Research Article

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KRAS Testing and Epidermal Growth Factor Receptor Inhibitor Treatment for Colorectal Cancer in Community Settings

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Abstract

Background: In metastatic colorectal cancer (mCRC), mutations in the *KRAS* gene predict poor response to EGF receptor (EGFR) inhibitors. Clinical treatment guidelines now recommend *KRAS* testing if EGFR inhibitors are considered. Our study investigates the clinical uptake and utilization of *KRAS* testing.

Methods: We included 1,188 patients with mCRCs diagnosed from 2004 to 2009, from seven integrated health care delivery systems with a combined membership of 5.5 million. We used electronic medical records and targeted manual chart review to capture the complexity and breadth of real-world clinical oncology care.

Results: Overall, 428 patients (36%) received *KRAS* testing during their clinical care, and 266 (22%) were treated with EGFR inhibitors. Age at diagnosis ($P = 0.0034$), comorbid conditions ($P = 0.0316$), and survival time from diagnosis ($P < 0.0001$) influence *KRAS* testing and EGFR inhibitor prescribing. The proportion who received *KRAS* testing increased from 7% to 97% for those treated in 2006 and 2010, respectively, and 83% of all treated patients had a *KRAS* wild-type genotype. Most patients with a *KRAS* mutation (86%) were not treated with EGFR inhibitors. The interval between mCRC diagnosis and receipt of *KRAS* testing decreased from 26 months (2006) to 10 months (2009).

Conclusions: These findings show rapid uptake and incorporation of this predictive biomarker into clinical oncology care.

Impact: In this delivery setting, *KRAS* testing is widely used to guide treatment decisions with EGFR inhibitors in patients with mCRCs. An important future research goal is to evaluate utilization of *KRAS* testing in other delivery settings in the United States. *Cancer Epidemiol Biomarkers Prev; 22(1); 91–101. ©2012 AACR.*

Introduction

KRAS testing is used to help make treatment decisions for patients with metastatic colorectal cancer (mCRC). The *KRAS* gene is present in tumors in 2 forms: mutated and wild-type. For patients whose tumor tissue expresses the wild-type *KRAS* genotype, combination treatment with EGF receptor (EGFR) inhibitors and chemotherapy has been shown to improve survival (1). Patients with the mutated form of *KRAS* do not experience this survival benefit. Thus *KRAS* testing allows oncologists to tailor the use of EGFR inhibitors, cetuximab (Erbitux, ImClone Systems Incorporated) or panitumumab (Vectibix, Amgen Incorporated), to increase treatment effectiveness, minimize adverse events, and be cost-effective.

In February 2009, the American Society of Clinical Oncology (ASCO) recommended that "All patients with mCRC who are candidates for anti-EGFR antibody therapy should have their tumor tested for *KRAS* mutations" (2). The National Comprehensive Cancer Network (NCCN) guidelines were revised in November, 2008, to recommend EGFR inhibitors only for patients with *KRAS* wild-type genotype (3). This was revised again to include cetuximab and panitumumab as first line therapies in 2009 and 2011, respectively (4, 5). The U.S. Food and Drug Administration (FDA) also changed labeling for EGFR inhibitors to describe the appropriate use of *KRAS* genetic testing (6). No studies have yet

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examined how *KRAS* testing has been disseminated in general practice in the United States. This study addresses this gap and is among the first to assess characteristics associated with *KRAS* testing across multiple integrated health care delivery systems serving diverse communities.

In this study, we examine factors previously associated with variable adoption of technologies for cancer diagnosis and treatment, such as advanced age, poor pretreatment health status, minority race ethnicity, lower socioeconomic status (SES), and higher comorbidity. Because EGFR inhibitors were recommended primarily as second-line therapies during the study period, we examined whether patient factors are associated with *KRAS* testing. We describe real-world trends in adoption of *KRAS* testing, timing of *KRAS* testing relative to cancer diagnosis and chemotherapy initiation, use of EGFR inhibitors by *KRAS* test status and result, and variations in testing and treatment across study sites. The overall purpose of these analyses is to help guide future efforts to disseminate other novel genomic tests.

Materials and Methods

Research environment

This research was part of the Comparative Effectiveness Research in Genomics of Colon Cancer (CERGEN) study, which includes investigators from 8 Cancer Research Network (CRN) sites and partners from academic institutions (7). We collected data at 7 CRN sites across the United States representing diverse populations. Integrated health care systems have: (i) a defined population; (ii) capitation payment; (iii) ownership of medical offices, hospitals, and pharmacies; (iv) an integrated medical record; and (v) exclusive relationships with one or more medical groups. Although not all integrated health care systems include all of these components, the key concept is that the health plan faces a single global budget which must pay for all medical care services. In 2008, about 25% of Americans received healthcare in Health Maintenance Organizations (8).

