PQI IN ACTION

Positive Quality Intervention

NCODA

Siltuximab (Sylvant®) in Patients with Idiopathic Multicentric Castleman Disease

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 IV oncolytics.

This PQI in Action is a follow up to the Siltuximab in Patients with Idiopathic Multicentric Castleman Disease and explores how the medically integrated teams at University of Michigan Health-Sparrow Herbert-Herman Cancer Center, Texas Oncology, and University of North Carolina (UNC) Health collaborate and utilize the information found in the PQI as part of their daily practice. This PQI in Action focuses on the use of siltuximab in patients with idiopathic multicentric Castleman Disease.

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PARTICIPANTS

UNIVERSITY OF MICHIGAN HEALTH-SPARROW HERBERT-HERMAN CANCER CENTER

Lansing, Michigan

Gordan Srkalovic, MD, PhD, FACP
Medical Director

Kevin Glaza, RPh
Pharmacist

Taylor Herlein, BSN, RN, OCN
Nurse

TEXAS ONCOLOGY

Dallas, Texas

Jessica Moore, PharmD
Pharmacist

Lipsi Melendez, Sr.CPhT
Pharmacy Technician

UNIVERSITY OF NORTH CAROLINA (UNC) HEALTH

Chapel Hill, North Carolina

Samuel Rubinstein, MD, MSCI
Malignant Hematologist

OVERVIEW OF IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE (iMCD)

WITH an estimated incidence of about 4,300 to 5,200 cases per year in the U.S, Castleman disease (CD) is rare and consists of a varied group of lymphoproliferative disorders that possess similar histopathologic features.[1,2] Notably, these disorders vary in their causes, clinical manifestations, treatment approaches, and outcomes.[2]

There are two main types of CD, which are distinguished by the patient's extent of lymph node involvement: unicentric (UCD) and multicentric (MCD). UCD affects one or more lymph nodes in a single region, while MCD involves multiple regions.[2] Further subcategorization of MCD into one of three groups is based on its etiological driver: POEMS-associated MCD (POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes), Human Herpes Virus-8 (HHV-8)-associated MCD (frequently seen in patients with human immunodeficiency virus (HIV) or otherwise immunocompromised), and HHV-8-negative MCD, also known as idiopathic MCD (iMCD). Finally, iMCD is broken down into two groups according to phenotype: iMCD-TAFRO, a severe form characterized by a consistent set of abnormal lab results and clinical features including thrombocytopenia, ascites, reticulin fibrosis, renal dysfunction, and organomegaly; and iMCD-not otherwise specified.[2,5]

Although the etiology of iMCD is not clear, interleukin-6 (IL-6) is recognized as a key driver in the disease process in some, but not all patients.[2,3,4] In terms of its function, IL-6 is a cytokine that influences the growth and differentiation of B-lymphocytes and plasma cells, oversees the immune response, and manages acute phase reactions. It also exerts various effects on inflammation and blood cell formation. IL-6, in addition to other cytokines, is believed to contribute to the widespread lymph node enlargement, clinical symptoms, and increases in inflammatory laboratory markers like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).[6]

MCD is marked by periods of remission and relapse, with a natural history that varies widely, from slow-progressing, indolent disease to acute and severe manifestations.[8,9] Patients with iMCD present with lymphadenopathy and may experience a range of other symptoms, from mild constitutional issues like severe fatigue, night sweats, weight loss, and fevers, to potentially life-threatening organ failure.[5,7]

As CD presents in a non-specific and diverse manner, it can frequently mimic other benign and malignant conditions. Combined with its rarity, this makes arriving at a CD diagnosis particularly challenging.[8] CD diagnosis relies on a combination of patient clinical presentation, imaging studies, and pathological examination of a lymph node biopsy.[7] The consensus diagnostic criteria for iMCD requires meeting two of two major criteria and at least two of eleven minor criteria, including one laboratory abnormality, while excluding other conditions like infections, malignancies, and autoimmune disorders that could mimic iMCD.[5,7]

Treatment for MCD is guided based on the presence of active or fulminant disease, organ failure, and HHV-8 status.[7] For iMCD in particular, chemoimmunotherapy and siltuximab are treatment possibilities, with siltuximab being the sole drug to have received FDA approval in this patient population.[7,10]

SILTUXIMAB: MECHANISM OF ACTION AND CLINICAL DATA

SILTUXIMAB

is a chimeric monoclonal antibody that targets interleukin 6 (IL-6), preventing it from attaching to both soluble and membrane-bound IL-6 receptors.[10]

