

BACKGROUND

The interpretation of multigene next-generation sequencing (NGS) tests can be complex, especially when the test report indicates tumoral heterogeneity or subclonal mutations.

Actionable genomic alterations may include somatic gene rearrangements, deletions, insertions, fusions, exon skipping, single nucleotide change, and copy number of variants. Germline pathogenic variants may also be actionable (eg, Poly (ADP-ribose) polymerase (PARP) inhibitors for patients with germline BRCA 1/2 pathogenic mutations).

A few examples include ¹:

- ➔ ALK gene rearrangements
- ➔ NTRK 1/2/3 gene fusions
- ➔ MET exon 14 skipping variant
- ➔ BRAF V600E point mutation
- ➔ KRAS G12C point mutation



The following tips have been developed to support greater understanding of newly identified actionable variants for the multidisciplinary cancer care team.

TIP



Appropriately Order NGS Panels

Multigene NGS panels have become very popular because they can identify a wide range of actionable genomic alterations in patients with cancer. The American Society of Clinical Oncology Provisional Clinical Opinion on somatic genomic testing provides guidance on when patients with advanced cancers may benefit from multigene NGS panels.²

The authors list some of the key benefits of broad profiling such as tissue conservation, cost efficiency and faster turnaround time for results (compared to a series of multiple single gene tests). Since several tumor-agnostic targeted therapies are approved by the U.S. Food and Drug Administration (FDA), patients with any type of solid tumor may benefit by receiving broad biomarker testing.

TIP



Utilize Molecular Tumor Boards

While oncologists are often familiar with common actionable genomic alterations, occasionally they may see an uncommon result or an unfamiliar gene. In those instances, they may present the case at a tumor board and gather input from pathologists and other experts in cancer genomics. A dedicated molecular tumor board that includes molecular pathologists and genetic counselors can be a valuable forum for multidisciplinary treatment discussion or for clinical education.

TIP



Recognize Different Types of Genomic Alterations

Cancer care teams may have varying levels of understanding regarding the different types of genomic alterations that may be found via NGS testing. A targeted therapy may only be approved for specific types of alterations found in each gene. For instance, a gene fusion is a different type of alteration compared to a point mutation. In the case of advanced non-small cell lung cancer, different agents are recommended for the treatment of patients with³:

- ➔ EGFR exon 19 deletion or exon 21 L858R variant
- ➔ vs EGFR exon 20 insertion
- ➔ vs EGFR T790M variant



It is important to recognize and distinguish the various types of somatic and germline genomic alterations to inform treatment plans and provide optimal care. Testing companies may use different language when reporting germline variants, so clinicians should familiarize themselves with the terminology used by each reference lab.

Cancer programs should use uniform and unambiguous language in their treatment plans to minimize confusion and ensure that eligible patients are considered for appropriate targeted therapies.

TIP



Ensure Collaboration to Optimize Reporting of Biomarker Test Results

At times, the biomarker test may be ordered by a member of the care team other than the treating medical oncologist.

For example, a pulmonologist performing a lung biopsy may order an NGS test on the tissue sample. In such instances, it may be beneficial to have an established and efficient protocol to alert the treating physician in a timely manner to the availability of these important test results so that care plans may be personalized based on biomarker results.



Clinical documentation should indicate whether the genomic alteration makes the patient eligible for targeted therapy in the first-line setting vs second-line or beyond. Treating physicians should work collaboratively with pathologists to optimize this process.

TIP



Review How Test Reports List Potential Targeted Therapies

NGS test reports may include a list of potential targeted therapies based on the identification of positive genomic alterations. However, some of this information may be incomplete or misleading, especially if the listed agents are not approved by the FDA for that specific indication.

For example, several HER2-directed agents are approved for patients with breast cancer who have positive HER2 overexpression (but not specifically for HER2 mutation in breast cancer, which is different from HER2 overexpression). If a patient with non-small cell lung cancer is found to have a HER2 mutation, it would be confusing to mention the same list of HER2-directed agents as potential targeted therapies. Currently, one agent is approved for the treatment of HER2-mutant non-small cell lung cancer.³ Therefore, it is essential to become familiar with how each reference lab formats their test reports and lists “potential” targeted therapies for each type of genomic alteration.

TIP



Involve Genetic Counselors in Treatment Planning

Historically, genetic counselors have focused on identifying hereditary cancer syndromes via germline genetic testing and were not typically involved in interpreting biomarker test results to identify targetable genomic alterations.⁴

Today, certain germline genetic test results (eg, BRCA 1/2 pathogenic variant) may inform targeted therapy (eg, PARP inhibitor) for certain types of common cancers.⁵

For example, many patients with ovarian, breast, and prostate cancer may undergo germline testing to determine eligibility for PARP inhibitor therapy. Also, when a genomic alteration like a BRCA 1/2 pathogenic variant is found on a somatic biomarker test report, the patient may also need to receive germline genetic testing to determine if the BRCA 1/2 pathogenic variant is spontaneous vs hereditary.⁶

As such, it is becoming increasingly important to involve genetic counselors when interpreting biomarker test results for certain types of cancers to inform systemic medical treatment planning. Genetic counselors can also discuss and explain future cancer risks and prevention strategies with patients who may be at risk for certain hereditary cancer syndromes and coordinate cascade testing with family members.

Learn more: acc-cancer.org/cancer-diagnostics.

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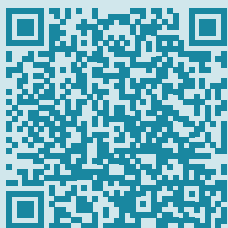
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