NTRK Gene Fusions

As advances in biomarker testing reveal more about the drivers that cause cancers, identifying and integrating guideline-concordant testing for rare cancer types, such as neurotrophic tyrosine receptor kinase (NTRK) gene fusion-positive cancers, is becoming increasingly necessary. NTRK gene fusions can result in activation of tropomyosin receptor kinases (TRK) proteins that act as oncogenic drivers. In 2018, larotrectinib was the first drug approved by the United States Food and Drug Administration (FDA) for the treatment of adult and pediatric patients with solid tumors with NTRK gene fusions. In 2019, the FDA approved entrectinib for the treatment of NTRK-positive solid tumors. The efficacy data for both agents came from several clinical trials that included patients with various types of advanced solid tumors, including salivary gland tumors, soft tissue sarcoma, non–small cell lung cancer (NSCLC), mammary analogue secretory carcinoma, breast, thyroid, and colorectal cancer. Despite the availability of these TRK inhibitors for “tissue agnostic” indications, the identification of NTRK gene fusions remains challenging in community cancer settings.

In 2022, the Association of Community Cancer Centers (ACCC) launched an education project, Emerging Biomarkers: Innovative Therapies for Rare Disease – A Spotlight on NTRK Gene Fusion Testing, in partnership with NTRKers, a non-profit patient support organization, and with support by Bayer, to explore ways to address barriers to optimal care for patients with TRK fusion-positive cancers. In this article, ACCC shares a look at the current NTRK testing landscape and identifies effective ways to optimize comprehensive biomarker testing in practice.

NTRK Testing Landscape

Many commercially available multigene panels using next-generation sequencing (NGS) include methods to detect fusions in the NTRK1, NTRK2, and NTRK3 genes. NGS tests may interrogate DNA, RNA, or both. Other methods used to detect NTRK fusions include immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and reverse transcriptase–polymerase chain reaction (RT-PCR).

The 2022 American Society of Clinical Oncology (ASCO) Provisional Clinical Opinion on somatic genomic testing recommends the use of multigene panel–based assays if more than one biomarker-linked therapy is approved for a particular type of cancer, and makes the following recommendations:

- “Site-agnostic approvals for any cancer with a high tumor mutation burden, mismatch repair deficiency, or [NTRK] fusions provide a rationale for genomic testing for all solid tumors. Multigene testing may also assist in treatment selection by identifying additional targets when there are few or no genotype-based therapy approvals for the patient’s disease.”
- “NTRK fusion testing should be performed in patients with metastatic or advanced solid tumors who may be candidates for TRK-inhibitor therapy, considering the prevalence of NTRK fusions in individual tumor types.”

The European Society for Medical Oncology (ESMO) consensus recommendations for NTRK testing include the following:

- In tumors where NTRK fusions are relatively common, FISH, RT-PCR or RNA-based sequencing panels can be used as part of the initial regimen of biomarker testing.
- In tumors where NTRK fusions are uncommon, pursue either frontline NGS (preferentially RNA-based NGS) or screening by IHC followed by RNA sequencing of positive cases.
Yet, despite multiple guideline recommendations for NTRK testing in patients with advanced solid tumors, sometimes tissue samples are not adequate, or pathologists may not know which testing method will yield the best results.8

Because there are clear pros and cons to different testing approaches, from IHC-based screening to the use of hybrid DNA/RNA NGS panels, molecular pathologists should be involved in shaping institutional biomarker testing policies and protocols.9 Molecular pathologists can also help clinicians interpret test results if an NTRK genomic alteration is noted on a test report. While NTRK gene fusions are actionable using FDA-approved therapies, other detectable genomic alterations (e.g., single nucleotide mutations or amplifications) may not be actionable.8

In October and November 2022, ACCC held a series of focus groups with multidisciplinary care team members from cancer programs nationwide to explore current practices in biomarker testing (including NTRK gene fusion testing), barriers to testing, and awareness and common misconceptions related to NTRK testing. During these discussions, ACCC members emphasized the importance of building strong communication channels between oncologists and pathologists to determine the optimal testing approach based on factors such as tumor type, in-house testing capabilities, tissue quantity, and turnaround time for results. Focus groups also formulated a series of suggested workflows and recommendations to optimize guideline-concordant testing, which are highlighted in this article (view the full report here).

