**Why Precision Oncology is not Very Precise**

**(and why this should not surprise us)**

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Dedicated to Karola Stotz

Abstract

Precision oncology seems for many the best bet for precision medicine generally. In the ideal case, there is a test provided to patients, which will either provide clear-cut prognoses, or targeted therapy, given the presence or absence of specific biomarkers, followed by significant improvement in overall survival, with fewer side effects than typical for many cancer therapies. I will argue that in the vast majority of applications of precision oncology, what we actually find, and indeed ought to expect, are rather different outcomes. Cut-offs for relevant biomarkers are contested and value-laden decisions, there appear to be moderate improvements in survival in the vast majority of cases, and overall, very few cancer patients are likely to benefit (cf. Hey et. al. 2016; Tannock et. al. 2016; Marquart et. al. 2018). In this paper, I’m going to first explain why this is true, and why this should (by now) not surprise us. Cancer’s heterogeneity and complexity ought, by now, to lead us to be skeptical of “magic bullet” thinking in cancer treatment. Moreover, I argue that better communication of the scope and limits of precision oncology is essential to avoiding the unethical engagement of prospective participants in clinical trials.

**Keywords:** Precision Oncology; Personalized Medicine; Cancer; Biomarkers

**1.0 Introduction: What is precision oncology?**

In 2015, President Obama launched his “Precision Medicine Initiative,” an ambitious effort at funding research that would ensure that patients receive care “tailored to them.” Though Obama granted that physicians have always sought to tailor care to individual patients, he argued that this initiative would launch a genuinely new kind of medicine. Care might be tailored to each patient in light of their genomic profile and personal characteristics, or perhaps, molecular and genetic characteristics of their particular disease.

The latter is seen as an especially promising avenue of research for cancer. Cancer is typically described as a “genetic” or “genomic” disease, in light of the fact that cancers are caused (in part) by genomic alterations that alter pathways in the cell governing cell birth and death. Each individual’s cancer has a unique suite of genomic changes, which in principle could help physicians predict the course of disease, or anticipate response to treatment. Indeed, several molecular biomarkers are already standardly used to make decisions about treatment, or predict risk of recurrence (NCI 2019). So, the ideal of precision oncology is often taken to be the model for precision medicine more generally.

In 2015, Francis Collins, director of the NHGRI, (National Human Genome Research Institute), Collins, and his colleague, Varmas, commented on Obama’s initiative: “Oncology is the clear choice for enhancing the near-term impact of precision medicine… Research has already revealed many of the molecular lesions that drive cancers, showing that each cancer has its own genomic signature, with some tumor-specific features and some features common to multiple types.” (Collins and Varmus 2015, 793).

As this passage suggests, advocates of precision oncology make the following fundamental assumptions: each individual’s cancer has a distinctive genomic profile – or set of mutations particular to that disease. These mutations are ‘**drivers**’ of cancer – they play central roles in the origin and process of disease progression. Such genomic features and their products can, potentially, be used as **biomarkers**. Many have argued that such biomarkers will eventually replace diagnostic criteria such as site of origin, node status, size of tumor, or degree of differentiation of cells, in service of more accurate prognoses, and targeted (and less harmful) treatment. Molecular features are often characterized as more “precise” than the pathologists’ assessments of grade and stage. Some cancer researchers speak of gross clinical features of cancer as soon to be, if not already – relatively obsolete.

This idea is not new; indeed, the hope for precision oncology was a deliberate outcome of investment in integrative research on cancer genomics and bioinformatics. In 2011, an ad hoc Committee of the National Research Council was convened to host a two-day workshop on the future of molecular medicine, and published *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease* – mapping out a plan for building an “Information Commons” and “Knowledge Network” for a new, “modernized” taxonomy of disease (NRC 2011) – one that draws upon the tools of “big data” and artificial intelligence. This more modern taxonomy would – in principle – remove any room for subjective or value-laden judgment in physicians’ diagnoses, or patients’ decisions.

 [Insert Box with Definitions of key terms here]

There are many questions one could raise about this ideal for medicine. This paper will focus on how effective precision oncology has been so far, as well as whether we ought to expect the promises made on behalf of precision oncology to be borne out in the future. The philosophical analysis is informed by a review of the scientific literature, analyses of the aims and scope of precision oncology by philosophers, historians, and social scientists, as well as insights from interviews with researchers and clinicians, who work both in basic science behind and clinical applications of precision oncology.

Part of the challenge of assessing the effectiveness of precision oncology is that the term is not used consistently. Some accounts are so permissive that they include any and all novel methods that draw upon molecular data. Others limit precision oncology to the use of NGS (next generation sequencing), to guide targeted therapy (Prasad and Gale 2017). This latter definition is so restrictive that it would exclude anything developed prior to roughly 2008, effectively ruling out some of the most famous exemplars of successful precision oncology (e.g., Tamoxifen, Herceptin).

