Capturing KRAS Testing for Stage IV Colorectal Cancer Cases: A Tale of Two States

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Background on the KRAS SSF

- Response to EGFR inhibitors is poorer among Stage IV colorectal cancer (CRC) patients with KRAS mutations
- Since 2009, NCCN and ASCO have recommended 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

KRAS Values

Primary outcome: Receipt of KRAS testing

KRAS Values

- Abnormal (mutated)
- Normal (wild type)
- Test ordered, results not in chart
- Test not done
- Unknown

Abnormal (mutated), Normal (wild type): Test Done

Test ordered, results not in chart, Test not done, Unknown: Test Not Done

Results from Analysis of 2010 Cases

ORIGINAL ARTICLE

Factors Associated With Guideline-recommended *KRAS* Testing in Colorectal Cancer Patients

A Population-based Study

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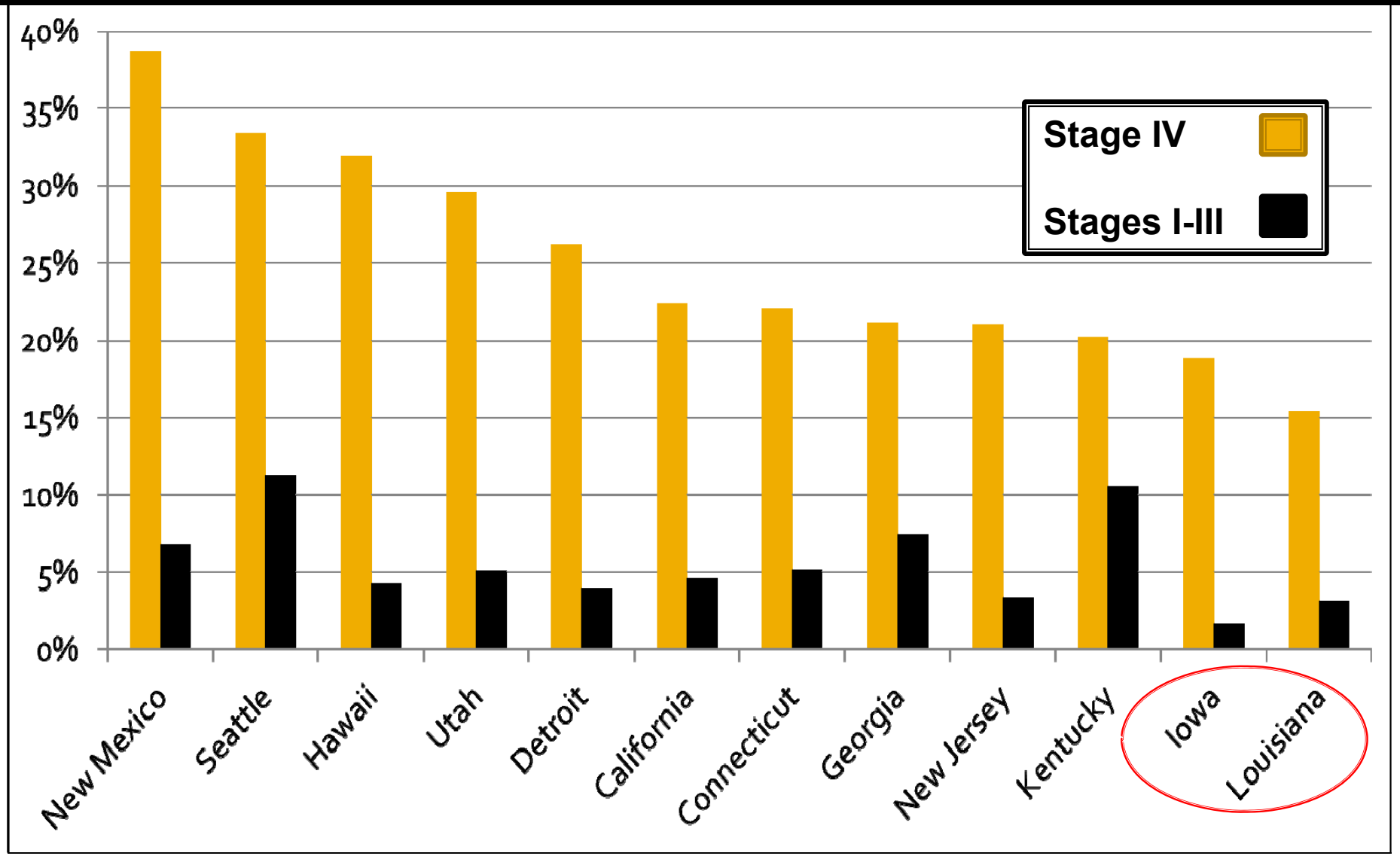
KRAS SSF Results, 2010 CRC Cases

	Overall	
N (column %)	**Stage IV**	**Stages I-III**
KRAS Values	(N=6119)	(N=24232)
Abnormal (mutated)	**588 (10%)**	462 (2%)
Normal (wild type)	**802 (13%)**	815 (3%)
Test ordered, results not in chart	72 (1%)	87 (0.4%)
Test not done	2718 (44%)	13365 (55%)
Unknown	1939 (32%)	9503 (40%)

