Journal of Patient-Centered Research and Reviews

Volume 11 | Issue 3 Article 4

10-15-2024

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Recommended Citation

Kruchko DH, Ali S, Hasan M, et al. Molecular tumor testing on colorectal adenocarcinoma specimens in a large community-based healthcare system. J Patient Cent Res Rev. 2024;11:215-21. doi: 10.17294/2330-0698.2074

Published quarterly by Midwest-based health system Advocate Aurora Health and indexed in PubMed Central, the Journal of Patient-Centered Research and Reviews (JPCRR) is an open access, peer-reviewed medical journal focused on disseminating scholarly works devoted to improving patient-centered care practices, health outcomes, and the patient experience.

Molecular Tumor Testing on Colorectal Adenocarcinoma Specimens in a Large Community-Based Healthcare System

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Purpose This study aimed to describe the adherence of National Comprehensive Cancer Network guidelines to perform genetic screening for all colorectal cancer (CRC) specimens with molecular tumor testing, eg, immunohistochemical (IHC) testing, in a large community-based healthcare setting. The study also identified trends involving characteristics of CRC, individual reporting physician, and physician location and examined the potential impact of these trends on the performance of molecular tumor testing.

Methods This was a retrospective, multi-center study using a centralized pathology database to assess molecular testing on CRC specimens. The primary endpoint was whether tumor testing of a CRC specimen was performed. Secondary endpoints included tumor location within the colon (ie, the right or left side), year of CRC diagnosis, and location of the pathologist within the Advocate Aurora Health (AAH) system. The data were collected from 2016 to 2020.

Results A total of 2469 CRC cases, reviewed by 47 pathologists practicing in five separate hospitals, were identified within the AAH system for the selected five-year time period. IHC testing was performed in 1666 of these specimens (67.5%). There was no statistical difference between CRC sidedness and IHC testing performed (p = 0.9). There were no discernible features or trends for the ordering of IHC testing among different pathologists.

Conclusions Molecular tumor testing for CRC specimens in this large community-based healthcare setting was inconsistent and below the ideal adherence rate of 100%. Secondary findings offered neither explanation nor trends in likelihood to send samples for IHC testing. Education would be beneficial for pathologists and all physicians who care for patients with CRC in community-based health care settings. (*J Patient Cent Res Rev.* 2024;11:215-221.)

Keywords colorectal cancer; molecular tumor testing; inherited cancer syndromes; cancer prevention; guideline adherence

Patient-Friendly Recap

- Colorectal cancer (CRC) among Americans under the age of 50 years old has been on the rise, yet there has been a lack of testing for inherited genetic cancer syndromes.
- In an effort to prevent early-onset CRC, the National Comprehensive Cancer Network (NCCN) recommended in 2015 universal immunohistochemical testing of all CRCs, which helps identify at-risk family members.
- Our study demonstrated inconsistent ordering of tumor testing in a large community-based healthcare system with a total of 67% of CRCs sent for tumor testing.
- Increased education for pathologists and other healthcare providers about the NCCN recommendation is advised.

Inherited cancer syndromes have been shown to represent 5-10% of all colorectal cancers (CRCs).[1] Identifying inherited syndromes is critically important, especially because CRC is increasing among adults younger than 50 years old. This is known as early-onset CRC (EO-CRC) in the United States.[2] In 2015, the National Comprehensive Cancer Network (NCCN) published guidelines recommending universal molecular tumor testing for DNA mismatch repair deficiency (dMMR) on all CRC specimens.[3] These guidelines were released in part to assist in the identification of family members of patients at increased risk of developing EO-CRC. This testing is accomplished with immunohistochemical

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staining (IHC) or microsatellite instability (MSI) on tissue (eg, colon cancer specimen). It is notable that testing by both IHC and MSI is a highly effective mechanism in screening for dMMR and subsequently inherited cancer syndromes, such as Lynch Syndrome (LS). If a patient is found to have an inherited cancer syndrome, such as LS, the patient would require frequent multi-system cancer screening. A diagnosis of LS carries a significant risk for family members to be affected as well, and testing of direct family members is suggested. Thus, following these guidelines has important clinical implications regarding the management of patients with LS and their family members. Despite society recommendations, little is known about the adherence to NCCN guidelines for IHC testing on CRC.

