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Closing the Gap in Cancer Genomic Testing

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Genomic analysis of tumor tissue and circulating tumor DNA is an increasingly important component of cancer care; such testing can be used to assess cancer risk, inform prognosis, and detect disease recurrence after treatment completion, for example. The most important application of genomic analysis has been in guiding therapy selection with the use of validated diagnostic tests, particularly companion diagnostics. The Food and Drug Administration (FDA) defines a companion diagnostic test as an in vitro diagnostic device that is essential for the safe and effective use of a corresponding therapeutic product. Such an approach was first used in 1998, when trastuzumab was paired with an immunohistochemical test that measured expression of human epidermal growth factor receptor 2 (HER2, also known as *ERBB2*) in breast cancer tissue to determine the likelihood that a tumor would respond to treatment. Since then, the use of molecularly targeted therapies and companion diagnostic tests has rapidly expanded.

As of June 2022, the FDA had cleared or approved companion diagnostic tests for approximately 27 molecular biomarkers that guide therapy selection for more than 40 FDA-approved drugs indicated in the treatment of 16 tumor types. Five molecular alterations — high microsatellite instability, high tumor mutation burden, *NTRK* fusions, *BRAF* V600E mutations, and *RET* fusions — have been linked to treatments that are approved for use regardless of tumor histologic type or site of origin.

Next-generation sequencing (NGS) tests, which reveal the mutational status of hundreds of genes in a single test run, are particularly useful to identify various genomic alterations in tumors that have the same histologic diagnosis. For example, alterations in as many as a dozen genes in non–small-cell lung cancer (NSCLC) tumors have been linked to FDA-approved treatments.[1] NGS tests are widely available from commercial and hospital laboratories, and the FDA has cleared three such tests for tumor molecular profiling. In 2018, the Centers for Medicare and Medicaid Services finalized a national coverage determination for NGS tumor profiling, concluding that testing is reasonable and necessary for patients with advanced cancer when the test has been cleared as a companion diagnostic and is performed in a laboratory certified under the Clinical Laboratory Improvement Amendments standards.

Medical professional societies have played an important role in guiding the appropriate use of tumor genomic testing. Recently, the European Society for Medical Oncology published recommendations regarding the appropriate clinical use of NGS testing for patients with metastatic cancers, and the American Society of Clinical Oncology (ASCO) recommended that multigene panel testing be performed in patients with advanced solid tumors whenever more than one genomic biomarker has been linked to an approved therapy. Patient organizations have informed their constituents about and advocated for evidence-based genomic testing, and information for patients is readily available from the National Cancer Institute (NCI), the American Cancer Society, ASCO, and many disease-focused groups.

Evidence from physician surveys and analyses of claims and electronic health record (EHR) data, however, indicate underutilization of tumor genomic testing. For example, a recent analysis of data from nearly 38,000 patients with stage IV NSCLC diagnosed between 2010 and 2018 revealed that only 22% had molecular test results in their medical record

and only 3% were treated with targeted therapy — even though guidelines during this period recommended that all such patients undergo testing for *EGFR*, *ALK*, and *ROS1* tumor alterations, at a minimum.[2] These findings are in keeping with those of other studies conducted in the United States and internationally that documented molecular-testing rates for NSCLC as low as 20%, depending on the geographic region, practice setting, period in which the study was conducted, and prevailing recommendations for molecular testing at the time.

A 2017 survey conducted by the NCI identified various provider- and organization-level factors that may contribute to undertesting. Oncologists cited difficulty in obtaining sufficient tissue for testing, insufficient time to order or review tests, and (less often) lack of expert personnel to assist in test interpretation as reasons for not ordering NGS tests.[3] These factors were most often cited by oncologists practicing in rural communities or in solo practices. When tests were ordered, they were most frequently used to select an FDA-approved therapy or determine eligibility for clinical trials. Analyses of the survey also found that oncologists with training in genomics or access to a molecular tumor board were more likely than other oncologists to use NGS tests.

What explains the apparent gap between the availability of tumor genomic tests and their utilization? Many factors have been identified that, taken together, suggest poorly coordinated efforts to implement precision oncology care. Necessary elements of the cancer precision-medicine workflow include comprehensive genomic analysis of tumors, interpretation of genomic test results by expert personnel, shared decision making with patients about the likelihood that test results will identify effective treatments, and employment of administrative services to help patients obtain access to therapies that are identified as potential treatment options (see table). Each of these processes involves multiple components that must be completed efficiently for care to be delivered within an acceptable time frame. Such components can include identifying or procuring tumor specimens suitable for genomic analysis and navigating the uncertainties surrounding clinical-trial eligibility or reimbursement for off-label treatments — issues that may be particularly challenging for patients who lack the resources to travel to clinical-trial sites or have no insurance or inadequate insurance to cover treatment costs.