Given this ambiguity, several philosophers of medicine have weighed in on how best to define “**p-medicine**” more generally (Lemoine 2017; DeGrandis and Halgunset 2016). Lemione uses “p-medicine” as a general category for a variety of expressions (“personalized,” “precision,” “stratified,” “individualized,” “P4,” “P5”) that have been used in service of either imagining the future of medicine, or characterizing exemplary instances of success in “molecularized” approaches to medicine. Precision oncology is only one instance of p-medicine, but arguably inherits from p-medicine some of the same ambiguity. Lemoine argues that we ought to define “p-medicine” by looking to exemplars of “what has been achieved, not what we should consider it is ‘by nature’” (2017). He takes **mabs** (monoclonal antibodies) as archetypal cases of success in p-medicine, not only because they are one of the most commonly cited exemplars, but also because they are the only case of a molecularly targeted therapy not “limited in principle to a narrow range of pathological conditions.”(Lemoine 2017, p. 19)

I agree with Lemoine’s emphasis on concrete exemplars of success, and in principle, I agree that if our aim is defining “p-medicine” generally, we ought to select exemplars that are not “limited to a narrow range of conditions.” However, one distinctive aim of precision *oncology* is designing therapies or prognostic tools that are beneficial to patients in light of their cancers’ unique molecular features. This creates a special challenge: both for defining precision oncology, and relatedly, for assessing effectiveness. Almost by definition, we should not expect a mode of intervention to target a wide range of conditions in precision oncology. Indeed, the wider range of conditions an intervention targets, the less it ought to serve as an instance of precision oncology.

The fact that precision oncology in principle involves developing prognostic tools and treatments unique to each patient yields a puzzle, also, in determining how we ought to measure “success” of such methods. Exactly because of the uniqueness of each cancer, we cannot and should not expect to conduct large randomized trials of novel prognostic tools or therapies. This has led to the controversial adoption of novel trial designs by the FDA (Kahn 2018), which, while getting drugs to market faster and thus arguably benefiting patients more quickly, also raise a suite of both epistemic and moral questions about whether such trials provide sufficient evidence of benefit. While small trials of several hundred patients with shared molecular features are problematic in themselves, “N-of-1” trials raise further questions about generalizability. In other words, the challenges facing how best to define precision oncology are intertwined with the problems of how best to measure success, and adjudicate failures.

For the purposes of this paper, I’ll adopt a middle ground that is (hopefully) neither overly inclusive, nor so exclusive as to rule out by definition some of the most celebrated cases.

The aim of precision oncology is to identify and deploy genetic and molecular features of cancer in service of diagnosis, prognosis, and treatment. By identifying particular markers of molecular features of the disease in each cancer patient, researchers and clinicians hope to better predict likely disease course, and tailor treatments to each patient.

This roughly captures the typical characterization of the aim of precision therapy, as providing “the right drug, at the right dose, for the right patient, at the right time.”[[2]](#footnote-2) Carolyn Hutter, the former director of the Cancer Genome Atlas Project (TCGA), explained that molecular characterization of cancer may be used for two main ends: to distinguish aggressive from non-aggressive forms of disease, and, in the ideal case, there will be “that perfect mutation that informs the drug to give, and the drug to not give.” (Hutter interview July 27, 2018) The aim of this paper is to consider why this goal has been so elusive, focusing on two key case studies: Avastin and TAILORx.

**2. Some Preliminaries: Cancer Complexity and the Goals of Precision Oncology**

The scientific and practical challenges facing both how best to measure and classify molecular features of cancer, and translate results to clinical medicine, are more daunting than the more optimistic visions of precision oncology suggest. Below, I identify the sources of such challenges, starting with the massive complexity and dynamic features of cancer itself, the “**curse of dimensionality**,” and then turning to practical challenges facing biomarker identification and validation. Problems of reversal of “fast tracked” drugs, I will argue, are likely to plague much of this research.

First, however, it’s important to note that cancer progression is a complex and dynamic process involving many factors in interaction. Cancers are not homogeneous, but heterogeneous populations of cells. Many tumors contain multiple subclones, and over time, these lineages of cells evolve in response to novel challenges (e.g., lack of oxygen supply), akin to branches in the tree of life, enabling invasion and metastasis, as well as the emergence of resistance to therapy (Greaves et. al. 2012). This makes reliance on a single biomarker, sampled at a single point in time, problematic as the sole criterion for prognosis, or treatment decisions. Thus, many clinicians and researchers suggest that multiple biopsies or samples of cells be taken over the disease course.[[3]](#footnote-3)

Moreover, interactions among both molecular and structural features of a tumor shape and are in turn, shaped by, features in the tumor microenvironment over time (Bissell and Hines 2011). While the very concept of the tumor microenvironment is one in flux (see, Laplane et. al. 2018), it’s clear that a variety of factors apart from the cancer genome contribute to how a cancer progresses, and in turn, how likely a patient is to respond to targeted treatment. In addition, patients’ age, treatment history, sex, stage of life (e.g., before or after menopause), metabolism, and other clinical characteristics, are likely to shape their response to therapy. Attention to these complex causal contributions to a cancer’s evolution and interaction with its microenvironment is absolutely essential to developing lasting, effective therapies. In sum, cancer progression is not fully determined by static, fixed, molecular properties. Molecular features vary in their expression within the same tumor, and over time. Tumors with the same expression profiles can have different responses to the same drugs, both because of differences in the tissue or organ affected, presence or absence of further molecular features, and much else.