A single study performed in 2018 at the University of Chicago showed that adherence to these guidelines was found to be 92%.[4] However, to date, no study has been performed to determine how well these NCCN guidelines are utilized in the community setting. Our study aims to determine the frequency of molecular tumor testing in a large community-based health system. The responsibility for IHC testing typically falls upon the pathologist who interprets the CRC specimen, as they are the first clinician aware of the diagnosis of CRC. However, all physicians are capable of coordinating IHC testing on CRC specimens, and this testing should be confirmed regardless of a clinician's specialty. For this reason, we reviewed which clinicians, other than pathologists, ordered IHC testing (eg, primary care physicians, oncologists, surgeons, and more). Adherence to society guidelines would likely increase if clinicians from all specialties were educated about the importance of universal IHC testing guidelines. We also reviewed individual factors resulting in high or low adherence to the NCCN guidelines. These factors included CRC-related features such as the side of tumor location within the colon (known as tumor sidedness), temporal factors such as the time since the issuance of the NCCN guidelines, and additional factors such as pathologist practice location within the hospital system.

METHODS

This was a retrospective, multi-site study involving patients from the Advocate Aurora Health (AAH) system from January 1, 2016, to December 31, 2020. The institutional review board at AAH classified this study as non-human subject research. At the time of the study, AAH had several hospital systems in the greater Chicagoland area, five of which were included in this study. These five hospitals encompass a wide area in Chicagoland and represent a diverse patient population in terms of socioeconomics and race.[5] The hospitals are listed as follows: Advocate Lutheran General Hospital (primary hospital of investigators, hospital with most resident and fellow training programs of the listed hospitals, and hospital with rotating pathologists at the time of study), Advocate Illinois Masonic Medical Center (hospital with residents and fellows), Advocate Christ Medical Center (hospital with residents and fellows), Advocate South Suburban Hospital, and Advocate Good Samaritan Hospital.

The patient population included only adult patients (≥18 years old) with pathology findings confirming colorectal adenocarcinoma in the specified time range. Subjects with pathology findings of intramucosal adenocarcinoma were excluded. The primary endpoint was whether molecular tumor testing of a CRC specimen was performed, recorded as yes or no. For this study, all molecular tumor testing was referred to as IHC testing. Secondary endpoints included the following: increased likelihood of molecular testing of CRC tumor based on sidedness of tumor (ie, right-sided colon tumor vs left-sided colon tumor), increased odds of molecular testing of CRC tumor based on pathologist location within AAH, or increased odds of molecular testing of CRC tumor based on the year following the release of the guidelines or year-to-year change.

For the initial query, the pathology department at Advocate Lutheran General Hospital (the primary site of the authors of this study) queried the pathology database system, CoPath (Cerner Corporation; Kansas City, MO). The query used the keywords "colorectal adenocarcinoma," "colon adenocarcinoma," and "rectal adenocarcinoma." The patients' electronic medical record system was not utilized. Eligibility was confirmed by manually reviewing the patients' pathology report to confirm that CRC was identified on pathology specimens. This was accomplished by reviewing the entire pathology report for each specimen. Once CRC was confirmed, the investigators determined whether the tissue was sent for IHC testing. This was accomplished by reading the comments section in the report, from which the pathologist incorporated the order for "IHC testing," "MSI testing," and "mismatch repair deficiency testing." If this text was not included in the pathology document, whether the original or any addendum, then IHC testing was not performed.

Each pathology specimen included the location of CRC (ascending colon, descending colon, etc), the associated pathologist, patient medical record number (MRN), and whether IHC testing was performed. The CRC locations were grouped by sidedness of the colon. Sidedness was determined by being either proximal or distal to the

splenic flexure, and thus, the cecum, hepatic flexure, ascending colon, and transverse colon were all identified as "right colon." The splenic flexure, descending colon, and sigmoid colon were all identified as "left colon." Rectosigmoid and rectal specimens were identified as "rectum." Rarely, the CRC location was not listed, or the specimen that was sent was from the total colectomy with the exact site not specified. These were identified as "unknown." Lastly, there were a small number of samples in which there were two separate CRCs arising simultaneously in distinct locations within the colon, and these were identified as "synchronous." Each pathologist worked at a primary hospital, so the pathologist practice location within AAH system was documented.

