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Opportunities and Challenges in Genomic Sequencing for Precision Cancer Care

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Cancer is a genomic disease defined by diverse somatic and germline alterations that promote aberrant cell growth. Tumor genomic profiling of single genes or limited gene panels to guide therapy selection is now part of standard management of several solid tumor types, including melanoma, lung cancer, colorectal cancer, and ovarian cancer. However, treatment of many solid tumors is still based on the site of origin rather than being personalized to the molecular alterations specific to an individual patient's cancer. Recent advances in next-generation sequencing (NGS) technology, coupled with decreasing costs, present a transformative opportunity to improve patient outcomes through implementation of routine, prospective tumor and germline genomic profiling.

Multiplexed NGS assays allow for characterization of hundreds or thousands of genes simultaneously, enabling patient matching to U.S. Food and Drug Administration (FDA)-approved therapies and molecularly driven clinical trials as well as novel biomarker discovery. Such assays are now available for prospective clinical use, both in academic settings and through commercial providers. A recent in-depth analysis of 10 000 patients with advanced solid tumors at our center identified potentially actionable alterations in 37%, with 11% enrolled into molecularly matched trials (1).

The recent FDA approval of pembrolizumab for un-resectable or metastatic solid tumors shown to be microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) is an important milestone in precision cancer medicine (2). This is the first regulatory approval of a systemic cancer therapy based on a specific genetic feature independent of tumor origin. Although the effectiveness of individual targeted therapies often varies across tumor types (3), further FDA approvals linked to pan-cancer biomarkers that are agnostic to the tissue site of origin are likely to follow. For example, compelling clinical data were recently reported for the pantropomyosin receptor kinase (TRK) inhibitor larotrectinib in patients

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across a range of adult and pediatric cancer types whose tumors harbor activating TRK fusions (4).

Clinical tissue specimens, especially those obtained through needle biopsies, often contain insufficient tumor material to assess all potential alterations of clinical interest using traditional laboratory methods (such as immunohistochemistry for mismatch repair proteins, fluorescence in situ hybridization for anaplastic lymphoma kinase [ALK] fusions, and real-time polymerase chain reaction for BRAF V600E). Next-generation sequencing can robustly define MSI-H or dMMR status through mutational signature analysis and simultaneously identify individual genetic variants that are predictive biomarkers of drug sensitivity, thus reducing the quantity of tissue needed for comprehensive molecular characterization (5). Furthermore, the cost of a single NGS assay is likely to be lower than the reagent and labor costs of multiple assays that interrogate a single gene. Finally, NGS assays can be iterated over time, with incorporation of newer investigational biomarkers at marginal additional cost.

Sequencing of plasma cell-free DNA (cfDNA) is an emerging strategy to noninvasively detect tumor genomic alterations in real time, potentially capturing tumor heterogeneity and disease evolution in a way not possible through biopsy of a single site of metastatic disease (6). Analysis of cfDNA may also mitigate procedural costs and delays associated with obtaining and processing tumor tissue for sequencing and allow for genomic profiling in patients who lack adequate tumor tissue for NGS. However, because the fraction of tumor versus germline DNA in plasma is low in most patients (especially those with earlier-stage disease), increased sequencing depth and greater reagent costs are required. Current commercial cfDNA assays therefore profile tens, rather than hundreds, of genes. Thus, despite the aforementioned advantages of cfDNA profiling, assessment of only limited gene panels may represent a step back in the breadth of genomic information available for clinical decision making and biomarker discovery. It is also not yet clear whether the ability to identify and target actionable but subclonal mutations—an advantage of cfDNA over tissue analysis-is an effective clinical strategy.

Although paired tumor-normal sequencing increases sequencing costs, we believe that this strategy for somatic mutation calling has several advantages over tumor-only sequencing platforms that rely on computational methods to filter germline alterations. The latter may label rare germline variants as somatic, especially in minority populations (7). The analysis of a paired normal sample also allows for the identification of germline alterations that confer increased cancer risk or are predictive biomarkers of drug response, such as germline *BRCA1/2* mutations. A universal germline screening approach also identifies a greater proportion of patients with pathogenic or likely pathogenic germline variants than would be discovered by germline genetic testing directed by conventional, family history-based guidelines (8). However, the optimal breadth of germline reporting remains debatable, especially with regard to variants not directly targetable within the scope of an individual patient's cancer treatment. There is also concern that future legislation may alter the protections conferred by the Genetic Information Nondiscrimination Act of 2008, which could make it difficult for patients with pathogenic germline variants to obtain adequate or

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affordable insurance coverage in the future. Until such issues are settled, an individualized or cancer-specific approach to germline reporting may be most appropriate.

Several additional challenges have slowed the broader adoption of precision medicine approaches. Treating oncologists may not readily recognize all potentially actionable alterations, and routine discussion of all patients at molecular tumor boards is not feasible. Clinical support tools are thus urgently needed to help clinicians and patients understand the clinical implications of individual genomic variants identified by genomic testing (9). Computational tools that prioritize novel variants for biologic and clinical characterization would also help to expand the utility of tumor genomic profiling (10). The optimal disease state at which to obtain genomic sequencing and the utility of broader assays, such as whole-exome and whole-transcriptome analysis, are additional areas of ongoing debate. Finally, the clinical utility of genomic profiling relies on patient access to targeted therapies, many of which are expensive. Thus, initiatives, such as the TAPUR (Targeted Agent and Profiling Utilization Registry) Study (ClinicalTrials.gov: NCT02693535), which provides investigational drug access in a community setting, will be critical in validating individual mutant alleles as predictive biomarkers of drug response.

In summary, we envision that comprehensive matched tumor-normal sequencing will be recognized as a component of standard care for patients with metastatic solid tumors in the near future. Broader adoption will be driven by the need to assess eligibility of patients for pembrolizumab across a range of advanced cancer types, given that MSI-H and dMMR status are not routinely assessed using other methods in most solid tumors. We believe that genomic profiling using NGS methods represents the optimal utilization of potentially limited tumor material and that continued development of cfDNA sequencing platforms is warranted. Although definitive cost-effectiveness data do not currently exist, we believe that the value of genomic sequencing will be validated over time as cancer therapy selection is increasingly dictated by molecular analysis.

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