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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Navigating mCRC: A Closer Look at Biomarker Testing

Announcer:
Welcome to ReachMD. You're listening to *Project Oncology* on ReachMD, and this medical industry feature titled "Navigating mCRC: A Closer Look at Biomarker Testing" is sponsored by Pfizer Oncology Medical Affairs.

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Here's your host, Dr. Charles Turck.

Dr. Turck:
According to a recent report from the American Cancer Society, colorectal cancer is one of the leading causes of cancer-related deaths. And this life-threatening disease is likely to take even more lives this year.[1] Could biomarker testing not only play a role in managing this disease but also in saving the lives of our patients?

This is ReachMD and I'm Dr. Charles Turck. Joining me to explore the role of biomarker testing in metastatic colorectal cancer, or mCRC for short, is Dr. Kristen Ciombor, Associate Professor of Medicine at Vanderbilt-Ingram Cancer Center in Nashville, Tennessee. Dr. Ciombor, welcome to the program.

Dr. Ciombor:
Happy to be here.

Dr. Turck:
Before we dive into treatment, Dr. Ciombor, what should be keep top of mind when discussing mCRC?

Dr. Ciombor:
Despite the improvements we've made in early detection and treatment, survival rates for mCRC are still poor. The five-year survival rate for mCRC is only 14 percent.[1] Additionally, we are seeing a significant increase in patients younger than 50 years old being diagnosed with colorectal cancer, some of whom already have metastatic disease at diagnosis, or who may recur after treatment.[1]

Now that we can perform biomarker testing on tumors, we can identify the genomic subtypes of mCRC that are prognostic, some of which can lead to poorer outcomes. And this type of testing has led to the discovery of newly approved biomarker-driven therapies which can help us personalize treatment based on the unique genomic characteristics of each patient's cancer.[2,3] So, in order to potentially improve survival rates for patients, we need to use this type of testing to help guide our treatment decisions.[2,3] Unfortunately, while we have these tools available, biomarker testing rates continue to fall behind guideline recommendations, so the implementation of test results doesn't always follow.[3,4]

If we have the potential to offer more personalized treatment options to these patients, then I believe we need to improve rates of biomarker testing and implementation of biomarker testing to become a routine part of clinical practice.

Dr. Turck:
Now with all of that in mind, can you tell us more about the burden of mCRC in the United States?

Dr. Ciombor:
Sure. Colorectal cancer is actually more common than we think and can be life-threatening. It's the third most diagnosed cancer overall, and the second leading cause of cancer deaths in both men and women after lung cancer. And about one in five patients have stage IV metastatic cancer at diagnosis.[1]

As an oncologist, it's heartbreaking when a patient comes to me, already at stage IV, knowing the challenges before us. We've learned that mCRC is a heterogenous disease and that genomic subtypes can differ in the aggressiveness of the disease, response to treatment, and prognosis.[3]

For example, in the almost 50 percent of patients whose tumors are wild-type for both RAS and BRAF, the median survival is about 30 months with systemic therapy. But in those 5-10 percent of patients with BRAF mutations, even with aggressive chemotherapy, the median survival can be just short of one year.[5]

I believe biomarker testing should be adopted as the standard of care for all of our patients. And it can't wait until after other treatment strategies have already failed. What we know now is that it's a necessary part of mCRC management and should be used as early as possible in diagnosis.[2]

Dr. Turck:
Now what do current clinical guidelines recommend regarding biomarker testing?

Dr. Ciombor:
Generally, CRC clinical guidelines recommend biomarker testing for KRAS/NRAS and BRAF mutations, MSI and/or MMR status, and HER2 amplification in patients with mCRC, as all of these are considered actionable alterations. In terms of the testing method, most guidelines accept individual gene testing or multiple tests together as part of a next-generation sequencing panel, also known as an NGS panel, which could either be tissue- or blood-based, or both.[3,6]

Dr. Turck:
It is important to note that certain approved treatments for mCRC have specific approved companion diagnostics, which may not include NGS. Please be sure to refer to approved product labeling and www.fda.gov/CompanionDiagnostics for information on FDA-approved companion diagnostics.

Dr. Ciombor:
The American Society of Clinical Oncology, known as ASCO, convened an expert panel with the American Society for Clinical Pathology, the College of American Pathologists, and the Association for Molecular Pathology to develop biomarker testing recommendations, as well as expert consensus opinions, for mCRC patients considering anti-EGFR therapy or conventional chemotherapy.[6]

In addition to recommending KRAS/NRAS mutational testing and MMR status testing, this expert panel recommends BRAF V600E mutational testing for prognosis stratification, predictive capabilities and Lynch Syndrome risk stratification.[6]

So, clinicians should be adopting these guidelines by including biomarker testing for every patient with mCRC as part of their early diagnostic workup. Then clinicians can often personalize treatment regimens, anticipate the treatment sequence with the initial therapy, and monitor treatment more effectively.[2,5] This way we can ensure we're using the most appropriate treatment for our patients as early as possible.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck and today I'm speaking with Dr. Kristen Ciombor about the role of biomarker testing in metastatic colorectal cancer.

