

Genomic Profiling for *KRAS*, *NRAS*, *BRAF*, Microsatellite Instability, and Mismatch Repair Deficiency Among Patients With Metastatic Colon Cancer

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PURPOSE Genomic testing is recognized in national guidelines as essential to guide appropriate therapy selection in metastatic colorectal cancer. Previous studies report adherence to testing guidelines is suboptimal, but current testing rates have not been assessed. This study reports testing rates in metastatic colon cancer (mCC) for guideline-recommended biomarkers in a US-based population.

MATERIALS AND METHODS A retrospective review of data extracted from electronic medical records was performed to identify patients with pathologically confirmed mCC and describe patterns of guideline-aligned biomarker testing. Data were extracted from the electronic health records of 1,497 patients treated at 23 practices across the United States. Both community and academic centers were represented.

RESULTS A total of 1,497 patients with mCC diagnosed between January 1, 2013 and December 31, 2017 were identified. Guideline-aligned biomarker testing rates for *RAS*, *BRAF*, and microsatellite instability/mismatch repair deficiency over this study period were 41%, 43%, and 51%, respectively. Patients were more likely to have guideline-aligned testing for *RAS* and *BRAF* if they were treated at an academic center, were diagnosed with de novo metastatic disease, and were female. In addition, patients < 65 years of age were more likely to have guideline-aligned *RAS* testing. Of the 177 patients (12% of cohort) who received anti-epidermal growth factor receptor therapy, only 50 (28%) had complete guideline-aligned biomarker testing.

CONCLUSION Despite guideline recommendations and significant therapeutic implications, overall biomarker testing rates in mCC remain suboptimal. Adherence to guideline-recommended biomarker testing would potentially reduce exposure to expensive and ineffective therapies, resulting in improved patient outcomes.

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INTRODUCTION

The promise of precision oncology requires the application of biomarker testing to direct appropriate clinical care. Among patients with metastatic colorectal cancer (mCRC), genomic profiling may identify somatic mutations that are prognostic for outcomes and/or predictive of response to approved treatments. In 2009, ASCO and the National Comprehensive Cancer Network (NCCN) published guidelines recommending that patients with mCRC undergo testing for activating mutations in codons 12 and 13 of *KRAS* exon 2 on the basis of data that patients with these mutations do not derive clinical benefit from the anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibody (MAb) therapies cetuximab and panitumumab.^{1,2} *KRAS* exon 2 mutation testing allows oncologists to avoid the use of ineffective anti-EGFR therapy in approximately 40% of patients with mCRC who may otherwise receive these drugs as second-line therapy.³

Over the subsequent 10 years, biomarker testing guidelines have been expanded (Fig 1). Testing for mutations in *KRAS* exons 3 or 4 and *NRAS* exons 2, 3, or 4 finds 20% more *RAS* mutations than exon 2 testing alone, adding another 8% of patients with mCRC who will have poor responses to anti-EGFR therapy (Fig 2).^{3,4} *BRAF* mutations, specifically V600E, predict lack of response to cetuximab and panitumumab in another 9%.^{5,6} *ERBB2* (HER2) amplification, present in approximately 2% of mCRC, is also a negative predictor of anti-EGFR MAb response, increasing the percentage of patients with mCRC in whom these ineffective agents could be avoided to almost 60%.^{7,8}

In addition to their clinical utility as negative predictors of cetuximab and panitumumab response, *BRAF* mutations and HER2 overexpression are positive predictors of response to targeted therapy. Guidelines recommend targeting both *BRAF* V600E and HER2-positive (*RAS* wild type) patients with combination targeted therapies, which have demonstrated durable

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CONTEXT

Key Objective

How often are patients with metastatic colon cancer (mCC) receiving guideline-aligned biomarker testing?

Knowledge Generated

This retrospective medical record review of patients treated at academic and community centers in the United States demonstrates that only 40% of patients with mCC received guideline-aligned biomarker testing between 2013 and 2017.

Patients were more likely to receive guideline-aligned biomarker testing if they were female, diagnosed at < 65 years of age, treated at an academic center, and diagnosed with de novo metastatic disease.