SILTUXIMAB CLINICAL TRIAL DATA IN MCD

FDA approval of siltuximab stemmed from a randomized, double-blind, phase 2 clinical trial (NCT01400503) that demonstrated its efficacy in HIV-negative and HHV-8 negative symptomatic multicentric Castleman disease (MCD).[11] The study compared siltuximab plus best supportive care (BSC) to placebo plus BSC. Durable tumor and symptomatic responses were observed in 34% of

Siltuximab: Mechanism of Action and Clinical Data - continued

the siltuximab group, compared to none in the placebo group. Further analysis revealed improved progression-free survival (PFS) with siltuximab; the median PFS was not reached in the siltuximab arm, while the placebo group had a median PFS of 14.5 months.[12] Siltuximab demonstrated good tolerability, with comparable rates of grade 3 or higher and serious adverse events to placebo.

The most common grade 3 or higher adverse events were fatigue, night sweats, and anemia.[11] The study concluded that siltuximab provides rapid symptom improvement and meaningful clinical benefits, although normalization of some laboratory values and lymph node size may take several months in responding patients.[12]

SILTUXIMAB INDICATIONS:

In April 2014, the FDA granted approval for siltuximab in the treatment of MCD patients who are negative for both HIV and HHV-8.[10] Based on the supporting data, the NCCN® guidelines recommend siltuximab as the preferred first-line treatment for this iMCD patient group.[7]

SILTUXIMAB PATIENT PROFILE:
HEALTHCARE PROVIDER INSIGHTS

A multidisciplinary panel of physicians, pharmacists, nurses, and pharmacy technicians from the University of Michigan Health-Sparrow Herbert-Herman Cancer Center, Texas Oncology, and UNC Health shared their insights on the challenges of diagnosing and managing treatment expectations in patients. UNC's Samuel Rubinstein, MD, MSCI initiated the discussion by pointing out that while CD "obviously is not cancer, its initial presentation often resembles cancer, leading hematologists/oncologists to frequently manage these patients." He continued, "The greatest challenge is diagnosis, which usually occurs before the patient even sees me. For a general internist, having clinical suspicion for CD is difficult due to the non-specific presenting symptoms. I am sure I would struggle to recognize rare CD cases among all the conditions that mimic it." Dr. Rubinstein further stressed, "Currently, diagnosis relies heavily on collaboration between experienced pathologists and clinicians, a resource not universally available. Most patients are not seen at academic centers specializing in rare diseases."

Gordan Srkalovic, MD, PhD, FACP a medical director at the University of Michigan Health-Sparrow Herbert-Herman Cancer Center, understands the challenges of diagnosing CD. He remarks, "Diagnosis is challenging and sometimes is a diagnosis of exclusion. However, we now have diagnostic criteria, which is a significant advancement. It is crucial to educate and raise awareness not only among oncologists but also rheumatologists and primary care physicians, as this will ultimately help more patients receive the correct diagnosis."

Dr. Rubinstein notes that siltuximab "generally has a high success rate, and patients often notice improvement after just one or two doses." When initiating siltuximab treatment, Dr. Srkalovic

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Siltuximab Patient Profile: Healthcare Provider Insights - continued

ensures that patients understand the expected course over the initial 1-3 months: first, symptom control, followed by potential control or shrinkage of lymph nodes. He explains, "The major question is whether we can stop treatment for patients who respond. Can we reduce the dose or extend the interval between treatments? Logically, reducing treatment intensity might be less effective. It's crucial to evaluate each case individually to understand why a patient or doctor might want to alter the protocol. For instance, if a patient lives 50 miles from the treatment center and their quality of life (QOL) is affected, protocol adjustments could be considered to improve QOL. Additionally, if financial toxicity is an issue, we may need to collaborate with the manufacturer to address it, ensuring the patient doesn't have to switch to a less effective treatment. My aim is to maintain treatment intensity for as long as possible to prolong the patient's response, but adjustments can be made if QOL is significantly impacted."

ELEVATING PATIENT CARE THROUGH MEDICALLY INTEGRATED PHARMACY (MIP)

ONCE a treatment regimen is decided upon, the multidisciplinary team springs into action to ensure optimized patient care. The presence of medically integrated pharmacy (MIP) services, which handle the processing and dispensing of IV and oral anti-cancer therapies in infusion centers or oncology clinic pharmacies, has enhanced medication management, streamlined patient care, and improved continuity of care.