All the listed data were then gathered into encrypted Microsoft Excel files. IHC testing was converted to a binary result: 0 indicated that IHC testing was not performed, whereas 1 indicated that IHC testing was performed. Location of CRC was recorded as follows: 0 = Right colon, 1 = Left colon, 2 = Rectum, 3 = Unknown, 4 = Synchronous. MRNs were recorded as they were, kept secured, and used to eliminate any duplicate recordings within CoPath. The data were then converted into quantitative values where each pathologist was assigned a number from 0 – 47, whereas 0 signified that the pathologist was unknown. The primary location was the pathologist's primary hospital within the health system and was also recorded as a quantitative value, ranging from 0 – 4, with 0 indicating Advocate Lutheran General Hospital, the primary hospital for the investigators of this study.

Descriptive statistics were presented as means and standard deviations for continuous data and as counts and percentages for dichotomous and categorical data. Statistical significance of trends for categorical variables was tested by Pearson Chi-square or Fisher's exact test for logistic regression categorical variables. Chi-squared test was performed to determine whether there was a trend of increased IHC testing year after year following the release of the NCCN guidelines.

RESULTS

A total of 2469 CRC cases, reviewed by 47 pathologists practicing in five separate hospitals, were identified within the AAH system for the selected five-year period. Of the total 2469 cases of CRC identified, IHC testing was performed in 1666 specimens (67.5%). CRC locations showed an equal distribution of right and left sidedness, with 1104 (44.7%) CRC cases identified in the right colon and 1054 (42.7%) CRC cases identified in the left colon. Two hundred thirty-nine (9.7%) CRC cases were identified in the rectum. Fifty-two (2.1%) synchronous CRC cases were identified, and 20 (0.8%) CRC cases were found in unknown locations. There was no statistical difference between CRC sidedness and IHC testing performed ($p = 0.9$, Table 1). IHC testing was performed in 768/1104 (69.6%) of cases with right-sided CRC, 693/1054 (65.7%) of cases with left-sided CRC, 161/239 (67.4%) of cases with rectal CRC, and 35/52 (67.3%) of cases with synchronous CRC.

Of the 47 pathologists that were included in this study, one pathologist (pathologist 12) performed IHC testing on 0% of specimens but interpreted 3 CRC specimens. One pathologist (pathologist 18) sent for IHC testing on 100% of specimens but only interpreted 2 CRC specimens. One pathologist (pathologist 30), who interpreted 90 total CRC specimens, sent for IHC testing 99% of the time, whereas another pathologist (pathologist 23) interpreted 74 total specimens but only sent for IHC testing on 11% of CRC specimens. Eight pathologists sent for IHC testing in ≥ 85% of CRC specimens. Despite such extreme differences among certain pathologists, there

Table 1. CRC Incidence and Percentage IHC Testing by Tumor Location

Location	Total Number of Cases	Percentage IHC Testing	p-value*
Right colon	1,104	768 (69.6%)	0.9
Left colon	1,054	693 (65.7%)	
Rectum	239	161 (67.4%)	
Synchronous	52	35 (67.3%)	
Unknown	20	12 (60%)	
Total	2,469	1,666 (67.5%)	

**Fisher's exact test*

IHC: Immunohistochemical Testing

Statistical significance was not found in comparing the tumor locations

were no discernible features or trends for the ordering of IHC testing at vastly different rates.

There were no statistically significant differences among pathologist locations and the likelihood that IHC testing was sent (p=0.5) when comparing all locations (Table 2). There was a total of nine examples of the ordering physician (ie, gastroenterologist, colorectal surgeon, and/or oncologist) requesting IHC testing on CRC specimens. This information was found in the comments of the pathology report, and because the electronic medical records were not accessed, there is no way to determine if this happened more frequently than was reported.