Evidence from community practices suggests that implementing practice-wide workflows that automatically trigger NGS testing for patients with advanced solid tumors, make use of molecular tumor boards to interpret results, and provide administrative assistance for clinical-trial matching and obtaining prior authorization are key to successful implementation of precision-medicine programs.[4,5] Building tools into EHRs that assess a practice's performance against established guidelines for tumor genomic testing is also essential to identify practice-level gaps in care. Capturing patient outcomes in EHRs using structured, common data elements will be important to enable sharing of real-world data that could advance knowledge on how best to use precision cancer medicines.

Prospective randomized trials, meta-analyses of single-group studies, and real-world registry data support the use of comprehensive tumor genomic testing to identify FDA-approved, guideline-recommended therapies for cancer patients. Critics of tumor genomic testing rightly contend that more evidence is needed to support its use outside clinical trials for identifying potential off-label treatments for patients who have exhausted standard therapies, since few such patients currently obtain meaningful clinical benefits from these treatments, and they are at risk for treatment-related and financial harm. Tumor genomic testing is appropriate to identify clinical-trial options for patients with advanced cancer, however. Studies such as the NCI's Molecular Analysis for Therapy Choice trial and ASCO's Targeted Agent and Profiling Utilization Registry (TAPUR) trial show that efficacious treatments can be identified using genomic profiling, even among patients with very advanced disease. In the TAPUR trial, for which one of us is the principal investigator, about two thirds of screened patients have been assigned to a treatment matched to a genomic alteration in their tumor, with mutations in *BRCA1* or *BRCA2*, *CDKN2A*, and *ERBB2* or *ERBB3* each being detected in 10 to 15% of patients with advanced solid tumors. Among 24 study cohorts (defined according to tumor type, genomic alteration, and study treatment) with available data, there has been a positive signal of drug activity in 16, with disease-control rates between 35% and 70%. Over time, new molecular tests that can provide information about the tumor epigenome, the transcriptome, the circulating proteome, and the gut microbiome could complement tumor genomic

Challenges and Potential Solutions to Improving Delivery of Precision Cancer Care.*

Workflow Element	Care Delivery Challenge	Potential Remedies	Resources
Tumor genomic testing	Oncologists must decide which biomarker tests to order after pathological confirmation of cancer diagnosis.	Biomarker testing could be incorporated into routine pathological workup. Evidence-based decision support within the EHR could be used to guide biomarker testing. Professional societies could develop quality measures to assess compliance with recommended testing. The FDA could assert its authority to regulate high-risk genomic tests to ensure test quality.	ASCO guideline on somatic genomic testing (https://ascopubs.org/doi/full/10.1200/JCO.21.02767) ESMO guideline on NGS testing (https://www.annalsofoncology.org/article/S0923-7534(20)39971-3/fulltext) ASCO quality measures (https://practice.asco.org/quality-improvement/quality-programs/quality-oncology-practice-initiative)
Reporting of test results	Turnaround time for genomic tests may delay initiation of cancer treatment, and results not reported into EHRs aren't readily accessible.	Testing labs could aim for a 7-day turnaround time, with reporting of results in electronic format directly into EHRs.	
Interpretation of test results	Interpreting complex genomic test results is challenging; multiple genomic knowledge bases are available but not harmonized with respect to content, format, or evidentiary standards for actionability, and oncologists may not know which to use.	The NIH could develop a universal public database for annotation of cancer genomic alterations that is regularly updated, is readily accessible, and has clinically actionable information. Guidelines could be developed for MTB review. Billing codes could be created to enable reimbursement for MTB review.	ClinGen (https://clinicalgenome.org/) cBioPortal for Cancer Genomics software (https://www.cbioportal.org/) CIViC (https://civicdb.org/welcome) COSMIC (https://cancer.sanger.ac.uk/cosmic) My Cancer Genome (https://www.mycancergenome.org/) Cancer Core Europe's Molecular Tumor Board Portal (https://www.nature.com/articles/s43018-022-00332-x)
Therapy selection based on test results	It can be unclear what level of evidence supports selection of a potential treatment.	Therapy options could be guided by evidentiary standards developed by professional societies.	ESMO Scale of Clinical Actionability for Molecular Targets (https://www.annalsofoncology.org/article/S0923-7534(19)34179-1/fulltext)
Obtaining access to preferred treatment	Oncologists may not know how to obtain access to the preferred treatment if it's investigational or would be used off label.	Clinical-trials matching software could continue to be developed. Clinical practice guidelines and compendia could be regularly updated to support reimbursement for off-label use. Pharmaceutical companies could provide premarketing access to promising targeted drugs by means of expanded-access programs and list these programs in a public resource.	Integrated Trial Matching for Cancer Patients and Providers (https://confluence.hl7.org/pages/viewpage.action?pageId=66938394) NCCN Biomarkers Compendium (https://www.nccn.org/compendia-templates/compendia/biomarkers-compendium) Reagan–Udall Foundation Expanded Access Navigator (https://navigator.reaganudall.org/)
Capturing patient outcomes	Incomplete and variable collection of data on patient outcomes complicates data sharing among practices and health systems and hinders ongoing evidence generation.	Clinical data standards could be incorporated in EHRs to simplify collation and sharing of data on patient outcomes.	Minimal Common Oncology Data Elements (http://hl7.org/fhir/us/mcode/)