Relevance

Biomarker testing plays an increasingly important role in treatment selection in mCC, and exploring new approaches to increase genotyping rates is essential for improved patient outcomes.

response and disease control rates in these specific populations.⁹⁻¹²

Microsatellite instability (MSI) is an important predictive biomarker for response to immune checkpoint blockade (ICB).^{13,14} In 2018, the tumor-agnostic approval of pembrolizumab for the treatment of patients with unresectable or metastatic MSI high (MSI-H) solid tumors after progression on prior approved therapies established this critical biomarker to guide ICB therapy selection.¹⁵ It is also an important screening test for the hereditary cancer syndrome, Lynch syndrome, and a prognostic marker in stage II CRC. The NCCN recommended mismatch repair deficiency (dMMR) testing (by MSI or immunohistochemistry [IHC]) for all patients > 50 years of age in 2011, and then for patients with mCRC at any age in 2015.^{16,17}

Although biomarker testing has been advocated for a decade in mCRC guidelines, published testing rates remain low. Carter et al¹⁸ reported 47.5% of patients with mCRC diagnosed between 2008 and 2011 had *KRAS* testing. A population-based study of > 20,000 patients in the SEER database reported only 30% of patients diagnosed with mCRC in 2010 were tested for *KRAS*.¹⁹ Shaikh et al²⁰ reported 28.2% of patients diagnosed with mCRC between 2010 and 2012 had testing for dMMR.

We hypothesize that genomic testing rates for guideline-recommended biomarkers have improved over time. To our knowledge, the current study is the first to report on undergenotyping rates and trends for all four guideline-recommended biomarkers in metastatic colon cancer (*KRAS*, *NRAS*, *BRAF*, and MSI/dMMR) and to characterize the tissue-based methodologies used in real-world practice settings.

MATERIALS AND METHODS

A retrospective review of the COTA Real World Data (RWD) database was performed to identify patients with pathologically confirmed metastatic colon cancer (mCC) diagnosed between January 1, 2013 and December 1, 2017.

Although guidelines recommend molecular testing for patients with mCRC, the current study included patients with mCC and excluded rectal cancer cases. At the time of data extraction, the COTA database included demographic, diagnostic, treatment, and quality-of-care information for patients with colon cancer abstracted from the electronic health records from 23 practices including 258 oncologists in Arkansas, Maryland, Michigan, New Jersey, New York, and Tennessee who contribute data under Business Associate Agreements. All data were de-identified to be compliant with Health Insurance Portability and Accountability Act and Office of Health Promotion Research regulations for purposes of secondary research use. The structure of the COTA database has been reviewed by the Western Institutional Review Board and has been deemed exempt from patient informed consent. The electronic medical records of each patient (all clinical progress notes, laboratory reports, and pathology reports) were reviewed by trained COTA abstractors for any mention of biomarker testing (including results placed in the record in both structured and unstructured formats, such as scanned pdf files). Approximately 10% of cases underwent a secondary review by a separate abstractor as part of quality control assurance procedures. The data were then merged with the study population using blinded patient identifiers for subsequent analysis. We defined a patient as “tested” if available biomarker data indicated relevant testing, regardless of method, vendor, or test completeness. Testing could have occurred at any time during the course of a patient’s disease, including before the dates of study and before metastatic progression. We defined a patient as receiving “extended RAS testing” if the laboratory or pathology report indicated analysis of exons 2, 3, and 4 for both *KRAS* and *NRAS* and as “limited RAS testing” if analysis was anything less than exons 2, 3, and 4 in both *KRAS* and *NRAS*. When available, testing methodologies including next-generation sequencing (NGS), polymerase chain reaction (PCR), and IHC were collected and reported. All statistical analyses were performed using the R statistical language.

