# PQI IN ACTION

Positive Quality Intervention

## Larotrectinib (Vitrakvi®) Overview

# INTRODUCTION

NCODA developed the peer-reviewed Positive Quality Intervention (PQI) as an easy-to-use and relatable clinical guidance resource for healthcare providers. By consolidating quality standards, real-life effective practices, clinical trial results, package insert, and other guidance, PQIs equip the entire multidisciplinary care team with a comprehensive yet concise resource for managing patients receiving oral or intravenous (IV) oncolytics.

This PQI in Action is a follow up to the Larotrectinib (Vitrakvi®) Overview and Larotrectinib (Vitrakvi®) Genomic Testing Management PQIs and explores how the medically integrated teams at Upstate Cancer Center, Wolfson Children's Hospital, and MD Anderson collaborate and utilize the information found in the PQI as part of their daily practice.

**Scan or click here to access Larotrectinib (Vitrakvi®) Overview Positive Quality Intervention**

**Scan or click here to access Larotrectinib (Vitrakvi®) Genomic Testing Management Positive Quality Intervention**

# PARTICIPANTS

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# TREATMENT LANDSCAPE FOR NEUROTROPHIC TYROSINE RECEPTOR KINASE (NTRK) FUSION SOLID TUMORS

NTRK gene fusion-positive solid tumors represent a rare, but clinically significant subset of cancers.[1-2] These tumors are driven by infusions involving NTRK1, NTRK2, or NTRK3 genes, leading to constitutively active tropomyosin receptor kinase (TRK) fusion proteins that promote oncogenesis.[1-2] This genetic alteration can be found across a wide range of solid tumors, including sarcomas and lung, thyroid, gastrointestinal (GI), central nervous system (CNS), salivary gland, and pediatric cancers.[3]

# VITRAKVI®: INDICATION AND CLINICAL DATA

## VITRAKVI® INDICATIONS, MECHANISM OF ACTION, AND CLINICAL TRIAL DATA

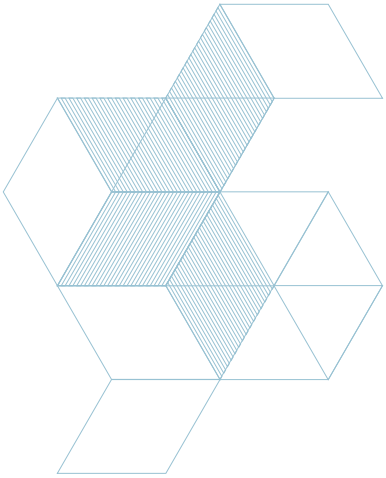
Larotrectinib is a kinase inhibitor that is indicated for the treatment of adult and pediatric patients with solid tumors that:[4]

- Have a NTRK gene fusion without a known acquired resistance mutation
- Are metastatic or where surgical resection is likely to result in severe morbidity
- Have no satisfactory alternative treatments or that have progressed following treatment

This indication received accelerated approval from the United States Food and Drug Administration (FDA) based on the overall response rate and duration of response.[4-5] It is important to note that larotrectinib is approved in patients with an NTRK fusion not just an NTRK mutation.

Larotrectinib inhibits TRKA, TRKB, and TRKC, which are encoded by the genes NTRK1, NTRK2, and NTRK3.[4] In-frame chromosomal fusions involving these genes create TRK fusion proteins that drive tumor growth by promoting cell proliferation and survival.[4]

The efficacy of larotrectinib was evaluated in three multicenter, open-label, single-arm clinical trials that included 55 adult and pediatric patients with unresectable or metastatic solid tumors with NTRK fusions: LOXO-TRK-14001, SCOUT, and NAVIGATE.[5-6] Larotrectinib demonstrated an overall response rate (ORR) of 75%, with a response duration of at least 6 months for 73%, at least 9 months for 63%, and at least 12 months for 39% of patients.[6] The most common adverse reactions (≥20%) with larotrectinib included nausea, vomiting, dizziness, fatigue, elevated aspartate aminotransferase (AST) and alanine transaminase (ALT) levels, constipation, diarrhea, and cough.[6] In an updated survival report presented at the European Society for Medical Oncology (ESMO) Congress 2024, an additional 120 patients with TRK fusion tumors treated with larotrectinib had an ORR of 78%, 12-month duration of response (DOR) of 81%, and median progression-free survival (PFS) of 36.8 months.[7] Adverse events were comparable to prior studies and were mainly grade 1 or 2.[7] Data presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting evaluated patients with non-primary central nervous system (CNS) solid tumors with brain metastases and primary CNS tumors harboring a TRK fusion treated with larotrectinib.[8] There was an objective response rate of approximately 60% in solid tumor patients with brain metastases and approximately 36% in primary CNS metastases, indicating efficacy in TRK fusion cancers with primary or metastatic intracranial disease.[8]



