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Factors associated with guideline-recommended *KRAS* testing in colorectal cancer patients: A population-based study

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Abstract

Objectives—Response to epidermal growth factor receptor inhibitors is poorer among Stage IV colorectal cancer (CRC) patients with *KRAS* mutations, thus *KRAS* testing is recommended prior to treatment. *KRAS* testing was collected by Surveillance, Epidemiology, and End Results (SEER) registries for 2010 CRC cases, and our goal was to provide the first population-based estimates of testing in the U.S.

Methods—SEER CRC cases diagnosed in 2010 were evaluated (n=30,351). Chi-square tests and logistic regression were conducted to determine patient characteristics associated with *KRAS* testing, stratified by Stages I-III vs. Stage IV. Log-rank tests were used to examine survival by testing status.

Results—*KRAS* testing among Stage IV cases ranged from 39% in New Mexico to 15% in Louisiana. In the model, younger age, being married, living in a metropolitan area, and having primary site surgery were associated with greater odds of receiving *KRAS* testing. Those who received testing had significantly better survival than those who did not (p<0.0001). Among those who received testing, there was no significant difference in survival by mutated vs. wild type *KRAS*. Five percent of Stage I-III cases received testing.

Conclusions—Wide variation in documented *KRAS* testing for Stage IV CRC patients exists among SEER registries. Age remained highly significant in multivariate models, suggesting it plays an independent role in the patient and/or provider decision to be tested. Further research is needed to determine drivers of variation in testing, as well as reasons for testing in Stage I-III cases where it is not recommended.

Keywords

colorectal cancer; epidemiology; *KRAS*; Surveillance; Epidemiology; and End Results Program

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Introduction

Approximately 136,830 new cases of invasive colorectal cancer (CRC) were diagnosed in 2014 in the United States (U.S.).¹ It is the third most commonly diagnosed cancer and third leading cause of cancer death in the U.S.¹ Twenty percent of CRC cases are Stage IV at diagnosis.² Anti-epidermal growth factor receptor (anti-EGFR) drugs have proven effective at slowing progression of Stage IV CRC.³⁻⁶ However, studies have demonstrated the presence of *KRAS* mutations, which occur in approximately 40% of Stage IV patients,^{7,8} make response to anti-EGFR therapy less likely.⁹⁻¹⁶

In 2009, both the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) published updated CRC treatment guidelines.^{9,17} NCCN recommends *KRAS* testing for all patients upon diagnosis of metastatic CRC, and that only those with tumors characterized by the wild-type *KRAS* gene should receive anti-EGFR therapy, while ASCO recommends *KRAS* testing in all patients for whom anti-EGFR therapy is being considered.^{9,17} Consequently, in 2010, *KRAS* was included as a site-specific factor (SSF) to be collected by the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) program.

While *KRAS* testing for Stages I-III CRC is not recommended, it has been suggested that *KRAS* status can be used as a prognostic indicator in all stages.¹⁸⁻²⁰ Our objectives were to document the U.S. population estimates of *KRAS* testing using data from the SEER Program for both Stage IV and Stages I-III CRC patients, as well as to determine factors associated with receipt of testing, including survival. In particular, geographic variation of *KRAS* testing was examined to highlight issues potentially related to differential diffusion, adherence or access to *KRAS* testing.

Materials and Methods

Data Source and Study Population

Cases of invasive CRC diagnosed in 2010 in any of the SEER 18 Registries: the states of California (including Los Angeles, San Francisco, San Jose and Greater California Registries), Connecticut, Georgia (including Atlanta, Rural Georgia and Greater Georgia Registries), Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah, as well as the metropolitan areas of Detroit and Seattle, were extracted using SEER*Stat (version 8.1.2). Cases were included in the analysis if they had diagnostic confirmation by positive histology and were of the histologic types included in the Colon & Rectal Cancer Collaborative Stage (CS) Schema v0204.²¹ Cases were excluded if they had an American Joint Committee on Cancer (AJCC) 7th Edition²² Stage equal to 'not applicable' (n=45) or 'unknown' (n=2093), if they were diagnosed on autopsy or death certificate only (n=28), if they were not microscopically confirmed (n=524), or if they had a histology of squamous cell neoplasms (n=161) or cloacogenic carcinoma (n=1). Furthermore, cases in the Alaska Natives registry (n=65) were excluded due to extremely small numbers. Special access to CRC SSF 9 (*KRAS* Testing) was granted by the NCI. This study was granted human subject exemption status by the University of Iowa Institutional Review Board.

Variables

The primary outcome variable was receipt of *KRAS* testing. Testing was considered done if the SSF 9 variable had a value of ‘abnormal (mutated)’ or ‘normal (wild type)’; otherwise *KRAS* testing was not considered to be done if coded as ‘test ordered, results not in chart’, ‘not done’ or ‘unknown’. Results of *KRAS* testing were also examined.

Patient demographic variables included age, gender, race, marital status, health insurance, SEER registry, and metropolitan (metro)/urban vs. non-metro/rural county of residence. Clinical variables included tumor location (colon vs. rectum and left/rectum vs. right side), histology, grade, first vs. subsequent primary cancer, and presence of other primary cancer(s). Treatment variables included primary site surgery and recommendation for, or receipt of, radiation therapy. The number of months survived post-diagnosis was also examined by stage and *KRAS* testing, with a maximum of 11 months of follow-up.

