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# Concepts of Actionability in Precision Oncology

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## Abstract

"Actionability" is a key concept in precision oncology. Its precise definition, however, remains contested. This article undertakes a philosophical analysis of "actionability" to aid in conceptual clarification. We map distinct concepts of actionability, arguing that each is best understood as a contextually objective category articulated to mitigate risk of "conceptual slippage." We defend "interactive pluralism," acknowledging the need for distinct concepts but also for conceptual interaction in practice. This article thus offers insights for both practitioners and philosophers, clarifying approaches to actionability for scientists and clinicians and serving as a case study to test competing views on scientific pluralism.

## 1. Introduction

Precision oncology aims to individualize cancer treatment using genomic information. Defining how and what genomic information is "actionable" has thus emerged as a central task for precision oncology (Nelson et al. 2013; Tempini and Leonelli 2021). A myriad of definitions, hierarchies, and scores to delineate and rank "actionability" of genomic data have been proposed, each serving distinct yet often overlapping purposes. That defining actionability should engender a diversity of approaches is unsurprising, given that what is considered actionable is linked to the nature and context of action. One might think it is just a matter of making colloquial senses of the term "actionable" more precise. However, as pivotal research and clinical decisions are increasingly staked on what genomic data is considered actionable, there is a pressing need to interrogate the concept of "actionability." Here, philosophical analysis can aid in conceptual clarification. Such analysis might also yield additional insights as a case study to test competing views in the philosophical literature on pluralism

with respect to scientific categories. To these ends, this article undertakes a philosophical analysis of the concept of "actionability" in precision oncology.[1]

The first section examines distinct motivations for developing concepts of actionability, proposing a taxonomy of different functions of actionable genes, and thus senses of actionability. The second section considers the relationship between different actionability concepts. Despite shared considerations across concepts, we argue that actionability is not reducible to a single concept with a single set of criteria for application, and we defend pluralism against two key challenges. The first is avoiding an "anything goes" pluralism where what is considered actionable simply varies with "subjective" stakeholder interests (Chae et al. 2017). While we grant that context and interests are important in assessing actionability, we argue that this does not make the concept "subjective." To the contrary, being precise about what it means to be actionable in any given context is critical, given a tendency for conflation among competing senses—"conceptual slippage"—and associated harms. We show how existing actionability frameworks are best understood as attempts to establish contextually specific, yet objective definitions of actionability. The second is avoiding a strictly "isolationist" pluralism, according to which "translating" across different senses or uses of the concept is impossible. We argue that in unique contexts, criteria for membership in one or another potentially overlapping sense of "actionable" is underdetermined. Such cases necessitate interaction between concepts, best captured by an "interactive" pluralism (Van Bouwel 2014). We illustrate this feature through a clinical case study, where problematic cases are reviewed by molecular tumor boards. We conclude by briefly considering what this view of actionability means for attempts to develop algorithmic definitions of actionability in precision oncology.

## 2. Concepts of actionability in biomedical research and practice

This section considers four different problems motivating concepts of actionability. These are then used to generate a taxonomy of actionability, reflecting different senses of the term. These problems include the need (1) to discriminate "actionable" mutations from an expanding set of "driver" mutations generated by research in cancer genomics; (2) to prioritize "actionable" mutations to guide enrollment in clinical trials of targeted therapies in oncology; (3) to define "actionable" mutations that require testing and treatment as part of the standard of care; and (4) to identify which variants are "actionable" if detected on genomic testing in asymptomatic individuals.

### *2.1. From "driver" genes to "actionable" mutations*

One unexpected finding of large-scale projects in cancer genomics, such as The Cancer Genome Atlas (TCGA) project, was that cancers harbored a much higher than expected number of "driver" mutations, a number that continued to climb as more tumors

[1] To be clear, genetic information is deployed to inform decisions in a variety of contexts in medical research and practice. The expression "genetic actionability" is used outside oncology, and different criteria for "action" should be considered in these contexts. We should be careful not to conflate criteria for action across such contexts. For a current review of the variety of ways in which genomic information is used in medicine, see, e.g., Shendure et al. (2019). See also Sarkar's (2021) discussion of the relevance of "specificity," e.g., in deploying CRISPR for genome editing.