## VITRAKVI® PATIENT PROFILE:
# MEDICALLY INTEGRATED TEAM INSIGHTS

THE medically integrated teams at Upstate Cancer Center, Wolfson Children's Hospital, and MD Anderson highlighted the critical role of NTRK fusion testing in identifying eligible patients for larotrectinib. Pediatric Hematologist-Oncologist Jody Sima, MD, from Upstate Golisano Children's Hospital emphasized the importance of evaluating patients' clinical presentation and selecting the appropriate testing platforms to interpret results. As an example, she shared, "a patient presented with infantile fibrosarcoma, so I notified our pathologist that we needed to look for this NTRK fusion upfront."

David S. Hong, MD, Clinical Medical Director at MD Anderson Cancer Center, recognized the transformational impact of identifying NTRK fusions through next generation sequencing (NGS) as a key advancement in precision oncology. He noted, "Larotrectinib is an amazing drug and I think it is crucial that patients in this generation of NGS get tested for this fusion. Vendors like Foundation Medicine and Tempus routinely perform these analyses, and medical oncologists are increasingly sending tissue samples for testing."

However, practical clinical considerations remain, such as patients with rapidly progressing disease where immediate therapy may be necessary. Dr. Hong explained, "If a patient is rapidly progressing, they sometimes can't wait for the NGS. You have to give upfront therapy, which is important. But if the patient can wait a week or two for that tissue analysis to come back—it's worth sending that tissue off." These insights underscore the importance of collaboration among oncologists, pathologists, and other healthcare providers to ensure tissue samples are tested whenever feasible, maximizing the benefits of precision medicine in improving patient outcomes.

> "A patient presented with infantile fibrosarcoma, so I notified our pathologist that we needed to look for this NTRK fusion upfront."
>
> – Jody Sima, MD

## ENHANCING PATIENT OUTCOMES THROUGH
# MEDICALLY INTEGRATED COLLABORATION

A multidisciplinary approach in providing TRK-targeted therapies ensures optimal outcomes for patients. Holly Kinahan, MSN,APRN, NP-C, AOCNP, Adult Nurse Practitioner at MD Anderson, believes collaboration with team members, such as pharmacists and supportive care specialists, enhances comprehensive care for patients. Kristie Fox, PharmD, Pediatric Clinical Pharmacist at Wolfson Children's Hospital, shares "it is important, especially for oncology patients, to consider the many factors involved in drug therapy and patient management. As a teaching hospital, our rounding process can include up to 20 people—pharmacy, dietitians, physicians, residents, fellows, and both medical and pharmacy students. Sometimes, team members from the clinic side also join." According to Rachel Bullock, CPhT, Patient Care Coordinator

> "Having your pharmacists provide education in the room with the patient makes a huge difference in drug effectiveness."
>
> – Jody Sima, MD

# Enhancing Patient Outcomes Through Medically Integrated Collaboration - continued

at Upstate Cancer Center, "having the pharmacy, the prescriber, social workers, and anyone else who might be involved, in the same spot just makes it so much easier" to prevent delays in treatment.

Our multidisciplinary oncology panel agreed that pharmacists play a crucial role within the multidisciplinary team by providing expertise on drug interactions, trial restrictions, and side effect management. Hoyt Slade, PharmD, BCOP, CMTM, Clinical Pharmacy Specialist at MD Anderson, highlighted his role in guiding physicians through complex therapeutic landscapes, especially when standard treatments for side effect management are not clear in trial protocols. Pharmacists work closely with physicians, nurses, and advanced practice providers to share expertise on treatments and provide patient education. Dr. Sima noted, "having your pharmacists provide education in the room with the patient makes a huge difference in drug effectiveness."

