 2015), accompanied by its first extensive conceptual discussion (Fernandes et al. 2017). Subsequently, research on precision psychiatry has been featured in edited collections (e.g., Baune 2019, Passos et al. 2019, Williams et al. 2021), across major psychiatric journals, and in specialized publications like Personalized Medicine in Psychiatry (first issue 2017) or Personalized Psychiatry and Neurology (first issue 2021).[3,4]

It is intriguing to note that not all domains within psychiatry have garnered equal attention in transitioning towards precision medicine. Although strides have been made in diagnostic enhancement through computational phenotyping (e.g., Patzelt et al., 2018) and promising research in genetically informed psychopharmacology (e.g., Butler, 2018),

[1] "People frequently cite the 1990s as the era for redefining mental disorders as brain disorders. While this conceptual shift was important, we now realize the greater importance of developing new tools: imaging techniques for quantitative studies of brain structure, function, and chemistry, as well as other comprehensive tools for mapping DNA and RNA. (...) These advances ushered in a decade of discovery that brings us to 2010" (Dana Foundation 2010).

[2] To just give one example of the early achievements of the pharmacogenetic instance of personalized medicine, let us consider an improvement in the treatment of HIV by the drug Abacavir. Abacavir was a relatively safe drug for most patients; in some patients, however (6%), it caused a life-threatening allergic reaction. This allergic reaction, however, could be correlated with a single genetic variant of the major histocompatibility complex class I (HLA-B*5701) (Hetherington et al. 2002, Mallal 2002). Subsequently, this discovery allowed them to implement screening procedures for HIV patients for the relevant genetic variant before the administration of the drug.

[3] The reader may wonder about the appearance of "personalized" instead of "precision" in this journal's names. In fact; both terms are often used synonymous (see e.g. Fröhlich 2018) as it is the case with these journals.

[4] The interested reader may find more details on the history of precision medicine, its (dis)continuity with previous developments in medicine in Ruaño (2004), Sykiotes et al. (2005), Steele (2009), Longo (2013), Michl (2015); Perlman et al. (2016), and Lee et. AL. (2019). For debates on how much progress was actually made through precision medicine and how much more should be expected, see e.g. Hedgecoe 2004, Green et. Al. (2011), Chabner et Al. (2013), Maughan (2017), Fröhlich et. Al. (2018), Denny et. Al (2021).

one fundamental aspect of psychiatric treatment remains relatively unexplored in theoretical discourse and has seen a limited number of empirical investigations: psychotherapy.

To address this gap, particularly in theoretical discourse, we propose a conceptualization of 'Precision Psychotherapy.' This endeavor aims to enrich the systematic exploration of the diverse sub-fields within precision medicine. We recognize that the significance of this undertaking extends beyond mere systematic exploration; it holds value in facilitating informed decision-making. Providing a conceptualization of precision psychiatry will offer valuable guidance to researchers and stakeholders in medical research and services, aiding in non-trivial decision processes. For instance, it can inform decisions regarding which research to include in reviews within the field of precision psychotherapy or determine the type of research and practices worthy of funding in projects aimed at advancing the implementation and research of precision psychotherapy. Such decision-making necessitates criteria for distinguishing precision psychotherapy and its associated research.

Our approach to formulating a viable definition of precision psychotherapy involves beginning with a broad comprehension of precision medicine and tailoring this understanding to accommodate the specific context of psychotherapy. This process will yield a nuanced understanding of precision psychotherapy, aligning it with the broader concept of precision medicine while capturing the unique attributes of psychotherapy. However, a significant challenge in this endeavor is the nebulous nature of precision medicine as a concept. As highlighted by several authors, “there is no officially recognized definition' for precision medicine (Jain 2015, 1). In many contexts, it simply serves as 'an expression for describing a methodologically heterogeneous field of different approaches that are only loosely connected by a very general objective” (Langanke et al. 2015, 26). Given this ongoing debate and lack of a clear definition for precision medicine, we recognize the need for foundational and clarificatory groundwork on precision medicine before narrowing down its application to the domain of psychotherapy. The structure of the paper will unfold as follows.

In Section 2, we initiate our discussion by delving into the sources and types of informational means typically utilized in precision medicine, extending this analysis to

encompass precision psychotherapy. This examination stems from the endeavors of philosophers who have sought to define precision medicine by considering the nature of the information that informs it. Within contemporary philosophical dialogues concerning precision medicine, we observe the utilization of a broad and narrow conceptualisation of precision medicine. The former asserts that precision medicine is solely grounded in microbiological and physiological data, while the latter extends its scope to encompass psychological, social, and environmental data as well. Although we refrain from committing to either stance for medicine at large, we advocate for adopting a broad understanding of the informational sources essential for achieving precision, particularly in the case of psychotherapy. We contend that an adequate understanding of precision medicine or psychotherapy cannot be derived solely from identifying the relevant types of information used. Consequently, we pivot to explore how the aim of this research — an enhancement of precision through these information sources — can be comprehensively understood beyond the slogan to provide "the right patient with the right treatment at the right time" (e.g. Haldorsen 2003, Blackstone 2019, European Parlament Research Service 2015, U.S. Food and Drug Administration Service 2018). A slogan not meeting requirements of conceptual scrutiny to expect from a serious definitional attempt as it only states the *purpose* of precision, not what precision consists in. Furthermore, some areas of medicine may not only be concerned with the treatment but might rather aim for an increase of precision in diagnostics. We argue for the idea that precision in medicine should be understood mainly as a reduction in indeterminacy more precisely semantic and epistemic indeterminacy.

Moving on to Section 3, we initially examine the ongoing discourse concerning precision medicine as a whole. However, it becomes apparent that the conceptualization of 'increasing precision' lacks sufficient detail within the context of precision medicine itself, making its direct application to subdomains like psychotherapy challenging. Commonly, precision is conceptualized through the phrase 'providing the right patient with the right treatment at the right time' (e.g., Haldorsen 2003, Blackstone 2019, European Parliament Research Service 2015, U.S. Food and Drug Administration Service 2018). This phrase, while evocative of the purpose of precision, falls short of the requisite conceptual scrutiny expected in a serious definitional attempt. Primarily, it outlines the

objective of precision without delving into what precision fundamentally entails. Moreover, certain medical domains may not exclusively focus on treatment but instead prioritize precision in diagnostics. We advocate for the understanding that precision in medicine primarily involves a reduction in indeterminacy, specifically targeting semantic and epistemic indeterminacy.