Table 3 shows no statistically significant change in IHC testing over the five-year period (p=0.69). In 2016, the year that immediately followed the release of the NCCN guidelines, 62% of CRC specimens were sent for IHC testing. The following year, in 2017, IHC testing was performed in 70% of CRC specimens. However, 2018 and 2019 had slightly lower IHC testing performed than that in 2017, and 2020 again demonstrated IHC testing in 70% of CRC specimens. There was therefore no identifiable trend in the year-by-year comparisons.

DISCUSSION

In 2015, regarding CRC pathology specimens, the NCCN recommended universal screening of all CRCs and endometrial cancers to maximize sensitivity for LS detection and simplify care processes.[3] Despite this guideline, there have been few studies that have assessed the adherence to this recommendation. In 2018, Muller et al[4] sought to identify the uptake of universal testing of all CRC specimens in an academic center and to determine if there were any associated demographic features that affected the likelihood that testing was performed (eg, race and ethnicity). Their study demonstrated that 92% of all CRC specimens were sent for IHC testing and that neither race nor ethnicity affected this universal testing. There have been no published studies to assess the adherence to this guideline in a community setting, although there was an abstract presented at the American College of Gastroenterology in 2016 that assessed 47 community-based patients in a retrospective analysis.[6] The authors of this abstract discovered that 43 of the 47 patients in their population (91.48%) with CRC had subsequent IHC testing.[3] Additional monitoring in the community setting was recommended by the authors.

We therefore approached our study with the intention of being the largest study by total number of patients and the study with the longest duration by total number of data collection years in assessing both adherence to these guidelines and the ordering behavior of pathologists in a community-based healthcare setting. Despite the findings of high adherence in prior studies, in both academic center and community-based settings, we did not find consistent adherence to this recommendation in our large community-based healthcare setting. We searched for factors associated with likelihood of performing IHC testing on CRC specimens, including the year the CRC was diagnosed by pathology, the sidedness of the CRC, and the pathologist's practice location. This analysis showed no significant associations among these variables and their relation to whether IHC testing occurred.

Table 2. Mean Likelihood of Sending for IHC Testing Based on Pathologist Location

Characteristic	**0**, N = 15[1]	**1**, N = 8[1]	**2**, N = 14[1]	**3**, N = 5[1]	**4**, N = 5[1]	p-value[2]
Likelihood of Send	0.71 (0.18)	0.67 (0.34)	0.61 (0.28)	0.54 (0.20)	0.70 (0.30)	0.5

[1]Mean (SD)

[2]Kruskal-Wallis rank sum test

Table 3. Total Percentage of IHC Testing by Year

Characteristic	**2016**, N = 1423[1]	**2017**, N = 531[1]	**2018**, N = 532[1]	**2019**, N = 548[1]	**2020**, N = 435[1]	p-value[2]
IHC Testing	263 (62%)	373 (70%)	360 (68%)	366 (67%)	304 (70%)	0.069
Unknown	0	0	0	0	1	

[1]n (%)

[2]Pearson's Chi-squared test

IHC testing on CRC specimens was determined by using manual data analysis and tabulation of pathology reports. Given that these orders were placed in a now inaccessible electronic medical record system, there was no way to directly view the order for a result of IHC testing. However, the pathology system (CoPath) acts as a simultaneous ordering/recording system, meaning once it is ordered, the pathology report populates the order. If a pathologist forgets to send for testing after signing the pathology report, but later decides to send for IHC testing, they would then have to go back into the closed pathology report, create an addendum, and send for testing. IHC testing was found as an addendum to several reports, which indicates an appropriate method in determining true testing for this study while eliminating the possibility that our method for data tabulation missed any IHC orders.

The five-year analysis began with assessing IHC testing on CRC specimens by year, starting in 2016, one year after the NCCN guidelines were released. The authors originally hypothesized that IHC testing would become more ubiquitous as awareness of the recent guidelines increased. However, our study showed no temporal change in IHC testing of CRC specimens. It is possible that if the study had been extended to present time, an increased trend would have been observed, but this requires additional studies.