were sequenced (Plutynski forthcoming). This finding was in part due to shifting criteria for how "driver" genes were detected and conceptualized. The concept of a driver mutation is contested and remains in flux, but roughly it refers to a genomic alteration that plays a causal role in tumor initiation or progression. The methods employed by large-scale sequencing projects meant that driver genes' causal roles were not assessed directly but inferred, initially simply based on their being overrepresented in tumor samples compared to controls (ibid.). Attempts were made to narrow this set of potential drivers with algorithms for sorting among variants; however, the overall set of drivers remained larger than expected. While this sensitive method for identifying potential genetic drivers of cancer was well suited to the goals of TCGA—namely, scaffolding future research—the project ultimately aimed to inform cancer treatment, creating a problem of how to identify which among this set of "driver" genes were genuinely "actionable" mutations. The category of driver genes, it seemed, had become too inclusive to meaningfully inform translational research.

The first concept of "actionability" thus evolved in a specific context in service of solving a specific problem: cancer genomics research and the identification of genetic variants of interest for translational research. A recent TCGA study of more than 9,000 tumors (Bailey et al. 2018), for example, predicted more than 3,400 driver genes using computational techniques. To narrow down this expansive set of drivers and identify variants with potential therapeutic implications, the authors applied further tools. One approach is PHIAL (Precision Heuristics for Interpreting the Alteration Landscape), an algorithm that ranks genomic variants according to clinical actionability from the database TARGET (Tumor Alterations Relevant to Genomics-driven Therapy) (Van Allen et al. 2014). TARGET evaluates clinical actionability using a range of information including preclinical and clinical data, existence of approved therapies, and expert opinion. Bailey et al. (2018) applied this approach to show that 52 percent of samples in their study contained actionable mutations.

TARGET and PHIAL are examples of how actionability is conceptualized and operationalized in basic science, ostensibly to aid in translational research. Other tools serve similar purposes, such as DEPO (Database of Evidence for Precision Oncology) (Sun et al. 2018), another approach employed by Bailey et al. (2018) that similarly involves a curated database and ranking system but with a focus on repurposing of existing cancer drugs. In this case, the main criterion for inclusion is the existence of a drug that targets a particular variant's associated pathway. Other researchers, drawing on different databases, use approaches with different inclusion and exclusion criteria. The Catalogue of Somatic Mutations in Cancer (COSMIC) is one of the largest and longest-standing genomic databases in cancer and plays a key role in data curation for precision oncology (Tempini and Leonelli 2021). Recently, COSMIC developed "COSMIC Actionability," a tool in service of translational research (Jupe et al. 2022). This tool is primarily concerned with the availability of drugs that target mutations and tracks the progress of novel drugs through clinical development.

These examples illustrate a first concept of actionability. We denote this concept *actionability*$_1$:

> Actionability$_1$ indicates a genomic variant's potential diagnostic, prognostic, or therapeutic relevance, most often based on evidence from curated genomic databases combined with ranking algorithms. This concept serves as a tool for translational research in oncology.

These approaches are not generally intended for clinical use but rather for delineating gene variants that may warrant further investigation. Bailey et al. (2018) acknowledge that the relatively high percentages of actionable variants thus identified likely represent a "ceiling of current molecular intervention potential." This concept is too inclusive to be useful in clinical practice, including far more variants than are relevant to clinical decisions. Therefore, *actionability$_1$* is a property of genomic data that is "upstream" of clinical research or practice.

### 2.2. "Actionability" for clinical trials in precision oncology

Using genomic information to directly guide cancer treatment is a central aim of precision oncology. Clinical trials in oncology increasingly incorporate genomic data to guide enrollment and choice of therapies (Carr et al. 2016). "Basket trials," trials designed to test targeted therapies where patients are matched to a drug based on mutations or biomarkers (rather than tumor histology), are frequently cited as exemplars. Some go as far as to argue that the success or failure of precision oncology hinges on the outcomes of these trials (Prasad 2020, 111–13). Successful design of such trials, however, requires appropriate selection of genomic variants likely to be useful as "biomarkers" for prognosis or treatment. The second concept of actionability responds to this challenge by attempting to establish criteria that provide sufficient warrant to enroll patients in a particular arm of an exploratory clinical trial based on the presence of specific mutations.