If we dive further into mCRC treatment, Dr. Ciombor, what kind of role does biomarker testing have in personalizing treatment?

Dr. Ciombor:
Approved biomarker-driven therapies have completely changed the way we treat mCRC.[2,3]

By implementing biomarker testing as early as possible after diagnosis, we can tailor treatment regimens and personalize regimen sequences based on approved biomarker-driven therapies, often referred to as precision oncology. This personalization can often

happen even in the first-line therapy setting.[2,3] And in patients who have disease progression on first-line therapy, biomarker-driven therapies are available that can potentially improve patient survival as well.[5]

For example, patients whose tumors have mismatch repair deficiency (dMMR) or microsatellite instability (MSI-H) now have immunotherapy options such as anti-PD1 antibodies with or without anti-CTLA4 antibodies that inhibit immune checkpoints. Those with RAS/BRAF wild-type tumors can potentially have improved survival using anti-EGFR antibodies with or without chemotherapy. And approximately 10 percent of mCRC patients whose tumors harbor BRAF V600E mutations are recommended by clinical guidelines to be treated with a combination of EGFR and BRAF inhibitors upon disease progression on first-line treatment.[5] And beyond current available therapies, biomarker testing can help identify new, actionable mCRC targets and determine patients who are eligible for clinical trials.[2,5]

Dr. Turck:
Now, are there any challenges providers face in adopting the guidelines for biomarker testing in mCRC patients?

Dr. Ciombor:
That's such an important question because consistent biomarker testing early in the diagnosis is the key to giving our patients their best chance in the fight against mCRC. Unfortunately, this type of testing has been challenging to adopt universally because of multiple barriers.[7]

In a six-year retrospective study of over 20,000 mCRC patients, only about two-thirds received any biomarker testing at all.[8] And although the rate of biomarker testing increased for each subtype studied over the years, by the end of the study, the rate of NRAS or BRAF testing was only 46 percent.[8]

And in a survey of 111 community oncologists who reported various barriers to biomarker testing, the ones most commonly mentioned included insufficient quantity or poor quality of tissue for testing, poor or nonexistent in-house testing laboratory capabilities, and long turnaround times for results. Some patient-related factors also affected their decision to test, including patient preference, general health and fitness, age, and lack of insurance coverage.[7]

In addition, studies show that there are some significant disparities when it comes to biomarker testing. Younger patients, those who have fewer comorbidities, better performance status, and access to an urban or academic treatment setting are more likely to receive this type of biomarker testing.[8,9,10,11]

Dr. Turck:
Now to bring all of this together, what are some strategies we can use to overcome these obstacles and improve biomarker testing rates?

Dr. Ciombor:
In the past, when RAS was the only known major gene mutation to affect treatment decisions, we were often testing individual genes one at a time. But now, we have more targets identified and newer ones being studied.[6]

In my opinion, ordering an NGS panel is best in biomarker testing because it allows us to test several genes at once and may make more sense in terms of time, test capability, and tissue sample efficiency. Also, NGS can detect rare biomarker variations that may be actionable now or are being studied in clinical trials.[2,3,6]

Next, we used to send these tests on our mCRC patients after the disease had progressed, many times only after first-line treatments had stopped working.[2] But testing early at the diagnosis of mCRC may help us avoid potentially ineffective therapies and instead make informed treatment decisions. And as new targets and therapies are identified, having a biomarker-driven treatment plan in place can help provide more personalized treatment options for our patients, from first-line treatment on.[2,6]

And finally, improving the adoption of biomarker testing, especially outside of academic centers, will require a multidisciplinary effort with oncologists, nurses, pathologists, patients, healthcare administrators, and payers working together to improve survival rates in our mCRC patients.[12]

Dr. Turck:
We're almost out of time today, Dr. Ciombor, but what key takeaways would you like to leave with our audience?

Dr. Ciombor:
The burden of mCRC is tremendous. Colorectal cancer is the second leading cancer-related cause of death in the United States and

despite improvements in screening and treatments, patients with mCRC often have poor outcomes.[1] This can be a life-threatening disease but testing for biomarkers can help us identify specific genomic subtypes of cancers so that we can tailor treatment to our patients' tumors' unique characteristics through precision medicine.[2,3,6]

So, the key take-home message here is that although providing guideline-recommended care can be challenging in clinical practice, in order to help improve outcomes for our mCRC patients, clinicians need to stay up-to-date on the guidelines and consistently implement biomarker testing at diagnosis to inform treatment decisions. Then, if appropriate, incorporate appropriate approved biomarker-driven therapies earlier in the treatment regimen.[2,3,4,5,11]

Dr. Turck:
Thanks for sharing these insights. They might help us combat metastatic colorectal cancer and perhaps even help our patients live longer. As we come to a close, I want to thank you, Dr. Ciombor, for helping us better understand biomarker testing for patients with metastatic colorectal cancer.

Dr. Ciombor, it was great speaking with you today.

Dr. Ciombor:
Thank you for having me.

Announcer:
This program was sponsored by Pfizer Oncology Medical Affairs. If you missed any part of this series, visit ReachMD.com/ProjectOncology. This is ReachMD. Be part of the knowledge.

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