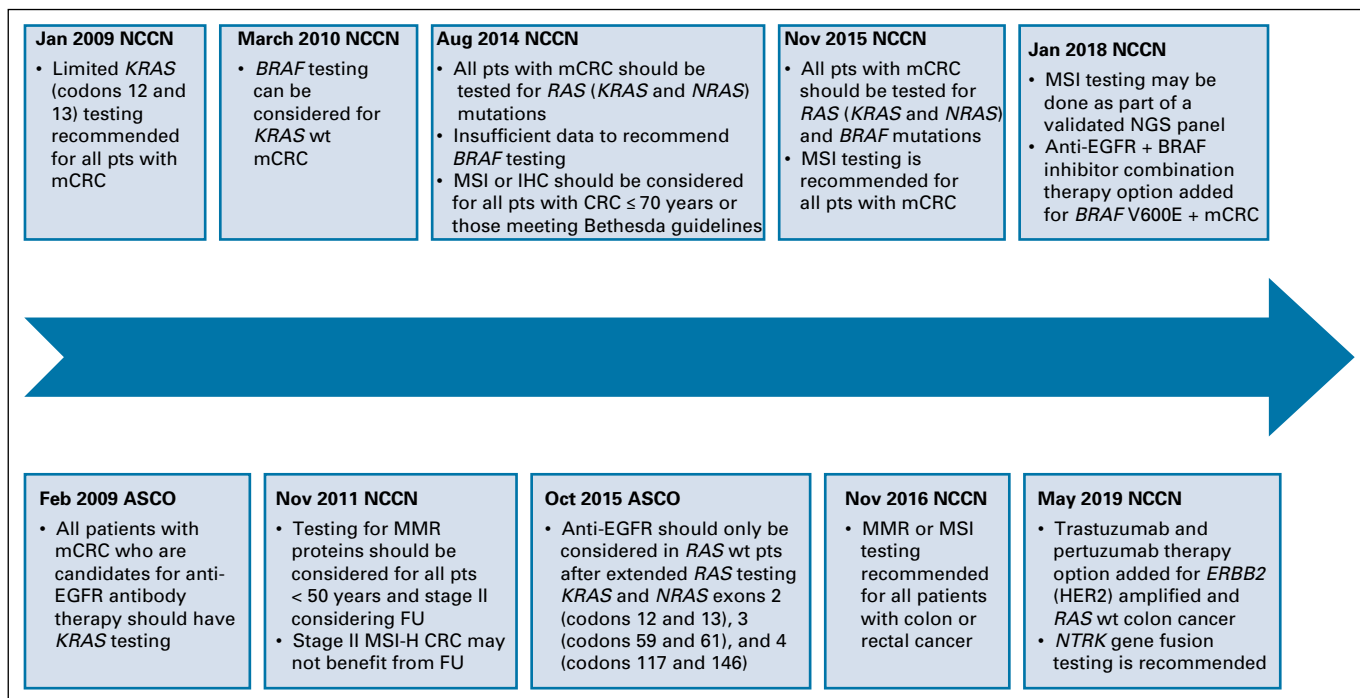


FIG 1. Evolution of guidelines for molecular testing in metastatic colorectal cancer (mCRC). FU, fluorouracil; IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability high; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; pts, patients; wt, wild type.

Testing for a given biomarker was considered “guideline aligned” if the NCCN guidelines recommended testing for that biomarker for the entire year being analyzed. Guideline-aligned testing in 2013 and 2014 included testing for *KRAS* by any methodology, in 2015 included extended testing of *NRAS* and *KRAS*, and in 2016 and 2017 included extended testing of both *KRAS* and *NRAS*, *BRAF* testing by any methodology, and MSI/dMMR analysis by any methodology. Before 2016, MSI/dMMR testing was recommended for patients < 50 years of age or patients meeting Bethesda criteria. Because the COTA database captures limited family history data, we did not include MSI/dMMR in the guideline-aligned genotyping analysis until it was recommended for all patients regardless of age or family history.

RESULTS

Patient Demographics

A total of 1,497 patients with mCC were identified in the observational database (Table 1). Of these patients, 1,325 (89%) had de novo presentation of metastatic disease, and 172 (11%) had been previously diagnosed with earlier stage colon cancer and became metastatic during the study time frame. The median age of the population at the time of metastatic diagnosis was 64 years. Women constituted 50% of the cohort. Six percent reported active tobacco use, 33% reported former use, and 52% denied any smoking history. Adenocarcinoma histology was reported in 94%, signet ring in 3%, mucinous in 1%, and

other histologies in 2%. The patients were treated at 23 centers, including 1,152 (77%) at academic cancer centers and 345 (23%) at community cancer centers.