Motivation for establishing such criteria is felt most strongly by pharmaceutical industry stakeholders, who place high importance on maximizing the success of early-phase clinical trials. The risks of "false positives" are higher than in earlier stages of translational research; failure of a novel targeted therapy to advance in the drug development pipeline can be costly. To give a sense of the stakes at play, the typical cost of a clinical trial (including phase 1, 2, and 3) is around $30 million (Hsiue et al. 2020). The cost varies with the number of enrolled participants, the type of trial, and so forth, but the financial investment and time required to complete the process (6–7 years) are both substantial. This creates a strong incentive to narrow the pool of actionable drugs. Carr et al. (2016) review existing approaches to defining actionability, many of which would fall under *actionability$_1$* in our taxonomy, arguing that "none of them fully satisfy the requirements for the practical application of selecting patients for basket and umbrella trials in which we in AstraZeneca are involved." Instead, they propose a framework of "actionable mutation tiers" that classifies mutations as "highly actionable," "potentially actionable," and "not currently actionable" for the purposes of exploratory trials. Which category a particular variant falls in is determined by rules that discriminate among preclinical and clinical evidence.

The "Digital Drug Assignment" system (Petak et al. 2021), for example, draws upon published preclinical and clinical data to assign and rank targeted therapies based on

expected response. The authors argue that use of this algorithm for drug assignment could improve response rates in basket trials in oncology. There are several other attempts to define actionability for investigational purposes (e.g., Meric-Bernstam et al. 2015). Together, these highlight a second concept of actionability, *actionability*$_2$:

> Actionability$_2$ indicates a genomic variant's role as a target of a novel therapy in the context of an early-phase clinical trial, most often based on a combination of preclinical and clinical evidence. This concept serves in the design of exploratory clinical trials in precision oncology.

*Actionability*$_2$ is a key concept for precision oncology given that most targeted drugs in oncology remain in early phases of clinical research. Most such trials do not pass the first phase. So, while this sense of "actionability" is narrower than *actionablity*$_1$, it is still wider than the pool approved for use in assignment of targeted therapies in routine clinical practice.

### 2.3. Actionability in clinical practice

While *actionability*$_1$ and *actionability*$_2$ serve important roles in basic science/preclinical research and early-phase clinical trials, respectively, there is a growing need to define how genomic data should inform decision making in routine practice. Some have raised concerns that these prior concepts of actionability may be confused with the senses typically used by clinicians and patients and could thus lead to harm (Tannock and Hickman 2016). This concern is also expressed by the authors of the ESMO (European Society for Medical Oncology) Scale for Clinical Actionability of Molecular Targets (ESCAT). ESCAT aims to help "oncologists in the clinic ... distinguish between findings that represent proven clinical value or potential value based on preliminary clinical or preclinical evidence, from hypothetical gene-drug matches and findings that are currently irrelevant for clinical practice" (Mateo et al. 2018, 1896).

In ESCAT, actionability is defined by means of an evidence hierarchy: Genomic alterations that are "ready for routine use" (tier I), that is, that support use of a targeted drug in routine practice, are distinguished from "investigational" (tier II) and "hypothetical" (tier III/IV) targets based on the type of evidence supporting the target-drug match. For a target to be considered ready for routine use, there must be evidence of improved outcomes in clinical trials, which is further subdivided into evidence from prospective, randomized controlled trials with survival end points (tier I-A), prospective nonrandomized trials (tier I-B), and basket trials demonstrating consistent clinical benefit (tier I-C).

The function of ESCAT's hierarchy is to establish what ought to be considered the highest level of evidence for effective intervention, which is the central criterion for membership in the category of "actionability" in a third sense, *actionability*$_3$:

> Actionability$_3$ indicates a genomic variant's role in informing decision making in routine clinical practice, typically based on evidence of clinical benefit with use of a targeted drug. This concept serves clinicians in routine practice and defines a standard of care in oncology.