Statistical Analyses

Analyses were stratified by Stage IV vs. Stages I-III. In order to address the effect of incomplete documentation and/or incomplete clinical work-up on *KRAS* testing as recorded by the SEER registries, a missing category for variables with large numbers of missing values was included in analyses. Differences in characteristics between those with and without *KRAS* testing were assessed using chi-square tests. Multivariate logistic regression analyses were conducted to determine patient characteristics associated with *KRAS* testing, with all variables listed above (except AJCC T and N stage as they are main components in determining overall stage) considered for inclusion in the models. Variables that were not significant predictors ($p > 0.10$) of *KRAS* testing were removed in a manual backward selection process. Kaplan Meier curves and log-rank tests were used to evaluate the association between *KRAS* testing and survival. All tests of statistical significance were two-sided. Analyses were conducted using SAS software (version 9.3, SAS Institute, Cary, NC).

Results

The study population included 6,119 cases of Stage IV and 24,232 cases of Stages I-III CRC. Variables with missing case information included race ($n=229$), insurance ($n=871$), marital status ($n=1,614$), county of residence ($n=5$), grade ($n=2,761$), T stage ($n=1,512$), nodal status ($n=890$).

Table 1 summarizes *KRAS* values by stage and location (colon vs. rectum). The overall proportion of *KRAS* testing captured by SEER registries was 22.7% among Stage IV cases and 5.3% among Stages I-III cases. Of the 1,390 Stage IV cases who received *KRAS* testing, 58% were classified as wild type and 42% were classified as mutated. Among the 1,277 cases of Stages I-III who received testing, 64% were classified as wild type and 36% were classified as mutated. There was no significant difference in *KRAS* testing or mutation rates between colon and rectum sites for stage IV or I-III (results not shown).

Stage IV Cases

Among those with Stage IV CRC, for whom *KRAS* testing is recommended either upon diagnosis or prior to initiating anti-EGFR therapy, the following demographic characteristics were associated with higher proportions of *KRAS* testing (Table 2): younger age, white, other, or missing race (marginal association, $p=0.06$), being married, and living in an urban/metro area. Substantial variation between registries was detected, ranging from 15% receiving *KRAS* testing in Louisiana to 39% in New Mexico. The following tumor and treatment characteristics were also associated with higher proportions of *KRAS* testing (Table 3): adenoma/adenocarcinoma and cystic/mucinous/serous histology, non-missing grade, more advanced T stage, nodal involvement, single primary cancer, no prior cancer history, and primary site surgery. Cases with ‘not otherwise specified’ (NOS), ‘other’ or ‘unknown’ tumor characteristics had a lower proportion of *KRAS* testing compared to cases with specific information.

In multivariate analyses (Table 4), younger age, residing in New Mexico, Seattle, Hawaii, and having primary site surgery were associated with greater odds of receiving *KRAS* testing. Being single (never married) or missing marital status, having histology of epithelial neoplasm NOS or other/unspecified, missing grade information, receipt or recommendation for radiation, and residing in Louisiana or in non-metro areas were associated with lower odds of receiving *KRAS* testing.

Stage I-III Cases

Among those with Stages I-III, for whom *KRAS* testing is not explicitly recommended, the following demographic characteristics were associated with higher proportions of *KRAS* testing (Table 2): younger age, being single or divorced, having insurance or Medicaid, and living in a metropolitan area. Again, there was substantial variation among registries. Earlier stage CRC cases residing in Seattle and Kentucky had the highest proportions of testing (11.3% and 10.5%, respectively), whereas those in Louisiana or Iowa had the lowest (3.1% and 1.7%, respectively). The following tumor and treatment characteristics were associated with higher receipt of *KRAS* testing (Table 3): tumors with histology of cystic/mucinous/serous or other/unspecified, poor to undifferentiated grade, higher stage, more advanced T and N stages, no prior cancer, primary site surgery and radiation therapy.

In multivariate analyses (Table 4), younger age, being single (never married) or divorced, missing race cystic/mucinous/serous histology, poor to undifferentiated tumor grade, and higher stage (II or III) were associated with greater odds of receiving *KRAS* testing, while missing marital status, living in a non-metro area, missing grade, and being uninsured or missing insurance information were associated with lower odds of *KRAS* testing. In addition, those residing in Seattle, New Mexico, Kentucky or Georgia had greater odds of receiving *KRAS* testing, whereas those in Iowa, and New Jersey had lower odds of receiving *KRAS* testing.

Survival Time

Survival months by *KRAS* testing status and stage (IV vs. I-III) are displayed in Table 5. Those with Stage IV CRC who survived the longest had higher receipt of testing compared

to those who survived a shorter time. Thirty percent of Stage IV cases surviving at least 11 months received *KRAS* testing, compared to 14% of Stage IV cases surviving less than one month. Figure 1 shows the Kaplan Meier curves for Stage IV cases who received *KRAS* testing compared to those who did not. A log-rank test indicated curves were significantly different ($p<0.0001$). Among Stage IV cases who received *KRAS* testing, there was no significant difference in survival by mutated vs. wild type *KRAS* status (Supplemental Digital Content Figure 1).