Definition of the eligible patient population

The study population includes 4,446 patients enrolled at 1 of 7 CRN study sites: Kaiser Permanente Northwest (OR and Washington), Kaiser Permanente Northern California, Kaiser Permanente Colorado, Kaiser Permanente Hawaii, Marshfield Clinic (WI), Henry Ford Health System (MI), and HealthPartners (MN and Western Wisconsin). Eligible patients were identified through tumor registries linked with electronic health information.

Eligible cases were those initially diagnosed with stage IV CRC between January 1, 2006, and December 31, 2009, and patients initially diagnosed with stage III CRC between January 1, 2004, and December 31, 2006, according to the criteria of the American Joint Committee on Cancer (AJCC; ref. 9). The earlier period for the stage III CRC cases allows adequate follow-up time to determine whether those cases eventually progressed to distant metastatic disease. Patients initially diagnosed at stage III were excluded if they did not progress to distant metastatic CRCs. Patients initially diagnosed at stage III were included to increase the available sample size and to evaluate whether *KRAS* test utilization differs depending on the initial stage at diagnosis. To ensure ascertainment of complete treatment data, we included only cases diagnosed while affiliated with the integrated health care delivery systems. Patients were excluded if they were diagnosed under the age of 18 years or if they did not maintain health plan affiliation for at least 1 year following diagnosis, allowing for a 3-month gap in affiliation. Patients with less than 1 year of follow-up were not excluded if the reason for disaffiliation was death. Patients were censored for death at any time after diagnosis or disaffiliation after 12 months following diagnosis.

This study was approved by the Institutional Review Boards (IRB) at Kaiser Permanente Northwest, Kaiser Permanente Hawaii, Kaiser Permanente Colorado, Marshfield Clinic Research Foundation, and Henry Ford Health System, and did not require written informed consent. The IRBs for the remaining sites ceded authority to the Kaiser Permanente Northwest IRB. A small number of members at each health plan have elected not to participate in anonymous or unconsented research protocols; thus, these patients were excluded.

Data collection

Each CRN site maintains electronic databases in a common, shared format called the virtual data warehouse (VDW; ref. 10), enabling us to use distributed code to extract clinical data on each participant. We used the vital signs, procedures, pharmacy, enrollment, encounter, diagnosis, and census databases. Each CRN site also maintains a tumor registry where clinical data are abstracted from the medical chart into an electronic database. We used the VDW tumor registry files to identify eligible cases and obtain electronic data. We queried electronic databases for patient characteristics (e.g., gender, age at diagnosis, race/ethnicity), tumor characteristics (cancer site, stage, histology), and treatment history (chemotherapies used and indicators of immunotherapy, radiation treatment, surgical treatment, hormone treatment, palliative care). We used group-level measures for SES derived from geo-coding (median household income and proportion of individuals in a census tract with a high school education), as individual-level factors were not available. The Charlson comorbidity index was computed on the basis of diagnosis information (11).

KRAS genetic testing

We used the *KRAS* genetic test data that was part of routine medical care. We obtained test information either by contacting each site's commercial vendor(s) for *KRAS*

testing directly and asking for a report, or through chart review. Data were abstracted from individual reports including the date of testing, ordering physician, and test result. We have described the methods used for genotyping and assessing the comparability in test results across testing laboratories (12).

Chart abstraction

Abstractors at each site manually extracted information on each study subject using standard data collection forms. Abstracted variables included verification of eligibility, demographics (race, ethnicity, smoking, alcohol use), family history of cancer, cancer treatment history including surgery, radiation, and chemotherapy, palliative care, genetic testing (including *KRAS*), and imaging to assess disease progression.

We trained abstractors by developing instructions and an abstraction manual and held a web-based training session. All abstraction forms were reviewed by a second reviewer to evaluate completeness and case eligibility. Abstraction forms were entered into an electronic database using double data entry to ensure accuracy.

Statistical analysis

Logistic regression modeling with *KRAS* testing as the outcome was conducted to identify factors that influence whether a patient was tested. Logistic regression was also used to evaluate factors affecting whether *KRAS* wild-type subjects were treated with EGFR inhibitors, using a binary variable indicating any use of cetuximab or panitumumab as the outcome of interest, and the covariates described below. Nonparametric ANOVA was used to characterize differences in interval to testing, as test interval was not normally distributed. All reported *P* values are for univariate models (unless otherwise stated) and are unadjusted for multiple testing. All confidence intervals reported from logistic regression are adjusted for the number of factors in the model using a Bonferroni correction.