Having presented our considerations regarding the appropriate understanding of precision in the context of medical research, we proceed to Section 4, where we substantiate the claim that precision entails the reduction of epistemic and semantic uncertainty in line with current medical research. We achieve this by examining the three key progress trajectories in medicine: Prediagnostic, Diagnostics, and Prognostics/Theranostics. We offer examples showcasing advancements in precision within each of these trajectories

In Section 5, integrating our considerations and applying them to the case of psychotherapy, we present our proposed definition of Precision Psychotherapy. We conclude that

An item of research increases the precision of psychotherapy if and only if it reduces a type of indeterminacy (i.e. reduces the range of plausible options) relevant for treating psychiatric illnesses (i.e. theranostics). It may do so by (a) refining psychiatric concepts and categories (reducing semantic indeterminacy), (b) providing evidences for or shifting certainty in line with psychiatrically relevant facts (reducing epistemic indeterminacy), or (c) increasing the likelihood with which a specific outcome is achieved by some intervention (reducing causal indeterminacy). For this, any type of information that reliably reduces such indeterminacies is suitable. Accordingly precision psychotherapy as practice is realized where such reductions of indeterminacy are used in the psychotherapeutic treatment of patients.

Finally, in Section 6, we summarize by affirming that our defined conceptualization offers a valuable foundation for researchers and philosophers to engage in meaningful discourse about precision psychotherapy, transcending existing commonplace yet vacuous slogans.

2. INFORMATIONAL SOURCES FOR PRECISION

The primary sources of information pivotal for the early progress in precision medicine originated from microbiological data. These insights initiated significant advancements in

precision within oncology and the study of rare diseases (Spear et al. 2001; Collins et al. 2001; Hamburger et al. 2010; Jones 2013; Carrasco-Ramiro 2017; Lemoine 2017).[5] As philosophers and scientists reflecting on the history of precision medicine have noted, "there have been a great many examples of interventions tailored to individual patient profiles, virtually all of them based on genetic profiles" especial "with genetically-mediated pharmacokinetic aspects of drugs" (Goetz, Schorl, 2018. p5). Others, who concerned themselves with systematic reviews of the literature in the field, such as Schleidgen et al. (2013) did for 'personalized medicine,' found that in research from the field we usually see attempts "to improve tailoring and timing of preventive and therapeutic measures by utilizing biological information and biomarkers on the level of molecular disease pathways, genetics, proteomics as well as metabolomics" (ibid.,9).[6]

Due to this widely shared observation, some authors support a *narrow* biomedical focused conception of precision medicine, excluding various non-biological kinds of information. Schleidgen et al. (2013), for instance, claim that precision medicine

"is not medicine with a special focus on the interests and preferences of the individual patient. For instance, PM does not include any reference to an adequate doctor-patient relationship. Hence, PM as such is not related to the term patient-centered medicine" (ibid., p 11).

A similar view is taken by Wiesing (2017), pointing out that

"the personal characteristics of human beings —their self-consciousness, their ability to reason and their rationality— are not even mentioned by personalized medicine in its search for molecular biomarkers. Personalized medicine refrains from the use of personal information, such as "psycho- and sociomarkers""

[5] At this point, the reader may wonder why we only talk about types of information used in precision medicine when discussing its means and not its methods as well. We exclude methods from our discussion simply because the sheer range of potential and actual methods employed to achieve the aims of precision medicine across various medical disciplines is so vast that attempting to address them all would be impractical. Additionally, it does not appear that any specific method is excluded from use in achieving precision, nor does there seem to be ongoing debate about this matter. Undoubtedly, in contemporary times, machine learning methods applied to large datasets of patient information are assuming an increasingly prominent role in medical research, and there is optimism that this may lead to a significant breakthrough (e.g. Love-Koh et al., 2018; Johnson et al., 2021). However, no particular method appears to be definitive or central to current discussions on what defines precision medicine.

[6] We continue to use the convention of using "personalized" and "precision" medicine interchangeably. However, it's important to note that this practice is not universally accepted. The National Research Council (NRC), for instance, prefers not to use them interchangeably. While both terms are sometimes used synonymously, the term "personalized medicine" has been used to convey the idea that unique treatments can be designed for each individual. Due to this, the NRC believes that the term "precision medicine" is a better choice to describe the large-scale medical movement they have in mind (NRC, 2011, 125). Similar concerns about the term "personalized" arise repeatedly in the literature. For instance, Feiler et al. point out that the focus on the personal in personalized medicine may generate a mystique of unrealizable promises and expectations about medicines and treatments perfectly tailored to each individual person (Feiler et al., 2017, 4).

(ibid.p2).

However this is not the only position taken in the debate.

The National Research Council of the United States, for example, considers that precision medicine will exploit the “variability in genes, environment, and lifestyle” (NRC 2011, 1) – a view also supported by authors like Abttan et al. (2020), who emphasize that

> “more recently, personalized medicine has taken an important turn by expanding the number and type of health-related data used [...] personalized medicine has moved beyond merely genetic data to include the full range of available patient information, from a molecular scale (proteome, transcriptome, metabolome, etc.) to an epidemiological one (foodome, sociome, environtome, etc.)". ibid, 3

In this view, the set of evidence used may also contain information about certain lifestyle factors such as the diet of subjects, their social situation (e.g., employments or friendships), and various environmental factors. Nothing in principle speaks against including 'psychomarkers', e.g., information about certain psychological traits such as personality traits. Taking into account all these factors, going beyond microbiology is what one might call the broad view, in contrast to the above-proclaimed narrow view focusing solely on biological information.