The relationship between survival months and receipt of *KRAS* testing was much less pronounced among Stages I-III cases (Table 5). Four percent of those surviving less than one month received *KRAS* testing compared to 6% of those surviving at least 11 months, but proportions of testing increased and decreased between those time points. Supplemental Digital Content Figure 2 shows the Kaplan Meier curves for Stage I-III cases who received *KRAS* testing compared to those who did not. A log-rank test indicated the curves were significantly different ($p<0.0001$).

Discussion

Despite the recommendation by NCCN that all patients diagnosed with Stage IV CRC undergo *KRAS* testing for treatment planning purposes, SEER data indicate that only 23% of Stage IV cases received testing in 2010, and that testing rates vary substantially by geographic region and patient characteristics. Our estimate is similar to the 29% of cases found to be tested for *KRAS* mutations within 90 days of diagnosis of metastatic CRC in seven Health Maintenance Organizations (HMOs) across the U.S. in 2009.²³ The proportion tested also falls within the range found on medical record review of 3,820 patients seen by participating physicians for Stage IV CRC in 2010 across 14 countries in Europe, Latin America, and Asia (40%, 27%, and 12%, respectively).²⁴ A variety of factors may explain the low proportion and geographic variation of *KRAS* testing in our national, population-based estimates.

First, the recommendation by ASCO differs from that of NCCN in that *KRAS* testing is recommended for those who are being considered for anti-EGFR therapy, not all stage IV CRC patients.^{9,17} For patients diagnosed with very advanced disease with short life expectancies, the oncologist and/or patient may decide to forego treatment with chemotherapy, hence eliminating the need for *KRAS* testing.⁹ A recent nationwide study of stage IV CRC patients who received chemotherapy between January 2004 and March 2011 found 26% of these patients had received anti-EGFR therapy, with its use falling by 18% after the US Food and Drug Administration limited anti-EGFR use to patients with wild-type *KRAS* expression.²⁵ Although a benefit has been established for anti-EGFR treatment in patients with wild-type *KRAS*, response rates to anti-EGFR therapy can be modest and even nonexistent in certain patients,¹³ perhaps causing some providers to be reluctant to offer anti-EGFR therapy/*KRAS* testing. Furthermore, some clinicians may be more comfortable with other recommended, more established chemotherapy regimens.

Second, SEER only collects incident cases of cancer, so it is possible the rate of *KRAS* testing among those initially diagnosed with Stage IV would be lower than would be

anticipated among all metastatic cases. Those initially diagnosed with earlier stage cancer that later progressed to metastatic disease may have been under more frequent surveillance. Therefore, their metastasis may have been detected at an earlier and potentially more treatable point, making them more likely to receive anti-EGFR therapy and consequently be *KRAS* tested. Conversely, those who were initially diagnosed as Stage IV may have had more advanced disease and less interest in pursuing treatment with chemotherapy. There were a number of cases with stage or site information categorized in a ‘NOS’ related category, which suggests they may not have undergone thorough staging procedures due to their general health. A recent nationwide study of patients with metastatic cancer at diagnosis found close to 16% of both colon and rectum cases received no form of anticancer therapy.²⁶ Another recent study which examined treatment in Medicare patients (66 years of age) with Stage IV CRC at diagnosis found only 45% received systemic chemotherapy.²⁷

There is wide variation in *KRAS* testing in Stage IV patients by SEER registry. The fact that the patterns of *KRAS* testing within registries differed somewhat between Stages I-III and Stage IV suggests that the variation between registries is not simply due to differences in data capture. Louisiana, Iowa and Kentucky had low *KRAS* testing in Stage IV cases. These states contain large, rural areas located long distances from academic medical centers. It is possible that *KRAS* testing and use of anti-EGFR therapy in these states is most commonly done in larger medical centers, but has not yet diffused out into smaller community hospitals and practices where CRC cancer cases are frequently treated. This was supported by the finding that patients residing in urban areas had higher rates of *KRAS* testing after controlling for other key factors.

Alternatively, it could be that providers in states such as Louisiana, Iowa and Kentucky conduct *KRAS* testing as frequently as providers in other states, but more frequently send their specimens to out-of-state private pathology laboratories, thus impeding the ability of cancer registrars to abstract the information. Future studies will focus on validating the *KRAS* SSF values to determine if instances of *KRAS* testing were missed. In addition, the Iowa and Louisiana registries will be classifying the treating facilities into academic medical centers vs. community hospitals with accredited cancer programs vs. community hospitals with no accredited cancer program to determine if *KRAS* testing patterns are substantially different by type of treatment facility.

A missing category was included in the analyses of variables with missing information (race, insurance, marital status, grade, AJCC T and N stage) in order to address the effect of incomplete documentation and/or clinical work-up on *KRAS* testing as recorded by the registries. In multivariate analysis, missing marital status and grade were associated with non-receipt of *KRAS* testing in stage IV cases, while missing marital status, grade, and insurance were associated with no *KRAS* testing for stages I-III. While this may be indicative of incomplete documentation, especially for stage I-III cases where both missing marital status and insurance were significant, missing grade information may also indicate an incomplete clinical work-up, perhaps due to patient preference for limited/no work-up or treatment, and/or advanced disease/comorbidities making treatment unfeasible. Interestingly, for stage I-III cases, having missing race information was associated with *KRAS* testing.

