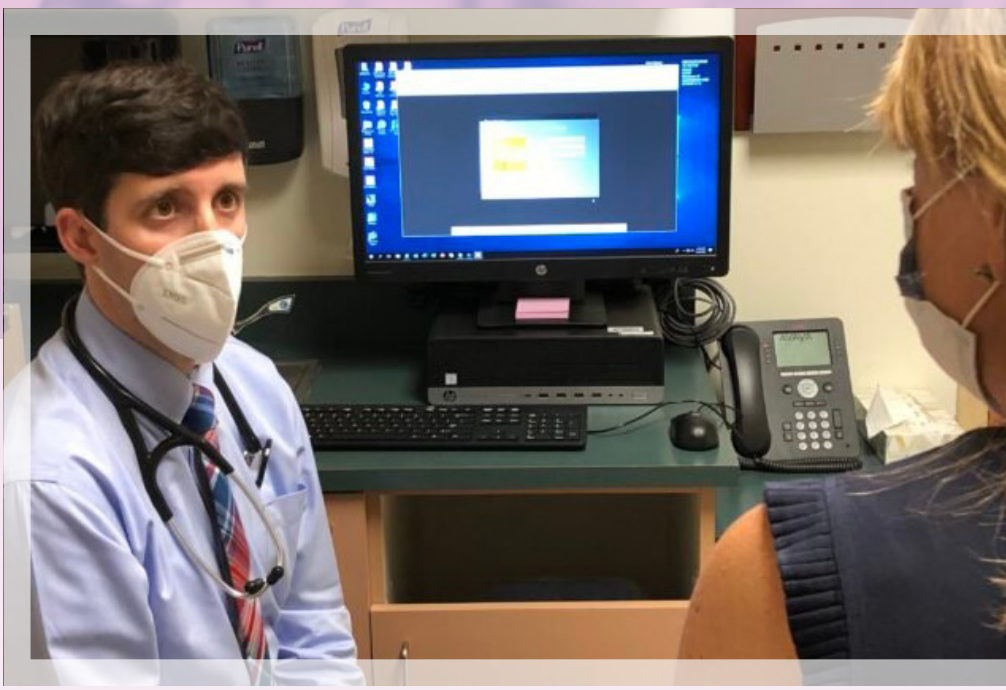
PQI IN ACTION



NERATINIB (NERLYNX®) DIARRHEA MANAGEMENT

NCODA'S POSITIVE QUALITY INTERVENTION IN ACTION

INTRODUCTION

To promote higher quality patient care, NCODA created the Positive Quality Intervention (PQI) as a peer-reviewed clinical guidance document for healthcare providers. By providing Quality Standards and effective practices around a specific aspect of cancer care, each PQI equips the entire multidisciplinary care team with a sophisticated yet concise resource for managing patients receiving oral or IV oncolytics. This PQI discusses the prevention/treatment of diarrhea, a major side effect of neratinib. The article, which expands on the **Neratinib (NERLYNX®) Diarrhea Management** PQI, explores how the medically integrated teams at Cancer Care Associates of York and Rocky Mountain Cancer Centers incorporate PQIs as part of their daily workflow and how the **Neratinib (NERLYNX®) Diarrhea Management** PQI elevates patient care.

Rocky Mountain Cancer Centers (RMCC) is Colorado's largest provider of cancer care with 56 physicians in 17 community-based locations statewide. A physician-led and -owned practice, RMCC offers a coordinated, strategic approach to cancer care dedicated to optimal patient outcomes and survivorship through evidence. A member of the U.S. Oncology Network, the RMCC has received the Highest Accruing Site Award, having more than 1,900 patients in major clinical trials and had played a role in more than 100 FDA-approved cancer therapies.

Cancer Care Associates of York (CCAY), Pennsylvania, is a private community practice that has served the historic York region for more than 40 years. Eight physicians, four advanced practitioners and a support staff deliver personalized care for local oncology and hematology patients. The multidisciplinary practice, located in the Apple Hill Medical Center, is dedicated to a compassionate team approach and coordinated care with specialists. Patients undergo treatment in a spacious 18,000-square-foot clinic with 33 chemo infusion chairs.