Both approaches, broad and narrow, are present in medical science and practice. Instances of a narrow perspective can be seen in the assessment of heritable genetic variations of subjects to determine whether they have a high risk of developing cancer (e.g., Shin, Bode, Dong 2017). On the other hand, recent developments in precision medicine focusing on type-II diabetes highlight the central relevance of lifestyle factors (e.g., Mutie, Giordano, Franks 2017). When considering the broad and narrow conceptualizations as competing positions, one may inquire about their suitability for psychiatry, particularly psychotherapy. Let us begin by examining psychiatry to determine whether, even at this level, a clear decision can be made in favor of one or the other source of information being more applicable.

Looking at existing discussions in precision psychiatry, we can observe both narrow and broad focuses. The narrow perspective is embraced by the author who coined the term 'precision psychiatry.' He anticipates that as precision psychiatry advances, “nobody will be able to work denying the biological substrate of mental diseases” (Vieta 2015, 117). This narrow emphasis on biological factors is shared by proponents who envision precision psychiatry concentrating on “Multi-omics, neuroimaging, big data and

high-density data approaches, exposome and molecular epidemiology and physiology [that] should converge towards specific biomarkers" (Köhne; Van Os, 2021, 1409).

However, other authors explicitly adopt a broader understanding, such as Fernandes et al. (2017), who acknowledge that precision psychiatry "rests on, and simultaneously contributes to, the evolving knowledge of the biological pathways involved in the major mental illnesses", ultimately leading to an "appropriately integrative understanding of mental illness as disorders of the brain" (ibid., p2). They make it clear that this appropriately integrative approach entails incorporating environmental and lifestyle factors into the modeling process. Similarly, Baune (2019) highlights that precision psychiatry is an approach "that takes into account individual variability of genes, environment, and lifestyle" (ibid, 1). Furthermore, he emphasizes that in the process of researching and applying precision medicine, consideration is given to "individual clinical characteristics of a patient," encompassing "neurocognitive, affective, and functional profiles," as well as the "personality, insight, and resilience" of patients (ibid, 2).

Shifting attention from medicine in general to psychiatry does not definitively resolve the debate between the narrow and broad understanding, as both continue to be applied. Consequently, the resolution of this issue needs to occur at the level of psychotherapy itself.

When would it, at least prima facie, be more plausible to assume the narrow or broad notion for the context of precision psychotherapy? The narrow notion would be *prima facie* plausible if efforts related to increasing the precision of psychotherapy should mainly rely on the use of biological information about patients. On the other hand, the broad notion would be prima facie more plausible if, in addition to the possibility that biological information might contribute to precision regarding psychotherapy, other information—such as neurocognitive, affective and functional profiles, personality traits, social information, and clinical characteristics of these patients—may also contribute to an increase in precision.

A brief look at psychotherapy research shows us that, at least up until now, we find examples supporting the apparent possibility to increase precision based on both biological and non-biological information. Let us illustrate this.

As an example of the use of biological information, we can consider the burgeoning understanding of the impact of psychotherapy on brain structures and functioning (see Beauregard 2022). Although this field of psychotherapy research is still relatively young, several promising examples have emerged. For instance, Colvonen et al. (2017) highlight that research suggests pre-treatment biomarkers (specific functional neural systems, glucocorticoid sensitivity and metabolism, heart rate, gene methylation, and certain genotypes associated with serotonin and glucocorticoids) can predict a positive response to psychotherapeutic treatment of PTSD. Riess (2011) points out that the quality of the therapeutic relationship between therapist and patient, assumed to be a relevant mediator or moderator of positive outcomes in psychotherapy, can be linked to (dis)concordances in the autonomic nervous system arousal in therapists and patients during therapy sessions. This is manifested by heart rate, respiration rate, muscle tension, galvanic skin resistance, electroencephalography, and brain imaging markers. Additionally, Marceau et al. (2018) found in their review that biomarkers (specifically hypoactivation in prefrontal and cingulate regions) can predict treatment response to psychotherapeutic interventions for patients suffering from Borderline Personality Disorder. These examples showcase the relevance of biological information in increasing the precision of psychotherapeutic treatments. However, we also find instances where non-biological information plays a crucial role.

Examples of cases where the use of non-biological information increases the precision of psychotherapy are numerous, constituting the standard information that has been crucial in psychotherapy research over the last decades. Here are some illustrations: The NIMH Treatment of Depression Collaborative Research Program found that baseline severity of depression predicts differential treatment effects. Generally, psychopharmacological treatments appear to be more effective than psychotherapy in severely depressed patients, while there is no difference found between pharmacotherapy and psychotherapies in subjects who are less severely depressed (Elkin et al., 1995). Another example pertains to research on personality traits and their role in the recovery from depression. It was revealed that the Big Five personality trait of neuroticism does not moderate the effects of CBT in treatment-resistant individuals (Spek et al., 2008; Fournier et al., 2009; Wiles et al., 2014). Nor did dysfunctional attitudes and

metacognitive awareness (Wiles et al., 2014), outcomes that discourage the practice of patient selection for CBT based on these features. Further, research highlights the significance of patients' preferences regarding the type of psychological intervention they receive on dropout rates in treatment and the magnitude of treatment effect. Aligning treatment with patient preferences significantly improves dropout rates as well as clinical outcomes (Swift et al., 2019; Windel et al., 2019). Lastly, in a more recent example, work by Saunders et al. (2020) analyzed routine data from 44,905 patients who received treatment. They linked patterns of recovery under different treatments (low intensity treatments - e.g., facilitator-led/guided self-help or computerized-CBT, and high-intensity treatments - e.g., CBT, interpersonal therapy (IPT), or counseling) and discovered clusters of patients responding differentially to treatments in terms of reliable recovery, improvement, and clinical deterioration. The information consistently used encompasses clinical measures (depression severity, anxiety severity, functional impairment, phobia self-rating), medical information (medical prescriptions), biological information (age at referral, sex), and social information (ethnic group, welfare status).