KRAS testing was coded as a binary indicator, with a value of 1 if a subject received *KRAS* testing at any point in the course of their clinical care, and 0 if there was no evidence of *KRAS* testing. The following characteristics were included in the model as binary variables: whether or not the subject had surgery, received a referral to medical oncology, received an EGFR inhibitor, had a Medicare insurance product, and had a family history of cancer. The following characteristics were included in the model as continuous variables: age, body mass index (BMI), survival (in years), average household income, average percentage of people with high school education or better in census tract, and year of metastatic diagnosis. Categorical variables included: number of chemotherapy regimens (categorized as 0, 1, 2, 3, 4, or 5+), Charlson comorbidity index (categorized as 0, 1, 2, 3, 4, or 5+; ref. 11), cancer stage (categorized as III or IV), race (categorized as White, Asian, Black, Pacific Islander, American Indian, other, or unknown), ethnicity (categorized as Hispanic or not Hispanic), gender (categorized as male or female), and integrated health system (categorized as A–G representing the 7 systems).

We used SAS (v9.2, SAS Institute) to conduct all analyses. We produced descriptive statistics using PROC UNIVARIATE, MEANS, and FREQ. We conducted Wilcoxon rank-sum tests using PROC NPAR1WAY. We used logistic regression (using PROC LOGISTIC) to model the likelihood of receiving *KRAS* testing. Using both forward and backward selection methods resulted in the same set of features being included in the model.

Results

A total of 4,446 patients met our eligibility criteria. To obtain more comprehensive data, a subset were selected for manual chart review, which was completed on 2,099 (47%) patient charts, including 1,152 (43% of 2,704) stage III CRC cases and 947 (54% of 1,742) stage IV CRC cases. We confirmed a diagnosis of mCRCs for 1,188 patients (266 diagnosed at stage III and 922 diagnosed at stage IV). This was the cohort used for the remaining analyses. With one exception, all sites conducted manual chart review on all (100%; 3 sites) or nearly all (>90%; 3 sites) of the eligible cases. The remaining site, the largest, randomly selected a subset of 22% of charts for review due to resource constraints.

We identified a clinical *KRAS* test result for 428 patients with mCRC (36%; Table 1). Of those tested, 40% had a mutation in codon 12 or 13 (Table 2), consistent with reported mutation frequencies from other studies (13, 14). There was insufficient biologic tissue available for 465 patients (39%).

Trends in KRAS test utilization

Beginning in June, 2008, there was a striking increase in utilization of *KRAS* testing (Fig. 1). The decline in the number of tests ordered toward the end of 2010 may be a product of study enrollment ending in December, 2009.

Of those who received *KRAS* testing, the median time between mCRC diagnosis and *KRAS* testing was about 10 months, with a range of 0 days to 4 years. There were significant changes in this interval over time (Wilcoxon rank-sum, $P < 0.0001$). From 2006 to 2009, the median interval between mCRC diagnosis and *KRAS* testing declined from 2.2 years to 2 months. Over the same time frame, EGFR inhibitors were used earlier within the patient's course of clinical care, with a median interval from metastatic diagnosis date to treatment with an EGFR inhibitor (among those receiving EGFR inhibitors) of 25 months in 2006 and 7 months in 2009. The interval between *KRAS* testing and initiation of EGFR inhibitor treatment increased from one month in 2006 to about 3 months in 2009. The percentage of patients tested within 90 days of mCRC diagnosis (an arbitrary threshold) is significantly associated with year of mCRC diagnosis, increasing from 5% in 2006 to 29% in 2009 ($P < 0.0001$; Table 3).

Table 1. Treatment status, health status, and demographic features of subject who did and did not receive *KRAS* testing as part of their clinical care for CRC