CRC sidedness did not have a statistically significant effect on whether IHC testing was performed. This is noteworthy because patients with LS have an increased risk of right-sided CRC, and if the findings had demonstrated an increased likelihood of IHC testing for right-sided CRC specimens, then perhaps pathologists were assessing which CRC specimens should be sent based on sidedness. Unfortunately, this trend was not demonstrated in our data. Additionally, there was no increased frequency of IHC testing in synchronous CRC cases. IHC testing of synchronous CRC was performed with similar frequency (35/52; 67.3%) as that for IHC testing of both rectal (161/239; 67.4%) and right-sided CRC (768/1,104; 69.6%). Although all CRC specimens should be sent for IHC testing based on NCCN guidelines, particular emphasis should be placed on synchronous CRC, including strong consideration for referral to genetic counseling.[7] The reason for this low IHC testing in synchronous CRC is unclear but certainly is an opportunity for education.

There was significant variability in IHC ordering by each pathologist with no identifiable trends for IHC testing among pathologists within their practice location. Our study was not designed to gather background data on each pathologist, such as pathologist time of training/residency, specialization in certain disorders, or if they worked with residents or fellows in an academic role. We can, however, make inferences regarding which practice locations were more likely to have pathologists practicing in an academic role. For example, pathologist location 0 is unique because it has multiple residencies and fellowships, although no dedicated pathology residency. However, pathology residents from nearby universities will periodically rotate at pathologist location 0, and therefore, these pathologists are more likely to engage in an academic role. The authors of this study hypothesized that pathologists who practiced at location 0 would therefore have a higher IHC testing percentage more in line with academic institutions. Studies have demonstrated that the rate of non-adherence to society guidelines is significantly higher in community-based settings, and therefore, academic physicians who engage in teaching residents and fellows have higher adherence to society guidelines.[8] This, however, was not demonstrated in our results.

Another consideration is who is responsible for sending CRC specimens for IHC testing. Although the decision to send for IHC testing historically is made by the pathologist, examples of colorectal surgeons, gastroenterologists, and oncologists requesting IHC testing on CRC specimens were found. This suggests that there is tremendous benefit in all practicing physicians who manage CRC, including primary care physicians, to be aware of the NCCN guidelines. This knowledge would allow any physician caring for a patient with CRC to review the pathology report and confirm that IHC testing was performed. Additionally, guideline awareness would facilitate continuity for follow up on the IHC result to ensure that appropriate follow-up testing is performed.

Up-to-date guideline awareness on the management of EO-CRC will improve patient-centered care and help in the effort to reduce EO-CRC incidence among family members. The increased incidence of EO-CRC contrasts with the decreasing rates of CRC among persons older than 50 years old. EO-CRC now accounts for approximately one in ten cases of CRC among adults.[2] The potential etiologies of EO-CRC are variable and out of the scope of this study, but one proposed mechanism is that certain individuals have an inherited genetic risk syndrome that predisposes them to CRC.[2,9] The key to identifying these individuals is increased genetic testing. Genetic testing can be accomplished by testing colorectal tissue after a diagnosis of CRC is made, as in our study, or by testing blood specimens (whole blood/germline testing). The issue becomes who to test and when testing is indicated. Germline testing in all adults is cost prohibitive and carries ethical concerns for some individuals.[10] For these

reasons and more, society guidelines do not yet universally recommend germline testing once CRC is diagnosed.

Molecular tumor testing on CRCs that demonstrate dMMR can be seen in LS, an inherited genetic condition with an increased risk for CRC, among other cancers.[11] IHC testing is an ideal screening method for dMMR, and if positive, follow-up testing including possible germline testing is performed to determine if this result represents an inherited condition, such as LS. Universal screening with IHC testing in patients with CRC demonstrates a sensitivity of 100% and a specificity of 93% in identifying patients with LS.[12] Although IHC testing in CRC specimens is not preventative testing, it is an ideal way to identify affected individuals and, just as importantly, their family members, who may unknowingly have LS and subsequently a predisposition to CRC and other cancers.