Considering all the above examples of the use of both broad and narrow information to support claims about how to more specifically select and target therapeutic interventions, it leads to a potential resolution of the debate regarding which types of information should be considered as sources of information for precision psychotherapy. If, as it prima facie appears, all the examples of psychotherapy research mentioned in the preceding paragraphs would qualify as research increasing the precision of psychotherapy, it would be appropriate to adopt the broad notion of information rather than the narrow one. This is because the narrow notion would only cover part of the described sources of information, while the broad one would encompass all the sources of information discussed above. However, whether these examples indeed qualify as increasing precision can only be answered once we establish our understanding of precision, a task we shall undertake in the next section. After presenting our understanding of precision, we will briefly revisit the above examples and demonstrate retrospectively that the antecedent of our presented conditional is indeed true.[7]

[7] Of course someone who would cling to any apriori reason why precision should only be restricted to the narrow notion might think otherwise and not be convinced by this presentation. In other words, one would

3. PRECISION FOR MEDICINE

When discussing precision medicine, and precision psychotherapy in particular, the question of how 'precision' in this context should be understood is natural and pivotal. There are several ways to conceptualize precision, broadly falling into two larger groups: the technical sense of precision within metrology, the science of measurement, and several commonsensical understandings that can be elaborated based on existing philosophical work on indeterminacy. However, we contend that the metrological account is inadequate in this context, and we should instead opt for a philosophically informed account. To establish the plausibility of this assertion, let us first delve into the metrological option and its inherent problems.

The International Vocabulary of Metrology (VIM, 2.15) defines precision as the proximity of several measurements on the same target. However, these measurements must only be close to each other, not necessarily to the true value. In this sense, one can be precise but wrong, highlighting the distinction between precision and accuracy, which refers to the closeness between the measured value and the true value. For instance, in a game of darts, you are accurate if your darts hit the bull's eye, and the degree of accuracy decreases as your darts land farther away from the bull's eye. Nevertheless, they might still cluster tightly if you throw precisely but inaccurately. It is precisely this independence of precision from accuracy, allowing for an increase in precision without a corresponding increase (and potentially even allowing a decrease) in accuracy, that renders the metrological understanding of precision unsuitable for precision medicine.

If the "very general aim" (Langanke et al. 2015, 26) of precision medicine assumed by stakeholders is encapsulated in the slogan "the right treatment for the right patient," it broadly encompasses what precision medicine is partly about. In this context, the metrological understanding of precision, as defined by the International Vocabulary of Metrology, seems unsuitable for precision medicine. If precision in medicine (and in

have to apply what Tabb, Lemoine (2022) pointed out, namely that “Given the amorphous role of the concept of precision, either precision medicine must be understood to mean different things in different fields or, if its usage in oncology is taken to be paradigmatic, psychiatry (and likely other fields as well) must be admitted to be imprecise.” (ibid. 194) Since the notion of precision in itself as spelled out earlier does not commit one to the narrow or broad notion of precision per se we for our part go with the first option.

psychotherapy as well) is indeed about determining the most appropriate (rather than inappropriate) treatment, it necessitates accurate judgments about potential treatment outcomes based on the specificities of patients. Mere metrological precision, where the measurements are close to each other but not necessarily to the true value, is inadequate. Simply arriving at the same conclusion regarding the treatment (precision) does not guarantee the correct treatment (accuracy). Epistemic progress in precision medicine should be intrinsically linked to an increase in accuracy. This progress should lead to a better understanding of how factors such as the specificities of a patient's condition influence different treatment outcomes. Therefore, whatever definition of precision in medicine is ultimately adopted, it should at the very least provide reliable, more accurate insights into medical facts that influence treatment outcomes. Epistemic progress, aiming for more accurate insights into medical matters, would not be guaranteed if a meteorology-based notion of precision were adopted to define precision medicine or psychotherapy.

Beyond the narrow confines of metrology, achieving precision is often associated with a reduction in some form of indeterminacy. This principle also extends to the 'precision' in metrology: the more precisely I throw darts, the more definite it becomes where they will land on the board after each throw. At the pinnacle of precision, all indeterminacy vanishes, and each throw hits the same point. But what exactly is indeterminacy? In a general sense, something, x, is considered indeterminate (to someone, to everyone, or in itself) if it is not obvious which of several options concerning x is correct. When our throws lack precision, it remains unclear where they will land. As we strive for precision, we can progressively eliminate potential landing sites on the board. By broadening our perspective beyond meteorology, we may arrive at an understanding of precision in terms of reducing indeterminacy that aligns more suitably with precision as pursued in medicine. This leads us to the alternative version, namely, the more commonsensical, philosophically informed understanding of precision that we propose to adopt.

Commencing with the common-sense understanding of precision as the reduction of indeterminacy, we can delve deeper into comprehending indeterminacy and its reduction by categorizing the various types of indeterminacy and identifying those

relevant in the context of medicine. The types of indeterminacy we will differentiate are *absolute* and *relative* indeterminacy. Absolute indeterminacy will be further subdivided into *ontological* and *causal* indeterminacy, while relative indeterminacy will be categorized into *semantic* and *epistemic* indeterminacy. Subsequently, we will argue that what primarily concerns medicine is semantic and epistemic indeterminacy and its subsequent reduction.

Something can be indeterminate with respect to something, for example a specific group, method, or framework, which we can denote as relative indeterminacy. Conversely, something can be objectively or inherently indeterminate, which we categorize as absolute indeterminacy. For example, the next number on a roulette wheel may be indeterminate to an individual, but given the metaphysical macroconditions of the ball and the wheel, it is objectively determinable. Physics narrows down the possibilities to a single outcome, but from the individual's perspective, all options remain uncertain. In this case, it is indeterminate relative to the individual but not in itself. This scenario exemplifies relative indeterminacy. In contrast, consider Schrödinger's cat in quantum mechanics: before observation, it is neither definitively dead nor alive. According to the Copenhagen interpretation of quantum physics, the status of Schrödinger's cat is inherently indeterminate. This is an instance of absolute indeterminacy, also referred to as metaphysical indeterminacy.