Drugs effective for some cancers with a particular genetic profile may also not be as effective in tumors arising in a different organ or tissue – for instance, a drug effective in skin may not be effective in the pancreas. Differences in non-genomic features of these tissues affect effectiveness of targeted therapy. Tissue microenvironment – e.g. the presence or absence of fibroblasts, blood supply to the stroma, etc. – can affect whether and how therapies arrive at the target. In sum, it should not surprise us that responses to therapy vary; and that treatment success is not uniform for patients who share a biomarker sampled at a single time. The presence of a shared biomarker is only one of several predictive factors in successful response to drugs targeting a specific molecular pathway.

It’s important to emphasize also that gene expression is a matter of degree – and, given the heterogeneity of cells in a tumor, can vary in space and time. Yet, for the purposes of prognostic tests or treatment decisions, cut-off points for measures of expression of proteins must be chosen, either to stratify patient’s risk of progression, or likelihood of benefiting from a particular drug. Choosing level of expression for such cut-offs thus requires complex processes of validation, and may also involve value-laden judgments about risk and benefit of over- and under-treatment. Line drawing problems in diagnosis and treatment decisions, in other words, will not be eliminated by molecular profile data. Precision medicine is no less subject to the rule that variation is the norm in biology.

There are, indeed, many reasons apart from the complexity of cancer biology that precision oncology has not proven as effective in clinical practice as one might be led to believe in the light of its frequent mention in the news cycle. Some of these reasons have to do with “upstream” problems with the basic science, but many more have to do with the institutional organization of cancer research, and challenges facing translation. Initial sequencing of the cancer genome faced many challenges – from improving quality of the samples used, to improving read depth and coverage of sequencing,[[4]](#footnote-4) to development of algorithms for analyzing the data in service of identifying actionable genes. Indeed, one core difficulty is that the very definition of what count as “actionable” genomic alterations varies substantially, making it difficult to implement large-scale genomic testing to enroll patients in clinical trials in the first place (See, e.g., Johnson et. al. 2014; Meric-Bernstam et. al. 2015; Schwaederle et. al. 2015; Scholl et. al. 2016). Drug design and testing is costly and (arguably) inefficient; most cancer drugs fail. Trial design is distinctive for therapies that are intended to target unique patient profiles, and even those that are approved by regulatory bodies run across many problems in translation (as in the Avastin case, discussed in some detail, below). In sum, not only is the genetics and biology of cancer prohibitively complex, but also the design and testing of precision therapies is enormously difficult, making “precision” as a goal elusive.

As we will see below, a central reason for the lack of uniformity of success has to do with *how we are assessing effectiveness*. Some of these are endemic to any research that is concerned with testing drugs that are intended to work for only small subpopulations of patients. But, some are problems with the design of trials, choice of endpoints, and consistency of tests for the presence and absence of biomarkers. For instance, critics of precision oncology have pointed out that early clinical trials often test an experimental group against a weak comparator that is infrequently used in practice (Tao et. al. 2018), that many surrogates used as the end-point of clinical trials do not represent outcomes that are important for patients (Prasad et. al. 2016), or, that clinical trials may use different levels of cut-off to designate molecular markers “present” or “absent,” leading to inconsistent outcomes (Hey et. al. 2016). A further (but related) concern is whether clinicians are in a position to interpret results of commercially available screening tools, let alone apply such results to treatment decisions (Hey et. al 2019b).

It also deserves mentioning also that most patients are simply ineligible for many precision therapies as defined here; a recent study showed that only 5% of patients were eligible for treatment with precision therapies, out of over 500 whose cancers were tested (ECOG-ACRIN Research Group 2017). That is, a relatively small proportion of cancer patients have specific markers for which targeted therapies have been demonstrated to be effective.

In sum, there are good reasons to think that the “magic bullet” model is unlikely (by itself) to lead to lasting and effective treatments in cancer, especially for advanced (metastatic) disease. Even the most successful exemplars of precision therapies face problems with tolerance and lasting response to treatment. For instance, TKIs for CML (**tyrosine kinase inhibitors**, such as imatinib, or Gleevec), targeting BCR-ABL1 fusion protein, have improved overall survival significantly – from 10-year OS from 10–20% to 80–90% in the last few decades. Yet resistance and intolerance to the drug is still a problem (Cortes et. al. 2019).

Below, I consider two case studies in precision oncology that illustrate how heterogeneity, complexity, and dynamic interactions create a variety of challenges for implementing precision oncology. Yet, each new generation seem very much in the thrall of this picture of the future of cancer medicine. As Strand, and colleagues argue (this volume), precision oncology as an imaginary or ideal seems to be far more at work here than the actual clinical practice of precision care. Perhaps more concerning, patients and families have been led to imagine that precision cancer care can and will be a panacea. This kind of optimism can be harmful – both to patients, and to the future of both upstream, and downstream, clinical research.

**3. Two Case Studies: Avastin and TAILORx**

Below I will consider two case studies in precision oncology: the approval and subsequent withdrawal of Avastin, and the recent TAILORx trial, and subsequent follow up. These cases illustrate both the limitations and potential successes of precision oncology.

First, Avastin received accelerated approval from the FDA in 2008, after a single, multi-center, open-label study showed improvement in progression free survival (PFS) for patients with HER2-negative metastatic breast cancer taking beacizumab in combination with paclitaxel (Taxol) over Taxol alone (Miller et. al. 2007). However, it was later withdrawn in 2011, when the evidence showed that while there was a statistically significant improvement in PFS, there was no significant improvement in overall survival. Even after it was withdrawn, however, Medicare and Medicaid were approving payment for the drug. This case is illustrative of several challenges facing precision oncology, and the oversight and regulation of drug approval in the US.