Dr. Rubinstein emphasizes the collaborative nature of this approach, stating, "it's obviously a team sport," and noting that his team includes an advanced practice provider (APP), a clinical pharmacist, and infusion center nurses. At the University of Michigan-Sparrow, a similar team structure exists. Pharmacist Kevin Glaza, RPh describes the advantages of the medically integrated team at his institution, stating, "Pharmacists have a unique role and are definitely part of a large team. We have excellent communication and work together face-to-face, which is ideal for addressing any questions. Our team meets weekly for 15-30 minutes to discuss patient-related issues, ensuring we're all aligned."

Glaza highlights the benefit to patients, noting, "We can speak directly with patients and address their concerns if the infusion nurse is unable to do so. In our experience, seeing an additional face really puts patients at ease." Beyond these benefits, Glaza points out the operational advantages pharmacists provide, such as checking labs, verifying doses, and monitoring for drug-drug interactions to ensure accuracy and appropriateness. He adds, "We catch many things. Working together, we are definitely improving patient safety and outcomes. It's crucial to have a multidisciplinary team on board."

When asked about the advantages of the multidisciplinary team, Taylor Herlein, BSN, RN, OCN, a nurse at the University of Michigan-Sparrow, highlights, "As a nurse, my training is holistic, focusing on the patient as a whole. This approach benefits patients by providing them with an advocate who can be the eyes and ears at the bedside. It also benefits physicians, as they can't always be present, making it crucial for the nurse to act as a liaison."

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>
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Regarding pharmacists, Herlein states, "As a nurse, I rely on pharmacists for drug-related inquiries, such as whether a filter is needed or the duration of infusion for medications. My pharmacist colleagues are medication experts, serving as a resource to help me provide safe and high-quality patient care."

SILTUXIMAB
ADMIXTURE PROCESS:

SILTUXIMAB'S admixture process, as noted by Glaza, is more time-consuming than most drugs. It begins by removing the medication from refrigeration and allowing it to reach room temperature. Reflecting on the University of Michigan-Sparrow's participation in the siltuximab Phase 2 clinical trial, Glaza recalls initial frustration from patients and nurses unaware of these preparation details. He proactively addressed this by informing infusion nurses about the 30-minute room temperature warming period and the subsequent 60-minute gentle swirling required for full dissolution. Glaza advises informing patients about this additional time and factoring it into scheduling. He estimates the total process, from admixture to administration, takes approximately three hours.

Jessica Moore, PharmD, a pharmacist at Texas Oncology, emphasizes siltuximab's incompatibility with normal saline, necessitating its mixture with D5W and utilization of a 0.02 micron in-line filter. To optimize efficiency, Moore explains, "Given the lengthy admixture process, we aim to complete lab work the day before treatment, minimizing the patient's time in the clinic on infusion day." Pharmacy technician Lipsi Melendez, Sr.CPhT, underscores the importance of securing siltuximab in advance due to the disease's rarity.

NCODA'S
PQI RESOURCE

THE PQI resource offers clinician-focused guidance and criteria that can benefit the entire team. Key sections demonstrate how medically integrated pharmacists assist physicians and clinical staff by providing their medical and administrative expertise. The Siltuximab in Patients with Idiopathic Multicentric Castleman Disease PQI includes information on clinical trials, side effects, monitoring, and patient-centered educational insights.

Regarding this PQI, Dr. Srkalovic remarks, "I find this useful because it's concise and helpful. This type of information is always beneficial, especially for nurses working with patients, and the first page provides a walkthrough of the drug and potential side effects." Heirlein adds, "It's valuable, particularly when administering a new drug, as it provides all the necessary information." Moore acknowledges that she had been creating similar documents to PQIs before discovering them but now plans to use the NCODA sheets to save a significant amount of time.

MONITORING PATIENTS AND ADVERSE
EVENT MANAGEMENT

IN each practice, pharmacists conduct a thorough review to ensure that treatment regimens align with labeled indications, national guidelines, and internal pathways, and that dosing is appropriate based on lab results and other patient or disease-related factors. Moore also notes that initially, she and her pharmacy team verify that patients test negative for both HIV and HHV-8 to comply with prescribing information.

Dr. Srkalovic emphasizes, "By far, the most crucial aspect of managing Castleman disease is clinical assessment. Regular clinical evaluations are necessary to monitor for both improvement and relapse, though relapse is less frequent." For his patients receiving siltuximab, he ensures a comprehensive metabolic panel (CMP), inflammatory markers, and a complete blood count (CBC) are ordered and completed with each dose to monitor safety and disease progression.