Prima facie, it seems that metaphysical indeterminacy and attempts to reduce it for the sake of precision might not be readily applicable in the field of medicine. Considering the ontological aspect, which pertains to the indeterminacy of whether something exists or not, it doesn't seem that medicine has a significant role here. The objective of medical diagnosis is to ascertain the existing values within a patient's body, not to create these values. Physicians aim to determine the specific illness a patient has, rather than conjuring an illness into existence for a patient. Similarly, medical interventions aim to modify certain values within a patient's body, not generate them from scratch. Consequently, a reduction of metaphysical indeterminacy in this ontological sense appears to be ill-suited for understanding precision medicine.

However, there is a metaphysical notion of indeterminacy that might be relevant, particularly considering that medical interventions involve a form of manipulation aimed

at making things happen. In this context, we could consider a form of causal indeterminacy. Unlike the momentary metaphysical indeterminacy, which is concerned with a specific moment in time (e.g., the moment before we open Schrödinger's box), causal indeterminacy pertains to the uncertainty regarding the outcome of a process. Stephen Jay Gould, for instance, suggested in *Wonderful Life* (1989) that evolution is causally indeterminate: if we were to rewind life's tape, we might not witness the emergence of the same individuals or even species. Similarly, could there not be medical interventions in which the outcome is uncertain? And could an increase in precision not imply that we gain a better understanding of the potential outcomes of our intervention?

These questions pose distinct inquiries. The first delves into the realm of absolute causal indeterminacy, where the outcome of an intervention is de facto uncertain, beyond control, and unpredictable as an inherent aspect of the intervention process. However, interventions characterized by such inherent uncertainty in outcomes would be less preferable than those where outcomes can be controlled. In the realm of medicine, the goal is to minimize uncertainty and benefit the patient, making interventions with inherently unpredictable outcomes less desirable. If such interventions exist, they would be phased out in favor of less indeterminate ones, a trajectory dictated not only by precision medicine but by the fundamental objectives of medical practice.

On the other hand, the second question pertains to relative causal indeterminacy. Here, the indeterminacy in outcomes arises not from the process of intervention itself but from previously uncontrolled factors that intervene in the process, factors that can be identified and controlled. Some of these influencing factors may have been previously unknown, hence not controlled. By identifying and bringing these factors into focus, they can be controlled to a certain extent. Consider the historical example of Ignaz Semmelweis, who increased control over maternal deaths during childbirth by recognizing and addressing the spread of materials from dissecting doctors to women in labor. The precision achieved in such cases stems from knowledge of and control over factors that intervene in the outcome of a process, rather than from the inherent indeterminacy of the process itself. In the context of medicine, precision primarily focuses on relative indeterminacy—relative to our current state of knowledge. It involves gaining knowledge

and control over factors that intervene in outcomes, moving from absolute, metaphysical indeterminacy to the realm of relative indeterminacy.[8]

For relative indeterminacy, which, to recall, occurs when something is not inherently indeterminate but is, for example, specific to a particular group, method, or framework, we may differentiate between *semantic* and *epistemic* indeterminacy.

Considering semantic indeterminacy first, it arises when the meaning of a term or utterance is not fixed—it could signify this or that. Ambiguity, a prominent form of semantic indeterminacy, occurs when several meanings are concealed under homophones, as seen with “bank,” which may refer to a financial institution or the edge of a river. However, the semantic indeterminacy underlying ambiguous phrases can be resolved by clarifying intended meaning. By exposing and resolving ambiguity, we achieve greater precision. Nevertheless, addressing ambiguity is a straightforward objective for precision medicine. However, not all types of semantic indeterminacy can be nullified by exposing them.

Unlike ambiguity, indeterminacy associated with vagueness cannot be resolved by being exposed. A term is considered vague if it possesses both clear-cut and borderline cases. For instance, Yul Brunner is clearly bald, and Dave Grohl is not. However, when considering individuals like Woody Harrelson or Jason Statham, there is disagreement among competent speakers. For these borderline cases, it remains unclear whether the concept of baldness applies or not. Consequently, statements attributing the concept to such borderline cases become uncertain in their truth value. Therefore, vagueness is often interpreted as a form of semantic indeterminacy, where it is indeterminate what falls under a concept and whether a statement with a vague concept is true or not for certain borderline cases.

Another form of indeterminacy arises with increased generality and quantification. With either general or existential quantification (using terms like 'all' and 'some'), we shift from referring to specific objects to speaking about everything within our universe of discourse. However, as our statements become more general, they also become less determinate. For instance, if I know that Bob is a builder, I have a clear idea of who to contact to fix my wall. On the other hand, if I only know that *someone* is a builder, it may take me considerable time to identify the right person.

[8] For a more detailed discussion on metaphysical indeterminacy see Williams (2008).

A third form of indeterminacy, associated with increased generality, arises from the subsumability of concepts, often discussed in terms of determinables and determinates. A concept is a determinable if and only if it subsumes several more specific concepts (its determinates). What makes a determinate-ascription true also makes the determinable-ascription true, but the truth of a determinable-description leaves open which determinate-ascription is true. For instance, if I know that your carpet is green, I know that it has a color, but I don't know whether it is forest green, moss green, teal, etc. So 'green' is more determinate than 'colored,' but less determinate than 'teal.' Green is a determinate relative to the determinable 'colored' but a determinable relative to more precise color concepts.[9]

If we consider these three forms of semantic indeterminacy, it appears that for the context of medicine, the reduction or elimination of vagueness of terms, as well as ambiguity, presents an adequate aim as they allow us to be more precise. However, there is also a catch: the concept 'vague' is itself vague because there are borderline cases of borderline cases. We might not know where the night begins or where the day ends, so we group all of the borderline cases under 'dusk'. That might make our use of 'day' more precise, but it leaves open the question: Where does 'dusk' begin and end? If vagueness is vague, so is its counterpart, precision. We can probably not eradicate vagueness fully in precision medicine – when exactly is blood pressure high? How long *exactly* do I have to be sad to count as depressed? – but we can rein it in more and more, which is already progress. Lets us next move to the other relevant form of relative indeterminacy, epistemic indeterminacy.