Avastin’s approval hinged upon improvements in PFS (progression free survival). When it was approved, there was no evidence that it would improve overall survival (OS). A recent metaanalysis by Hey, et. al. (2019a), reviewed fifty-two studies of Avastin in patients with metastatic HER2-negative breast cancer, both before and after the FDA’s accelerated approval. None found a significant association between PFS and OS. Of those 52 studies, only six showed statistically significant outcomes favorable to the drug (namely, in PFS), but none showed overall survival benefit. Ten of these 52 studies were terminated, and in 14, trial results are unknown; one of these showed a statistically insignificant benefit in PFS in combination with another drug, but the toxicities were so significant that results did not indicate benefits to the drug. In other words, in multiple studies, with a total of 11,897 patients participants, there was no improvement in overall survival, and significant enough costs in terms of toxicities and quality of life to terminate a majority of trials. Arguably, this case shows a failure of oversight; though it also illustrates several challenges in designing and developing exactly this sort of targeted therapy.

First, while Hey et. al. (2019a) argue that the FDA did use appropriate oversight in the sense that it withdrew approval when they should have, it seems well worth asking why as many as 37 trials with such nearly identical protocols were conducted between 2006 and 2009. Arguably, many more trials were conducted than were appropriate or necessary, given the minimal benefit demonstrated. Indeed, redundancy, or lack of coordination among researchers seems fairly common in precision oncology research (Carlisle et. al. 2020).[[5]](#footnote-5) This wastes valuable time, money, and arguably, causing potentially unnecessary harm (in the form of toxicities, or worth, early death), and unwarranted hope among participants in the trials. There is also a concern about either underreporting or inadequate reporting of toxic side effects, which preclude giving these drugs in combination with other therapies, for instance. Many trials prior to approval were discontinued, but it’s not clear from the reporting of this data whether this was because of toxicity of the drug in some combinations with other therapies, or simply because of lack of evidence of benefit.

Second, in accelerated trials, approval for drugs often hinges on improvements in surrogate measures like progression free survival. But, several have raised concerns about whether PFS is a legitimate surrogate for outcomes that concern patients: namely, overall survival (OS). Validating PFS as a surrogate for OS is difficult at best. Hey, et. al. review the data, and show that even after seven clinical trials, it was unclear whether PFS was a good surrogate for overall survival in the case of metastatic BC. In principle, subsequent follow up for accelerated approval is expected to either validate PFS as a surrogate, or warrant removing the drug’s approval. But, even though there is a mandate that the FDA conduct follow up research for accelerated trials, it seems that (a) there has not always been adequate follow up, given the rapid expansion of approval for drugs on the basis of these surrogate measures, and (b) it is not easy (or possible) to determine whether and if so, the surrogate is a valid measure of outcomes of interest. In this case, the follow up studies showed no benefit, and Avastin was withdrawn. But, even after withdrawal, Medicare and Medicaid was approving reimbursement for the drug.

Even though the Avastin case is an instance of “success” in that it was (appropriately) withdrawn, there seems to be at least three kinds of concerns cases like this raise. First, there should have been more coordination of research, to avoid redundant or unnecessary trials. Second, there needs to be greater coordination of regulatory decisions and reimbursement decisions by Medicare and Medicaid. With greater investment in the process of translation to the clinic, this kind of organization of research could be more efficient, and ideally, less harmful. Third, the question of whether and why PFS is a valid surrogate ought to be considered in light of the widest array of relevant evidence, including the nature of the drug, and the disease. While PFS is often taken to be an unproblematic surrogate for OS, it seems that there is good reason to question this as a general rule.

Arguably, it’s unsurprising that PFS was not a good surrogate for OS, particularly in the case of metastatic disease. Avastin targets one pathway, endothelial growth factor. In advanced solid tumors, there is likely to be a great deal of genetic variation – i.e., multiple lineages or subclones, and thus great potential for resistance to such drugs (Greaves and Maley 2010). Natural selection in response to a drug (for instance, in the case of antibiotic resistance) typically leads to a short-term response, followed by treatment failure. Targeting a single pathway is likely, by and large, to lead a cancer to return in a far more aggressive form. Particularly in a heterogeneous population of cells typical of metastatic disease, there will be ample variation available for natural selection, and thus ample opportunity for resistance to evolve. In this case, the response in the short term (PFS) may have been good, but overall response (OS) is likely to be poor. In short, these outcomes could have been predicted. Mathematical modeling of cancer’s evolutionary dynamics has predicted responses such as these going back to the early 2000s (see, e.g., Nowack et. al. 2004). If greater attention were paid to the evolutionary dynamics of advanced cancer, the outcomes of such trials could be predicted, and less confidence may have been placed in PFS as a proxy for OS. This could have saved thousands of women taking Avastin from unnecessary harm and unwarranted hope.