Monitoring Patients and Adverse Event Management - continued

He adds, "Imaging is also important, as patients often present with enlarged lymph nodes visible on scans. However, imaging improvements typically lag behind clinical improvement. Patients may feel better and show improved lab results while imaging appears unchanged or even slightly worse. Waiting to repeat imaging may eventually reveal lymph node shrinkage long after the patient's condition improves. While imaging is essential, it's not definitive and should likely be performed later than initially anticipated."

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-Gordan Srkalovic MD, PhD, FACP

PATIENT-CENTERED ACTIVITIES

- Educate patients on siltuximab therapy and recommend appropriate interventions.
  - Counsel on most common side effects: skin disorders (rash, pruritis), respiratory tract infection, edema, weight gain, hyperuricemia, fatigue, diarrhea.
  - Avoid live vaccinations.
  - Report signs of infection (fever, chills, cough, or sore throat) to your care team immediately.
  - Increased risk of fetal harm; discuss risk/benefits. Patients who could become pregnant should use effective contraception during treatment and for 3 months after the last dose of siltuximab.
- Patient Assistance: NCODA Financial Assistance Tool, Recordati Patient Liaison.

EDUCATION ENHANCES PATIENTS' UNDERSTANDING OF SILTUXIMAB

EDUCATION is imperative when patients are starting treatment with siltuximab.

At UNC Health, Dr. Rubinstein begins by discussing the risks and benefits of siltuximab with his patients, followed by a high-level overview of the treatment. Pharmacists then provide detailed counseling on the specifics of the therapy and symptom management strategies. Dr. Rubinstein points out that patients spend the most time with infusion center nurses, and highlights the crucial role of nurse navigators, who assist patients with insurance, payment, appointment coordination, and obtaining outside archival tissue if needed.

Dr. Srkalovic stresses to the local referring oncologist the importance of informing both patients and physicians that siltuximab requires "long-term treatment" and does not "provide an immediate response." He further highlights that "Siltuximab is a treatment that does not really treat the disease itself because we don't know where the disease is ultimately coming from. We know what is driving the disease and this treatment is used to block the

Education Enhances Patients' Understanding of Siltuximab - continued

PQI PROCESS

DOSING:

01 **FDA approved: 11 mg/kg IV over 1 hour every 3 weeks until treatment failure**

02 **Off-label (severe disease in critically ill patients): 11 mg/kg IV once weekly x 4 then every 3 weeks until treatment failure**

03 **Dosing Considerations**

Prior to First Infusion	Absolute neutrophil count ≥1000 cells/mL Platelet count ≥75 cells/mL and 50 cells/mL for retreatment Hemoglobin ≤17 g/dL Severe impairment (Child-Turcotte-Pugh class C): No dosage adjustments provided in the manufacturer's labeling (has not been studied)
Initial Disease Control	Adjunctive corticosteroids may be also administered for 4 to 8 weeks, followed by a corticosteroid taper; patients who are more symptomatic may require higher initial dose corticosteroids and a more gradual taper
Altered Kidney Function	CrCl < 15 mL/min/End stage renal disease: No dosage adjustments provided in the manufacturer's labeling (has not been studied)
Cytokine Release Syndrome	Permanently discontinue
Hematologic Toxicity	Consider delaying treatment until ANC ≥1,000 cells/mL, platelets ≥50,000 cells/mL, and hemoglobin <17 g/dL
Severe Infection	Withhold siltuximab until infection resolves
Infusion Related Reactions	Immediately interrupt infusion for reaction of any severity and manage symptoms as clinically appropriate • Grade 1 or 2 (mild to moderate) infusion reactions: Once symptoms resolve, resume infusion at a lower infusion rate; consider antihistamines, acetaminophen, and corticosteroids; if patient does not tolerate infusion following intervention, permanently discontinue • Grade 3 (severe) or Grade 4 (anaphylactic reaction or life-threatening) infusion reactions: Permanently discontinue

Education Enhances Patients' Understanding of Siltuximab - continued

MONITORING

01	Complete blood count (CBC) with differential should be reviewed prior to each dose for the first 12 months and every 3 dosing cycles thereafter