LS, also referred to as hereditary nonpolyposis colorectal cancer syndrome (HNPCC), is an inherited condition that is defined by a deficiency of MMR genes. MMR genes are responsible for repairing incorrect nucleotide pairing during DNA replication.[10] An error in this process leads to accumulation of nucleotide bases, referred to as microsatellites. These microsatellites accumulate and can lead to DNA alterations known as frameshift mutations and thereby lead to colorectal adenocarcinoma. The progression from normal colorectal tissue to CRC in patients with LS is two to three times faster than the progression observed in the general population.[13] Due to the earlier progression from normal colorectal tissue to CRC, colonoscopies are performed on a more frequent basis to identify and resect pre-cancerous polyps prior to CRC development. This frequent colonoscopy recommendation helps to prevent CRC in patients with known LS and is thus a key actionable step that can be taken after a confirmed positive IHC result on a CRC specimen. To prevent CRC and specifically EO-CRC, hospital systems and physicians need to be aware of these 2015 NCCN guidelines and, more importantly, implement them into their practice.

Follow-up testing for tumors with a positive IHC result is critical and includes a variety of suggested methods; however, our study was not designed to assess the follow-up testing performed after identifying positive IHC results.[12] Future studies assessing follow-up testing in a large community-based healthcare system would be beneficial. There is a need for future prospective studies in large community-based healthcare settings to demonstrate the uptake of these NCCN guidelines, frequency of follow-up testing performed, and the results of follow-up genetic testing.

Limitations

Our study has multiple limitations. First, this study was a retrospective study. Second, because a pathology-specific database was used in place of the electronic medical record system, demographic information for each patient was not reported. Additionally, clinical data were not included, so rate and results of downstream testing such as BRAF and MLH1 were unable to be assessed. Lastly, in this database, the ordering physician was not included. Since pathologists, gastroenterologists, colorectal surgeons, and oncologists can all request IHC testing on CRC specimens, this data analysis could have provided insight to encourage further compliance. Third, there were some specimens with "unknown" locations listed. In some of these cases, patients had total colectomies performed, so the specific area (right vs left) was not listed. In other cases, the report did not provide an exact location, whereas the electronic medical record may have provided the exact location of the sample. Location, however, did not appear to affect whether IHC testing was performed. Finally, we were unable to obtain information regarding the individual pathologist, such as residency training, years in practice, or sub-specialty experience – all factors that could affect practitioners' propensity to send for IHC testing. In addition, there was a very large range in the number of CRC cases seen by individual pathologists. Some pathologists had a small number of cases of CRC, such as pathologist 12 and 18, who interpreted 3 and 2 samples, respectively. We kept all results from these pathologists, per the original design of the protocol. Our study was not designed to assess the average number of CRC specimens that each pathologist reviews. We could not therefore assign a threshold for number of CRC specimens reviewed for a pathologist to be included in this study.

Future studies are planned to further assess the downstream testing of positive IHC results. Additionally, assessing the effect of having an educational program with medical trainees on the rate of testing would be beneficial.

CONCLUSIONS

Inconsistent ordering of IHC testing of CRC specimens was observed in a large community-based healthcare system. Ordering of IHC testing in CRC specimens by individual pathologists was not dependent on practice location, year of CRC diagnosis, or CRC tumor location. Certain pathologists are adherent to the NCCN guidelines, while others are completely non-adherent to the guidelines. The patient-centered implications of this study are therefore that increased clinician education on IHC testing of CRC are recommended. Improved society guideline adherence will have a direct positive impact on patient care. This

education should predominantly be geared toward pathologists who practice in a large community-based healthcare system; however, all physicians who care for CRC patients should also be aware of the importance of these guidelines. Additionally, an automatic reflex order for IHC testing, once a diagnosis of CRC is made by a pathologist, should be considered and incorporated into electronic medical record systems. The creation of an order reflex for IHC testing could reduce the risk of guideline non-adherence and thereby maximize the effort in reducing EO-CRC incidence.

Author Contributions

Study design: Kruchko, Ali, Sesselmann, Ehrenpreis. Data acquisition or analysis: All. Manuscript drafting: All. Critical revision: All.

Conflicts of Interest

None.

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