ASCO
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Next Generation Sequencing

POLICY BRIEF

KEY TERMS

Analytic Validity – The accuracy of a test to detect the specific entity that it was designed to detect. This accuracy does not imply any clinical significance, such as diagnosis.

Biomarker – A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention.

Clinical Utility – With respect to a biomarker test, the evidence of improved measurable clinical outcomes, or usefulness and added value to clinical decision making, compared with current management without testing.

Clinical Validity – The accuracy of a test for a specific clinical purpose, such as diagnosing or predicting risk for a disease.

Companion Diagnostic – Food and Drug Administration designation for a biomarker test "that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of [a] … companion diagnostic device with a therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, including the labeling of any generic equivalents of the therapeutic product."

Next-Generation Sequencing – Also referred to as 'massively parallel sequencing' or 'high-throughput sequencing,' refers to technologies that perform DNA sequencing in parallel, allowing for the production of thousands or millions of sequences concurrently.

Precision Medicine – Also known as personalized medicine, this refers to the tailoring of medical treatment to the individual characteristics of each patient, by classifying individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment.

Background

Biomarker tests have many uses in cancer care. They can be used for prognosis and risk assessment, screening, diagnosis, and treatment/post-treatment monitoring. These tests are also often used to select optimal treatment plans by predicting response to molecularly targeted therapies. Historic examples of this approach include the biomarker *BCR-ABL* which directs use of imatinib for chronic myeloid leukemia, or the use of *HER-2* status and trastuzumab treatment in breast cancer. Such personalized cancer treatments hold great promise, so long as accurate and reliable biomarker tests exist which enable clinicians to discern the most effective therapy for a specific patient.

Originally, the tests that were used to predict response to targeted therapies were single-biomarker tests, performed using relatively simple sequencing technologies. The test charactertistics (e.g., analytic and clinical validity) were eventually well-characterized, and long-term data ultimately supported the clinical utility of the test-treatment combination to improve patient outcomes. As research continued and more potentially therapeutic targets were discovered, it became necessary to test for more than one biomarker to determine optimal therapy. These tests would often be ordered by a clinician as a panel of separate tests for use in a specific clinical context (e.g., estrogen receptor/progesterone receptor [ER/PGR] expression and *HER2* amplification for guiding treatment for breast cancer). These panels would soon expand to include other targets of interest, either for research purposes or to help identify patients suitable for a clinical trial. Eventually, an entire patient's genome could be sequenced using next-generation sequencing (NGS) technology, although initially this was cost-prohibitive.

Rapid advances in technology have continued to reduce the per-biomarker cost of NGS testing, but persistent regulatory, reimbursement, and clinical practice issues continue to impede the broader clinical use of NGS testing in cancer care. At the national or global level, NGS testing is capable of generating enormous amounts of data that could be used to refine our ability to personalize cancer treatments, but only when paired with clinical outcomes from the medical record. To date, gaps in infrastructure and interoperability have impeded this potential although progress is ongoing.

In an attempt to help inform ASCO's membership and their patients, this brief reviews the policy issues influencing the availability and uptake of NGS testing in cancer care.

Concerns for ASCO Members & the Cancer Community

Three main areas of concern exist regarding clinical use of NGS tests: coverage and reimbursement, regulatory oversight, and clinical practice issues. Coverage and reimbursement has been historically complex, due to the inconsistent nature of both public and private payer policies. This is in part due to the number of analytes being assessed via NGS tests. Historically, payers have only been willing to include within a person's insurance plan a limited number of biomarker tests of well-characterized clinical validity and utility, with the understanding that the results would directly bear on an impending treatment decision. A comprehensive cancer center may nevertheless see value in pathology protocols that routinely assess a large number of biomarkers via NGS for any tumor tissue acquired from patients, in order to maximize information obtained from an individual sample and to reduce the per-biomarker cost of testing to the institution.

Such protocols help not only to inform initial treatment options, but also suggest subsequent treatment options or candidacy for clinical trials, sparing patients from the need for re-biopsy and associated delays/complications. Depending on payer policy, some or much of an NGS test may be un-reimbursed. The reason given may be due to being designated experimental or not medically necessary, or because the payer would prefer that certain biomarkers be assessed in a stepwise fashion or by specific testing methodologies. For Medicare, these determinations historically varied at the local Medicare Administrative Contractor (MAC) level. What this resulted in, in practice, was different policies regarding coverage and reimbursement depending upon geographic location in the country.