Epistemic indeterminacy deals with not knowing what is the case even though the concepts are clear. It is sometimes understood as degrees of uncertainty regarding the truth of a proposition. As the mathematician De Finetti famously suggested, this will show itself behaviorally in the way we bet: The more certain we are that *x* happens, the more we are willing to bet on *x*, and vice versa. This fits well with the different areas of medicine: In diagnostics, we may want to develop more fine-grained tools to know more about the status of a patient; and in therapy, we may want to develop more fine-grained interventions or learn more about intervening variables or underlying mechanisms in order to be more certain about producing specific outcomes.

[9] For a longer discussion different kinds of semantic indeterminacy see Sorensen (2022).

Since medicine, as it is practiced today, is evidence-based and therefore guided by the empirical sciences, medical knowledge, like all scientific knowledge, must be considered fallible. We should expect precision medicine to aim at better methods to gather information and decrease uncertainty. However, achieving full precision or absolute certainty may not be a realistic goal. Instead, a reduction in uncertainty may suffice. According to the imminutability account of certainty, advocated by Stanley (2008), one's belief that proposition p is considered certain when it is justified to the highest degree. This idea traces back to Russell, who wrote that “a proposition is certain when it has the highest degree of credibility, either intrinsically or as a result of argument” (1948, p. 396). The challenge lies in defining what constitutes 'the highest degree' of certainty.

As pointed out by Reed (2022), spelling out the phrase 'the highest degree' is a complex task. If we interpret it to mean 'justified to the highest degree' in comparison to all other beliefs an individual holds regarding a subject matter, the notion of the highest degree will vary based on the other beliefs the subject holds, which might be relatively low. This could lead to the highest degree of certainty being low as well (i.e., being as certain belive *p*, as I am certain of anything). The same issue could arise if we broaden the certainty comparison to the intersubjective field, considering the beliefs regarding a topic held by everyone else. It appears that we do not want a standard that is too relative. An elegant solution to this problem is offered by Chisholm:

> *p* is certain for *S* =df for every *q*, believing *p* is more justified for *S* than withholding *q*, and believing *p* is at least as justified for *S* as is believing *q*. (1989, p. 12)

This definition of certainty ensures, on one hand, that a supported belief *p* is the belief that can be held with the highest certainty, surpassing all beliefs *q*. On the other hand, it also guarantees that p is supported to a significant degree. This is achieved by stipulating that supporting p must not only be more rational than withholding *p* but also more justified than the evidence for propositions q, compelling us to withhold judgment about their truth. Such an understanding of epistemic precision in terms of certainty, as proposed by Chisholm, is suitable in the context of medicine. It avoids an approach to certainty that may *prima facie* appear incompatible with medical knowledge, such as understandings of certainty as being inviolable in the face of contrary evidence. Instead, it posits that

certainty depends on degrees of evidence that sufficiently support a proposition, making it better supported than its alternatives to be certain of it. Consequently, there is room to discuss certainty resulting from varying degrees of evidential support. This approach aligns well with the practical handling of knowledge in medicine, which involves the accumulation of evidence of different sorts for or against certain medical propositions.

Summarizing our discussion on relative indeterminacy, semantic and epistemic indeterminacy, and their reduction in the context of medicine, the idea of increasing precision in medicine can manifest in two main forms. Firstly, by enhancing the precision of medical terms through reducing vagueness, ambiguity, or uncertainty in their applications, aligning them more closely with medical objectives. Secondly, by formulating medical propositions that can be held with a higher degree of certainty, or by elevating the certainty level we have for existing medical propositions.

It's important to note that these ways to increase precision in medicine are likely to interact regularly. Determining whether a novel formulation of a medical proposition or changes in a medical concept qualify as improvements (i.e., being more precise) cannot be decided in the armchair; it often requires clinical expertise and empirical support for its adequacy. Conversely, some increases in epistemic precision might stem from using more fine-grained concepts. In conclusion, the strongest moments of precision increase, the ideal case if one will, would be one in which all aspects are present. Consider a historic example in Robert Koch, who discovered the etiological role of Mycobacterium tuberculosis as the cause of tuberculosis, establishing and supporting a new medical proposition regarding the cause and mode of transmission. Previous researchers like Jean Antoine Villemin (1865) had already demonstrated that tuberculosis is an infectious disease by infecting rabbits with material from cadavers of individuals who died from tuberculosis (Villemin 1865). However, Koch showed that it was a bacterium causing the outbreak and transmission (Kaufmann, Schaible 2005). This increased semantic precision as we transitioned from Villemin’s insight that something causes a tuberculosis infection to Koch’s understanding that Mycobacterium tuberculosis causes a tuberculosis infection. It increased epistemic precision as Koch provided evidence making this specific bacterium the most likely cause. Additionally, it increased causal precision of an

intervention as a function of the increase of epistemic precision regarding insight into causes, allowing for a more targeted intervention to prevent tuberculosis infections.

To conclude this section let us ask what exactly is the advantage of our push for the idea of precision in medical contexts being understood in terms of decreasing epistemic and semantic indetermancy over the meteorological notion of precision. To put it simple, while the metrological idea of precision does bear no inherent relationship to truth-tracking (measures can become pore precise without becoming more accurate) thinking of precision in terms of reducing semantic or epistemic uncertainty does. Decreasing semantic and epistemic indetermancy seems to bring us closer to the right semantics, and adequate believes about medical matters.Furthermore, as we'll illustrate in the next section, precision improvements in medical research appear to be primarily achieved through reducing semantic and epistemic uncertainty, rather than through meteorological precision enhancements.

4. DIAGNOSTICS, PROGNOSTICS, AND THERANOSTICS

If we accept that an increase in precision in a medical field would mean a decrease in semantic or epistemic indeterminacy, one may complain that this is a rather abstract aim. But how shall this aim be realized? Considering the different domains of medical practice in which precision might be improved and looking at some examples may help. The areas we want to examine for this purpose will be called Prediagnostic, Diagnostics, Prognostics, and Theranostics

The task of prediagnostic is to identify prodromal factors allowing to predict the future occurrence of disease.[10] Such factors might be its predictive markers or causal precursors. The latter case is especially interesting as it provides avenues for early

[10] This aspect of precision for example occurs in the National Institute of Health´s (NIH) discussion what precision medicine is (NIH, 2022), in that the NIH paraphrases the position of the American Research Council (2011), saying that precision medicine among others is about “the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease.”

preventive interventions. Prediagnostic therefore falls into the domain of *Predictive Medicine* (Jen et al. 2021).