While not significant, the black and other stage I-III race categories had lower odds of testing, suggesting many of those missing race information were white.

After controlling for registry site, it appears that several patient characteristics are important in the decision to order *KRAS* testing. Younger patients, for example, underwent *KRAS* testing at a more frequent rate. This may be due to better general health and longer life expectancy or due to seeking treatment at medical centers where *KRAS* testing is more frequently performed. In the aforementioned study of HMO Stage IV CRC cases, non-receipt of chemotherapy, older age, higher Charlson co-morbidity index score, and mortality within six months of Stage IV CRC diagnosis were all associated with not receiving *KRAS* testing.²³ Interestingly, in this current analysis, having health insurance was not associated with *KRAS* testing among Stage IV patients, but was among Stages I-III patients.

Those with Stage IV disease who were single (never married) had lower odds of *KRAS* testing, which suggests that having a spouse or other family support was important in a patient or provider's decision to recommend testing and anti EGFR therapy. Conversely, being divorced or single (never married) was actually associated with higher odds of having *KRAS* testing among patients with Stage I-III disease, which suggests a different decision-making process among patients and providers when dealing with earlier vs. later stage disease. Stage was clearly an important consideration in the non-metastatic population given that Stage III patients had more than three times greater odds of *KRAS* testing compared to Stage I patients, and Stage II patients had twice the odds of *KRAS* testing compared to Stage I patients. While *KRAS* testing is not recommended for earlier stage cancers, studies suggest *KRAS* mutations may have prognostic significance, and thus may be used for reasons beyond anti-EGFR therapy.²⁸ A recent CRC chemotherapy trial of stage III cases found *KRAS* mutations were independently associated with disease free survival, suggesting *KRAS* testing should be expanded to stage III CRC.²⁹ In addition, some patients might have clinically diagnosed metastatic CRC and therefore were *KRAS* tested, but were down-staged after more diagnostic procedures were performed.

In terms of survival, a clear advantage was demonstrated among those who received testing. As there was no significant survival difference detected between those with *KRAS* mutations and those with wild-type status, it appears the survival advantage was more likely related to the selection of patients for *KRAS* testing rather than treatment with anti-EGFR therapy. Poor prognostic factors negatively associated with receipt of testing, including older age, more advanced T and N stage, and prior cancer, may have influenced the decision to forego testing at the time of diagnosis. In fact, more than 50% of Stage IV CRC cases who had no *KRAS* testing died less than 3 months after diagnosis, compared with 30% who had *KRAS* testing, suggesting those not receiving *KRAS* testing were generally in poorer health.

The survival advantage could also be related to those living longer having more of an opportunity to be tested. Anti-EGFR therapy may have only been considered after the patient failed other chemotherapeutic agents. Therefore, patients would have had to live long enough to fail one regimen and be considered for a second regimen involving anti-EGFR therapy in order to be tested. While this approach is not totally consistent with NCCN guidelines for *KRAS* testing, it is in accordance with ASCO guidelines.^{9,17}

Limitations of this study must be considered when interpreting results. SEER does not collect information about specific *KRAS* testing methods, and it is not possible to assess rates of false positives or negatives. However, our estimate of *KRAS* mutations occurring in 42% of Stage IV patients is consistent with previously published estimates of approximately 40%.^{7,8} This analysis was based on a new variable collected for the first time in 2010. The primary source of information used by cancer registrars to collect information across all cancer cases is the hospital medical record. The primary source of *KRAS* testing information is the hospital pathology report. *KRAS* results are part of the College of American Pathologists (CAP) protocol, but reporting is optional; partly because this result is not always available when the pathology report is issued.³⁰ Thus, *KRAS* testing may not always be documented in the pathology report, or it may be added as an addendum at a later time, potentially after the report was abstracted by the cancer registrar. In addition, physician offices, or even hospitals, may send specimens to private out-of-state pathology laboratories for *KRAS* testing, and some of these laboratories may not be a case finding source for the registries. Thus, *KRAS* results not incorporated into the patient's hospital medical record could be missed by registries.

Furthermore, SEER only collects information related to first-course therapy. If anti-EGFR therapy was offered as a second line option and *KRAS* testing was deferred until that point, it is possible the testing occurred outside the registry chart abstraction window. SEER also only captures cases who reside within SEER areas, but the current SEER 18 Registries cover 28% of the population,³¹ and the cancer cases included in SEER are widely considered to be representative of the U.S. cancer population.³² Finally, SEER data do not capture patient or provider preferences or reasons for refusal of testing.

In conclusion, this is the first U.S. study to provide both population estimates and patient characteristics associated with *KRAS* testing among CRC patients, and provides the oncology community with baseline testing rates for stage IV patients for whom targeted treatments are available. The results show that just over one in five Stage IV colorectal cancer patients receives *KRAS* testing, and substantial variation exists by geographic region and patient characteristics. Somewhat surprisingly, it was also found that approximately 5% (and in certain geographic areas up to 10%) of non-metastatic patients received *KRAS* testing despite it not being recommended in the guidelines. Our findings suggest the need to clarify *KRAS* testing protocols and improve the uptake of these guidelines across all geographic areas of the U.S., as it is possible that testing and/or anti-EGFR therapy are not uniformly accessible to those who could benefit. The results can also guide the development of future studies to evaluate variations in *KRAS* testing and its impact on patient outcomes.