# NCODA'S PQI RESOURCE

THE PQI resource contains peer-reviewed clinician-directed guidance and criteria designed to support the multidisciplinary team in treatment approaches. It illustrates how medically integrated pharmacists support physicians and health care staff through clinical and administrative expertise. The Larotrectinib (Vitrakvi®) Overview and Larotrectinib (Vitrakvi®) Genomic Testing Management Positive Quality Interventions cover clinical trial data, genomic testing strategies, dosing considerations, side effects management, monitoring strategies, and patient-centered counseling pearls. Dr. Sima values the PQI because it consolidates key clinical information, particularly major studies and references, into a single tool. This is a helpful supplement when providing side effect management and counseling to patients. Fox appreciates the PQI because it supports patient-centered activities, which aligns with the core role of a pharmacist in patient care.

## BEST PRACTICES IN NTRK FUSION TESTING

To effectively identify patients eligible for TRK-targeted therapies, it is essential to perform NTRK fusion testing using sensitive and specific methodologies.[9] Current assays available to identify NTRK fusions in tumor samples include NGS-based analysis, immunohistochemistry (IHC), fluorescent in situ hybridization (FISH), and reverse transcriptase–polymerase chain reaction (RT-PCR).[9] NGS enables highly sensitive and specific detection of NTRK fusions while simultaneously identifying other oncogenic drivers.[9] A key consideration for patients with significant tumor burden is it generally takes 2-4 weeks to result.[9]

In October 2024, the FDA approved the NGS-based FoundationONE CDx test (F1CDx) as a companion diagnostic for NTRK1, NTRK2, and NTRK3 in DNA or RNA isolated from tumor tissue from eligible patients.[10] IHC is widely available in clinical laboratories and has a typical 24-hour turnaround time to result, however, it has lower sensitivity for NTRK3 fusions.[9] FISH is a highly sensitive DNA-based assay that requires multiple tests to be run to detect NTRK gene fusions at multiple locations.[9] RT-PCR detects gene-fusion RNA transcripts and requires knowing both the fusion partner and exon breakpoints when designing the primers.[9] This approach can be considered with known fusion partners, such as detection of ETV6-NTRK3 fusions in secretory breast cancers and infantile fibrosarcoma.[9]

# THE PQI PROCESS: VITRAKVI® DOSING CONSIDERATIONS

ONCE confirmed that NTRK fusion has been identified, clinicians verify correct dosing for their patient population. Larotrectinib is available in 25 mg and 100 mg capsules, as well as a 20 mg/mL oral solution, which are interchangeable.[4]

The recommended dosage for adult and pediatric patients with a body surface area (BSA) of ≥ 1 $m^2$ is 100 mg orally twice daily with or without food.[4] Pediatric patients with a BSA of <1 $m^2$ is 100 mg/$m^2$ orally twice daily with or without food.[4] No renal dose adjustments are required; however, dose adjustments may be required based on hepatic impairment and coadministration with strong CYP3A4 inhibitors/inhibitors.[4] Dose adjustments are shown in Table 1.

**Table 1: Larotrectinib Dose Adjustments[4]**

| **Hepatic Dose Adjustments for Hepatic Impairment Prior to Initiating Therapy** | |
|---|---|
| Child-Pugh Class A | No dose adjustment necessary |
| Child-Pugh Class B and C | Reduce initial dose by 50% |
| **Coadministration with Strong CYP3A4 Inhibitors/Inducers if Coadministration Cannot be Avoided** | |
| Coadministration with CYP3A4 Inhibitors | Reduce larotrectinib dose by 50% |
| Coadministration with CYP3A4 Inducers | Double the larotrectinib dose |
| Upon Discontinuation of CYP3A4 Inhibitor/Inducer | Resume larotrectinib at the original dose after 3-5 elimination half-lives of the CYP3A4 Inhibitor/Inducer (half-life 2.9 hours) |

# THE PQI PROCESS: ADVERSE EVENT MANAGEMENT AND MONITORING PATIENTS

COMMON adverse effects (> 20%) occurring with larotrectinib include increased AST/ALT, alkaline phosphatase (ALP), dizziness, musculoskeletal pain, fatigue, cough, constipation, diarrhea, nausea, vomiting, abdominal pain, lymphopenia, pyrexia, neutropenia, hypocalcemia, and hypoalbuminemia.[4,6] Although grade 3 or 4 adverse events are low, it is important to note that the most observed in the LOXO-TRK-14001, SCOUT, and NAVIGATE trials were anemia (11%), increased AST/ALT (7%), weight increase (7%), and decrease in neutrophil count (7%).[4,6] Monitoring AST/ALT, ALP, and bilirubin levels for hepato-