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MID, THE PQI, AND NERATINIB: A NEW OPTION FOR TREATING HER2-POSITIVE BREAST CANCER

The FDA approved a robust 53 novel therapeutics in 2020. This is the second highest total ever, falling just short of 2018's all-time high of 59. Oncology products dominated the approval list, with the FDA approving a record 18 (34%) cancer drugs.[1] Among them: Neratinib, approved in combination with capecitabine for adult patients with advanced HER2-positive breast cancer.[2]

Three years earlier, the FDA approved neratinib for extended adjuvant treatment of adult patients with early stage HER2-positive breast cancer pretreated with trastuzumab.[3] For oncologists, the approvals spotlit the targeted therapy drug as a contender among breast cancer therapies. Studies show that patients pretreated with trastuzumab and capecitabine who then receive neratinib have significant, better-progression free survival and overall survival outcomes that trastuzumab and capecitabine alone.[4,5,6]

Understandably, this targeted cancer drug has emerged as a viable option for the world's most commonly occurring cancer. Breast cancer now accounts for one of every eight cancers in 2022.[7] Up to 20% of breast cancers are HER2-positive (the cancer overexpresses human epidermal growth factor receptor 2) and up to half of patients with metastatic HER2–positive disease may develop brain metastases.[8,9]

Here is where symptom-management discussion comes into critical play. The diarrhea issue near-overshadowed the new therapy's potential when it debuted on the market five years ago. "Women were kind of scared to use it," said Evan Slater, PharmD, pharmacy director of Rocky Mountain Cancer Centers. Explaining the pros and cons "was a pretty delicate balancing act."

The results of the original ExteNET trial showed the majority of patients (95%) experienced diarrhea in the first month of treatment. Median time to onset of any grade diarrhea was 2 days (8 days for Grade 3) and median cumulative duration of diarrhea was 59 days (5 days for Grade 3). According to manufacturer, Puma Biotechnology, Inc., the cause of diarrhea is unknown, but may be triggered by epidermal growth factor reception inhibition. Preclinical models suggest the etiology of neratinib-related diarrhea includes elements of secretory and inflammatory diarrhea and bile acid malabsorption.

The Phase 2 CONTROL trial eased concerns, addressing preventive strategies to reduce the incidence, duration and severity of diarrhea as well as reduced neratinib discontinuation compared to the pivotal ExteNET trial. Dose escalation and various anti-diarrheal combinations emerged as the key approaches.[10,11] Mature data is available for budesonide and colestipol; interim data is available for titration in the Phase 2 CONTROL trial.[11]

According to neratinib prescribing information, antidiarrheal prophylaxis with loperamide should be initiated with the first dose of neratinib and continued during the first two treatment cycles (56 days); and as needed thereafter, titrated to one to two bowel movements per day. The neratinib full prescribing information was updated to include dose escalation in June 2021.

Neratinib can be dispensed by the Medically Integrated Team, and thus offers patients more comprehensive care. NCODA defines Medically Integrated Dispensing (MID) as a dispensing pharmacy within an oncology center of excellence that promotes a patient-centered, multidisciplinary team approach. The MID is an outcome-based collaborative and comprehensive model that involves oncology healthcare professionals and other stakeholders who focus on the continuity of coordinated, quality care and therapies for cancer patients.[5] The MID model can improve management of patients on therapies like neratinib in several ways including enhanced communications, measuring adherence, managing regimen changes, quicker therapy initiation, improved patient satisfaction, financial assistance, cost avoidance and producing less waste.

NCODA offers multiple tools to aid the MID practice in managing oncolytics. This toolbox contains a patient survey, Financial Assistance Database, Treatment Support Kits, Oral Chemotherapy Education sheets, and PQI clinical resource documents. "They are all helpful," said Dr. Ma, of Rocky Mountain Cancer Centers. "The diarrhea management is the most practical part."

THE POSITIVE QUALITY INTERVENTION

The PQI **Neratinib (NERLYNX®) Diarrhea Management** provides updated standard protocols, dosages and therapy regimens, "keeping the provider and support team are all on the same page," said Chanh Huynh, MD, of Cancer Care Associates of York.

"There are new drugs in the market all the time. So, it's hard to keep up," said Dr. Huynh, whose practice sees a high volume of breast cancer patients. "To have quick resources and to know how to intervene with evidence-based medicine is the best thing." Which adds to the complexity when diarrhea management enters the equation, adding the threat of painful cramping, loose stools and anxiety to diminish the quality of life. When it comes to side effects, "diarrhea is the big one," Dr. Ma said. "It's good for pharmacists, for physicians – and also for patients and nurses, maybe even financial counselors – to understand the full picture."

"TO HAVE QUICK RESOURCES AND TO KNOW HOW TO INTERVENE WITH EVIDENCE-BASED MEDICINE IS THE BEST THING."

Chan Huynh, MD

The PQI Process lays out the intervention step by step, with clinician-directed guidance and criteria that can benefit the whole team. The first step is to identify eligible HER2-positive patients as potential candidates for neratinib, discuss side effects, then share approaches to the prevention and management of diarrhea. As stated earlier, strategies include drug escalation and variations of anti-diarrheal combinations outlined by the Phase 2 CONTROL Trial.