### Liquid Biopsy

The use of liquid biopsy (circulating tumor DNA [ctDNA]; cell-free DNA [cfDNA]) is rapidly expanding and is ordered when biopsy tissue quantity is not sufficient (QNS) for testing or when patients are unable to tolerate a biopsy.9 Although liquid biopsy results can be helpful when they are positive, they may have up to a 30 percent false-negative rate in advanced lung cancer.10

Research has shown that liquid biopsy can be used to detect NTRK gene fusions in patients with multiple types of advanced solid tumors.11 In a recent study, NTRK fusions detected by liquid biopsy were confirmed in tissue tests in 88 percent of patients with various advanced solid tumors.12 Liquid biopsy may also be used to detect resistance mutations and identify patients who may be eligible for clinical trials investigating next-generation TRK inhibitors.10

Therefore, understanding the nuances between testing types and when to utilize the various approaches becomes critically important. One focus group participant, Mary Walters, PharmD, BCOP, clinical pharmacist and co-director of the Oncology Precision Medicine Program at Aurora Health Care in Milwaukee, Wisconsin, described their solution—a robust precision medicine program in place to support oncologists. “We help curate when orders are made for our NGS panels, if they have a specific disease state or if they are at a specific place within their cancer treatment, and help them [oncologists] determine which panel may be appropriate for that patient based on their characteristics, whether or not they want to do a tissue-based specimen, or whether it should be liquid-based testing- we help them make that decision.”

### Optimizing Biomarker Testing Policies and Procedures

As cancer programs review their current biomarker testing practices, they may benefit by exploring ways to optimize processes to ensure that every eligible patient is considered for comprehensive biomarker testing. ACCC focus groups suggest the following recommendations:

- **Develop NGS testing policies and procedures:** Implement a workflow that ensures that patients with advanced or metastatic solid tumors have NGS testing performed on their tumors. This will enable timely and equitable testing and increase the likelihood of finding NTRK gene fusions.

- **Incorporate liquid biopsy for appropriate patients:** Aim to establish consensus around when and how liquid biopsy should be used in patients with advanced...
solid tumors. Remind oncologists that the ASCO Provisional Clinical Opinion states the following about liquid biopsy:6

- “cfDNA testing has the additional advantage of capturing tumor heterogeneity because of pooling in the blood of DNA from throughout the tumor or from multiple tumors.”

- “Fusion testing may be more limited in common cfDNA tests used currently.”

- **Leverage technology to track the status of send-out tests:** If most biomarker tests are sent out to reference labs, create electronic orders that allow clinicians to track the status of these tests. Establish direct access to reference lab portals. This will reduce the potential for duplicate orders and provide an easier way to measure turnaround time for results.

- **Clearly label somatic vs. germline test reports:** As somatic and germline tests may both use NGS platforms, this may cause confusion when test reports are reviewed. Find ways to clearly label reports as somatic vs. germline. The Consistent Testing Terminology Working Group recommends that clinicians use the following terms:13
  
  - “Biomarker testing” to discuss tests that identify characteristics, targetable findings, or other test results originating from malignant tissue or blood
  
  - “Genetic testing for an inherited mutation” and “genetic testing for inherited cancer risk” for tests to identify germline mutations

- **Address disparities in biomarker testing:** Certain patients with cancer may be at risk for experiencing testing disparities. Studies have shown lower rates of NGS testing in Black and Hispanic patients compared with White patients.14 Reflex testing protocols may be the most effective way to improve testing equity and to ensure that every eligible patient is tested, regardless of race, ethnicity, or socioeconomic factors. These recommendations have proven successful at several cancer programs, including Aurora Health Care. “We have a standardized reflex testing algorithm. So, for certain disease states that have a high prevalence of targetable alterations, like non–small cell lung cancers and colorectal cancers, our pathologists are authorized to order reflex testing for in-house NGS panels, which includes 50 genes, including common NTRK fusion variants as well,” explained Walters. At their center, a multidisciplinary committee that includes pharmacy, precision medicine experts, medical oncologists, pathologists, oncology leadership, and others meet monthly to review updates, new targeted therapies, and new recommendations to update these reflex testing standards.