Overall Guideline-Aligned Biomarker Testing

Guideline-aligned biomarker testing was completed in 40% of patients in this study (601 of 1,497). Patients were more likely to have guideline-aligned biomarker testing if they were treated at an academic center versus a community center (44% v 29%; $P < .001$), if they presented with de novo metastatic disease versus progressing from an earlier stage (42% v 24%; $P < .001$), if they were diagnosed at age < 65 years versus age ≥ 65 years (44% v 35%; $P < .001$), and if they were female versus male (44% v 36%; $P < .01$).

KRAS and *NRAS* Testing Rates

Guideline-aligned *RAS* testing was completed in 41% of patients (610 of 1,497) during this study. Patients were more likely to received guideline-aligned *RAS* testing if they were treated at an academic center versus a community center (44% v 29%; $P < .001$), if they presented with de novo metastatic disease versus progressing from an earlier stage (43% v 25%; $P < .001$), if they were diagnosed at age < 65 years versus age ≥ 65 years (44% v 35%; $P < .001$), and if they were female versus male (45% v 37%; $P < .01$).

Between 2013 and 2017, 777 (52%) patients had *KRAS* testing by any methodology, with 62% of tested patients harboring an alteration. A total of 566 (38%) patients had

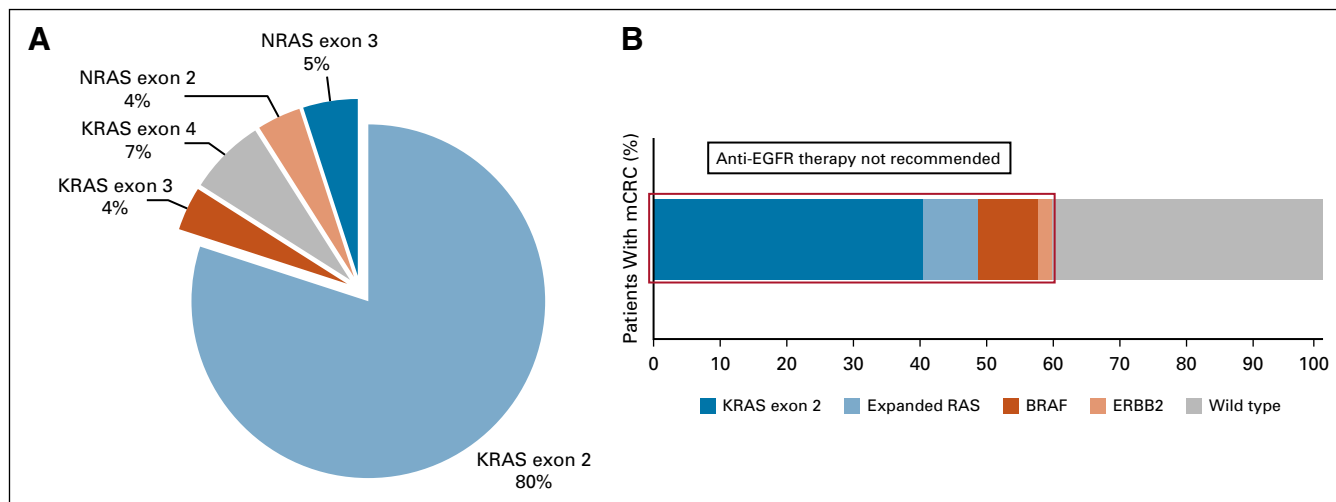


FIG 2. Prevalence of negative predictors to anti-EGFR therapy. (A) Frequency of mutations identified in expanded *RAS* testing.^{4,20,21} (B) Approximately 60% of patients with metastatic colorectal cancer (mCRC) will have a genetic alteration that may predict poor response to anti-EGFR monoclonal antibody (MAb) therapies cetuximab and panitumumab. Most of these nonresponders will have *KRAS* exon 2 mutations, but expanded *RAS*, *BRAF*, and *ERBB2* analysis identifies an additional 20% of patients who will not benefit from therapy.

NRAS testing by any methodology, with 7% of tested patients harboring an *NRAS* mutation (Fig 3).