According to manufacturer Puma, the recommended dose of neratinib is 240 mg, taken orally as a single dose of six 40 mg tablets, continuously for one year. The dose escalation procedure: The patient takes 3 of the 40 mg tablets (for a total of 120 mg) daily for seven days. Titration helps the patient's system adjust to the drug. Prophylaxis begins with the first dose of neratinib and continues for two cycles depending on the regimen and the patient's response.

The dosage escalates to four tablets daily (160mg daily) for Week 2, then to six tablets daily (240 mg) for Week 3. Patients are advised to hydrate, and phone the office if diarrhea persists despite medications. Other reportable side effects include nausea (43%), abdominal pain (36%) and stomatitis (14%).

The PQI outlines dosage adjustments for moderate to severe treatment-emergent diarrhea, when to maximize use of anti-diarrheal agents, and to assess diet and aggravating substances. Referenced medications include loperamide, colestipol and budesonide.

The proactive, at-a-glance guidelines appeal to Dr. Ma. The oncologist, whose RMCC practice is comprised of nearly 70% of breast cancer patients, frequently utilizes neratinib with trastuzumab-based therapy. "Then we give another year of neratinib to further decrease the chances of recurrence and also to improve survival," she said.

PQI PROCESS: UPON RECEIPT OF NERATINIB PRESCRIPTION

- Consider dose escalation based on data from CONTROL trial (see supplemental information for dosing)
- Diarrhea Prophylaxis - Diarrhea occurs in 95% of the patients without prophylaxis protocol
  - Begin prophylaxis with the first dose or neratinib and continue for 2 cycles depending on the regimen selected and the patient response
  - Ensure patient has instructions and supply of loperamide and consider colestipol or budesonide (see Supplemental Information for dosing)
  - The clinician should exercise his/her best professional judgment in making recommendations for interventions for individual patients
  - Identify drug-drug interactions and side effect profiles of loperamide, colestipol, and budesonide when making clinical recommendations
  - Consider weekly assessment of diarrhea throughout the first 2 cycles
  - Drug-Drug Interactions
- Avoid concomitant use of PPIs
  - If H2-antagonists must be used, administer neratinib 2 hours before or 10 hours after
  - Other antacids (Tums, Maalox) should be separated by at least 3 hours
- Verify in EMR that patient is scheduled for CMP to assess liver function
  - Consider monthly CMP for the first 3 months then every 3 months as clinically indicated

PUTTING THE NERATINIB (NERLYNX®) DIARRHEA MANAGEMENT PQI INTO ACTION

This PQI is a peer-reviewed clinical guidance document that provides quality standards and effective practices around a specific aspect of cancer care. The Medically Integrated Pharmacy team is in a unique position to ensure appropriate treatment, increase compliance and maximize clinical outcomes. Each Positive Quality Intervention (PQI), an NCODA Quality Standard, is designed to operationalize and standardize these practices to achieve positive clinical outcomes. The **Neratinib (NERLYNX®) Diarrhea Management PQI** is written in sections beginning with a description and ending with patient-centered activities and references.

Following the description, the background section gives pertinent historical date and information, clinical trial experience and the main focus of the intervention. Regarding neratinib, the background discusses the approval, indication and published data leading to approval. It also focuses on management of diarrhea, the drug's most common side effect.

Ongoing communication about preventive protocols is essential. "If you prescribe a medication, you want your patients to get the benefits, but if they get side effects that decrease their quality of life, there's a chance of them not being complaint with the medication" said Dr. Ma. "Dose escalation – which I've been using in my practice – helps a lot … I think we've had a lot of patients able to stay on the drug longer – especially on the one-year adjuvant therapy – and able to tolerate it better." Clinicians agree that frank, ongoing conversations—regarding pre-emptive measures from titration to anti-diarrheal agents – are essential to good outcomes for patents on neratinib.

Melissa Shimanek, PharmD, oversees medically integrated dispensing (MID) of oral drugs at more than a dozen RMCC clinics. Patient consults serve as "deep dives," opportunities to explain drug regimens, interactions and diarrhea management. The PQI information and resources "are huge in terms of really getting patients to stay on treatment," she said. "And our doctors really are utilizing that dose escalation now."

PATIENT-CENTERED ACTIVITIES: KEEPING THE FOCUS ON PATIENTS

Pharmacist Evan Slater notes that neratinib's toxicities offset its potential when the drug debuted on the market five years ago. "Women were kind of scared to use it," said Slater, PharmD, of Rocky Mountain Cancer Centers. Explaining pros and cons "was a pretty delicate balancing act."