Paradigmatic examples of genomic targets that have the highest evidence (tier I-A) according to the ESCAT include *ERBB2* (HER2) amplification for use of trastuzumab in breast cancer and *EGFR* activating mutations for use of gefitinib or other EGFR inhibitors in non–small cell lung cancer. *Actionability*$_3$ captures how the term is used in guidelines that dictate the standard of care in oncology, indicating that clinicians ought to routinely test for these biomarkers and use them to guide treatment decisions.

A fourth concept of actionability, *actionability*$_4$, addresses the problem of identifying actionable variants to guide reporting of genomic testing in asymptomatic individuals:

> Actionability$_4$ indicates a genomic variant's warrant for medical action if identified in asymptomatic individuals.

This actionability concept enables predictions of disease likelihood and severity and is associated with clinical recommendations based on the risks and benefits of particular interventions (Hunter et al. 2016). An "actionability score" guides how and which findings are reported to clinicians. Using this taxonomy as a starting point we now turn to some philosophical questions regarding the nature of actionability.

## 3. What is actionability?

What is the relationship between these different concepts of actionability? Is "actionability" one thing or many? Are *actionability*$_1$, *actionability*$_2$, and *actionability*$_3$ distinct concepts with distinct referents? Or are *actionability*$_1$ and *actionability*$_2$ better understood as mere approximations, developed with the ultimate aim of identifying what is "truly" clinically actionable, best captured by a single concept, such as *actionability*$_3$? There are two general responses to these questions, each revealing different views on the nature of actionability: monism and pluralism.

### 3.1. Actionability monism versus pluralism

The monist with respect to actionability would answer the last question in the affirmative: Actionability describes a singular property of genomic data, namely its ability to engender specific clinical action, especially use of a targeted therapy. For the monist, this direct clinical impact is fundamental to the concept of actionability in precision oncology. Monism may seem to be the position endorsed by ESCAT (Mateo et al. 2018), insofar as merely "hypothetical" and "investigational" uses are ranked lower down in the "actionability" hierarchy, and only variants that are "ready for routine use" meet the most restrictive criteria. Here, there seems to be one actionability concept at play, and different thresholds of evidence that determine whether targets meet the standards necessary for "true" clinically actionability.

Monism, however, focuses on one set of actions to the exclusion of others, thus ignoring potential uses of the concept in biomedical research. As discussed in the preceding text, distinct concepts of actionability play distinct roles in genomics research, clinical trials, and routine clinical practice. Even if we limit our focus to the clinical domain, there is a diversity of ways that genomic information can be

actionable in different clinical contexts. These go beyond simply drug-target matching to include diagnosis, prognosis, further testing, counseling, and follow up. What actions are involved, and thus what is considered actionable, even in "routine" practice, is varied, raising doubts as to whether a single concept can capture all considerations and uses.

This argues for pluralism with respect to actionability. Such a position might seem rather obvious and almost trivial. After all, invoking "actionability" invariably raises questions—such as "actionable for whom?" and "actionable for what?"—which may lead one to posit as many actionability concepts as there are stakeholders and uses for genomic information. The challenge, then, lies in articulating what exactly this pluralism consists in and why it is important to keep these discrete senses of actionability distinct.

### 3.2. Actionability and contextual objectivity

Varieties of scientific pluralism have been discussed at length by philosophers to help explain the diversity of theories, models, and concepts found in contemporary science. For example, Stotz and Griffiths (2004; Griffiths and Stotz 2006, 2013) highlight the plurality of gene concepts employed by different research communities in biology, with molecular, evolutionary, and developmental biologists relying on distinct gene concepts, each emphasizing unique features and properties. The "postgenomic" gene concept refers to different types of objects, with different properties than the "Mendelian" gene concept, though there are (partial) overlaps in referent. Though one could argue that gene concepts are after all simplified representations of what are in reality much more complex entities and processes, arguably, each concept genuinely refers to a distinct class of phenomena, with distinct properties. How a diversity of contexts of application of a concept can be nonetheless objective is further illustrated by Alexandrova's (2017, 17) analysis of the concept of well-being. She likewise argues for well-being contextualism indexed to "objective features of the practical environment."