BRAF Testing Rates

Guideline-aligned *BRAF* testing was completed in 43% of patients (235 of 546) in 2016-2017 when *BRAF* testing was guideline recommended. Patients were more likely to receive guideline-aligned *BRAF* testing if they were treated at an academic center versus a community center (47% v 25%; $P < .001$), if they presented with de novo metastatic disease versus progressing from an earlier stage (46% v 23%; $P < .001$), and if they were female versus male (48% v 38%; $P < .05$).

Over the whole study period, including the years 2013-2015 when *BRAF* testing was not yet recommended in guidelines, 613 patients (41%) were tested by any methodology for *BRAF* mutations, with 17% of tested patients harboring a mutation.

MSI and dMMR Testing

Guideline-aligned dMMR testing was completed in 51% of patients (276 of 546) in 2016-2017 when dMMR testing was recommended for all patients with mCC. None of the evaluable factors in this study were correlated with a higher likelihood for a patient to have dMMR testing.

Over the whole study period, including the years 2013-2015 when MSI/dMMR testing was only recommended for a subset of patients with mCC, 667 patients (45%) were assessed for dMMR, and 46 (7%) were MSI-H or harbored at least one MMR deficiency.

Testing Methodology

Testing methodology was specified in the majority of cases (79% for *KRAS*, 92% *NRAS*, 87% *BRAF*, and 94% MSI/

dMMR). Although PCR was the most common testing methodology for *KRAS* in 2013, NGS was the dominant testing methodology for *KRAS* after 2013 and for *NRAS* and *BRAF* throughout the entire period of this study. The proportion of patients who had testing for *KRAS*, *NRAS*, and *BRAF* by NGS increased each year over the course of the study (Fig 4).

Use of Anti-EGFR Therapy

In this study, 177 (11.8%) patients received cetuximab or panitumumab between 2013 and 2017. Of these patients, 50 (28%) had guideline-aligned testing for *RAS* and *BRAF*. Sixty-three (36%) were tested for *KRAS* by any methodology, 37 (21%) were tested for *NRAS* by any methodology, and 44 (26%) were tested for *BRAF* by any methodology. In addition, 7% of patients (12 of 177) who received cetuximab or panitumumab were positive for mutations of either *KRAS* or *NRAS*. It is not known whether *RAS* testing occurred before or after initiation of therapy.

DISCUSSION

Evidence-based national guidelines for biomarker testing have been developed to assist in the care of patients with mCRC.² However, this retrospective review demonstrates significant undergenotyping for recommended biomarkers, with only 40% of patients receiving guideline-aligned biomarker testing between 2013 and 2017. We expected increased awareness of guidelines with time and therefore increased testing rates in more recent years. Although the proportion of patients tested for individual markers increased, because guidelines significantly expanded between 2013 and 2017, the number of patients receiving guideline-aligned genotyping in 2017 was lower than it was at the start of the study. There was a trend toward increasing guideline-aligned testing from 2015 to 2017,