Characteristic	Value	Tested	Not tested	*P*	Characteristic	Value	Tested	Not tested	*P*
Chemotherapy	0	13	171	<0.0001	Race	White	306	520	<0.0001
Regimens	1	28	146			Asian	42	52	
	2	75	99			Black	37	90	
	3	117	53			Pacific Is.	13	11	
	4	80	49			Am. Indian	2	4	
	≥5	264	93			Other	10	31	
						Unknown	15	55	
Surgery[a]	No	105	351	<0.0001	Ethnicity	Not Hispanic	319	592	0.0984
	Yes	322	410			Hispanic	27	45	
Referral to Med.	No	5	166	<0.0001	Gender	Male	222	379	0.1368
oncology	Yes	407	610			Female	205	381	
BMI Category	<20	17	61	<0.0001	Household	<$40K	95	221	0.0024
	20–24	89	165		income	$40K–$59K	142	263	
	25–29	122	182			$60K–$79K	90	141	
	≥30	114	150			≥$80K	63	107	
Age at diagnosis, y	<50	63	75	<0.0001	% High school	<50%	4	12	<0.0001
	50–59	124	110		education	50–69%	36	63	
	60–69	143	149			70–89%	197	383	
	70–79	73	230			≥90%	166	260	
	≥80	22	199						
Charlson Co-morbidity	0	291	356	<0.0001	Year of metastatic	2006	50	211	<0.0001
index	1	170	176		diagnosis	2007	123	228	
	2	54	80			2008	179	194	
	3	12	18			2009	93	110	
	4	8	13		Medicare	No	274	581	<0.0001
	≥5	2	8			Yes	150	183	
Any EGFR inhibitor	No	262	674	<0.0001	Organization	A	44	57	<0.0001
	Yes	164	88			B	170	256	
Survival interval, y	0.5	28	438	0.0010		C	57	92	
(if deceased)	0.5–1	36	94			D	66	127	
	1–2	73	131			E	37	87	
	≥2	241	147			F	18	44	
Family history of cancer	No	129	220	<0.0001		G	37	96	
	Yes	214	296		Cancer stage	III	120	146	<0.0001
	Unk	86	243			IV	313	609	

NOTE: *P* values are unadjusted, from χ^2 tests.
[a]Colectomy or hemicolectomy.

KRAS test association with patient treatment

Overall, 252 patients (21%) received an EGFR inhibitor during the course of their clinical care. When looking solely at EGFR inhibitor use, the majority received cetuximab alone (214; 85%). The remainder received both cetuximab and panitumumab in different lines of therapy (26; 10%) or panitumumab alone (12; 5%). These drugs were received either alone or in combination with other therapies.

Most patients who received EGFR inhibitors (65%) also received *KRAS* testing, and nearly all patients who received EGFR inhibitors (83%) had a *KRAS* wild-type genotype. Of the 25 patients who had a *KRAS* mutation and yet received EGFR inhibitors, 16 were tested after EGFR inhibitor treatment was initiated, and an additional 7 were tested before mid 2008. Only 2 were tested and treated with an EGFR inhibitor after the recommendations went into place. Among those who received EGFR

Table 2. Association of *KRAS* testing and treatment with EGFR inhibitors among patients with mCRCs

	Treated with EGFR inhibitors[a]	Not treated with EGFR inhibitors	Total
No *KRAS* test	89 (35%)	671 (72%)	760 (64%)
KRAS test[b]	163 (65%)	265 (28%)	428 (36%)
WT	136 (83%)	110 (42%)	246 (57%)
Mutation	25 (15%)	152 (57%)	177 (42%)[c]
Insufficient sample	2 (1%)	3 (1%)	5 (1%)

[a]Patient was treated with cetuximab or panitumumab at any time during the course of their clinical care.

[b]A *KRAS* test was ordered as part of the patient's clinical care. Insufficient sample = a test was ordered but no *KRAS* genotype was reported.

[c]About 40% had mutations in codon 12 or 13. An additional 2% had a mutation detected in codon 61. However, not all labs tested codon 61 as part of their *KRAS* sequencing protocol.

Abbreviations: WT, wild-type genotype; mutation, any *KRAS* mutation for any codon tested, primarily codons 12 and 13 for most patients.

inhibitors, the year EGFR therapy was initiated was strongly associated with receipt of *KRAS* testing at any time and also strongly associated with receipt of *KRAS* testing before initiating treatment with EGFR inhibitors (Fig. 2; Table 3). By 2009, more than 96% of patients who received EGFR inhibitors were tested for *KRAS* status before initiating therapy.