Similarly, the plurality of actionability concepts can be seen as arising from specific, practical problems faced in different research and clinical environments.[2] As the preceding discussion makes clear, these problems are discrete. The need for the genomics researcher to narrow down an expanding set of driver genes is a distinct problem from the need for practicing oncologist to determine a standard of care. The oncologist who applied $actionability_1$ for the latter task, for example, considering *in silico* evidence of functional impact as sufficient grounds for attributing actionability, just as the researcher who applied $actionability_3$ to the former task, would clearly be in

[2] Some have argued that there is a tension between pluralism and contextualism, where contextualism is interpreted as a more modest position, i.e., there is broad conceptual unity and only apparent differences in sense, resulting from application of a single concept in different contexts. However, we argue that it is exactly the vagueness of this "broad" sense of actionability that can lead to confusion in application. Thus, we argue for pluralism, where there are contextually distinct (and objective) applications of the term. We do not take pluralism and contextualism in the senses described here to be in conflict. Rather, we see different concepts arising from different research interests and contexts as entirely consistent with contemporary views of scientific pluralism (e.g., Longino 2013).

error. Such cases can be understood as instances of "conceptual slippage."[3] The definitions, tools, and hierarchies proposed in each area are best understood as attempts to establish contextually objective concepts of actionability to prevent conceptual slippage and its associated harms.

The worry about conceptual slippage may lead some readers to think that the matter at hand is all semantic, that is, we need only use different terms to refer to distinct concepts and thus appropriate criteria for "actionability." However, in some contexts, the criteria for application of a concept may be much more open to interpretation, and thus conceptual interaction may be appropriate.[4] Although defining an objective context can be straightforward in some situations, the diversity of contexts and possible actions, particularly in the clinical domain, sometimes warrant suspension of narrow criteria of application and allow for more fluid, interactive approaches to actionability. Close attention to the "objective features of the practical environment" (Alexandrova 2017, 17) can help decide what considerations ought to apply; however, some cases may demand the integration of considerations from different contexts. Thus, the conceptual pluralism seen with actionability is not a strictly *isolationist* pluralism, according to which challenges attributing actionability might be wholly resolved by employing distinct terms to refer to distinct concepts in distinct domains. Rather, it is an *integrated* or *interactive* pluralism (Mitchell 2003; Chang 2012; Van Bouwel 2014). This feature of actionability is illustrated by an emerging activity in precision oncology developed to assist with determinations in clinical practice: molecular tumor boards.

### 3.3. Interactive pluralism in action: Molecular tumor boards

According to defenders of integrated and interactive pluralism, different theories, models, or concepts interact in meaningful ways in scientific practice, and this interaction has epistemic benefits. Following Chang (2012) and Van Bouwel (2014), we adopt the term "interactive pluralism" but likewise draw inspiration from Mitchell's (2003) "integrative pluralism." For Mitchell, the need for integration arises from the complexity of natural phenomena and the recognition that science requires not only a diversity of theories and models but also interaction between them. In contrast, Van Bouwel (2014, 109) argues for "interactive pluralism," which he takes to be a more modest position that does not stipulate an "integration imperative." For Van Bouwel, interactive pluralism is a view midway between integrative pluralism and isolationist pluralism, where the need for interaction is contingent upon the explanatory,

[3] Concepts of actionability are prone to conceptual slippage, especially with preclinical concepts being inappropriately applied to inform patient care decisions. An example from one author's personal experience occurred in a patient with relapsed acute leukemia where genomic testing from a private company indicated the presence of "actionable" variants and suggested use of certain targeted therapies based on mechanistic evidence and data from other cancers. However, there was no clinical evidence for the effectiveness of this therapy in the patient's specific disease. Such cases are increasingly encountered in practice with the proliferation of direct-to-consumer genomic testing in cancer (Kilbride et al. 2018). This susceptibility to conceptual slippage in clinical applications of genomic data, even in the absence of clinical evidence, reflects how naïve genetic determinist viewpoints persist in precision medicine and oncology (Tabery 2023).

[4] Thanks to an anonymous reviewer for raising this point.

predictive, or interventionist interests or questions arising from within a context of inquiry.