Another interesting workaround for community hospitals that do not have an in-house molecular pathologist but could benefit from molecular pathology expertise when diagnosing and ordering biomarker testing is pathology services collaboration. Michelle Shiller, DO, AP/CP, MGP, medical director of Genomic and Molecular Pathology Services and cancer liaison physician at Baylor Sammons Cancer Center in Dallas, Texas, shared how they created a dedicated email group with a team of molecular pathology experts (including physicians who are certified molecular pathologists as well as PhD-level molecular biologists, bio geneticists, cytogenetic specialists) to support providers from community hospitals, who can access guidance from this expert network. As Shiller explained, “Between this number of people [molecular pathologists], there is someone watching it [the email] at almost any given moment. So, the community pathologist can email the group with a question, and an expert will answer, usually within 15 minutes or less.”

**Opportunities for Future Development**

Although interest and utilization of comprehensive biomarker testing for rare cancers continues to increase, there are important opportunities for improvement that both community and academic cancer programs have identified. One such area relates to shared decision-making with patients. Many patients may not understand the importance of biomarker testing, especially if they hear similar terms such as “genomic or genetic testing.”
er patients may be reluctant to undergo testing because of privacy concerns or they may believe the results will worry their family members. Furthermore, in some instances—when test ordering is reflexive or at centers without a precision medicine navigator—tests are ordered without having a dedicated patient conversation.

Many focus group participants agreed on the need for improvement, including Shiller, who shared these insights. “From a germline perspective, patients may be referred to genetic counseling, but they rarely know why they are referred and so they are unlikely to follow up with an appointment. For somatic testing, because it happens reflexively, providers may not think about explaining it [somatic testing] to the patient, so that the patient can understand why testing may be an important thing to consider. And therefore, I think that’s why patients may say they don’t want to be tested. But I think if they understood that this kind of testing informs therapy that’s much more tolerable, they might be more open-minded toward it. So, I think there is a very long runway of improvement, both in the somatic and germline space, with respect to communication about the need for testing and/or meaning of testing.”

Clearly explaining how test results may guide treatment decisions that potentially provide better outcomes and clarifying the difference between biomarker testing vs. genetic testing for an inherited mutation can enhance patient communication and improve shared decision-making. Cancer clinicians should also be prepared to discuss the potential costs associated with biomarker testing. While state policy initiatives are underway to ensure coverage of NGS testing by commercial insurers, currently certain insurance companies may not cover NGS testing. Thus, cancer programs should have financial advocates in place who can work with patients and help them apply for patient assistance programs.

Focus group participants also identified a need to address disparities in access to testing for underserved populations. With multiple layers of barriers, such as geographic location, transportation, insurance coverage, and high out-of-pocket costs, ensuring access to comprehensive biomarker testing for underserved populations is a growing concern.

Although most cancer programs recognize that there are disparities, many institutions are simply trying to get an idea of the scope and size of the problem. By examining testing rates across different patient populations and leveraging data from electronic health records (EHR) systems and external testing vendors, they hope to get a clearer picture to develop tools to combat these disparities. In the meantime, providing guideline-concordant broad biomarker testing for every patient who requires it, while working with navigators to identify opportunities for financial and other means of support, is the best route.

Carla Strom, MLA, and Director of Operations in the Office of Cancer Health Equity at Atrium Health Wake Forest Baptist in Winston-Salem, N.C. adds this: “You do have to be able to recognize concerns, but not let them [social determinants] keep you from offering and talking about things like biomarker testing or clinical trials.”

**Final Thoughts**

Because NTRK fusions are relatively uncommon, it remains imperative to perform broad biomarker testing that includes both DNA and RNA testing in patients with advanced solid tumors. The use of a multigene NGS panel may represent the optimal balance across effectiveness, efficiency, and cost for most patients with solid tumors. Optimal communication is necessary to coordinate timely testing on tissue, plasma, or both.

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For more information and resources, visit the ACCC program webpage **Emerging Biomarkers: Innovative Therapies for NTRK Gene Fusion Testing.**
REFERENCES


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A publication from the ACCC education program, “Emerging Biomarkers: Innovative Therapies for NTRK Gene Fusion Testing.” Learn more at accc-cancer.org/emerging-biomarkers-NTRK.

The Association of Community Cancer Centers (ACCC) is the leading education and advocacy organization for the cancer care community. For more information, visit accc-cancer.org.

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