Percent with KRAS Testing By Registry & Stage



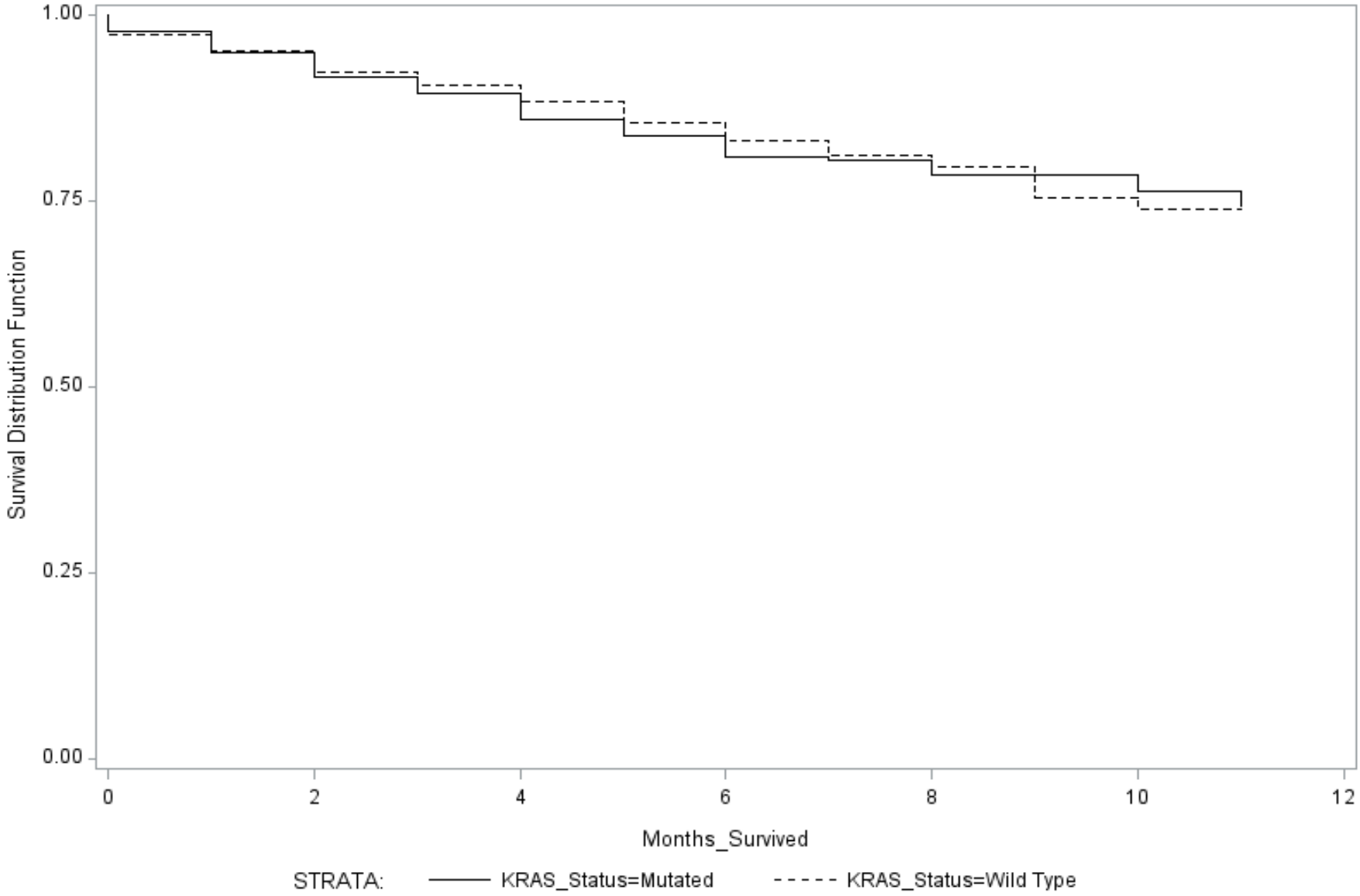
Factors associated with KRAS Testing in 2010 cases in Multivariate Logistic Regression Model

Stage IV

		O.R. (95% CI)
Age	≤ 39	**5.20 (3.62-7.49)**
	40-49	**4.35 (3.32-5.70)**
	50-59	**3.29 (2.57-4.20)**
	60-69	**2.52 (1.98-3.19)**
	70-79	**2.19 (1.72-2.80)**
	80+	1.00 (Referent)
Marital Status	Married	1.00 (Referent)
	Divorced/Separated	0.89 (0.73-1.09)
	Single (Never Married)	**0.70 (0.59-0.84)**
	Widowed	0.87 (0.71-1.08)
Area of Residence	Metro/Urban	1.00 (Referent)
	Non-Metro/Rural	**0.75 (0.61-0.92)**
Histology	Adenoma/Adenocarcinoma	1.00 (Referent)
	Epithelial	**0.48 (0.27-0.86)**
	Cystic/Mucinous/Serous	1.02 (0.83-1.26)
	Other	**0.19 (0.05-0.78)**
Surgery	Performed	**1.41 (1.22-1.62)**
	Not Performed/Unknown	1.00 (Referent)