WARNINGS AND PRECAUTIONS

01	Do not administer with concurrent active severe infections; hold until resolution
02	Avoid administration of live vaccinations to patients or infants born to patients receiving siltuximab
03	Increased risk of gastrointestinal perforation; promptly evaluate at first signs/symptoms

ADMIXTURE

01	Available in 100 mg and 400 mg single dose vials
02	Prepare using a 21-gauge, 1.5" needle; infusion bag 250 mL D5W, polyvinyl chloride (PVC), polyurethane (PU), or polyethylene (PE) set which contains a 0.2-micron inline polyethersulfone (PES) filter
03	Note: only stable with D5W
04	Allow vial to come to room temperature (approximately 30 min), reconstitute using sterile water for injection (SWFI), and gently swirl (do not shake)(approximately 60 min to fully dissolve)
05	100 mg vial – 5.2 mL SWFI (reconstituted concentration 20 mg/mL)
06	400 mg vial – 20 mL SWFI (reconstituted concentration 20 mg/mL)
07	Inject calculated volume for final concentration into 250 mL D5W and invert bag gently

Education Enhances Patients' Understanding of Siltuximab - continued

ADMINISTRATION

01 **Administer over one hour using a polyurethane (PU), or polyethylene (PE) set which contains a 0.2-micron inline polyethersulfone (PES) filter(PU), or polyethylene (PE) set which contains a 0.2-micron inline polyethersulfone (PES) filter**

02 **Do not infuse in the same line as other medications**

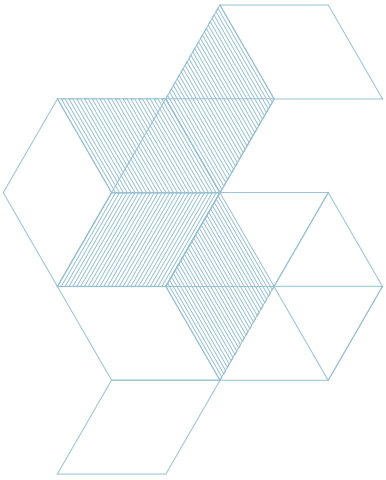
03 **Complete the infusion within 4 hours of dilution of the reconstituted solution to the infusion container**

04 **Administer in a setting to provide resuscitation equipment in case of an infusion related reaction; bronchodilators, antihistamines, and corticosteroids should be readily available**

driver of disease." Of the patients he has treated, Dr. Srkalovic emphasizes that in terms of side effects, "typically, it will be some type of infusion reaction. Most of the cases are mild and can be controlled with standard hypersensitivity reaction treatment. Other than that, patients tolerate siltuximab really well." He mentions that he had two patients who experienced mild reactions, which were treated with antihistamines and steroids and subsequently resolved. Following this, he contacted the local oncologist, and no further hypersensitivity reactions occurred. When educating patients, Dr. Srkalovic often covers the basics of Castleman disease, as most patients—and even some physicians—are not familiar with it. He finds the Castleman Disease Collaborative Network's (CDCN) educational resources very helpful and his practice distributes a packet from them to patients. Srkalovic notes, "When discussing treatment, we talk about expectations, particularly regarding the likelihood of success, because it's clear that the treatment doesn't work for everyone, so expectations need to be managed. It's also important to communicate that there is a good chance symptoms won't be controlled but can be reduced." He concludes with "Our goal is to transform this disease into a chronic condition without it impacting the patient's lifestyle or quality of life. We don't want it to reduce life expectancy, and that is what we want to achieve."

At UNC Health, Dr. Rubinstein explains that patient education is a collaborative effort between him and the pharmacist. His main responsibility is to inform patients about the risks associated with siltuximab and to explain why, in his opinion, the benefits outweigh these risks before treatment begins stating "Typically, patients with Castleman disease are quite unwell when they consult with us, making them eager for relief and improvement in their condition, as well as to avoid hospitalizations. As a result, convincing them of the treatment's value is not such a tough sell."

From a nursing perspective, Herlein highlights that while physicians discuss major side effects when recommending treatment, nurses are responsible for obtaining informed consent and providing detailed patient education. Utilizing resources from the Oncology Nursing Society, nurses offer one-on-one sessions to discuss side effects, answer questions, and provide information packets and videos on chemotherapy safety. Additionally, Herlein sees value in having nurse educators from pharmaceutical companies provide team overviews, especially for rare diseases.