The Food & Drug Administration (FDA) attempted to introduce a level of consistency into the biomarker testing regulatory space through the FDA-approved companion diagnostic designation. However, because non-approved (including NGS) tests could assess the same biomarkers as companion diagnostics (and were more flexible to modify at the institutional level), and because companion diagnostic status did not automatically assure coverage by payers, this designation alone largely failed to address the underlying issue.

Clinical use of NGS is also complicated by the opacity of testing platforms to ordering physicians, as well as the sheer number of potential biomarkers that can be tested. A physician requesting results from testing for *HER2* amplification status for a patient with breast cancer, for example, may be unaware of the testing methodology being used in the pathology laboratory. Depending upon institutional or laboratory preferences, this could result in more biomarkers being reported out from the NGS test than were specifically requested. While these additional results could be useful for selecting therapy or evaluating clinical trial eligibility in case of disease progression, they are also able to suggest treatment with targeted agents for which evidence of efficacy does not yet exist in a specific clinical context (i.e. off-label use). This can be exacerbated in cases where marketing of these tests to patients leads to expectations for certain treatments that may be outside the standard of care.

Surveys of oncologists, even those at academic medical centers, have demonstrated lack of confidence to optimally assess treatment plans when presented with so many options.[1] This also suggests a large unmet need to better integrate NGS test results into electronic health records.[2]

Where ASCO Stands on NGS Testing

ASCO unequivocally supports personalized cancer therapy: delivering the right treatment, to the right patient, at the right time. NGS testing represents the leading edge of technological innovation in this space, with potential to drive down overall testing costs and improve treatment outcomes. Our concerns mainly center upon the uncertain coverage and regulatory environments for these tests, as well as the harm that could be done to patients who fail to receive appropriate therapy, or receive costly or toxic ineffective therapy, that is chosen on the basis of an inaccurate test. ASCO is also concerned that these testing services remain expensive and are not always readily available to underserved or low-income populations. Caution and planning are needed to ensure clinical uptake of NGS testing does not run the risk of exacerbating cancer disparities. The diversity of clinical research participants is a long-standing priority for ASCO and is essential to the process of generalizing outcomes of biomarker-driven clinical trials.

For this reason, ASCO has supported opportunities to improve our ability to learn from NGS testing, such as coverage with evidence development proposals from CMS. ASCO supports improved regulatory oversight to help ensure oncologists are able to have confidence in NGS test results. For this reason, ASCO continues to be involved in dialogue about the future of regulation for these highly complex and frequently ordered tests. ASCO believes future oversight for NGS tests will need to balance the potential

[1] Gray, Stacy W., et al. "Physicians' attitudes about multiplex tumor genomic testing." Journal of Clinical Oncology 32.13 (2014): 1317.
[2] Cox, Summer L., et al. "Patterns of cancer genetic testing: a randomized survey of Oregon clinicians." Journal of Cancer Epidemiology 2012 (2012).

role of FDA with existing lab accrediting organizations, as well as the Clinical Laboratory Improvement Amendments (CLIA), in order to preserve access to medically necessary testing. CMS has also recently finalized a national coverage determination (NCD) for certain patients with cancer, providing Medicare reimbursement for any NGS test that is either an FDA-approved companion in vitro diagnostic (for somatic mutations in advanced cancer) or is FDA approved or cleared (for germline mutations in patients with ovarian or breast cancer), and whose test result is used to direct treatment. This NCD applies differently to tests for somatic mutations (advanced cancer only) compared to tests for germline mutations (ovarian or breast cancers of any stage). The NCD also allows MACs to cover NGS tests that are not FDA-cleared/approved, provided the test is a somatic test for advanced cancer or a germline test for any cancer and the MAC believes the supporting evidence is adequate to direct cancer treatment based upon the test result. The impact this NCD will have on the landscape of NGS coverage and reimbursement remains to be seen, but ASCO is committed to ensuring that existing access remains preserved until more satisfactory oversight is fully in place.

The decision to order an NGS test to assist with clinical decision making should be left to the physician and the patient. Assuming a well-regulated testing environment, such tests should be covered and reimbursed as routinely as the therapy whose selection is enabled by the test result.

For More Information

American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility