Introduction

Through broad molecular testing, cancer care providers can match cancer treatments to the specific genomic alterations driving tumors in many patients, allowing for more informed treatment decisions. Neurotrophic tyrosine receptor kinase (NTRK) fusion-positive cancers and TRK inhibitors present a case in point. 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, to explore ways to address the barriers around NTRK testing and to identify practical solutions for integrating NTRK gene fusion testing into practice.

Focus Groups

In October and November 2022, ACCC held focus groups with members of the multidisciplinary cancer care team from oncology programs around the country to explore how these programs are performing broad biomarker testing, including NTRK gene fusion testing. Focus group discussions centered around: biomarker testing practices; awareness and potential misconceptions of NTRK testing; barriers to testing, including the need for somatic next-generation sequencing (NGS) testing policies and procedures; disparities in testing; and optimal workflows and key recommendations to ensure that guideline-concordant testing is provided for patients who may require it.

Awareness about NTRK Testing

Focus group participants indicated that an increasing number of patients with advanced cancers were now receiving broad genomic profiling via NGS of somatic tissue and/or plasma. NGS tests may use DNA, RNA, or both. While some cancer care team members may not be aware of the advantages and/or limitations of different NGS testing modalities to detect NTRK fusions, which can lead to potential misconceptions, molecular pathologists can provide guidance around technical nuances and help formulate testing policies that balance effectiveness, efficiency, and cost.

Recent studies assessing the diagnostic sensitivity and specificity for NTRK fusion detection methods have shown variable results across immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), reverse transcription–polymerase chain reaction (RT-PCR), DNA-based NGS, RNA-based NGS, and DNA/RNA hybrid sequencing assays. Recognizing that there may not be a single “best” way to test for NTRK fusions, focus group participants commented that broad NGS (either DNA, RNA, or both) seemed to be the most practical and efficient approach. One focus group participant indicated that their cancer program utilized IHC to screen for NTRK fusions, followed by FISH or NGS for confirmation.

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

- In tumors where NTRK fusions are frequently identified, 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 front-line NGS (preferentially including RNA-based NGS) or screening by IHC followed by RNA sequencing of positive cases.
Focus group participants also considered potential misconceptions about NTRK testing, NTRK fusions, and targeted therapies among cancer clinicians. These included:

- “Germline genetic testing can detect NTRK fusions.” This may be generally misleading because the term “NGS” may be used when referring to somatic and/or germline testing. There are conditions that are associated with germline NTRK alterations, but those are NOT fusions.

- “DNA- or RNA-based NGS produces the same results.” Technical differences between DNA-based vs. RNA-based NGS may not be fully understood.

- “Any abnormal NTRK result (e.g., point mutation) is an NTRK gene fusion.” Clinicians may need to be reminded that these other mutations are not gene fusions and may not respond to pan-TRK inhibitors.

Some focus group participants expressed the need for formal policies around NGS testing, as many cancer programs rely on the oncologists’ discretion for selection of reference labs and NGS test ordering. Other cancer programs have “reflex” NGS testing protocols for common advanced solid tumors (e.g., non-small cell lung cancer or colorectal cancer) and at these centers, their pathologists mainly utilize in-house NGS testing. However, in-house NGS tests may not include as many genes as some commercially-available NGS tests.

Most participants agreed that NGS testing is very common in patients with advanced lung and colorectal cancers. Patients with advanced breast, ovarian, and pancreatic cancers are frequently referred for hereditary genetic counseling and testing, but may be less likely to receive somatic NGS testing.

Of note, when the 2022 American Society of Clinical Oncology (ASCO) Provisional Clinical Opinion on somatic genomic testing was released, many oncologists advocated for the use of broad NGS testing in patients with more types of solid tumors beyond lung and colorectal cancers.

Oncologists are increasingly using “liquid biopsy” tests, which detect circulating cell-free tumor DNA (ctDNA) or cell-free DNA (cfDNA), to find actionable genomic alterations in patients with advanced cancers. In some cancer programs, liquid biopsy is mainly used in patients with lung cancer when tissue quantity is not sufficient (QNS). In other centers, its use appears to be expanding into additional cancer types. None of the focus group participants worked in cancer programs that offered their own in-house liquid biopsy tests, although these methods are starting to be deployed in some centers.

In-House NGS Testing on Tissue

During focus group discussions, participants considered how each cancer program appears to have developed its own criteria to determine when and how broad NGS testing is ordered in adult patients with advanced cancers. A key factor seems to center around a cancer program’s capacity to perform in-house NGS testing on tissue. In centers where the local pathology group has NGS testing capabilities, pathologists often collaborate with the cancer programs to develop reflex testing protocols that integrate with diagnostic clinical workflows to ensure that testing occurs near the time of diagnosis in appropriate patients with advanced cancers.

When the local pathology lab does not perform NGS testing, there is a need to ensure effective communication and coordination so that tissue samples are sent out for testing in a timely fashion. Furthermore, it may be difficult to track the status of send-out tests unless orders are entered electronically, and/or if clinicians have direct access to reference lab portals to view results.

Even when an institution performs in-house NGS testing, oncologists may want to send a tissue sample out for broader testing or specific analyses. Several focus group participants explained how their cancer programs handled these requests. In one example, an oncologist is required to submit a special request that is reviewed by the precision medicine team. If the request is approved, then the sample is sent for outside testing and in-house testing is not performed. The precision medicine team holds a weekly molecular tumor board to review the results of NGS tests and to check if any patients may be eligible for clinical trials based on their test results.

Shared Decision-Making

Focus group participants were asked to describe who explains NGS testing to patients and engages them in shared decision-making conversations about the need for testing. While oncologists often perform this task, several indicated that other clinical staff (e.g., a cancer biomarker navigator/precision medicine steward) may meet with the patient, explain the need for biomarker testing, and educate patients about how the results will be used.

If an institution utilizes a reflex testing protocol for advanced cancers, then patients may not always know which tests will be ordered on their diagnostic biopsy tissue. Focus group participants also mentioned that a growing number of patients with advanced cancers are now receiving both somatic and germline testing. As a result, these patients are being seen by medical geneticists or certified genetic counselors who are explaining the clinical importance and potential implications around both somatic and/or germline test results.

Disparities in Testing

Focus group participants discussed ways to increase access to broad cancer biomarker testing, especially for patients with cancer who may be at risk for experiencing disparities. Studies have shown lower rates of NGS testing in Black and Hispanic patients compared to White patients. Analysis of CMS claims data has revealed that Medicaid patients with lung cancer are 40 percent less likely to get tested than patients with private health insurance. Focus group participants noted that 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. Certain insurance companies and Medicare may not always cover NGS testing, so cancer programs should have financial advocates who can work with patients and help them apply for patient assistance programs.
Recommendations

Focus group participants identified some key recommendations to improve NGS testing processes:

- **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.

- **Clarify the role of liquid biopsy**: Recognize that the science around liquid biopsy is rapidly changing. Aim to establish consensus around when and how liquid biopsy should be used. Remind oncologists that the ASCO Provisional Clinical Opinion states the following about liquid biopsy:
  - “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**: Create electronic orders that allow pathologists and cancer clinicians to track the status of send-out tests. Establish direct access to reference lab portals. The use of an integrated electronic system that is accessible by pathologists and cancer clinicians will help 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.

Conclusion

Since NTRK fusions are relatively uncommon, it remains imperative to perform broad biomarker testing in patients with advanced solid tumors when appropriate. NGS may be the most practical approach, but optimal communication is necessary to coordinate timely testing on tissue, plasma, or both. Since in-house NGS testing is not always available, clinicians may continue to work on streamlining the send-out process and removing barriers that may hinder timely or equitable testing for patients.

For more information and resources, visit the ACCC program webpage

[accc-cancer.org/emerging-biomarkers-NTRK](accc-cancer.org/emerging-biomarkers-NTRK)

REFERENCES


Acknowledgements
ACCC would like to thank those who participated in the Focus Groups for this project:

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A publication from the ACCC education program, “Emerging Biomarkers: Innovate 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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