Increasing precision in this domain can occur by: (i) providing evidence for certain factors to be meaningfully predictive (and perhaps causally relevant) for a disease; (ii) broadening the evidence base so that we can predict with greater certainty and less bias from a single source; (iii) presenting evidence against a likely factor being predictive and minimizing its interference with our prediction; (iv) revising established hypotheses in light of incoming evidence to make the proposition more precise or probable.

Let's consider an example of a potential increase in precision, achieved by reducing generality. Consider the hypothesis that higher overall leukocyte counts in women are associated with an increased risk of breast cancer. This proposition is unspecific regarding whether any specific leukocyte subtypes play a crucial role in breast cancer risk or not. Identifying leukocyte subtypes and testing whether some are more relevant than others thereby specifies and precisifies the hypothesis. Doing so, this reduction of generality contributes not only to theoretical interest but also to practical interest—by homing in on more specific predictive factors.[11] Next to diagnostics.

The task of diagnostics is to identify current diseases in patients. Here, we may achieve greater precision by assessing the patient's condition more accurately or by distinguishing between potential diseases, such as distinguishing tuberculosis from a bacterial infection. Precision can therefore be achieved by: (i) providing evidence for diagnostic markers that reliably identify a specific medical condition; (ii) increasing the reliability of certain diagnostic markers; (iii) providing evidence against certain factors being diagnostically relevant, minimizing their interference with determining medical truth; (iv) revising diagnostic categories or factors based on empirical evidence, making them more precise or useful for diagnostics.

Consider, as an example, the lumping and splitting of diagnostic categories. Lumping of diagnostic categories (consolidating two or more into one) might not always increase precision, though it could still be beneficial. On the other hand, splitting often decreases ambiguity and vagueness. While for a long time, identifying disease entities in medicine relied on pure phenotype-based categorization, the rise of molecular biology

[11] This example is taken from the research of Kresovich et al. 2020.

has changed this practice in recent decades, prompting the medical community to consider both disease genotypes and phenotypes in determining disease entities (Biesecker, 1998). More recently, the Splitting and Lumping Working Group (SLWG) of ClinGen (Lumping and Splitting - ClinGen | Clinical Genome Resource) has made efforts to formulate the factors that should guide decisions to lump or split diagnostic categories and the procedures by which evidence should be weighed as reasons for lumping or splitting, including factors like phenotypical differences, molecular mechanisms of development, genetic basis, and inheritance patterns (Thaxton, Goldstein, et al., 2022). An instance of kind splitting that would reduce ambiguity and therefore increase semantic precision in diagnostics discussed by the workgroup is the case of Multiple Endocrine Neoplasia 2 (MEN2). MEN2 is a type of cancer associated with mutations in the RET-Gene. This disease is considered to have two symptomatically distinct subtypes: MEN2-A (sometimes called Sipple-Syndrome) and MEN2-B (sometimes called Wagenmann-Froböse-Syndrome). Based on reviews of evidence on the genetic basis, phenotypical differences, molecular mechanisms of development, and inheritance patterns, the SLWG concludes that instead of considering the conditions named MEN2-A and MEN2-B subtypes of the same disease, they should be regarded as two different diseases altogether (ibid). This move, if accepted, increases the precision of diagnostic categorization by disambiguating MEN2, formally referring to two different disease entities as subtypes, into two entirely different conditions (ibid). Moving on to prognostics.

The task of prognostics involves identifying factors that enable predictions regarding how a patient might prevent, recover from, or potentially relapse into a certain disease, either with or without specific treatments.[12] This is a facet of predictive medicine closely related to s*tratified medicine* (Bell, 2014), which aims to predict the interventions that will yield the most benefits and have the fewest side effects for a reference group of

[12] This aspect of increase of precision is e.g. pointed out by (Cherny et. Al. 2014, p1): “Rather than having medications recommended on the basis of diagnosis and staging, “personalized medicine” suggests that tailored treatments based on assessment of biological parameters of the individual or the underlying disease can improve patient outcomes by identifying those patients most likely to benefit from specific therapies and, simultaneously, diminishing the use of medications for patients who can be predicted not to derive benefit from them.” Also this aspect appears in the earlier referenced statement of the NIH saying that precision medicine is among others about “American Research Council (2011), saying that precision medicine among others is interested in ““prognosis of those diseases they [patients] may develop, or in their response to a specific treatment” so that “preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not” (NIH 2022).

patients based on prognostic factors. This ideally allows for more finely-grained recommendations than those based solely on diagnostic categorization. The intervention may aim to prevent, cure, or at least improve a patient's condition. When discussing the topic of treatment in this context, some authors prefer to frame it in terms of *theranostics*.

The domain of prognostics can be enhanced by: (i) providing evidence that prognostic factors, including the type of intervention, enable predictions about whether an intervention increases the chances of recovery, or prevents, offsets, or mitigates a disease's outbreak, progression, or relapse; (ii) increasing the reliability of predictive factors to serve the aims of (i); (iii) providing evidence against some considered factors being predictive; (iv) revising the conceptualization of predictive factors in light of empirical evidence. An example of increased precision in prognostics can be seen in research on the effectiveness of monotherapies for cancer (Adam et al., 2020). In this field, large-scale in vitro tests are conducted to associate molecular profiles of cancer cells with their response to drugs. The National Cancer Institute Developmental Therapeutics Program published data on the response of 60 cancer cell lines (known as NCI60) to tens of thousands of chemical compounds, including a large number of drugs. One important result of these efforts was the discovery of the 26S proteasome inhibitor bortezomib, now used in multiple myeloma treatment (Shoemaker, 2006). Since then, in vitro drug screens of cancer cell lines have become a popular approach to discovering the multi-omic underpinnings of drug sensitivity and resistance (Macaroon et al., 2011).