The second case study in some ways suggests a great benefit of genomic data, but in other ways highlights similar problems with oversight, translation, and the elusive benefit of genetic information. Using the 21-gene Oncotype DX assay (Genomic Health, Redwood City, CA), the recent Trial Assigning Individualized Options for Treatment (TAILORx) study demonstrated that the majority of women with ER+, HER2-negative, node-negative breast cancer derive no benefit from adjuvant chemotherapy (Sparano, et. al., 2018). In other words, they demonstrated that chemotherapy provides no benefit to 70% of women with early stage (node-negative, ER+, HER-2-negative) disease. The way the research study was framed in the news was that prior to the TAILORx study, many women were not receiving a benefit from chemotherapy; now, with greater understanding of the genetics associated with risk of recurrence, patients can avoid chemotherapy and its harmful effects, and clinicians can recommend treatment to only those patients who will likely benefit.

While this spin on the results of the trial seems very impressive, a closer look at the standard of care prior to the completion of TAILORx reveals a somewhat more complicated story. Arguably, many of the women shown to benefit from the genetic assay would have opted out of chemotherapy anyway, and for good reason. In premarket studies, oncologists were already recommending the Oncotype-DX test as a way to urge women with low-risk profile to not take chemotherapy. That is, they were preferentially offering the test to women with low-risk disease – i.e., those who were ER+, node-negative, and HER2-neu negative – because oncologists knew already that such women were unlikely to benefit from chemotherapy. The test was used to provide patients with additional reassurance that chemotherapy was unnecessary. In other words, *it was well known almost a decade prior to the TAILORx study that women with node-negative status, ER+ and HER2-neu profiles were at low risk of recurrence*, and so oncologists were *already* not recommending chemotherapy for these patients (Oratz et. al. 2007; Henry,et. al. 2008; Asad et. al. 2009). Adjuvant! Online (Ravdin 1995), a program designed to generate treatment plans to women based on ER status, age, node positive and negative status, and size of tumor, starting in the late 1990s, and early 2000s, would have already urged most women with node-negative cancer to opt out of chemotherapy, and opt either for surgery and radiation, or simply surgery and tamoxifen (Olivotto et. al. 2005).

In sum, the genetic information was – more or less – redundant. So, while the TAILORx study is hailed as a celebrated victory for prognostic genetic testing, it is unclear whether it as a matter of fact led to any change in standard of care typical for practicing oncologists. Indeed, a recent review in NEJM showed that in terms of absolute risk of recurrence, imaging and other clinical data (stage, grade, patient age, ER status HER2-neu status) are *as if not more predictive of rates of recurrence*, and relative benefit of chemotherapy. Given that the test is expensive (approximately $4000 per patient in the United States), it’s worth noting that imaging and histologic markers already available could be used to predict the ODRS and ultimately obviate the need for the more expensive assay.

It is not surprising that the vast majority of node-negative, HER2-neu breast cancers are at lower risk of recurrence, and so that patients with this status are unlikely to benefit from chemotherapy. Such cancers were not expressing a protein that was known as early as the 80s to increase risk of recurrence. Indeed, anyone familiar with the development of genomic assays for cancer would already realize that the particular genes identified in the OncotypeDX assay were in fact identified as associated with some of the same risk factors associated with higher relative risk of recurrence well-known decades prior to the test: (e.g., one of the genes is associated with HER2-neu status, one of the best predictors of recurrence risk) According to Dialani et al. (2016), “combining imaging features (on mammographic, US, and MR images, whenever available) with tumor histologic grade and progesterone receptor and human epidermal growth factor receptor 2 status can reliably be used to identify tumors with high recurrence scores with a sensitivity of 89% and a specificity of 83%, thereby obviating OncotypeDX testing (Genomic Health) and thus potentially substantially reducing health care expenditures.” A recent review of a subset of the TAILORx dataset showed that in terms of reduction of absolute risk, traditional histologic and imaging data is equally as effective in predicting risk of recurrence and thus benefits of chemotherapy.

**4. Upshots**

Where do these case studies leave us? If, as some studies (LeTorneau et. al. 2017) suggest, the success of precision therapies is minimal, then why are so many scientists convinced of it potential? Are the successful cases unique? If so, what explains the relative success of these cases?

It seems clear that there are several central challenges facing precision oncology – not only with establishing and measuring effectiveness, but also, with regulation, design and implementation of research. First, arguably, the problem of precision oncology is a direct consequence of the complex and heterogeneous biology of cancer. As Shrager et. al. (2019) characterize this problem, it’s a consequence of what computer scientists call the “**curse of dimensionality**” problem. While this summary of the problem is somewhat oversimplified, it makes the nature of the fundamental epistemic challenge facing design and implementation of precision oncology very clear:

Computer and cognitive scientists have long though of problem solving in terms of the search for good solutions in a potentially very large space of possible solutions… Classically, this search space was not considered very large, so a fairly simplistic search strategy based on large clinical trials was effective. At the peak of the success of classical clinical trials, say 25 years ago, cancer was thought of as what might be called a “10 by 10” disease: there were ten types of cancer, corresponding to tissue of origin, crossed with roughly 10 types of chemotherapy. This way of thinking is represented by a 100-cell matrix… Each cell in this matrix represents a biomarker-treatment relationship which needs to be tested… and the search for the right treatment would involve conducting large, randomized trials for each of the ten chemotherapies… as our understanding of cancer has evolved – recognizing that there are potentially thousands of molecular biomarkers that influence whether a treatment will be effective… The space of possible treatment decisions is enormously larger… With thousands of molecular features, leading to tens of thousands of combinatorial subtypes, and hundreds of plausible combination therapies, there may be many millions of treatment-decision rules (i.e., matrix cells) that have to be tested… The number of dimensions that determine the size of this search space is called the “dimensionality” of the data, and the number of independent observations is sometimes referred to as the sample size, or “n” of a study. As a result of the combinatorial structure of the problem, each new feature grows the size of the search space exponentially (Shrager et. al. 2019, 363).