# The PQI Process: Adverse Event Management and Monitoring Patients - continued

toxicity is recommended every 2 weeks during the first 2 months of larotrectinib treatment, then monthly thereafter or as clinically indicated.[4] Monitoring for signs and symptoms of CNS effects, such as dizziness, cognitive impairment, mood disorders, and sleep disturbances is also advised.[4] In the event of grade 3 or 4 toxicity, Table 2 presents guidance on dose modifications. For patients with withdrawal pain, consider tapering doses at discontinuation.[4]

### Table 2: Dose Reductions for Grade 3 or 4 Toxicity[4]

**For Grade 3 or 4 Toxicity; Hold Until Resolution, Then as Follows:**

| Dose Modification | Patients with BSA ≥ 1 $m^2$ | Patients with BSA < 1 $m^2$ |
|---|---|---|
| 1st Dose Modification | 75 mg orally twice daily | 75 mg/$m^2$ orally twice daily |
| 2nd Dose Modification | 50 mg orally twice daily | 50 mg/$m^2$ orally twice daily |
| 3rd Dose Modification | 100 mg orally once daily | 25 mg/$m^2$ orally twice daily |

Permanently discontinue for any Grade 3 or 4 adverse event that does not resolve within 4 weeks, or any patients unable to tolerate after 3 dose modifications

## MANAGING ADVERSE EFFECTS OF LAROTRECTINIB

**The multidisciplinary team reviewed adverse effect management for larotrectinib.**

**Tolerability:** Dr. Hong noted it is generally well-tolerated, with dizziness as the most common side effect, often resolving within weeks. "If side effects like dizziness occur, they typically start within the first few days or weeks and improve over time," he said. "Older patients may experience worse symptoms, but these often subside when the drug is held or the dosage is reduced."

**Other Side Effects:** Mild GI issues (nausea, vomiting, diarrhea), slight weight gain, and elevated liver function tests.

**Pediatric Considerations:** Fox emphasized liver function monitoring in children due to ongoing organ development. "Pediatric patients experience organ growth at varying rates, which can influence drug metabolism. If long-term treatment is needed, continuous liver function monitoring is essential," she explained.

# The PQI Process: Adverse Event Management and Monitoring Patients - continued

**Liver Function:** Elevated liver function tests occur in ~15% of patients but rarely severe. Dr. Hong advised, "It's crucial to rule out other causes, such as excessive acetaminophen use, alcohol consumption, or herbal medications. Many cancer patients take herbal supplements like St. John's Wort or mushroom extracts, which can interfere with liver enzymes."

**Rare Pain Syndrome:** NTRK receptor inhibition may cause muscle and bone pain if doses are missed. "If the drug is not taken consistently, particularly if doses are skipped, patients can develop pain syndrome over time," Dr. Hong said. "With a half-life of around 8 hours, missing doses can trigger this pain signal."

**Adherence & Myalgias:** Kinahan highlighted that myalgias are common, especially if patients deviate from a strict dosing schedule. "Myalgias can develop even with a slight timing deviation," she said. "Additionally, when the drug is temporarily discontinued for procedures like radiation therapy, some patients may experience withdrawal symptoms, including muscle aches."

**Weight Gain & Neurological Effects:** Kinahan noted weight gain around the midsection, particularly in women, and neurological effects like gait imbalance, which often improve during therapy breaks. Slade reinforced the importance of monitoring and patient education, adding, "Patients may come with myalgias, loss of coordination, or ataxia." Strict adherence, proactive monitoring, and patient education are key to optimizing outcomes.