In contrast, among those who did not receive treatment with EGFR inhibitors ($n = 936$), only 265 (28%) were tested for *KRAS*. There were 152 (57%; of 265) patients with a *KRAS* mutation who did not receive EGFR inhibitors, consistent with current recommendations. There were 110 (42%) patients with *KRAS* wild-type genotype who did not receive EGFR inhibitors. These *KRAS* wild-type patients were diagnosed more recently (median mCRC diagnosis month of August 2008 vs. December 2007; Wilcoxon rank-sum, $P = 0.0026$), had received *KRAS* testing more recently (median *KRAS* test month December 2009 vs. May 2009; $P = 0.0036$), and had received fewer lines of therapy (mean number of 1.7 vs. 2.4 lines of therapy; Wilcoxon rank-sum, $P < 0.0001$) compared with patients with *KRAS* wild-type genotype who received EGFR inhibitors. These patients had similar age at diagnosis ($P = 0.71$), BMI ($P = 0.82$), comorbidity index ($P = 0.58$), interval to *KRAS* testing ($P = 0.38$), gender ($P = 0.35$), race ($P = 0.90$), ethnicity ($P = 0.35$), Medicare status ($P = 0.91$), and length of survival ($P = 0.07$) compared with patients with *KRAS* wild-type genotype who received EGFR inhibitors. Patients with *KRAS* wild-type who had not yet received EGFR inhibitors are at an earlier point in their cancer treatment and may have received EGFR inhibitors after the close of the study window or have yet to receive them.

Most patients (60%) received EGFR inhibitors as part of their last reported line of therapy; 22% received EGFR inhibitors as a middle line treatment, and 18% as their first-line treatment. For patients diagnosed before mid 2008, only 45%, 53%, and 63% of patients who received EGFR inhibitors as their first line, middle line, or last line of therapy, respectively, ever received *KRAS* testing. For patients diagnosed after mid 2008, the proportion who received *KRAS* testing increased to 82%, 88%, and 94% of patients who received EGFR inhibitors as their first line, middle line, or last line of therapy, respectively.

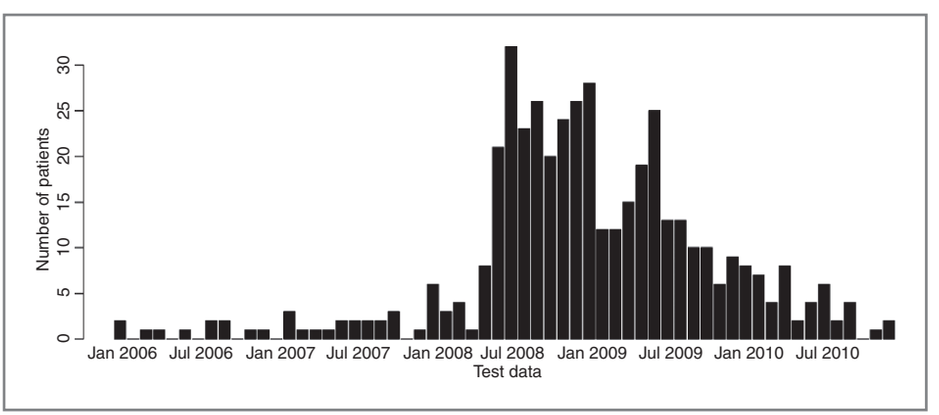

Figure 1. Overview of *KRAS* test utilization for study participants.

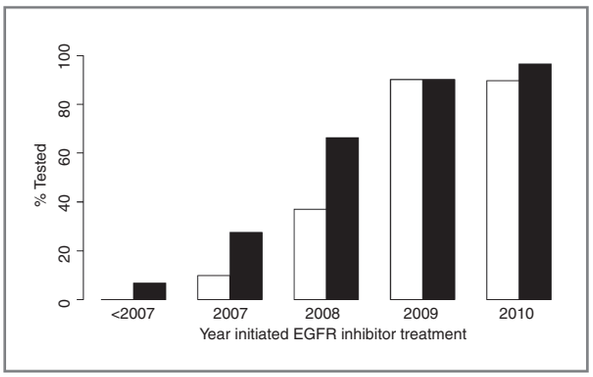

Figure 2. Percentage of patients who received *KRAS* testing before EGFR Inhibitor treatment (white bars) and at any time in their clinical care (black bars) by year that EGFR inhibitor treatment was initiated, among patients who received EGFR inhibitors.

Patient characteristics

Several aspects of patients' treatment history, health status, and demographics were significantly associated with *KRAS* testing status.

Treatment history. Patient treatment history was a strong predictor of receipt of *KRAS* testing (Table 4). Patients who did not receive any chemotherapy were significantly less likely to receive *KRAS* testing than patients who received at least one line of chemotherapy (7% vs. 60%, adjusted $P < 0.0001$). Patients receiving more lines of chemotherapy were more likely to receive *KRAS* testing. The remaining treatment history variables that we considered were no longer significant after adjusting for cancer stage, number of lines of therapy, age at diagnosis, survival interval, Charlson comorbidity index, and metastatic diagnosis date.