Given the dimensions of the problem space, it is not surprising that success in precision oncology is elusive. The “low-hanging fruit,” or instances where a single biomarker can be targeted effectively without recurrence, are likely to be rare. In particular, effective targeted therapy is particularly likely in cancers with low genomic complexity – e.g., cases of cancer driven by only a handful of driver mutations, and cancers with low heterogeneity. And, this is what we find: very rarely (e.g., in CML) have we found a single genomic feature that predicts with great precision how a patient is likely to respond to targeted therapy. This is because such cancers are relatively simple (from a genomic perspective) (Lawrence et. al. 2013). For more complex disease (indeed, in the vast majority of cancers), we ought to expect the effectiveness of novel precision cancer therapies to be limited.

Particularly in metastatic disease, even the most effective precision interventions are – by and large – not likely to be curative. I.e., “exceptional” responders are exceptional for a reason. Indeed, there are new research programs designed around determining why such responders do in fact respond so well.

The vast majority of cancer deaths are in treatment-resistant, recalcitrant, or advanced stage disease – typically those identified relatively late in the game. Advanced tumors are likely to recur, or evolve resistance to both standard chemotherapies and targeted therapies, exactly because they have been subject to multiple rounds of therapy. Intratumor heterogeneity in advanced tumors makes the effectiveness of such therapies particularly precarious, because such tumors are more likely to evolve resistance to both standard chemotherapies and targeted therapies.

In the face of this challenge, researchers have attempted to develop methods that deploy AI and big data methods – like network models – that help reduce the number of dimensions of the problem. However, such methods are only successful (as Shrader et. al. point out), when there are well-defined criteria of successful solutions of a problem, when the data concerning success is readily available, cheap and plentiful, when experts can teach AI using data from easy and cheap to run experiments, and when there are highly accurate simulators of the underlying processes. These conditions are not met in cancer research.

In sum, defining “success” – as we’ve seen – is a highly contested matter. As several critics of precision oncology have pointed out (Tannock et. al. 2016; Prasad et. al. 2018; Hey et. al. 2019), the endpoint measured in trials is often not “overall” survival, but typically “progression free survival” or “time to tumor growth.” The latter are not the outcome patients are most concerned to intervene upon, and may or may not track the former. Follow up studies can improve upon this problem, but coordination of research is a problem, as we’ve seen with the FDA’s rapid approval (and removal) of drugs. In addition, sometimes tests of novel therapies are not done against standard of care, such that results are not very informative for clinicians (Tao, et. al., 2018).

As I’ve argued, there are further reasons to be concerned about the informational value of cancer biomarkers, or molecular data, in service of prognosis and treatment decisions. First, while gene expression is continuous, biomarkers are often “binned” as discrete variables, for the purposes of prognosis, diagnosis and treatment decisions. This means that two different cancers – say, one advanced stage metastatic breast cancer, and another a treatment naïve early stage cancer – could “score” the same in terms of gene expression profile, even though they are very different disease. This could lead to clinicians assigning the same drug to two very different patients (as has happened, in some ovarian cancers), leading to inconsistent results (see, e.g., Hey et. al. 2016).

To be sure, as in many contexts in medicine, a cut-off has to be made for continuous variables in making decisions about care. This is not a challenge unique to precision oncology; while it introduces some arbitrariness, as long as researchers attend to the widest array of relevant evidence in making such decisions about cut-offs, it's not necessarily a devastating problem. The problem comes with the presupposition that molecular data trumps or obviate the need to attend to the many other variables that need to be taken into account. The key here is to use a wider array of information – not only more molecular data, but to sample a tumor at multiple time points, as well as attend to gross histological features of the tumor itself, to better understand the likely response to the drug. For, whether a drug gets to the target may have to do with some basic facts about the blood supply to a tumor, properties of the tissue in the surrounding organ, immune response, and patient metabolism. Prioritizing the genomic and molecular features of a tumor can lead to loss of important information.

Indeed, commercial tests of presence and absence of molecular variants are not always consistent in their results. A comparison of two commercially available next-generation sequencing platforms revealed rampant disagreements in mutation and recommended drugs for the same nine patients.

Another study found that different commercially provided tests for breast cancer patients arrived at divergent classifications of patients, depending in part on how many cores were taken of a tumor. In other words, intertumor heterotenetiy (ITH) can lead to prognostic misclassification in of patients, because some tumors have regions of both indolent and aggressive disease (see also, Green, et. al., this volume). Gene expression panels (GEPs) such as Oncotype Dx, MammaPrint, PAM50 (Prosigna), EndoPredict, and Breast Cancer Index (BCI) use a small number of selected genes. So, “in patients with highly heterogeneous tumors, multiple cores might be required to estimate risk prediction and that it might be a useful strategy to include both representative and atypical cores while selecting multiple samples to fully account for the ITH-driven variation in risk prediction.” (Gyanchandani et. al. 2016).