## PQI PROCESS[4,11]

01 Monitor liver function tests (LFT) every 2 weeks during the first month of treatment and monthly thereafter or as clinically indicated

02 Monitor for signs/symptoms of neurotoxicity

03 Modify doses for Grade 3 or 4 toxicity

04 Permanently discontinue for any Grade 3 or 4 adverse event that does not resolve within 4 weeks, or any patients unable to tolerate after 3 dose modifications

05 For withdrawal pain, consider tapering at discontinuation

## SIDE EFFECTS[4,6]

01 Common adverse effects (> 20%): Increased AST/ALT, ALP, dizziness, musculoskeletal pain, fatigue, cough, constipation, diarrhea, nausea, vomiting, abdominal pain, lymphopenia, pyrexia, neutropenia, hypocalcemia, and hypoalbuminemia

02 Grade 3 or 4 adverse effects: Anemia (11%), increased AST/ALT (7%), weight increase (7%), and decrease in neutrophil count (7%)

"Myalgias can develop in patients if their medication schedule is not strictly followed, even with a slight timing deviation. Additionally, when the drug needs to be temporarily discontinued for procedures like radiation therapy, some patients may experience withdrawal symptoms, including muscle aches."

- Holly Kinahan, MSN,APRN, NP-C, AOCNP

# PRIORITIZING PATIENT-CENTERED CARE

THE Patient-Centered Activities section follows the PQI Process and gives patient-centered guidance for the multidisciplinary team. The Larotrectinib (Vitrakvi®) Overview Positive Quality Intervention suggests providing the patient with an Oral Chemotherapy Education (OCE) sheet. OCE sheets are an NCODA-led initiative that provides information about oral chemotherapy drugs and their side effects to cancer patients and caregivers. In the 2019 ASCO publication Patient-Centered Standards for Medically Integrated Dispensing: ASCO/NCODA Standards, formal education by an experienced clinical education (e.g., nurse, physician, pharmacist, nurse practitioner, or physician assistant) should be conducted prior to initiating an oral anticancer drug.[12]

**Scan or click here to access Larotrectinib (Vitrakvi®) Oral Chemotherapy Education Sheet**

# EMPOWERING PATIENTS THROUGH LAROTRECTINIB EDUCATION

THE next steps involve educating the patient on adverse effects that may be experienced while on larotrectinib. Patients are advised to report adverse effects such CNS symptoms, paresthesia, numbness/burning sensation of the hands/feet, loss of appetite, nausea or vomiting, and pain in the upper right quadrant.[4,11]

## PATIENT EDUCATION & ADHERENCE STRATEGIES FOR LAROTRECTINIB

**The multidisciplinary team reviewed adverse effect management for larotrectinib.**

- **Educating patients on larotrectinib's adverse effects is a key step in treatment.**
- **Adverse Effects to Report:** Patients should monitor and report CNS symptoms, paresthesia, numbness or burning in hands/feet, loss of appetite, nausea, vomiting, and upper right quadrant pain.
- **Multidisciplinary Approach:** Education involves pharmacists, physicians, nurses, and advanced practice providers. Slade emphasized, "Pharmacists are a drug information resource for the team; we help navigate drug interactions and side effects from the patient standpoint."

"Pharmacists are a drug information resource for the team; we help navigate drug interactions and side effects from the patient standpoint."

– Hoyt Slade, PharmD, BCOP, CMTM

# The PQI Process: Adverse Event Management and Monitoring Patients - continued

## PATIENT EDUCATION & ADHERENCE STRATEGIES FOR LAROTRECTINIB CONT.

**Role of Advanced Practice Providers:** Kinahan highlighted the strong patient relationships built by APPs, who often manage side effects and supportive care. In her practice, the team collaborates with study coordinators to educate patients on clinical trial drug side effects.

**Dosing Adherence:** Oncology clinicians stressed strict adherence to avoid rebound effects. If a dose is missed, patients should take it upon remembering unless it is within 6 hours of the next scheduled dose. If vomiting occurs after taking a dose, the next dose should be taken as scheduled.[4]

**Pediatric Considerations:** Dr. Sima acknowledged limited data in pediatric patients, requiring careful discussions with parents. "There is sufficient data to show that larotrectinib is well-tolerated, but we remain transparent about uncertainties to help families weigh risks and benefits."

**Administering Oral Solution:** Fox emphasized counseling families on proper dosing and storage. "We typically have patients or family members physically practice drawing up a dose using water or another substitute to confirm they can measure it correctly with the syringe. We also assess their comfort level with administering it at home. Depending on the child's age, they may be able to do it themselves, so we tailor the education accordingly." Comprehensive education and adherence support ensure safe and effective treatment.