NCODA's Treatment Support Kits (TSKs), encourage patients and caregivers to continue "deep dives" with hands-on, one-stop resources. An effective option for practices where unbranded materials and products is welcome, TSKs features staff-approved educational and practical materials for patient use. These materials include both education and over-the-counter (OTC) products.

CLICK HERE TO ORDER TSKs

THE NERATINIB TSK IS A GO-TO THAT INCLUDES INFORMATION ABOUT THE DRUG "WHICH IS VERY HELPFUL FOR PATIENTS AND HELPFUL TO US – AND HOW TO HELP WITH SIDE EFFECTS."

Valerie Stites, RN

The Neratinib (Nerlynx®) Treatment Support Kit (TSK) outlines how dosage titration and diarrhea prophylaxis can help prevent and ease side effects. Contents include:

- Treatment booklet with OCE sheet
- Customizable treatment calendar
- Voucher for anti-diarrheal medication
- Neratinib PQI for healthcare professionals

The key to diarrhea management is to repeat – often – the benefits of an escalated dose and preventive medicines, RMCC and CCAY clinicians agree. Encouragement elevates compliance. While they emphasize pre-emptive measures in clinics, virtual visits and phone calls, the take-home kits are 24/7 resources. "The more they have on hand to grab when they need, the better," Shimanek said. There is a lot of information to absorb, said Valerie Stites, RN, Oral Oncology Nurse Navigator of Cancer Care Associates of York. That's why the one-stop source neratinib TSK "is great," she said.

Consider the patient's plight. First, the physician briefs them about neratinib. Nurses, physician assistants and other staff members follow up, discussing the mechanism of action, potential bowel irregularities and anti-diarrheal measures. Each session – which includes dosages, side effects, hydration and financial assistance – lasts 40 minutes to an hour. It's a lot to process and remember.

The neratinib TSK is a go-to that includes information about the drug "which is very helpful for patients and helpful to us – and how to help with side effects," Stites said. "The materials are easy reads. It's an easy kit to work with." Patients gravitate in particular to OCE sheets, handouts, and the voucher for anti-diarrheal medications. "They love them," the nurse navigator said.

MEDICALLY INTEGRATED DISPENSING: A TEAM APPROACH

Both RMCC and CCAY clinicians place a heavy emphasis on teamwork and patient education. The term "we" is deployed often. A collaborative approach is critical, "from the beginning, when the patient enters our door," said Dr. Ma of Rocky Mountain Cancer Centers. "We start the conversation. What is our long-term and short-term goal? How long is the treatment going to be?"

For colleague Julie Messina, PA-C, her role spans "the whole spectrum" of patient care. "We manage pain, we do palliative care," she said. The team effort enables her to intervene when she recognizes, for instance, when a patient is suffering from treatment-related stress. Her one-on-one chats with the patient can segue into referrals to clinical social workers, psychosocial counseling, support groups and community resources.

The patient-centric climate is equally passionate at CCAY. Dispensary manager Christina Patterson, PA-C, serves as a front-line line educator, communicator and patient liaison. Besides dispensing, Patterson tracks patients' progress, evaluates electrolyte levels and labs, and relays key findings to clinicians. Patients reluctant to share bowel issues at appointments are often more comfortable confiding in Patterson and pharmacy techs, who share the information with clinicians.

Patterson, who regards neratinib as a high-risk drug that requires compassionate, ongoing support, also serves as patient advocate and cheerleader. When patients question the side effects – and the necessity of a year-long regimen – she reminds them that the extended adjuvant therapy decreases the risk of recurrence. "We definitely have been able to keep patients on (neratinib)," she said. "Maybe not to 240 days (straight), but we are able to keep them on therapy at least a majority of the year."

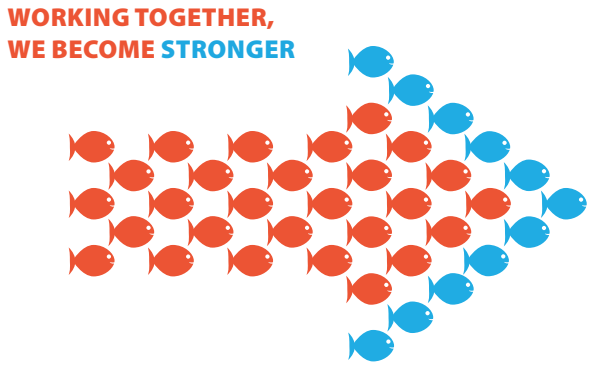
CONCLUSION: ALWAYS COLLABORATIVE: NCODA, THE MID, AND PQI

Patients on neratinib "are so invested in their treatment, in their recovery and their health," Slater said. Dr. Ma, of RMCC, is hopeful that neratinib adjuvant treatments will advance, eventually decreasing cancer recurrence rates by up to 50 percent, especially for pretreated patients who can opt for surgery for residual cancer. Whether the goal is short-term (palliative care) or long-term (survivorship), discussions about symptom management are essential to well-being. "It's a big topic, from the moment the patient enters our door," she said. She believes the dialogues should continue, even after the treatment concludes.