* ASCO denotes the American Society of Clinical Oncology, CIViC Clinical Interpretation of Variants in Cancer, COSMIC the Catalogue of Somatic Mutations in Cancer, EHR electronic health record, ESMO the European Society for Medical Oncology, FDA the Food and Drug Administration, MTB molecular tumor board, NCCN the National Comprehensive Cancer Network, NGS next-generation sequencing, and NIH the National Institutes of Health.

testing and further refine therapy selection for patients.

Ensuring equitable and efficient deployment of precision medicine is a global challenge that requires patient access to validated molecular tests, a consistent regulatory and reimbursement environment offering incentives for test development, and concerted efforts by practice and health system leaders to develop the multidisciplinary workforce and information infrastructure necessary to create a precision cancer care delivery system. Putting these pieces in place would not only close the genomic testing gap in cancer care but could transform outcomes for many patients with cancer.

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Deciding on My Dimples

Liz Salmi, A.S.

"OK, boss, it's time for us to make a few decisions," my neurosurgeon, Shawn Hervey-Jumper, announced. He was removing a malignant tumor from my brain, and we were nearing the end of the procedure. It wasn't my first craniotomy — it was my fourth — but this time the stakes were much higher. As someone who has been living with a grade 2 astrocytoma for 15 years, I've long since accepted reality. Though initially indolent, these tumors commonly progress to a more aggressive grade.

As the director of the Glial Tumor Neuroscience Program at the University of California, San Francisco, Shawn specializes in removing tumors from within functional regions of the brain using brain-mapping techniques. He has dedicated his life to understanding how the brain maintains and recovers language, sensory, motor, and cognitive abilities. For my part, I'm not only a patient, but also a patient advocate and scholar, part of a burgeoning movement in which patients are becoming patient-investigators. Open, transparent communication between clinicians and patients is a key focus of my work, and this moment captured something essential about my nontraditional journey toward academic medicine.

"I've removed as much tumor as I can see," Shawn explained. "Based on what you're telling me, Liz, we're in your face. If I go any farther in this area, I'm putting you at an increased risk of sensory and motor loss due to the tumor's proximity to the motor cortex. How do you want to proceed?"

Shawn and I had discussed contingencies in advance. We knew there would be sensory loss, although we didn't know exactly where. We'd explored the real possibility that I would eventually develop weaknesses, ranging in severity from foot drop to complete inability to move my right leg. Shared decision making can be uncomfortable for all involved. More than talking about my overall prognosis, discussing mobility deficits made me cry . . . and made him go silent.

As much as Shawn and I had prepared for such possibilities, and though I have learned more about my own neuroanatomy with each passing surgery, the imminent prospect of sensory, and especially motor, loss in my face came as a shock. Time stopped as I gamed out the possible ramifications: *Will I be unhappy with my appearance? Would these dimples I inherited from my father never be seen again?*

Throughout my life, people have complimented me on my dimples — a defining feature. My husband jokes that I have a "resting smiley face," and by giving the impression that I'm always smiling, my dimples may have indirectly shaped my persona. I've learned that a kind and smiling face is welcome in nearly any setting. Moreover, my dimples have additional meaning for me: I'm pretty sure my father's genes can take credit for them. But might he have given me a brain tumor gene as well? Most neuro-oncologists will tell you that no familial links exist in glioma, yet 7 years ago my father had a seizure and then a scan: "Bifrontal tumor mass suggestive of glioblastoma." I still have a photo I took of our MRIs side by side. Our scans are our last father–daughter portrait.

If my tumor becomes more aggres-