Health status. Patient overall health status was another significant determinant of receipt of *KRAS* testing (Table 4). Patients with increasing age ($P = 0.003$), more comorbidities ($P = 0.03$), or who were deceased within 6 months of diagnosis with mCRCs ($P = 0.001$) were significantly less likely to receive *KRAS* testing after adjustment for other factors. These patients were also significantly less likely to receive any form of chemotherapy (e.g., 33% vs. 76% received any chemotherapy for those over/under 80 years old, respectively; 50% vs. 76% received any chemotherapy for those with more/less than 5 comorbidities, respectively; 61% vs. 72% received any chemotherapy for those with less/more than 6 months survival following diagnosis with mCRCs, respectively).

Demographics. None of the demographic characteristics were associated with receipt of *KRAS* testing after adjusting for treatment history, clinical characteristics, and health status (Table 4).

Provider characteristics

For three sites, we were able to collect information on the ordering physician. Across these sites, 89% (117 of 131) of medical oncologists ordered at least one *KRAS* test. Because the *KRAS* test is so widely adopted among clinicians at these sites, we did not explore provider characteristics further, as this is unlikely to be a major explanation for practice variation in this study.

System characteristics

Insurance product. Although there is limited variation on type of insurance for patients in this study, patients with Medicare coverage were more likely to receive *KRAS* testing than patients without this coverage; however, that difference appears to be explained by other clinical factors, as evidenced by the insignificant Wald χ^2 P value in the multivariate modeling (45% vs. 32%, adjusted $P = 0.19$).

Geographic distribution. We observed significant variation across sites in the proportion of patients who received *KRAS* testing ranging from 28% to 44% ($P = 0.02$; Fig. 3). There was more substantial variation in the median interval between diagnosis and receipt of *KRAS* testing by site ranging between about 3 months and 1 year (Wilcoxon rank-sum test, $P < 0.0001$).

Table 3. Timing of *KRAS* test within the course of mCRC diagnosis and treatment among patients who received *KRAS* testing

	Tested, *n* (%)					
Year of mCRC diagnosis	Before mCRC diagnosis	At mCRC diagnosis (<90 d)	Between diagnosis and treatment[a]	Before treatment[a] (<90 d)	After treatment initiated[a]	Total
2006	2 (6%)	3 (9%)	3 (9%)	13 (38%)	15 (44%)	34
2007	3 (5%)	4 (7%)	14 (24%)	16 (27%)	23 (39%)	59
2008	3 (5%)	19 (31%)	13 (21%)	21 (34%)	12 (19%)	62
2009	3 (12%)	13 (50%)	4 (15%)	9 (35%)	3 (12%)	26

NOTE: *KRAS* test dates are unknown for 71 participants.

[a]Treatment with EGFR inhibitors. Includes those tested but not yet treated.

Table 4. Multivariate modeling of relationship of mCRC patient characteristics to receipt of *KRAS* testing as part of clinical care

Treatment status characteristics						Demographic characteristics					
Characteristic	**Value**	***N***	**% Tested**	**OR (95% CI)**	***P*[b]**	**Characteristic**	**Value**	***N***	**% Tested**	**OR (95% CI)**	***P***
Chemotherapy regimens	0	184	7	0.02 (0.003–0.10)	<0.0001	Race	White	826	37	–	0.8221
	1	174	16	0.08 (0.06–0.10)			Asian	94	45	0.6 (0.3–1.2)	
	2	174	43	0.43 (0.33–0.57)			Black	127	29	0.8 (0.4–1.7)	
	3	170	69	1.05 (0.86–1.30)			Pacific Is.	24	54	1.0 (0.3–3.0)	
	4	129	62	0.41 (0.36–0.44)			Am. Indian	6	33	0.8 (0.1–7.9)	
	≥5	357	74	–			Other	41	24	1.6 (0.4–2.8)	
							Unknown	70	21	1.0 (0.4–2.5)	
Surgery[a]	No	456	23	0.63 (0.40–0.91)	0.0187	Ethnicity	Not Hispanic	911	35	–	0.5002
	Yes	732	44	–			Hispanic	72	38	0.7 (0.3–1.4)	
Referral to Med. oncology	No	171	3	0.77 (0.21–2.5)	0.6569	Gender	Male	601	37	–	0.5899
	Yes	1017	40	–			Female	586	35	0.8 (0.6–1.2)	
Any EGFR inhibitor	No	936	28	–	0.0014	Household income	<$40K	316	30	0.8 (0.5–1.4)	0.4753
	Yes	252	65	2.0 (1.3–3.1)			$40K–$59K	405	35	–	
Health status characteristics							$60K–$79K	231	39	1.3 (1.1–1.4)	
Characteristic	**Value**	***N***	**% Tested**	**OR (95% CI)**	***P***		≥$80K	170	37	1.2 (1.1–1.5)	
Age at diagnosis, y	<50	138	46	1.4 (0.8–3.0)	0.0034	% High school education	<50%	16	25	0.7 (0.1–3.3)	0.9924
	50–59	234	53	2.4 (2.3–3.0)			50–69%	99	36	1.4 (1.0–1.8)	
	60–69	292	49	1.7 (1.3–2.5)			70–89%	580	34	–	
	70–79	303	24	–			≥90%	426	39	1.2 (1.0–1.4)	
	≥80	221	10	0.4 (0.3–0.7)							
Charlson Co-morbidity index	0	647	45	–	0.0316	Year of metastatic diagnosis	2006	261	19	0.06 (0.02–0.1)	<0.0001
	1	346	49	0.5 (0.1–1.4)			2007	351	35	0.2 (0.2–0.5)	
	2	134	40	0.3 (0.1–0.8)			2008	373	48	–	
	3	30	41	0.5 (0.2–1.7)			2009	203	46	0.9 (0.7–1.1)	
	4	21	38	0.6 (0.2–2.0)		Medicare	No	855	32	–	0.1883
	≥ 5	10	20	0.3 (0.1–0.8)			Yes	333	45	1.8 (0.9–2.2)	
BMI Category	<20	78	22	0.9 (0.4–2.0)	0.7945	Organization	A	101	44	0.7 (0.4–1.1)	0.0220
	20–24	254	35	0.9 (0.8–1.0)			B	426	40	–	
	25–29	304	40	–			C	149	38	0.6 (0.5–0.8)	
	≥30	264	43	1.2 (1.1–1.3)			D	193	34	0.6 (0.4–0.8)	