Our analyses also highlight the need for more complete reporting and standardization of data included in medical records and registries, as important clinical variables can only be analyzed when they are accurately documented and captured. Complete capture of *KRAS* testing information will provide an opportunity to evaluate therapy options and quality of care, and to assess survival outcomes. This could be facilitated by inclusion of *KRAS* testing in CAP protocols for all stage IV CRC cases. Given increased interest in tumor biomarkers and their impact on prognosis and prediction of cancer treatment response, it is highly likely that researchers will be interested in using *KRAS* and other similar prognostic and predictive

factors in their analyses. It is anticipated that data capture and quality will improve with time and will allow researchers to assess the pattern of dissemination and diffusion in clinical practice of *KRAS* testing in different regions of the country.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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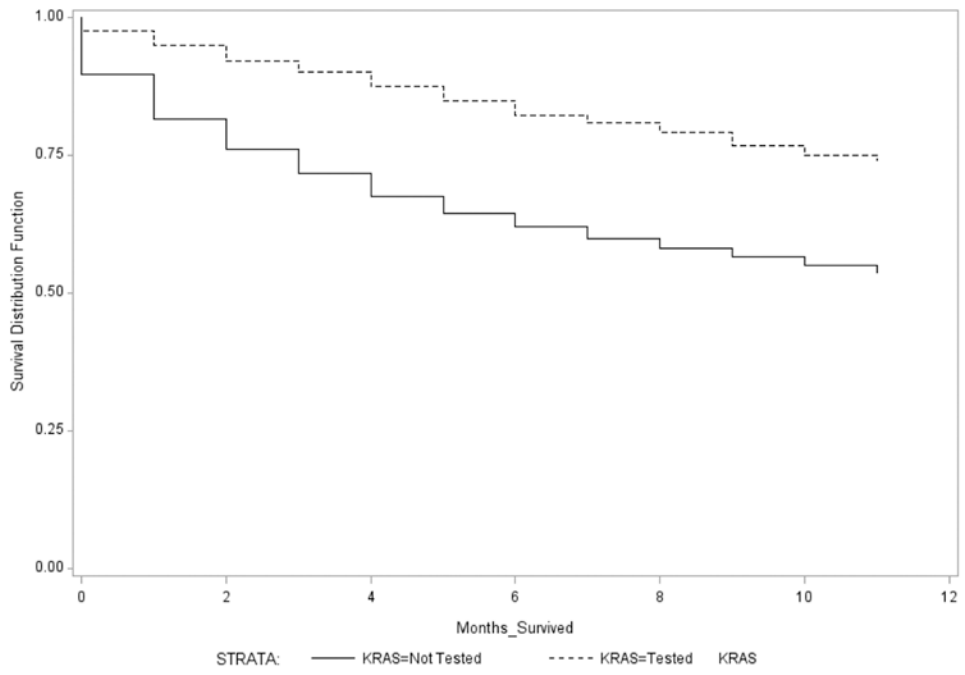


Figure 1. Kaplan Meier survival curves for Stage IV colorectal cancer cases who received *KRAS* testing compared to those who did not, 2010

Table 1
Number (%) with Site Specific Factor 9: KRAS Testing by Colorectal Cancer Stage and Site, 2010

N (column %)	Overall		Colon		Rectum	
	Stage IV	Stages I-III	Stage IV	Stages I-III	Stage IV	Stages I-III
KRAS Values						
010: Abnormal (mutated)	588 (9.6%)	462 (1.9%)	447 (9.9%)	331 (1.9%)	141 (8.8%)	131 (1.9%)
020: Normal (wild type)	802 (13.1%)	815 (3.4%)	586 (12.9%)	606 (3.5%)	216 (13.6%)	209 (3.1%)
997: Test ordered, results not in chart	72 (1.2%)	87 (0.4%)	54 (1.2%)	76 (0.4%)	18 (1.1%)	11 (0.2%)
998: Test not done	2718 (44.4%)	13365 (55.1%)	2008 (44.4%)	9729 (55.7%)	710 (44.6%)	3636 (53.8%)
999: Unknown	1939 (31.7%)	9503 (39.2%)	1431 (31.6%)	6726 (38.5%)	508 (31.9%)	2777 (41.0%)
Total	6119 (100%)	24232 (100%)	4526 (100%)	17468 (100%)	1593 (100%)	6764 (100%)