TABLE 1. Study Population and Genomic Testing Patterns

Variable	Total (%)	KRAS		NRAS		BRAF		dMMR	
		Tested	Not Tested	Tested	Not Tested	Tested	Not Tested	Tested	Not Tested
Patients	1,497	777 (52)	720 (48)	566 (38)	931 (62)	613 (41)	884 (59)	667 (45)	830 (55)
Sex									
Female	742 (50)	403 (54)	339 (46)	309 (42)	433 (58)	333 (45)	409 (55)	356 (48)	386 (52)
Male	754 (50)	373 (49)	381 (51)	256 (34)	498 (66)	279 (37)	475 (63)	310 (41)	444 (59)
Age group ^a									
< 65 years	935 (62)	497 (53)	438 (47)	377 (40)	558 (60)	412 (44)	523 (56)	446 (48)	489 (52)
≥ 65 years	559 (37)	279 (50)	280 (50)	188 (34)	371 (66)	200 (36)	359 (64)	220 (39)	339 (60)
Race									
White	1,047 (70)	528 (50)	519 (50)	387 (37)	660 (63)	418 (40)	629 (60)	435 (42)	612 (58)
Black	131 (9)	69 (53)	62 (47)	49 (37)	82 (63)	53 (40)	78 (60)	65 (50)	66 (50)
Asian	79 (5)	49 (62)	30 (38)	46 (58)	33 (42)	47 (59)	32 (41)	46 (58)	33 (42)
Other	80 (5)	47 (59)	33 (41)	25 (31)	55 (69)	33 (41)	47 (59)	41 (51)	39 (49)
Undeclared	61 (4)	28 (46)	33 (54)	28 (46)	33 (54)	28 (46)	33 (54)	23 (38)	38 (62)
Year of metastatic diagnosis									
2013	229 (15)	121 (53)	108 (47)	74 (32)	155 (68)	87 (38)	142 (62)	57 (25)	172 (75)
2014	355 (24)	189 (53)	166 (47)	132 (37)	223 (63)	141 (40)	214 (60)	162 (46)	193 (54)
2015	367 (25)	197 (54)	170 (46)	130 (35)	237 (65)	150 (41)	217 (59)	172 (47)	195 (53)
2016	372 (25)	175 (47)	197 (53)	139 (37)	233 (63)	143 (38)	229 (62)	177 (48)	195 (52)
2017	174 (12)	95 (55)	79 (45)	91 (52)	83 (48)	92 (53)	82 (47)	99 (57)	75 (43)
Stage at diagnosis									
0-III	172 (11)	103 (60)	69 (40)	35 (20)	137 (79)	47 (27)	125 (73)	90 (52)	82 (48)
IV (IVA, IVB, IVC)	1,325 (89)	674 (51)	651 (49)	531 (40)	794 (60)	566 (43)	759 (57)	577 (44)	748 (56)
Practice type									
Academic	1,152 (77)	564 (49)	588 (51)	511 (44)	641 (56)	523 (45)	629 (55)	517 (45)	635 (55)
Community	345 (23)	213 (62)	132 (38)	55 (16)	290 (84)	90 (26)	255 (74)	150 (43)	195 (57)

NOTE. Data presented as No. (%).

Abbreviation: dMMR, mismatch repair deficient.

^aIn 3 cases, age was unspecified.

which corresponds with increasing usage of NGS. Observed undergenotyping rates in this analysis are consistent with previous reports of *KRAS* testing rates (30%-48%) between 2008 and 2013.^{18,19,21}

Undergenotyping for guideline-recommended biomarkers may place patients at risk for receiving ineffective anti-EGFR MAb therapy and/or missing the opportunity to receive appropriate immunotherapy options. Although *RAS* and *BRAF* testing is recommended for all patients with mCRC, it may be reasonable to omit testing for patients who are not candidates for targeted therapy. However, in this cohort, 72% of patients receiving cetuximab and/or panitumumab were undergenotyped, providing evidence against the hypothesis that low testing rates are explained by patients not being considered for anti-EGFR therapy.

Using the observed real-world mutation rates for *KRAS*, *NRAS*, and *BRAF* (62%, 7%, 17%), we estimated the proportion of patients who would have been considered

candidates for anti-EGFR therapies had all patients undergone complete biomarker testing. Only 14% of patients with mCC (210 patients) would have tested *KRAS*, *NRAS*, and *BRAF* wild type and thus qualified for anti-EGFR therapy. However, using the actual testing rates, 895 patients (60%) had no documented mutation, leaving 685 patients who might have erroneously been offered anti-EGFR therapy. Giving anti-EGFR therapy to patients who are *RAS/RAF* positive poses risks to patients, in particular severe infusion reactions, which occur in 3% of patients given cetuximab and 1% of patients given panitumumab.^{22a} In addition, MAb therapies are expensive relative to testing costs. Assuming a conservative cost of \$6,500 for comprehensive NGS, and \$6,000/wk for cetuximab 250 mg/m², only 4.6% (32 of 685) of the undergenotyped patients receiving inappropriate therapy for 1 year would cover the costs for testing of all 1,497 patients in this study.²²