While this section focused on the domains in which medicine might increase its precision in general to illustrate our claims about semantic and epistemic uncertainty decrease being adequate conceptualizations of what it might mean for medicine to become more precise, the next section focuses on bringing these ideas and our other points from the previous section to bear on the case of precision psychotherapy. But before we move on, there is a remaining argumentative depth from Section 2 that is still open. To recall: there, we claimed we would later show that the examples we used to plausibly support the wide, rather than the narrow, notion of psychotherapy to be used are indeed examples of research in psychotherapy that would qualify as increasing precision. This point is easy to make now given our work in this and the last section.

The first examples, using biomarkers such as PTSD biomarkers for treatment outcome prediction (Colvonen et al., 2017), biomarkers for the prediction of the therapeutic relationship (Riess, 2011) , and biomarkers for outcome prediction in borderline patients, increase epistemic precision in theranostics by establishing new medical propositions concerned with factors whose presence or absence predicts the success of therapeutic treatment outcomes. The same holds true for the findings from the NIMH Treatment of Depression Collaborative Research Program (Elkin et al., 1995). On the other hand, the mentioned research on relevant features of treatment-resistant depressive patients that showed several features to be irrelevant in predicting outcomes in therapy increased precision in theranostics by decreasing certainty in incorrect medical propositions (Spek et al., 2008; Fournier et al., 2009; Wiles et al., 2014). Similarly, the research on the relevance of patient preferences on dropout rates and outcomes in therapy contributes to increasing precision by providing evidence for a certain medical proposition falling into the trajectory of theranostics that would increase certainty in certain medical propositions (Swift et al., 2019; Windel et al., 2019). The same applies to the clustering studies for dividing patients into groups that benefit from low and high-intensity treatment. Perhaps they may find a helpful refinement in what we attempted to do by providing this definition, as it provides evidence that certain factors (e.g., gender, age, personality) of a patient predict some psychotherapeutic interventions' potential to lead to recovery from a mental illness or, respectively, prevent, offset, or mitigate its outbreak, progression, or relapse (Saunders et al. 2020).

Now that it is clear that the examples used to support the broader notion of information in the context of psychotherapy indeed seem to increase precision, and thus the antecedent of our earlier claim in section 2 holds true, let us take all our considerations from the last sections and apply them to the question of how we should define precision psychotherapy.

5. DEFINING PRECISION PSYCHOTHERAPY

We have discussed the informational sources that should be considered as drivers of precision medicine or, respectively, psychotherapy in section 2. In section 3, we explored

how to best conceptualize precision as an aim in precision medicine. We also provided a differentiation of general trajectories of progress in precision and showed examples of how progress, in line with our proposed understanding of precision, can be made in each of them in section 4. In this section, we will draw together our theoretical considerations from the last sections and apply them to arrive at a working definition of precision psychotherapy. Our proposal is as follows:

An item of research increases the precision of psychotherapy if and only if it reduces a type of indeterminacy (i.e. reduces the range of plausible options) relevant for treating psychiatric illnesses (i.e. theranostics).. They may do so by (a) refining psychiatric concepts and categories (reducing semantic indeterminacy), (b) providing evidences for or shifting certainty in line with psychiatrically relevant facts (reducing epistemic indeterminacy), or (c) increasing the likelihood with which a specific outcome is achieved by some intervention (reducing causal indeterminacy). For this, any type of information that reliably reduces such indeterminacies is suitable. Accordingly precision psychotherapy as practice is realized where such reductions of indeterminacy are used in the psychotherapeutic treatment of patients.

More precisely, this would mean that a research item contributes to precision psychotherapy if:

(i) it provides evidence that a certain factor (e.g., gender, age, personality) of a patient predicts the potential of some psychotherapeutic interventions to lead to recovery from a mental illness or, respectively, prevent, offset, or mitigate its outbreak, progression, or relapse.

(ii) it increases the reliability and credibility of a predictive factor to be used in cases like (i).

(iii) it provides evidence against some considered factor, thereby decreasing its potential to interfere with tracking medical truth.

(iv) it revises the conceptualization of predictive factors in light of empirical evidence, making the medically relevant concepts more precise and testable, i.e., less ambiguous, vague, or general.

This definition, developed from our theoretical considerations on precision medicine in general and applied to the specific case of psychotherapy, offers two additional benefits beyond the reasoning we have presented so far to support it. The first benefit is that this understanding is in line with, but more general and detailed, than other suggestionsin the literature. For example, the goal of precision psychotherapy is described as "increasing the success of psychological interventions by identifying predictors of response" (Martinez-Aran, Vieta, 2021). It also aligns with the mandate for individualization presented by Gordon Paul, which emphasizes finding the optimal treatment for a specific individual under particular circumstances (Paul, 1967). Moreover, it fits the aim of predicting "the optimal treatment for a given individual and the magnitude of the advantage" (Bronswjik et al., 2021). This deeper understanding of precision not only points out the rough aims but proposes how these aims are meant to be achieved. Thus, among those who have articulated their opinions and work in the field of precision psychotherapy, our proposal is likely to find no strong opponents at first glance, suggesting that it is not obviously in conflict with what scientists in precision psychiatry actually do and want.

6. CONCLUSION

In this paper, we take significant strides toward a more rigorous understanding of precision psychotherapy. We accomplish this by conducting a thorough review of the ongoing discourse on precision medicine (section 2) and by introducing novel insights on how to conceptualize precision in medicine (sections 3 and 4). Building on this foundation, we propose a new and robust definition of precision psychotherapy. This definition not only aligns with what we argue constitutes precision medicine in general but is also in line with the limited existing discussions within the emerging field of precision psychotherapy. We believe this definition will serve as a solid basis for further conceptual debates and will offer practical utility, aiding entities such as funding agencies and lawmakers in determining what qualifies as research in precision psychotherapy. Furthermore, it will empower researchers to discern what research can be classified as precision psychotherapy and what cannot.

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