Table 2
KRAS testing for colorectal cancer by stage and demographics, 2010

	Stage IV, n (row %)			Stages I-III, n (row %)		
	No KRAS testing	KRAS testing	p-value	No KRAS testing	KRAS testing	p-value
TOTAL	4729 (77.3%)	1390 (22.7%)		22955 (94.7%)	1277 (5.3%)	
Age (years)						
<40	130 (63.7%)	74 (36.3%)	<.0001	493 (89.5%)	58 (10.5%)	<.0001
40-49	430 (66.3%)	219 (33.7%)		1674 (92.7%)	132 (7.3%)	
50-59	923 (72.7%)	346 (27.3%)		4226 (94.3%)	256 (5.7%)	
60-69	1205 (77.1%)	357 (22.9%)		5416 (94.0%)	344 (6.0%)	
70-79	1034 (79.1%)	273 (20.9%)		5756 (95.4%)	279 (4.6%)	
80+	1007 (89.3%)	121 (10.7%)		5390 (96.3%)	208 (3.7%)	
Gender						
Female	2177 (77.2%)	643 (22.8%)	0.88	11110 (94.8%)	616 (5.2%)	0.91
Male	2552 (77.4%)	747 (22.6%)		11845 (94.7%)	661 (5.3%)	
Registry						
California ^a	1798 (77.6%)	518 (22.4%)	<.0001	9194 (95.4%)	441 (4.6%)	<.0001
Connecticut	212 (77.9%)	60 (22.1%)		1053 (94.8%)	58 (5.2%)	
Detroit	234 (73.8%)	83 (26.2%)		1215 (96.1%)	50 (3.9%)	
Georgia ^b	554 (78.9%)	148 (21.1%)		2226 (92.6%)	179 (7.4%)	
Hawaii	81 (68.1%)	38 (31.9%)		465 (95.7%)	21 (4.3%)	
Iowa	212 (81.2%)	49 (18.8%)		1166 (98.3%)	20 (1.7%)	
Kentucky	327 (79.8%)	83 (20.2%)		1444 (89.5%)	169 (10.5%)	
Louisiana	378 (84.6%)	69 (15.4%)		1600 (96.9%)	51 (3.1%)	
New Jersey	554 (79.0%)	147 (21.0%)		2588 (96.6%)	91 (3.4%)	
New Mexico	87 (61.3%)	55 (38.7%)		494 (93.2%)	36 (6.8%)	
Seattle	211 (66.6%)	106 (33.4%)		1080 (88.7%)	138 (11.3%)	
Utah	81 (70.4%)	34 (29.6%)		430 (94.9%)	23 (5.1%)	
Race						
White	3604 (77.1%)	1069 (22.9%)	0.06	18415 (94.7%)	1029 (5.3%)	0.49
Black	719 (80.1%)	179 (19.9%)		2489 (94.9%)	134 (5.1%)	
Other	383 (73.9%)	135 (26.1%)		1867 (95.0%)	99 (5.0%)	
Missing	23 (76.7%)	7 (23.3%)		184 (92.5%)	15 (7.5%)	

	Stage IV, n (row %)			Stages I-III, n (row %)		
	No KRAS testing	KRAS testing	p-value	No KRAS testing	KRAS testing	p-value
Insurance						
Insured	3671 (76.9%)	1102 (23.1%)	0.58	19258 (94.7%)	1080 (5.3%)	0.0006
Medicaid	687 (79.0%)	183 (21.0%)		2279 (94.0%)	145 (6.0%)	
Uninsured	249 (77.6%)	72 (22.4%)		717 (95.1%)	37 (4.9%)	
Missing	122 (78.7%)	33 (21.3%)		701 (97.9%)	15 (2.1%)	
Marital Status						
Married	2319 (74.3%)	801 (25.7%)	<.0001	12256 (94.8%)	676 (5.2%)	<.0001
Divorced/Separated	529 (76.8%)	160 (23.2%)		2235 (92.9%)	172 (7.1%)	
Widowed	785 (84.3%)	146 (15.7%)		4131 (95.9%)	176 (4.1%)	
Single/Never married	845 (78.8%)	227 (21.2%)		3061 (93.4%)	218 (6.6%)	
Missing	251 (81.8%)	56 (18.2%)		1272 (97.3%)	35 (2.7%)	
Area of Residence						
Metro area	4003 (76.7%)	1219 (23.3%)	0.004	19750 (94.5%)	1143 (5.5%)	0.0005
Non-Metro area/Rural/Alaska	726 (81.0%)	170 (19.0%)		3201 (96.0%)	134 (4.0%)	
Missing	0 (0%)	1 (100%)		4 (100%)	0 (0%)	

^aLos Angeles, San Francisco, San Jose, and Greater California registries combined;

^bAtlanta, Rural Georgia, and Greater Georgia registries combined

Table 3
KRAS testing for colorectal cancer by stage and tumor/treatment characteristics, 2010

