Surveillance, Epidemiology, and End Results Registry and Patient Characteristics Associated with Receipt of KRAS Testing

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Background

Treatment Guidelines for KRAS Testing

- Response to epidermal growth factor receptor (EGFR) inhibitors is poorer among Stage IV colorectal cancer (CRC) patients with KRAS mutations
- Since 2009, NCCN and ASCO have recommend KRAS testing prior to treatment with EGFR inhibitors
- KRAS testing was collected by SEER registries as a site specific factor (SSF) beginning with 2010 CRC cases

Study Aim

- To provide the first population-based estimates of KRAS testing in the U.S. and examine factors related to testing

Methods

Study Population

- Inclusion criteria:
  - SEER 18 Registry (except Alaska Natives Registry)
  - Diagnostic confirmation by positive histology
  - Included in Colon & Rectal Cancer Collaborative Stage Schema v0204
- Exclusion criteria
  - Diagnosed at autopsy or by death certificate only

Analysis

- Primary outcome: receipt of KRAS testing
  - Considered done if SSF9 ='abnormal (mutated)' or 'normal (wild type)'
  - Considered not done if SSF9 = 'test ordered, results not in chart', 'not done' or 'unknown'
- Bivariate analyses and multivariate logistic regression used to examine associations between KRAS testing and:
  - Patient demographic characteristics
  - Clinical/tumor characteristics
  - First course treatment
- Kaplan Meier curves & log-rank tests used to evaluate the association between KRAS testing and survival (max of 11 months follow-up)
- Analyses stratified by Stage IV vs. Stages I-III

Results

Table 1. KRAS SSF Results, 2010 CRC Cases

	Overall	
N (column %)	**Stage IV**	**Stages I-III**
KRAS Values	(N=6119)	(N=24232)
010: Abnormal (mutated)	**588 (10%)**	462 (2%)
020: Normal (wild type)	**802 (13%)**	815 (3%)
997: Test ordered, results not in chart	72 (1%)	87 (0%)
998: Test not done	2718 (44%)	13365 (55%)
999: Unknown	1939 (32%)	9503 (40%)

Figure 1. Percent with KRAS Testing By Registry & Stage*

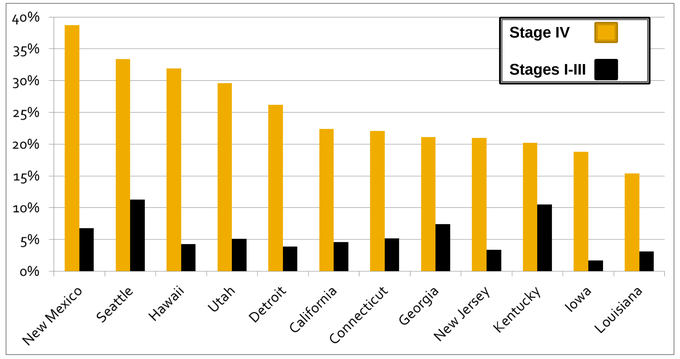

Figure 2. Stage IV Survival by KRAS Testing Receipt

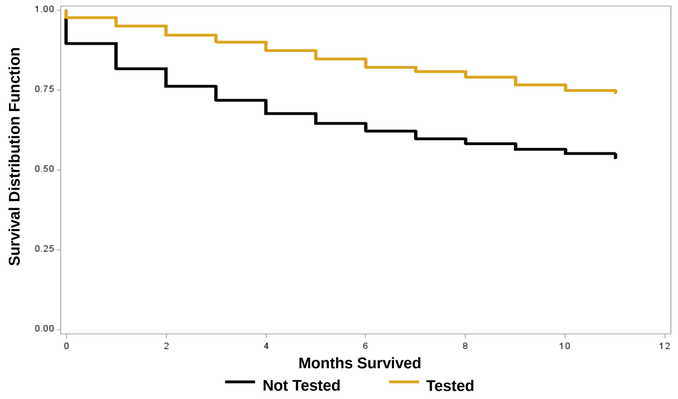

Table 2. Factors associated with KRAS Testing in Multivariate Logistic Regression Models**