(Continued on the following page)

Table 4. Multivariate modeling of relationship of mCRC patient characteristics to receipt of *KRAS* testing as part of clinical care (Cont'd)

Treatment status characteristics						Demographic characteristics				
Characteristic	**Value**	***N***	**% Tested**	**OR (95% CI)**	***P*[b]**	**Characteristic**	**Value**	***N***	**% Tested**	**OR (95% CI)**	***P***
Survival interval, y (if deceased)	0.5	466	6	–	0.0010		E	124	30	0.3 (0.2–0.4)	
	0.5–1	130	28	1.9 (0.8–4.3)			F	62	29	0.6 (0.4–0.8)	
	1–2	204	36	2.9 (1.4–6.3)			G	133	28	1.0 (0.6–1.3)	
	≥2	388	62	5.1 (2.3–11.4)		Family history of cancer	No	349	37	0.9 (0.6–1.3)	0.5208
							Yes	510	42	–	
Cancer stage	III	266	45	1.7 (1.1–2.5)	0.0078		Unknown	329	26	0.7 (0.4–0.9)	
	IV	922	34	–							

NOTE: The largest group in each category is used as the basis of the OR.
Abbreviation: CI, confidence interval.
[a]Colectomy or hemicolectomy.
[b]All reported Wald χ^2 *P* values and ORs are from a logistic regression model including all factors in Table 4, and a binary variable indicating presence or absence of *KRAS* testing as the response variable. As the reported percent tested is based on the raw, unadjusted counts, there can be apparent discrepancies between the percent tested and the reported adjusted ORs.

Figure 3. System characteristics. Practice variation in (A) the proportion of patients who received *KRAS* testing and (B) the median test interval (number of days between diagnosis with mCRCs and receipt of *KRAS* testing) across integrated health systems participating in this study.

Discussion

This study illustrates the remarkably rapid and wide adoption of *KRAS* testing by clinicians in integrated health care delivery settings. In these settings, *KRAS* testing programs began in mid 2008 before changes in professional or regulatory guidance. Since 2009, more than 94% of patients who received EGFR inhibitors were tested for *KRAS* status before initiating therapy. Eighty-three percent of patients treated with EGFR inhibitors had a *KRAS* wild-type genotype. Most patients with a *KRAS* mutation (86%) were not treated with EGFR inhibitors. Almost 90% of oncologists in our study ordered at least one *KRAS* test. Although overall only 36% of the patients in the study population received *KRAS* testing, these decisions appear to be personalized and tailored to individual patient characteristics. Major factors influencing testing were related to patient treatment history (e.g., patients who did not receive any chemotherapy were less likely to be tested) and also to overall health status—those who were elderly, had multiple comorbidities, or who were deceased within 6 months of mCRC diagnosis were less likely to be tested.