	Stage IV, n (row %)			Stages I-III, n (row %)		
	No KRAS testing	KRAS testing	P-value	No KRAS testing	KRAS testing	P-value
TOTAL	4729 (77.3%)	1390 (22.7%)		22955 (94.7%)	1277 (5.3%)	
CS Schema						
Colon	3493 (77.2%)	1033 (22.8%)	0.74	16531 (94.6%)	937 (5.4%)	0.29
Rectum	1236 (77.6%)	357 (22.4%)		6424 (95.0%)	340 (5.0%)	
Sub-site						
Right Side*	1846 (78.0%)	520 (22.0%)	0.27	9961 (94.7%)	563 (5.3%)	0.63
Left Side	2883 (76.8%)	870 (23.2%)		12994 (94.8%)	714 (5.2%)	
Histology						
Epithelial neoplasm, NOS	121 (89.6%)	14 (10.4%)	<.0001	80 (94.1%)	5 (5.9%)	0.0006
Adenoma/adenocarcinoma	4106 (77.0%)	1228 (23.0%)		20841 (94.9%)	1115 (5.1%)	
Cystic/Mucinous/Serous	459 (75.9%)	146 (24.1%)		1943 (92.8%)	150 (7.2%)	
Other/Unspecified	43 (95.6%)	2 (4.4%)		91 (92.9%)	7 (7.1%)	
Grade						
Well (I) to Moderately (II) differentiated	2541 (75.5%)	824 (24.5%)	<.0001	17626 (95.0%)	924 (5.0%)	<.0001
Poor (III) to Undifferentiated (IV)	1119 (75.9%)	356 (24.1%)		3892 (92.7%)	308 (7.3%)	
Missing	1069 (83.6%)	210 (16.4%)		1437 (97.0%)	45 (3.0%)	
Stage						
I	--	--	--	7638 (97.7%)	180 (2.3%)	<.0001
II	--	--	--	7715 (95.3%)	381 (4.7%)	
III	--	--	--	7602 (91.4%)	716 (8.6%)	
T Stage						
T3	2275 (76.9%)	682 (23.1%)	<.0001	20495 (95.3%)	1009 (4.7%)	<.0001
T4a	1204 (73.0%)	446 (27.0%)		2460 (90.2%)	268 (9.8%)	
TX (Unknown)	1250 (82.7%)	262 (17.3%)		0 (0%)	0 (0%)	
N Stage						
N0	1478 (81.2%)	343 (18.8%)	<.0001	15353 (96.5%)	561 (3.5%)	<.0001
N1a	2502 (73.4%)	906 (26.6%)		7602 (91.4%)	716 (8.6%)	
NX (Unknown)	749 (84.2%)	141 (15.8%)		0 (0%)	0 (0%)	
Primarys						
Single primary	3709 (76.2%)	1161 (23.8%)	<.0001	17122 (94.6%)	972 (5.4%)	0.22
Multiple primaries	1020 (81.7%)	229 (18.3%)		5833 (95.0%)	305 (5.0%)	
Prior Cancer						
No prior cancer	3863 (76.2%)	1207 (23.8%)	<.0001	18194 (94.6%)	1045 (5.4%)	0.03
Prior cancer	866 (82.6%)	183 (17.4%)		4761 (95.4%)	232 (4.6%)	

	Stage IV, n (row %)			Stages I-III, n (row %)			P-value
	No KRAS testing	KRAS testing	P-value	No KRAS testing	KRAS testing	P-value	
Surgery							
Yes	2595 (73.8%)	921 (26.2%)	<.0001	21885 (94.6%)	1242 (5.4%)	0.001	
No or Unknown	2134 (82.0%)	469 (18.0%)		1070 (96.8%)	35 (3.2%)		
Radiation							
Yes or recommended	572 (78.5%)	157 (21.5%)	0.42	3259 (93.7%)	218 (6.3%)	0.004	
No/Unknown/Refused	4157 (77.1%)	1233 (22.9%)		19696 (94.9%)	1059 (5.1%)		

* Right-sided sites include cecum, ascending colon, hepatic flexure, transverse colon; left-sided sites included splenic flexure, descending and sigmoid colon, rectosigmoid junction, rectum and the classification of 'large intestine NOS'.

Table 4
Odds Ratios (95% Confidence Intervals) from Stage-stratified (IV vs. I-III) Logistic Regression Models Examining the Association between KRAS Testing and Colorectal Cancer Patient Demographic and Clinical Characteristics, 2010

Variable	Stage IV			Stages I-III		
	Age (years)	Odds Ratio* (95% CI)	Variable	Age (years)	Odds Ratio* (95% CI)	SEER Registry
Age (years)	39	5.20 (3.62-7.49)	Age (years)	39	2.25 (1.63-3.12)	California
	40-49	4.35 (3.32-5.70)		40-49	1.64 (1.28-2.09)	Connecticut
	50-59	3.29 (2.57-4.20)		50-59	1.45 (1.18-1.78)	Detroit
	60-69	2.52 (1.98-3.19)		60-69	1.57 (1.30-1.90)	Georgia
	70-79	2.20 (1.73-2.80)		70-79	1.23 (1.02-1.49)	Hawaii
	80+	1.00 (Referent)		80+	1.00 (Referent)	Iowa
SEER Registry	California	1.00 (Referent)	SEER Registry	California	1.00 (Referent)	Kentucky
	Connecticut	1.11 (0.81-1.51)		Connecticut	1.26 (0.95-1.68)	Louisiana
	Detroit	1.32 (1.00-1.74)		Detroit	0.90 (0.67-1.22)	New Jersey
	Georgia	0.93 (0.75-1.15)		Georgia	1.86 (1.53-2.25)	New Mexico
	Hawaii	1.71 (1.13-2.59)		Hawaii	1.02 (0.63-1.64)	Seattle
	Iowa	1.02 (0.72-1.45)		Iowa	0.48 (0.30-0.76)	Utah
	Kentucky	0.91 (0.69-1.21)		Kentucky	3.33 (2.72-4.09)	
	Louisiana	0.64 (0.48-0.85)		Louisiana	0.78 (0.58-1.06)	
	New Jersey	0.98 (0.80-1.22)		New Jersey	0.77 (0.61-0.98)	
	New Mexico	2.67 (1.83-3.89)		New Mexico	1.83 (1.28-2.63)	
	Seattle	1.87 (1.44-2.43)		Seattle	2.84 (2.31-3.50)	
	Utah	1.26 (0.83-1.93)		Utah	1.14 (0.73-1.76)	
Marital Status	Married	1.00 (Referent)	Marital Status	Married	1.00 (Referent)	
	Divorced/Separated	0.89 (0.73-1.09)		Divorced/Separated	1.30 (1.08-1.55)	
	Single (Never Married)	0.70 (0.59-0.84)		Single (Never Married)	1.26 (1.07-1.49)	
	Widowed	0.87 (0.71-1.08)		Widowed	0.90 (0.74-1.08)	
	Missing	0.62 (0.45-0.85)		Missing	0.61 (0.43-0.88)	
Area of Residence	Metro/Urban	1.00 (Referent)	Area of Residence	Metro/Urban	1.00 (Referent)	