Some breast cancer survivors get nervous – the fear of relapse is common -- when office visits become less frequent. Some, though healthy, feel lost without their support team. The RMCC MID helps fill this void, checking in with patients during prescription refills and alerting the oncologist about issues. "It's very helpful," Ma said. "I feel like it's a tighter team, doing a much better job to take care of the patients in the long run," she said. And ultimately, a long, cancer-free, symptom-free run is the goal. "You know, we may not always cure patients, but we do our best," Messina said. "We can always be kind and we can always be there for them and help them navigate through their procedures and do our best for survivorship. We're really hoping to give them meaningful survivorship."

Neratinib, still a young drug, remains a subject of studies that support improved invasive disease-free survival for breast cancer patients treated with the drug. These include: a Phase III ExteNET trial,[12] a five-year analysis of these patients,[13] and a 2021 review of real-world cases where participants chose to stay on therapy after dosage titration and prophylaxis relieved their side effects.[14]

All team members agree the MID model, PQI, TSK and OCE sheets are valuable tools for medical teams as well as patients. The most-reviewed protocols: the guidelines for dose escalation and anti-diarrheal protocols. The PQI for neratinib fosters ongoing communication, education, and involvement to help clinical teams help patients manage side effects, improve compliance, and be self-advocates in their care. Self-empowerment is integral to the collaborative process, especially when symptom management can be a daily challenge.



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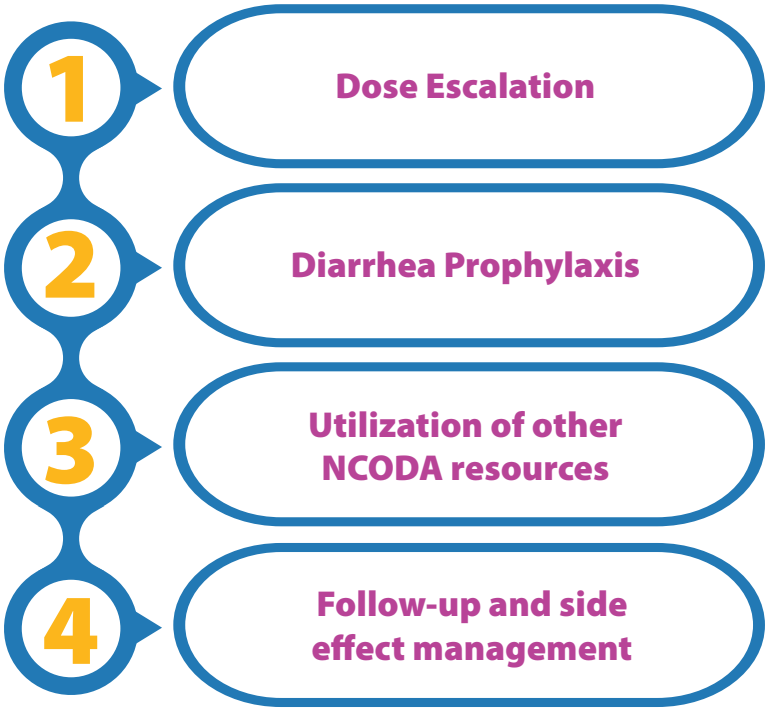
PQI PRINCIPLES:



Helpful Online Resources

- Neratinib (NERLYNX®) Diarrhea Management PQI
- NCODA Website
- Positive Quality Interventions
- Oral Chemotherapy Education Sheets
- Order TSKs

ON THE COVER:

- Patrick Eulitt, MD, of Rocky Mountain Cancer Centers, counseling a patient prior to the start of therapy.

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Each Kit Contains:

1. Treatment Booklet
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3. Product Education Resource
4. Supportive Care Voucher
5. Positive Quality Intervention (PQI) Resource
6. Patient Survey

For More Information Visit: **www.ncoda.org/treatment-support-kits**

NOTES:

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

Important notice: NCODA has developed this Positive Quality Intervention in Action platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatsoever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional.

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