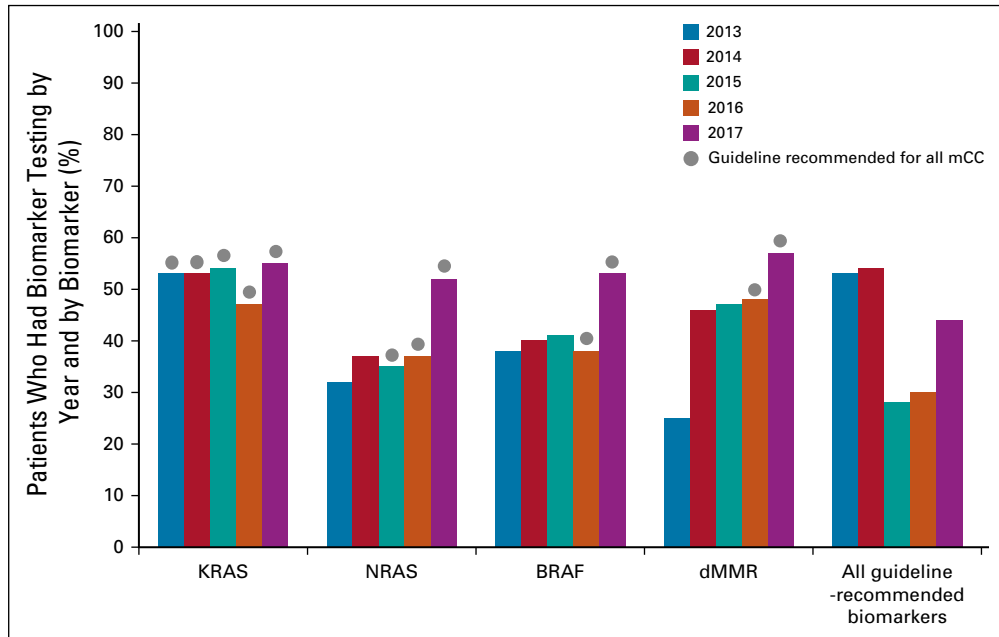


FIG 3. Observed testing rates over time by biomarker. Percentage of patients who had biomarker testing for each biomarker by any methodology (including both limited and expanded analysis) by year. The last category represents the proportion of patients who had guideline-aligned testing by year. Guideline-aligned testing in 2013-2014 included testing for *KRAS* by any methodology, in 2015 included extended testing of *NRAS* and *KRAS*, and in 2016-2017 included extended testing of both *KRAS* and *NRAS*, *BRAF* testing by any methodology, and microsatellite instability/mismatch repair deficiency (dMMR) analysis by any methodology. mCC, metastatic colon cancer.

Although NCCN guidelines do not specify a preferred methodology for biomarker testing, a sequential approach to testing multiple biomarkers amplifies challenges with tissue insufficiency, turnaround time, and cost.²³ We saw increased use of NGS for biomarker testing between 2013 and 2017 for *KRAS*, *NRAS*, and *BRAF*. Broader adoption of NGS multigene panel testing in mCC may improve undergenotyping rates. If every patient in this study who was tested for at least one biomarker had a tissue- or plasma-based NGS panel with comprehensive coverage of

extended *RAS*, *BRAF*, and MSI, we would have observed a nearly 50% increase in the percentage of patients who had guideline-aligned biomarker testing (from 40% to 59%). Still, > 40% of patients would have received no biomarker testing. Therefore, additional barriers must exist, preventing adoption of tissue-based biomarker testing in mCC.

Barriers to molecular testing in mCC have not been well studied but may include tissue availability, turnaround time, physician education/knowledge, cost/insurance coverage, patient preference, and patient eligibility for therapy on the basis of performance status and comorbidities.^{18,24} A qualitative study of oncologists' perspectives on *KRAS* testing in 2010 found all participating clinicians reported ordering *KRAS* testing and endorsed the value of testing, but there was a lack of consensus on test timing and confusion about what tissue sample to test (fresh v archival and primary v metastatic).²⁵ A 2018 survey of US oncologists, pathologists, and surgeons about MSI/dMMR testing practices in mCRC found 84% were aware of published guidelines for dMMR/MSI testing in patients with mCRC, and 78% followed published guidelines. Although the majority of physicians (69%) stated they perform universal testing for all patients with mCRC, nearly 30% of physicians selected patients for testing on an individualized basis. The most commonly cited barriers to MSI/dMMR testing were insufficient tissue (48.3%), patient refusal (35.8%), and insurance cost concerns (31.1%).²⁴ In the