Stage IV		Stages I-III	
Variable	Odds Ratio* (95% CI)	Variable	Odds Ratio* (95% CI)
Non-Metro/Rural	0.75 (0.61-0.92)	Non-Metro/Rural	0.57 (0.46-0.69)
Histology		Histology	
Adenomas/Adenocarcinomas	1.00 (Referent)	Adenomas/Adenocarcinomas	1.00 (Referent)
Epithelial	0.48 (0.27-0.86)	Epithelial	1.11 (0.44-2.83)
Cystic/Mucinous/Serous	1.02 (0.83-1.26)	Cystic/Mucinous/Serous	1.24 (1.03-1.48)
Other	0.19 (0.05-0.78)	Other	1.18 (0.53-2.60)
Grade		Grade	
Well (I) to Moderately (II) differentiated	1.00 (Referent)	Well (I) to Moderately (II) differentiated	1.00 (Referent)
Poor (III) to Undifferentiated (IV)	1.02 (0.88-1.19)	Poor (III) to Undifferentiated (IV)	1.24 (1.08-1.43)
Missing	0.80 (0.66-0.97)	Missing	0.72 (0.53-0.98)
Surgery		Insurance	
Performed	1.41 (1.22-1.62)	Uninsured	0.63 (0.45-0.90)
Not Performed/Unknown	1.00 (Referent)	Medicaid	1.02 (0.84-1.23)
		Missing	0.39 (0.23-0.66)
		Insured (Other Than Medicaid)	1.00 (Referent)
Radiation		Race	
Yes or recommended	0.81 (0.67-0.99)	White	1.00 (Referent)
No/Unknown/Refused	1.00 (Referent)	Black	0.89 (0.73-1.09)
		Other	0.94 (0.75-1.19)
		Missing	2.19 (1.26-3.83)
		Stage	
		I	1.00 (Referent)
		II	2.00 (1.66-2.40)
		III	3.59 (3.02-4.26)

* Adjusted for all variables listed within this stage column

Table 5
KRAS testing in colorectal cancer cases by number of months survived and cause of death, stratified by stage, 2010

Survival Months	Stage IV, n (%)				Stages I-III, n (%)				p
	N	No KRAS testing	KRAS testing	p	N	No KRAS testing	KRAS testing	p	
0	972	835 (85.9%)	137 (14.1%)	<.0001	2659	2544 (95.7%)	115 (4.3%)	0.07	
1	768	623 (81.1%)	145 (18.9%)		2179	2057 (94.4%)	122 (5.6%)		
2	688	538 (78.2%)	150 (21.8%)		2053	1958 (95.4%)	95 (4.6%)		
3	551	427 (77.5%)	124 (22.5%)		2009	1882 (93.7%)	127 (6.3%)		
4	553	423 (76.5%)	130 (23.5%)		2031	1917 (94.4%)	114 (5.6%)		
5	452	338 (74.8%)	114 (25.2%)		1878	1794 (95.5%)	84 (4.5%)		
6	433	311 (71.8%)	122 (28.2%)		2185	2071 (94.8%)	114 (5.2%)		
7	361	265 (73.4%)	96 (26.6%)		1829	1717 (93.9%)	112 (6.1%)		
8	365	260 (71.2%)	105 (28.8%)		1822	1727 (94.8%)	95 (5.2%)		
9	368	276 (75.0%)	92 (25.0%)		2094	1986 (94.8%)	108 (5.2%)		
10	309	224 (72.5%)	85 (27.5%)		1806	1715 (95.0%)	91 (5.0%)		
11 (or still alive)	299	209 (69.9%)	90 (30.1%)		1687	1587 (94.0%)	100 (6.0%)		
Status at 11 months									
Alive	4308	3131 (72.7%)	1177 (27.3%)	<.0001	22578	21354 (94.6%)	1224 (5.4%)	<.0001	
Deceased	1811	1598 (88.2%)	213 (11.8%)		1654	1601 (96.8%)	53 (3.2%)		
Cause of Death									
Colon, rectum or rectosigmoid	1443	1267 (87.8%)	176 (12.2%)	0.19	871	835 (95.9%)	36 (4.1%)	0.08	
Miscellaneous malignant cancer	89	77 (86.5%)	12 (13.5%)		39	39 (100%)	0 (0%)		
Heart or cerebrovascular disease	64	55 (85.9%)	9 (14.1%)		275	271 (98.6%)	4 (1.4%)		
Other or Unknown	215	199 (92.6%)	16 (7.4%)		469	456 (97.2%)	13 (2.8%)		