## COUNSELING PEARLS

- ❍ Do not make up a missed dose within 6 hours of the next scheduled dose
- ❍ If vomiting occurs after taking dose, take the next dose at the scheduled time
- ❍ Store the glass bottle of oral solution in the refrigerator and discard after 90 days of first opening
- ❍ Patients should not eat grapefruit or drink grapefruit juice while taking this medication
- ❍ Females of reproductive potential and patients with female partners of reproductive potential should use effective contraception during and for at least 1 week after the final dose
- ❍ Do not breastfeed during treatment and for 1 week after last dose

# The PQI Process: Adverse Event Management and Monitoring Patients - continued

## ENSURE PATIENTS ARE AWARE OF SIDE EFFECTS TO MONITOR AT HOME

- ❍ Patients should report symptoms such as confusion, difficulty speaking, dizziness, coordination problems, tingling, numbness/burning sensation in hands/feet
- ❍ Patients should report symptoms such as loss of appetite, nausea or vomiting, pain in the upper right side of the stomach area

## ORAL SOLUTION COUNSELING POINTS:

- ❍ Always use the bottle adaptor and oral syringes provided to ensure accurate measurement
- ❍ 1 mL and 5 mL syringes are provided * Do not use a household teaspoon*
- ❍ Each syringe may be used over a 7-day period and replaced thereafter
- ❍ Place the tip of the oral syringe into the mouth against the side of the cheek and slowly squirt
- ❍ Remain in the upright position for a few minutes following dose administration
- ❍ If spit up, do not give another dose; wait until the next scheduled dose
- ❍ Always place the child-resistant cap back on the bottle *Do NOT remove the bottle adaptor*
- ❍ Clean the oral syringes by removing the plunger from the barrel and rinse with warm water

"We typically have patients or family members physically practice drawing up a dose using water or another substitute to confirm they can measure it correctly with the syringe. We also assess their comfort level with administering it at home. Depending on the child's age, they may be able to do it themselves, so we tailor the education accordingly."

- Kristie Fox, PharmD

# BREAKING BARRIERS IN ACCESS TO TREATMENT

RACHEL Bullock, CPhT, Patient Care Coordinator at Upstate Cancer Center, outlined the workflow of her medically integrated pharmacy (MIP). A significant portion of her work involves managing prior authorizations, ensuring medications are accessible, and addressing cost-related barriers through medication assistance programs. She highlighted the importance of tracking and monitoring to ensure patients receive their medications promptly, which often requires overcoming hurdles such as incomplete documentation or insurance requirements.

Bullock emphasized the advantages of medically integrated teams, where pharmacists, prescribers, and other healthcare professionals collaborate in a shared system. Having all services in one location streamlines communication, enables immediate resolution of prescription issues, and reduces delays commonly associated with external specialty or retail pharmacies. This setup enhances both efficiency and patient care, as team members can access shared medical records and maintain direct communication. Given the requirements under the 340B program, patients must meet specific criteria for applying drug discounts to larotrectinib. For those who do not qualify, such as patients on Medicaid, the team facilitates referrals to alternative pharmacies while providing support to minimize confusion and delays.

Bullock detailed the use of manufacturer coupons, patient assistance programs, and income-based discounts to mitigate the financial burden of medications. However, prior authorization remains a challenge, often due to incomplete documentation or denials requiring appeals. Insurance-mandated step therapy—where patients must try and fail other treatments before approval—is a common obstacle. Despite these challenges, the integrated team works efficiently to expedite the process compared to external pharmacies. By addressing logistical, financial, and educational needs, MIPs can ensure that patients receive timely, effective, and personalized care.

**Scan or click here to access the NCODA Financial Assistance Tool**

"I think, for us specifically, our patients aren't just a number. That's not to say other pharmacies treat patients that way, but we spend so much time reviewing medical charts, talking to patients, and truly understanding their needs. Many of our patients feel comfortable calling us, even when their concerns aren't directly related to their prescriptions. Having that broader connection allows us to understand their needs and nuances better, helping us determine the best next steps for their care."

