Precision medicine in oncology aims to exploit patient-specific molecular alterations present in tumors to identify treatments with the greatest probability of clinical benefit. Numerous studies utilizing preclinical models, such as cell lines, organoids, and patient-derived xenografts (PDX), have shown that distinct molecular alterations can be used as biomarkers to identify patients who are most likely to benefit from a specific treatment. Molecular diagnostic tests to guide the use of targeted therapeutics are used for the treatment of patients with lung, colon, skin, breast, blood, and ovarian cancers (for a review, see ref. 1). Next-generation DNA-sequencing pipelines are often used to sequence large numbers of cancer-associated genes in patient tumors, which in some cases can identify therapeutic options to guide clinical decision-making (2). However, for patients with advanced disease who have exhausted standard clinical care approaches, or where genetic testing fails to nominate effective treatments, there is a need to identify additional therapeutic options.

In this issue of Cancer Discovery, Pauli and colleagues report the development of an integrated precision care platform incorporating genetic and functional testing to nominate treatments for patients with advanced cancers who have exhausted options for standard clinical care (Fig. 1; ref. 3). This includes whole-exome sequencing (WES) of patient tumors to nominate clinically actionable molecular alterations, systematic derivation and in vitro drug testing of patient-derived tumor organoid (PDTO) cultures, and the use of organoid-derived PDX models for validation and safety testing. This timely study is at the cutting edge of individualized precision medicine, addressing a major technical, logistic, and clinical challenge, and thereby provides a road map for the implementation of functional testing to guide clinical care.

The authors utilized the EXaCT-1 test, a WES pipeline designed to inform therapeutic decision-making for patients with advanced cancer. To date, 769 tumors derived from over 500 patients with advanced cancer, obtained from primary and metastatic sites, have been sequenced and analyzed. Although known somatic alterations in cancer genes were identified in the majority of samples, less than 10% of samples had somatic alterations in targetable cancer drivers, enabling potential off-license drug use. Less than 1% of samples had an alteration actionable with an FDA-approved drug. Although this study includes only patients with advanced disease, the small percentage of patients with therapeutically actionable molecular alterations is consistent with other studies from large patient cohorts (2). There is currently a lack of consensus in the community with respect to the interpretation of cancer variants and their potential actionability in the clinical setting. Some analyses of genomic datasets from large patient cohorts, utilizing an inclusive definition of targetability, estimate that many more patients' tumors (up to ~70%) could potentially have a targetable somatic alteration (4). Nonetheless, the data from Pauli and colleagues, which are based on current best practice, underscore that genetic testing in the clinic fails to nominate therapeutic options for many patients.

For those patients with few or no clinical options, advances in methods to propagate patient-derived in vitro and in vivo tumor models, such as organoids, conditionally reprogrammed cells, and PDX, provide an opportunity to directly test the sensitivity of patient tumor cells to a large number of drugs. This type of functional profiling has been exploited in hematologic malignancies with encouraging results (5, 6), and has been used, for example, as a preclinical discovery platform in breast and drug-resistant lung cancers (7, 8). In their study, Pauli and colleagues systematically derived a living biobank of PDTOs (n = 56) and xenografts (n = 19) from a subset of patient tumor samples profiled by WES, and where sufficient fresh tissue was available. Remarkably, PDTOs were successfully derived from primary and metastatic tumors, including tissue biopsies and surgical resections, originating from prostate, bladder, kidney, colon, brain, pancreas, and a range of other cancers. This is despite a modest 39% success.
rate for PDTO derivation (56 of 152 specimens), the majority of which failed due to insufficient tumor with viable cells. Access to high-quality tissue suitable for organoid derivation is not always currently possible, particularly in the setting of advanced disease where patients may have poor performance status. Improved minimally invasive methods to access tissue, together with optimized derivation and culturing methods, particularly when working with small poor-quality samples, could expand the use of such advanced preclinical platforms beyond the current set of patients.

The disease relevance of the PDTO and PDX models was supported by demonstrating that their genetic and histopathologic features were well matched to the original tumor. For example, copy-number analysis of putative cancer genes and somatic nucleotide variants showed high concordance between the PDTO, PDX, and tumor from the same patient. This is consistent with work by others in the breast, colon, and pancreas, demonstrating that PTDO and PDX generally recapitulate many of the histologic and genetic features of the primary tumor from which they were derived (8, 9). When using patient-derived preclinical models, the preservation (or not) of intratumor heterogeneity and ongoing clonal evolution during propagation are important considerations when interpreting results (10). Similarly, there is a risk of sampling bias when generating a model from tissue taken from a single primary or metastatic lesion, or from a small tumor fragment from a large heterogeneous tumor. As a result, patient-specific preclinical cancer models may give an incomplete view of the intratumor and interlesion genomic heterogeneity present, including the presence or absence of alterations in cancer genes, which could negatively affect the ability of preclinical models to faithfully recapitulate clinical response.

To nominate new therapeutic opportunities for patients, PDTOs from 4 patients with uterine, endometrial, or colon cancer were subjected to high-throughput single-agent and combination compound screens. The drug library consisted of 160 compounds, including current FDA-approved chemotherapeutics and targeted agents under clinical development. Through an iterative screening process, combination therapies were identified for all 4 patients. For 2 of these patients, the most promising combinations were prioritized for in vivo confirmation and safety studies in the corresponding patient-matched PDX models. In each case, the newly nominated therapies gave a similar response in the PDX models as was observed in the PDTO. These promising results attest to the ability of this platform to nominate potential new therapeutic avenues for individual patients with advanced disease.

As Pauli and colleagues state, the use of functional testing to guide individualized precision cancer medicine is currently in its infancy, and there are obstacles in the road ahead. The next logical step from this study is to use this precision cancer platform to actually inform individual patient care. Efforts to evaluate the clinical effectiveness of nominated treatments, including determination of patient objective response rates, progression-free survival, and adverse side effects, will be essential for this next stage. Existing clinical trial design is not possible for an N = 1 personalized treatment approach. However, the aggregation of genomic and clinical response data from many patients could provide justification to initiate a new clinical trial to evaluate promising biomarker-driven therapies identified using this platform. In addition, the success of this approach is dependent on the ability to feed back information in a time frame compatible with clinical decision-making. In this study, the timeline to progress through the pipeline for the 4 patients ranged from 8 to 13 weeks, and 3 of 4 patients were alive when drug choices were selected, indicating that this will indeed be possible for some patients. To interpret information from this platform to affect the course of clinical care will require a multidisciplinary team of scientists, oncologists, clinical geneticists, and pathologists. They will have the difficult challenge of balancing the possible clinical benefit of nominated treatments with factors such as patient eligibility and clinical trial capacity.
as experimental variability from PDX studies, drug toxicity, access to drugs, and the increased likelihood of poor patient performance status in the setting of advanced disease. Beyond informing individual patient care, the authors correctly highlight the wealth of genomic, *in vitro* and *in vivo* functional, and clinical data generated by this precision medicine platform. There is no doubt that this will be a valuable source of information to guide the design of new therapeutic biomarkers and clinical trials on the road to precision cancer medicine.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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