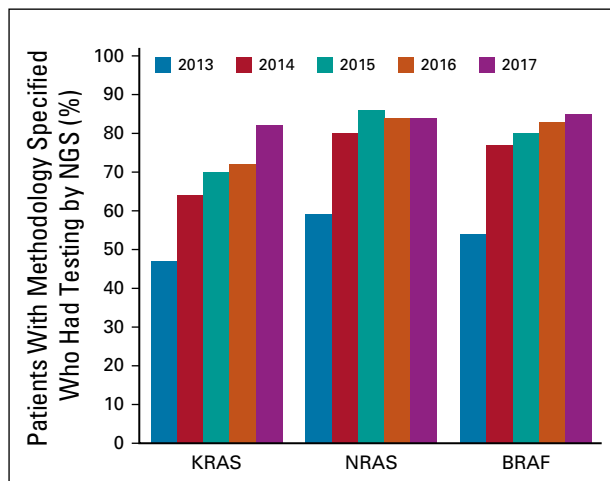


FIG 4. Percentage of testing completed by NGS by year.

current study, guideline-aligned testing was significantly more likely if the patient was diagnosed with de novo metastatic disease. More complete testing in patients with de novo metastatic disease versus patients who experienced progression from an earlier stage may suggest challenges in obtaining archival tissue specimens or patient or physician resistance to repeat tissue biopsy related to complication risks or financial pressures.

Several well-validated plasma-based NGS assays that include comprehensive analysis of biomarkers from circulating tumor DNA (ctDNA) have demonstrated high sensitivity, specificity, and concordance with tissue genotyping. As with tissue genotyping, ctDNA testing can predict response to targeted therapies (MSI-High, *BRAF* V600E mutated, *ERBB2* amplified, *NTRK* fusions) and lack of response to anti-EGFR treatment but may also reduce barriers associated with obtaining archival tissue or rebiopsy (Gupta et al, manuscript in review).^{25a,26-35} Given the relative ease of use and rapid turnaround time, plasma-based NGS offers one method of overcoming barriers associated with tissue testing, but other strategies to reduce undergenotyping must be explored, including physician education, implementation of testing protocols like universal MSI/dMMR screening, and use of electronic health records to identify patients who require genotyping.

There are multiple limitations of this study. Mainly, the study relied on medical record input for database review. Patients whose genomic testing was not documented in the medical record could have led to errors of omission. It is also possible that patients had biomarker testing before being referred to the centers included in this data set, and this testing was not documented in the record. In addition, data were collected only on patients with colon cancer. Guideline recommendations for *KRAS*, *NRAS*, *BRAF*, and MSI all specify testing for metastatic colorectal cancer. Prior

studies suggest that patients with rectal cancer are tested less frequently than those with colon cancer.¹⁹ Therefore, true testing rates for mCRC may be lower than what is presented in this mCC study. It is also important to note that more than three-quarters of the patients in the cohort were treated at academic centers. In 2017, 94% of the cohort was treated at academic centers. Our data demonstrate that patients were more frequently tested for *NRAS*, *BRAF*, and dMMR if they were treated at an academic center. With only 19% of the cohort being nonwhite, we were unable to make statistically significant conclusions about the impact of race on genotyping rates. This is an important factor that should be further explored in diverse patient cohorts.

Mutation-positive rates reported for *KRAS*, *NRAS*, and *BRAF* in this study were higher than previously published literature, including a large cohort of mCRC tumors sequenced by MSK-IMPACT, which cites *KRAS*, *NRAS*, and *BRAF* mutation rates of 45%, 4%, and 12%, respectively.³⁶ We acknowledge a potential for positive result bias, with physicians documenting positive results in their clinical notes more often than negative results. This would only affect the findings of this study if result were not documented elsewhere (in the laboratory or pathology sections of the record). Last, reasons for undergenotyping were not documented in the COTA database. There may have been factors such as treatment ineligibility or refusal that contributed to undergenotyping rates.

The results of this study indicate that adherence to evidence-based biomarker testing guidelines in mCC remains poor in both academic and community settings in the United States, with only 40% of patients completing guideline-aligned biomarker testing. Improving guideline-recommended biomarker testing in this disease would potentially reduce exposure to expensive and ineffective therapies, resulting in improved patient outcomes.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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