Tumor Genetic Screening Programs: A Call to Action

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The clinical development of targeted therapies has increasingly incorporated precision medicine strategies that require molecular selection or enrichment. Given the rapid expansion in the number of potential targets under active investigation, the low prevalence of many targets, and the diverse range of cancer types involved, the use of molecular profiling technologies capable of detecting actionable alterations in dozens or even hundreds of genes simultaneously has become an increasingly important tool to screen patients for trial eligibility.1,2 To date, however, the ability of such screening programs to accelerate accrual to genotype-matched clinical studies has not been rigorously evaluated.

In the article that accompanies this editorial, Meric-Bernstam et al3 report the MD Anderson Cancer Center experience of using multiplexed genomic profiling to facilitate enrollment onto genomically matched clinical trials. After consent to a dedicated profiling study, patients were offered testing using one of two “hotspot” focused multiplexed assays, initially a mass-spectroscopy-based test and later a more comprehensive amplicon-capture, next-generation sequencing test. All profiling was performed in a Clinical Laboratory Improvement Amendment–certified laboratory, and the results were entered into the medical record, where they could be used to guide treatment decisions. Importantly, testing was offered to patients regardless of whether they had a tumor type for which such testing was required to guide standard-of-care therapy. The top-line finding of this report was that although 39% of patients had at least one potentially actionable alteration, only 11% of these patients (4% of patients overall) were subsequently enrolled onto a genomically matched study. The actionable genomic alterations that most commonly prompted enrolled to a genotype-matched trial were mutations in PIK3CA (41%), BRAF (28%), EGFR (8%), KRAS (5%), and ERBB2 (5%). Interestingly, patients with an actionable alteration were only marginally more likely to enroll onto a clinical trial (either matched or unmatched) when compared with patients without an actionable alteration (28.4% v 24.4%).

This prospective tumor profiling effort was conducted at a large cancer center with an extensive clinical trial portfolio. Therefore, we are forced to consider whether the 4% enrollment rate to a genotype-matched study may be the upper limit of what can be expected from similar profiling efforts in a diverse patient population. It is important to recognize, however, that this figure likely underestimates the true clinical utility of multiplexed somatic mutation testing. Patients with tumor types for which genomic profiling was required to guide routine care decisions (for example, lung adenocarcinoma, melanoma, and colorectal cancer) were underrepresented. As insurance typically covers the cost of testing for these common solid tumors for which targeted agents have been definitively shown to improve patient outcomes, these patients had less incentive to participate in the study. Similarly, patients treated with commercially available therapies, either in accordance with US Food and Drug Administration approval or on an off-label basis, were not counted as having received a matched therapy, although they may have benefited from testing. Finally, several actionable alterations for which matched agents are commercially available, including ERBB2 amplification and ALK/ROS1/RET rearrangements, were likely missed as the profiling platforms used are not well suited to detect these classes of alterations. Alternate approaches such as hybrid-capture, next-generation sequencing are more capable of detecting copy number alterations and structural rearrangements and thus may have identified additional actionable alterations and further increased the utility of testing.3,4 To date, no prospective screening study using hybrid-capture, next-generation sequencing has reported the rate of subsequent enrollment to genotype-matched studies in a similarly heterogeneous patient population.