Further, many of these new drugs are tested in small populations of patients, and often patients with advanced cancers. Whether the results of such studies are relevant to the vast majority of patients (and particularly those with treatment naïve cancers) is unclear. Even when patients share the same biomarkers, the “same” cancer can have very different properties. So, what we discover about such therapies in trials may or may not be relevant to other patients.[[6]](#footnote-6)

Last but certainly not least, cost of precision care makes many new diagnostic tests and therapies unavailable to a vast majority of patients. Last but not least, apart from questions about effectiveness, it’s worth mentioning that the cost of newly approved agents is also staggering. The OncotypeDX test is prohibitively expensive for many patients, and it not apparently all that beneficial, over and above information already available (patient ER status, node status, etc.). Even the most effective targeted therapies, however, are also routinely priced far outside the range available to most patients. The Institute for Clinical and Economic Review has released its Draft Evidence Report assessing the comparative clinical effectiveness of the PARP inhibitors (ICER 2017), and suggests that even in the best circumstances, maintenance therapy in recurrent disease would require discounts of approximately 50–80% on current list prices to meet acceptable thresholds ($50 000–150 000 per QALY gained) (cf. Volpe et al. 2018). Similarly for the TKIs for non-small cell lung cancer, costs would need to be reduced some 20-40% (depending on the drug) for current list prices to achieve $100,000 per QALY gained) (ICER 2016). In other words, the costs of these drugs – in some cases as much as $400,000 plus per year – would need to be reduced substantially to warrant their continued administration to patients, given the time and quality of life gained from treatment. This is genuinely disheartening, considering especially that many patients might be using up their life savings – or worse, suffering bankruptcy – to pay for such drugs.

It’s not even clear (as in the case of TAILORx) that most patients are likely to benefit from what – for most – would be a prohibitively expensive test. Yet many patients clamor for such tests, even if they’re unlikely to benefit. As mentioned above, very few patients overall are likely to benefit from precision oncology, as most cancer patients do not have actionable mutation. That is, most cancers are not even candidates for precision therapy. There simply are not (yet) targeted drugs likely to assist them (Marquart et. al. 2018). Of course, this may well change with advances in biologics and immune therapies.

In sum, there are a variety of reasons why precision therapy has not been as successful as one might hope – some to do with cancer itself, and some to do with what and how we are testing novel cancer therapies, and last but not least, how approvals for novel therapies regulated and translated into the clinic.

**5. Conclusions**

To be clear, one ought not to downplay the significance of successes of precision oncology, both for researchers, and of course, for patients and their families. However, it’s worth noting that many exemplars of successful precision oncology were developed and approved before the first human genome was sequenced in 2001. For instance, tamoxifen Herceptin (traztuzumab) for Her2+ BC, was approved by the FDA in 1998. The initial test for test for HER2-neu positivity used fluorescent in situ hybridization–based gene amplification, or immunohistochemistry, to demonstrate overexpression of the protein – not NGS (next generation sequencing). Imatinib was approved for targeted treatment in chronic myeloid leukemia in patients with the BCR-ABL rearrangement in in 2001, almost a full decade before the first cancer genome was sequenced. Gefitinib was approved by the FDA for treatment in 2003 for non–small cell lung cancer patients with a specific mutation to the epidermal growth factor receptor gene.

Some of these precision therapies are now part of the standard of care. HER2-neu is considered essential to classifying patients, not only in service of providing them with targeted therapies, but also for giving them prognoses of likely disease course. Small cell lung cancer patients with EGFR mutation benefit from a tyrosine kinase inhibitor, which can help them also to avoid aggressive and toxic chemotherapies. Some of these treatments improve outcomes significantly. Prior to the development of Imatinib, the median survival among patients with CML is about five years, but ranged from a few months to ten years or longer for those who have indolent, chemoresponsive CML. With Imatinib, The 5-year estimated overall survival rate for patients who received imatinib as initial therapy (89%) is higher than that reported in any previously published prospective study of the treatment of CML. (Druker et. al. 2006). Molecular profile can help predict disease course for glioblastomas.

What the above case studies suggest is that in the vast majority of cases, the actual (as opposed to the hyped) benefit of precision oncology is rather minimal. As Strand and colleagues have emphasized (this volume), personalized medicine presents a vision or imaginary of desired futures, but this state may be very far from reality. For instance, what TailoRX succeeded in showing, at best, is a substantial proportion of patients were overtreated. To be sure, this means that one thing that genetic profiling can do well is demonstrate lack of benefit of current treatment modalities. But, it turns out that clinicians already were aware that a variety of markers indicated low benefit of chemotherapy, and so the case of TAILORx did not (or should not have) radically changed the standard of care. At best, what it might do is prevent overenthusiastic (and ill informed) clinicians from overtreating patients with aggressive chemotherapy.

More seriously, it’s not clear how much in absolute terms precision oncology yields benefits that matter. The endpoint measured in trials of new targeted treatments is typically not “overall” survival, but “progression free survival.” That’s a problem because patients by and large are not simply concerned with slowing the growth of a cancer for a few months, especially when these months of life are accompanied by substantial toxicities. This ought to be communicated to patients with end-stage disease who sign on for clinical trials, as so often such patients are subject to false hope.