	Stage IV	Stages I-III
Variable	**O.R. (95% CI)**	
Age		
≤ 39	**5.10 (3.53-7.37)**	**2.31 (1.64-3.23)**
40-49	**4.23 (3.21-5.57)**	**1.66 (1.28-2.13)**
50-59	**3.19 (2.49-4.10)**	**1.46 (1.18-1.81)**
60-69	**2.48 (1.95-3.16)**	**1.61 (1.32-1.97)**
70-79	**2.19 (1.72-2.80)**	**1.26 (1.04-1.54)**
80+	1.00 (Referent)	1.00 (Referent)
Marital Status		
Married	1.00 (Referent)	1.00 (Referent)
Divorced/Separated	0.89 (0.73-1.08)	**1.31 (1.09-1.57)**
Single (Never Married)	**0.71 (0.60-0.85)**	**1.26 (1.06-1.49)**
Widowed	0.87 (0.70-1.08)	0.89 (0.74-1.08)
Area of Residence		
Metro/Urban	1.00 (Referent)	1.00 (Referent)
Non-Metro/Rural	**0.73 (0.59-0.90)**	**0.59 (0.47-0.72)**
Histology		
Adenomas/Adenocarcinomas	1.00 (Referent)	1.00 (Referent)
Epithelial	**0.48 (0.27-0.85)**	1.11 (0.39-3.17)
Cystic/Mucinous/Serous	1.04 (0.85-1.28)	1.21 (1.00-1.46)
Other	**0.09 (0.01-0.68)**	1.47 (0.66-3.29)
Surgery		
Performed	**1.57 (1.38-1.80)**	Not Significant in model
Not Performed/Unknown	1.00 (Referent)	
Insurance		
Uninsured	Not Significant in model	**0.55 (0.38-0.81)**
Medicaid		0.96 (0.79-1.16)
Insured (Other Than Medicaid)		1.00 (Referent)
Grade		
Well to Moderately differentiated	Not Significant in model	1.00 (Referent)
Poor to Undifferentiated		**1.24 (1.07-1.43)**
Stage		
I	Not Significant in model	1.00 (Referent)
II		**1.93 (1.59-2.33)**
III		**3.42 (2.86-4.08**

* Los Angeles, San Francisco, San Jose, and Greater California registries combined; Atlanta, Rural Georgia, and Greater Georgia registries combined

**Using California residents as the referent group, residing in the Hawaii, New Mexico or Seattle Registry catchment areas was associated with greater odds of KRAS testing for Stage IV cases while residing in Louisiana was associated with lower odds. Among Stage I-III cases, residing in the Georgia, Kentucky, or Seattle catchment areas was associated with greater odds of testing while residing in Iowa, Louisiana or New Jersey was associated with lower odds

Summary and Conclusions

- Only 23% of Stage IV CRC cases received KRAS testing
- Wide variation in documented KRAS testing for Stage IV CRC patients exists among SEER registries
- Age remained highly significant after controlling for Registry, suggesting it plays an independent role in the patient and/or provider decision for KRAS testing
- Possible explanations for low rates of testing:
  - Uptake of EGFR inhibitors and KRAS testing has been slower in some areas
  - Those initially diagnosed as Stage IV may have had more advanced disease and less interest in having chemotherapy compared to those initially diagnosed at earlier stages who had recurrence/progression (not captured by SEER)
  - Testing may be more frequent at time of second- or third-line therapy vs. at time of first-line therapy and therefore more challenging to capture within abstraction period
  - Some providers may have sent specimens to out-of-state private pathology laboratories not known to the Registries
  - The survival advantage of those with KRAS testing was likely related to selection of younger patients for testing and the need to live long enough to get testing (50% without testing died <3 months post-diagnosis vs. 30% with testing)
  - 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

Future Studies

Further research is needed to:

- Validate the KRAS SSF values to determine if instances of KRAS testing were missed
- Determine drivers of variation in testing, as well as reasons for testing in Stage I-III cases where it is not recommended.