This approach provides a useful framework for our views on actionability. Certain actionability concepts, such as *actionability*$_3$ may be straightforwardly applied in some cases, for example, to determine use of trastuzumab in the treatment of an individual with stage III HER2-positive breast cancer, where there is strong evidence of clinical benefit. Here the context is well defined, and a single concept offers the necessary resources to make an attribution of actionability. However, other cases require drawing on multiple concepts of actionability and careful consideration of the potential for interaction between criteria of application of these concepts. Often this occurs when the context or problem is less well defined. In oncology, such scenarios might include (but are not limited to) cases of relapsed/refractory disease, multiple potential drug targets, rare cancer subtypes, or ambiguous genomic information. Molecular tumor boards were developed to assist with decision making in these complex cases and show how different concepts of actionability can interact in practice.

Molecular tumor boards aid in the interpretation of genomic information and make determinations of actionability in individual, concrete cases. Bourret and Cambrosio (2019) show how in such cases, nonclinical practitioners such as bioinformaticians and molecular biologists, "far from merely providing technical information," are rather "fully-fledged reasoning partners," who leverage a unique set of conceptual resources toward the "common goal of enacting actionable interpretations." In molecular tumor boards, no single concept of actionability or single framework is applied (Luchini et al. 2020). Rather, by incorporating different specialists with a range of expertise, different concepts of "actionability" are deployed to facilitate interpretations of relevant data and prioritize clinical actions.

What molecular tumor boards allow for is a dialogue where participants appeal to a variety of concepts of actionability. Preclinical evidence may be considered in service of addressing unique cases, such as where a given pathway is implicated and a drug that intervenes in this pathway may abrogate this. Such discussion may involve reasoning by analogy or invoking potentially relevant mechanistic evidence. Such approaches, however, are not without risk of harm—not only because decisions being based on merely potentially relevant mechanistic evidence in the absence of clinical trials are far from ideal, but also because of the potentially pernicious effects of economic interest shaping how mechanistic evidence is investigated and communicated (Holman 2019). This is one of several reasons why it is not only important to recognize distinct uses of the term "actionable" but also to scrutinize the types of evidence that inform attributions of actionability. Molecular tumor boards thus not only provide an example of a practice in which distinct concepts of "actionability" are in play but also in which there is need for critical reflection on the interaction between these different concepts in service of decision making.

## 4. Conclusion

"Actionability" is a key concept in precision oncology. There is, however, disagreement on how to best define and apply this concept. In this article, we have argued in favor of treating distinct senses of "actionability" as genuinely

distinct, contextually objective categories to prevent "conceptual slippage," while acknowledging the need for conceptual interaction to handle concrete cases in practice.

There are several upshots of this view. Firstly, it should make researchers and clinicians skeptical of efforts aimed at developing a single definition of actionability. The "Digital Drug Assignment" system (Petak et al. 2021), mentioned previously, is one such example, which attempts to operationalize actionability by means of a computational algorithm. Although developed for use in research to help assign therapies in clinical trials, and thus arguably only an example of *actionability*$_2$, the authors of this tool have larger ambitions: "the ultimate goal of DDA [Digital Drug Assignment] is to help the work of molecular tumor boards planning of personalized treatment strategies for *all lines* of treatment *for each* patient" (Petak et al. 2021; emphasis added). The authors' goal for this algorithm is to offer a single, overarching concept of actionability that encompasses not only *actionability*$_2$ but also *actionability*$_3$. In our view, such algorithmic tools are unlikely to be successful beyond narrow domains of application, given the diverse set of actions the concept of "actionability" responds to in practice.

Secondly, clinical cases sometimes require interaction between multiple concepts of actionability, where practitioners negotiate different forms and thresholds of evidence appropriate within different contexts. This is exemplified by the interdisciplinary dialogue at work in molecular tumor boards. The underdetermination and complexity of such decision making should make one doubt that one can formalize this process. Attempts to replace tumor boards by algorithmic approaches may operationalize actionability concepts in ways that underdetermine their appropriate application in specific cases. Watson for Oncology tried to do this (unsuccessfully) for conventional tumor boards (Chin-Yee 2022).

In summary, we offer a provisional taxonomy of concepts of actionability used in precision oncology research and practice, and defend pluralism and contextualism. We grant these concepts are in flux; nonetheless, outlining current actionability concepts serves as a useful starting point for philosophical analysis. Our arguments draw attention to the need to carefully attend to context in conceptual application and to further examine the norms of conceptual interaction in the practice of precision oncology.

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