Two events immediately preceded the rapid increase in *KRAS* testing beginning in June 2008. First, at ASCO's annual meeting in late May 2008, retrospective analyses of the CRYSTAL (15) and OPUS (16) randomized clinical trials were presented show the lack of effect for EGFR inhibitors in patients with *KRAS* mutations. Second, the European Medicines Agency (EMEA) Committee for medicinal products for human use (CHMP) issued an opinion in May 2008 indicating the use of EGFR inhibitors for treatment of patients with mCRCs who are *KRAS* wild-type (17). It is remarkable that this increase occurred before release of guidance in the United States from ASCO, the FDA, or the NCCN.

Our findings illustrate a low risk for disparities in access to testing and/or treatment in these settings. Although measures of SES (i.e., household income, education, and Medicare status) were associated with *KRAS* testing status in unadjusted comparisons, these associations were no longer significant after adjustment for other patient characteristics. We did observe unexplained variation across sites in the proportion of patients who receive *KRAS* testing and in the timing of *KRAS* testing, suggesting that system-wide factors (e.g., institutional policies, treating physician preference) may influence test use even after accounting for the patient's disease status and treatment.

The variation across sites has practical implications for the effectiveness of the *KRAS* testing program. Ideally, the *KRAS* test will only be used for patients who are eligible and considered for this treatment, but most patients (up to 80% in this study) may never receive EGFR inhibitors. As the interval between mCRC diagnosis and *KRAS* testing is decreasing over time, we evaluated whether the sites with the shorter median testing interval were simply late adopters of *KRAS* testing. Although this may be an explanation for one site with the shortest median interval, it does not explain the overall trend across the remaining sites.

The primary limitation of this study is that it was conducted only within integrated health care delivery systems, which may differ significantly from other types of delivery systems. An important future research goal is to evaluate utilization of *KRAS* testing in other delivery settings in the United States. Outside of the United States, a recent report evaluated the uptake of the *KRAS* test in Asia, Latin America, and Europe (18). They also noted rapid uptake of testing from 3% in 2008 to 69% in 2010, with significant regional variation of 78%, 63%, and 44% receiving *KRAS* testing in 2010 in Europe, Latin America, and Asia, respectively. The majority of patients in the Ciardiello study were selected for inclusion because they were receiving chemotherapy. Our results are not precisely comparable because we included all or nearly all (>90%) patients with mCRCs regardless of treatment status, and 32% of patients in our study did not receive any chemotherapy. Of the people who received any chemotherapy in 2010, 78% were tested for *KRAS* status.

Other limitations are related to the retrospective, observational nature of the study design. We did not collect information directly from patients and thus our findings are based solely on information from medical records and *KRAS* testing vendors. There is variation in the available follow-up time as patients diagnosed in 2009 were more likely to be censored. Also, there may be other unmeasured confounders that impact the interpretation of study results. For example, complications or poor health status not fully captured by our comorbidity measure also may have contraindicated chemotherapy.

The environment was also a strength of our study design. We leveraged the CRN research infrastructure to draw upon our coordinated systems of electronic data and tumor registries. Consistency of file structures and data definitions allows us to have efficiency in multi-institution research, such as facilitating use of the same criteria across sites in case definition and selection. Our work also highlights limitations to our research databases and electronic medical records. Importantly, (i) we had to use manual chart review to identify progression to mCRC (these study data will be used to develop and validate better prediction algorithms for future work), and (ii) we were not able to identify either who received the genetic test or the test results from electronic sources. Improved coding and recording of genetic test orders and results would greatly facilitate future studies.

The availability of new technologies is not usually sufficient for their optimal implementation in clinical practice (19–21). For example, utilization rates are typically low (~30%) for testing of inherited mutations in the *BRCA1/2* gene even among patients at high risk for breast cancer who are referred to genetic counseling (22–25). Observational studies such as ours have a larger sample size, a greater diversity of patients, and potentially a greater diversity of care models compared with the clinical trial settings that formed the basis of the professional recommendations. Thus, this study informs the ultimate purpose of improving patient outcomes and reducing population health disparities.

This study was one part of the CERGEN project, a comprehensive research program in comparative effectiveness research for genomic applications. This includes interviews with patients, providers, and health plan decision makers about the implementation of *KRAS* testing. This methodology may allow us to explore some of the unexplained practice variation across sites that we observed in this study. We also plan to compare outcomes for patients whose treatment decisions are guided by *KRAS* testing versus patients who did not receive testing. Through comparative effectiveness research, we have been able to describe the sequence of diffusion of mCRC treatment decision making guided by *KRAS* testing, made more valuable by the multisite and wide diversity of patients and geographic diversity of providers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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