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| Key Terms |  |
| Biomarkers | Measurable properties of a patient believed to be predictive of a particular clinical status. In cancer, biomarkers may be the presence or absence of a particular mutation, or, protein levels indicating the activity of a particular gene; “biomarker endpoints” are measures of endpoints used in clinical trials as a proxy for the actual clinical endpoint. Thus, “progression free survival” (PFS) is sometimes used as a “biomarker” for “overall survival” (OS), to reduce the time and cost needed to assess the relative efficacy of new treatments.  |
| Functional categories of biomarkers | The U.S. FDA and NIH BEST (Biomarkers, Endpoints and other Tools) document (2015) identify seven: diagnostic, monitoring, assess pharmacodynamics and/or response to drug, predict which treatments are likely to benefit a particular patient, determine prognosis, detect safety, or assess susceptibility/risk. Hey, et. al., 2019 identify an eighth function: acting as surrogate measure or substitute for direct measure of outcomes. |
| Biomarker Validation  | Formal assessment showing that a measure or biomarker is a reliable indicator of patient’s clinical status or outcome. |
| Driver genes | Genes, mutations to which are thought to play an important role in cancer onset and progression |
| “p-medicine” | Lemoine’s (2017) term for forms of medicine that link biomarkers to highly effective, specific therapies, through innovative means – including shared repositories of data, such as genomic databases, or a biological network. |
| Precision oncology | The use of molecular markers (including but not limited to presence and absence of particular mutations) in service of stratifying patients, diagnosis, prognosis, and tailoring therapy to molecular features of the cancer itself. |
| Adaptive Trials | An adaptive clinical trial is a clinical trial that evaluates a medical device or treatment by observing participant outcomes on a prescribed schedule, and modifying parameters of the trial protocol in accord with those observations. |
| N-of-1 trials | In this case, a single patient is the entire trial. Random allocation can be used to determine the order in which an experimental and control intervention are given to a patient, a “randomized controlled” N-of-one trial. In cancer, a tumor may be sequenced, whole exome, genome, and/or RNA expression analysis, this information is analyzed to identify the distinct drivers in that patient’s tumor, and then a search is conducted drugs known to target those drivers. Drugs are tested on the patient’s tumor sample, either in cell culture or after being implanted into a mouse model (technically called a patient-derived xenograft), and if treatment is effective, it may be investigated in the patient, serially, over time. |
| Mabs  | These fall in the class of “biologics”: Monoclonal antibodies: drugs that target proteins, and in particular, antibodies. In the case of cancer, they bind to specific antigens associated with cancer cells, in order to induce immune response, or slow replication of cells, as in the case of trastuzumab for HER2neu breast cancer. |
| TKIs | Also fall in the class of biologics: Tyrosine kinase inhibitors inhibit the activity of kinases that enable signaling transduction – thus halting the activity of certain pathways associated with cancer. For instance, imatinib is a first line treatment for CML patients with a particular chromosomal abnormality.  |
| “Accelerated” approval for “breakthrough” drugs  | “Accelerated” approvals by the FDA are meant to expedite access to a drug, based on evidence of impact on a surrogate endpoint rather than evidence of impact on the actual clinical benefit the drug is intended to provide; “breakthrough” processes expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s). |
| curse of dimensionality | The greater the number of molecular biomarkers that influence whether a treatment will be effective, the higher the dimensionality of the space of possible treatment decisions (based on combinations of these drug-biomarker pairings), requiring many more observations to test for effectiveness. |

1. Department of Philosophy, Washington University in St. Louis. Email: aplutyns@wustl.edu [↑](#footnote-ref-1)
2. Indeed, this slogan has even been deployed as a label for a clinical trial, the “Right Drug, Right Dose, Right Time Using Genomic Data to Individualize Treatment Protocol (RIGHT Protocol)” a study using pharmacogenomic testing to develop electronic health records infrastructure to deliver clinical decision support and study the effects of integrating preemptive pharmacogenomics testing into clinical practice (<https://clinicaltrials.gov/ct2/show/NCT03803293>) [↑](#footnote-ref-2)
3. See also, Green (this volume), where a potential drug match for an organoid often leads to discussion at a tumor board meeting, as to whether the biopsy is sufficiently recent. To ensure acting on a match is warranted, they often need to re-biopsy patients. [↑](#footnote-ref-3)
4. This criterion refers to the number of times a particular base position in the DNA is read during the sequencing analysis. The greater the coverage of a particular alteration, the more likely it is to be detected, which is especially important in tumor samples with low tumor content (where most cells in a biopsy or sample are not tumor cells, but stromal cells). By covering the same area of the gene fragment multiple times, the likelihood of picking up a variation of low allelic frequency is enhanced. [↑](#footnote-ref-4)
5. One reader suggested that this may be a consequence of the structure of incentives and institutional support for competitive grants for research on new drug’s approval. There may be benefits in being the first institution or researcher to implement precision medicine, which make it more attractive to conduct (redundant) trials. (Thanks to Green for this suggestion.) [↑](#footnote-ref-5)
6. For further discussion, see also: Green et. al. (this volume). Green notes: This is also a problem in PreCan. Incurable cancer patients with advanced cancers are the only ones “experimentally accessible” but it is a patient population group that is very different from the majority of cancer patients. [↑](#footnote-ref-6)