How we interpret the clinical utility of broad genetic screening also rests, in part, on the definition used to define an “actionable” somatic alteration. Meric-Bernstam et al3 acknowledge and attempt to address this complexity by presenting multiple secondary analyses. Activating mutations in KRAS illustrate this challenge well. A recent randomized phase II study of docetaxel with or without the MEK inhibitor selumetinib in KRAS-mutant non–small-cell lung cancer found that patients treated with selumetinib had improved progression-free survival.5 The broader clinical experience with MEK inhibitors in a variety of other KRAS-mutant solid tumors has, however, been disappointing to date.6 Thus, although there exists a body of preclinical and early clinical data suggesting that MEK inhibitors may have modest clinical utility in a subset of KRAS-mutant tumors, the level of evidence supporting the routine use of such agents is not at this point compelling. A classification system that acknowledges and communicates to the treating physician the varying levels of evidence that exist to support the “actionability” of individual mutational events is thus urgently needed to guide the clinical interpretation of profiling results. This is quite challenging, as differing levels of evidence or contradictory findings may exist based on tumor type or even the individual mutant allele within a gene. As an example of the former, BRAF inhibitors are US Food and Drug Administration–approved and active in most patients with BRAFV600E mutant melanoma but are inactive as single agents in BRAFV600K–mutant colorectal cancer.7 Given this clinical experience, should we remove BRAFV600K mutations that occur in colorectal cancer from the list of actionable alterations, or do preliminary data of modest activity with combined BRAF and EGFR
inhibitors imply that BRAFV600E mutations remain actionable in these patients? Individual mutant alleles within a single gene may also have different sensitivities to targeted agents with important implications for treatment selection. For example, while the selective EGFR inhibitor erlotinib is active in patients with nonsmall cell lung cancer harboring EGFR exon 19 deletions and L858R mutations, exon 20 insertions which are activating are resistant to this agent.10 As clinicians struggle to interpret evolving and sometimes conflicting data and researchers attempt to evaluate the utility of genomic screening efforts, the field will need to move toward a more nuanced definition of actionable that accounts for varying and constantly changing levels of evidence.

The frequency with which patients with tumors harboring actionable alterations are enrolled onto genotype-matched clinical trials is also heavily influenced by the portfolio of studies available at a particular institution. Even when a matched study is enrolling, patients may be unable to participate as a result of limits on slots per month, cancer type restrictions, or other exclusions such as the number of prior therapies. One particularly efficient way to expand access to matched therapies is through multihistology, biomarker-selected basket studies. Basket studies define eligibility on the basis of the presence of a particular genetic alteration as opposed to tumor type. Such studies are most appropriate when a mutation is found at low incidence in multiple different cancer types (NCT01524978, NCT01953926). Patients are enrolled regardless of tumor type, but those whose histologies have the highest anticipated rates of the actionable alteration are enrolled onto their own cohort and analyzed independently for efficacy. Basket studies depend on independent screening programs, such as the genomic profiling study presented by Meric-Bernstam et al, to identify potentially eligible patients.

Although genomic screening programs are a necessary requirement for the success of biomarker-driven studies, fully leveraging the genomic data these programs generate to drive clinical trial enrollment presents unique challenges. At large centers, it is difficult for treating physicians to remain aware of every precision medicine study actively accruing patients. Frequently, the principal investigator of the most appropriate phase I study or basket study for a patient does not share the same disease specialty as the treating physician. In this setting, the ability of the principal investigator to efficiently identify patients who potentially qualify for participation in their precision medicine study and notify the treating physician in real time becomes a critical programmatic capability. Demonstrating these significant logistical challenges, Meric-Bernstam et al found that of the 230 patients with actionable alterations in PIK3CA, AKT, PTEN, or BRAF who received further treatment at their center and for whom a genotype-matched study was available, the matched study was discussed with only 106 (46%) of these patients. These results highlight that increasing the number of patients on matched trials requires not only a broad screening programs and robust clinical trial portfolios, but also investments in information technology infrastructure to facilitate the timely notification of treating physicians and patients as to potential genotype-matched studies so that precious opportunities are not missed.

Perhaps the most important question raised by the study by Meric-Bernstam et al is whether enrollment onto a genotype-matched protocol is really the metric by which these important profiling efforts should be judged. We would instead argue that the standard should be whether these programs identify sufficient patients with specific alterations to allow researchers to design and conduct previously impractical, but potentially transformative, precision medicine studies. Meric-Bernstam et al found that mutations in only three actionable genes (PIK3CA, KRAS, and BRAF) were present in > 5% of the patients tested. Moreover, far lower rates of actionable alterations in many other genes, including AKT, EGFR, and ERBB2, were observed across a wide variety of tumor types. These findings clearly demonstrate the necessity of uncoupling highly multiplexed next-generation genomic screening from the therapeutic studies that seek to enroll these rare genetic subpopulations. To be certain, this type of outcome is much more difficult to measure but ultimately far more clinically meaningful. In sum, despite the challenges highlighted, we feel that the type of genomic screening initiative undertaken by Meric-Bernstam et al will be an increasingly critical part of a robust clinical trials program, and the authors should be applauded for their efforts.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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