– Rachel Bullock, CPhT, Patient Care Coordinator

# SUMMARY

Larotrectinib offers a novel therapy for adult and pediatric patients with NTRK fusion, expanding the advancement in precision oncology. The multidisciplinary team agreed that the PQI Clinical Resource delivers accessible, evidence-based drug information to support patient eligibility identification and care management. The primary objective of the PQI is to equip the team with the tools and education needed to enhance patient-centered outcomes.

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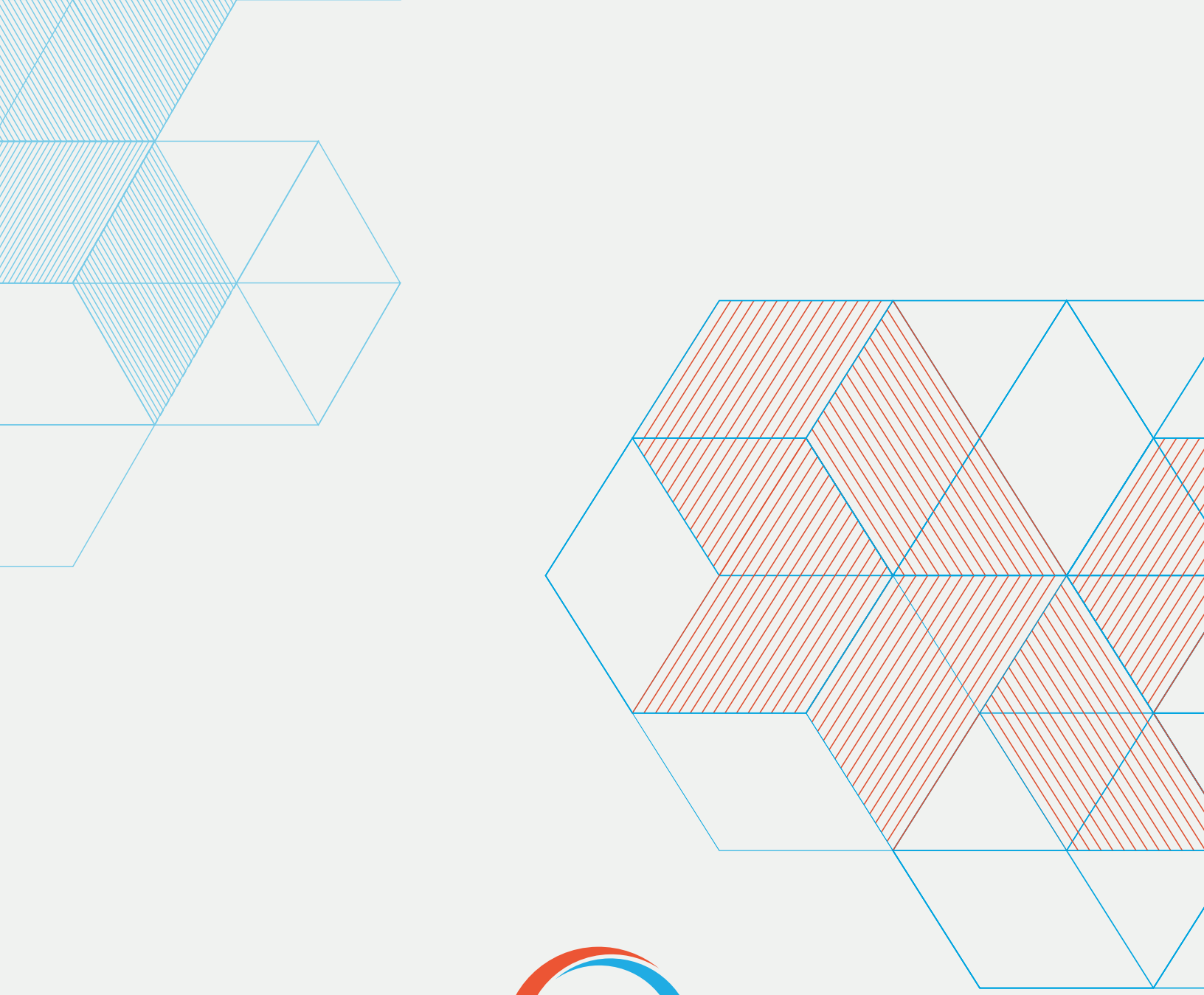

*Practice panelist's comments reflect their experiences and opinions and should not be used as a substitute for medical judgment.*