SUMMARY

CASTLEMAN disease is rare and often resembles other conditions, making diagnosis challenging. The cause of iMCD remains unclear, but IL-6 is identified as a key driver of the disease process, contributing to symptoms and potentially influencing treatment choices, such as the use of siltuximab, a monoclonal antibody targeting IL-6. Siltuximab is currently the only FDA-approved treatment for iMCD.

Clinicians from diverse practices shared their insights on diagnosing, treating, and managing expectations for patients with iMCD. The panel members agreed that a medically integrated team provides several benefits, including improved medication management, enhanced communication, and increased patient safety.

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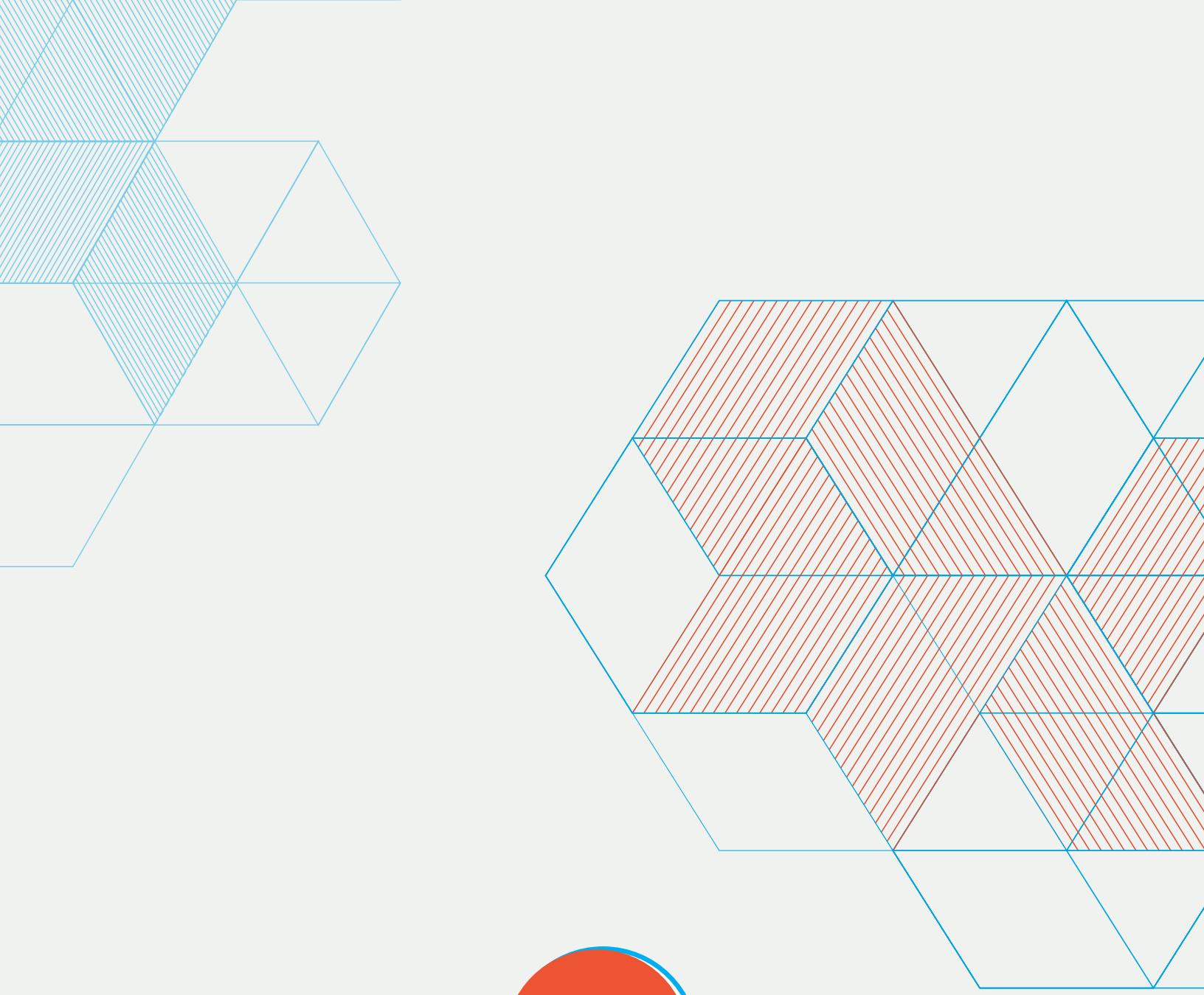

Practice panelist's comments reflect their experiences and opinions and should not be used as a substitute for medical judgment.