*SEER Registry also included in model

Kaplan Meier survival curves for mutated vs. wild type *KRAS* status among stage IV colorectal cancer cases who received *KRAS* testing, 2010



Conclusions from Analysis of 2010 Cases

- 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 Percent with KRAS Testing

- Slow uptake of EGFR inhibitors and KRAS testing
- Testing may be more frequent at time of 2nd- or 3rd- line therapy vs. at time of 1st-line therapy and therefore more challenging to capture
- KRAS testing may be ordered after the patient is discharged from the hospital and results may therefore only be sent to the oncologist's office

Next Steps

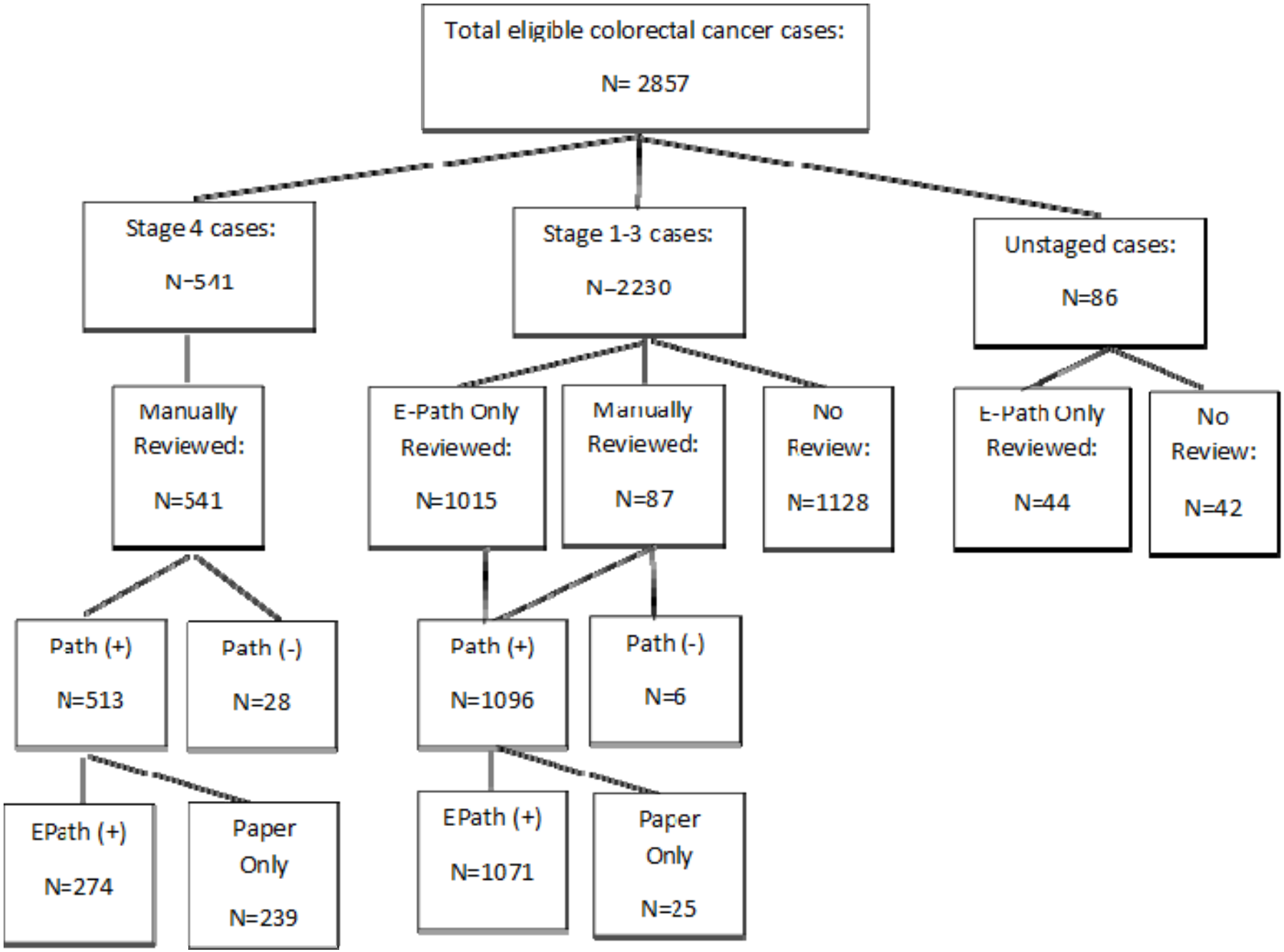
Since KRAS testing information was ‘missing/unknown’ in a large percentage of Stage IV cases, and there were wide variations by Registry, NCI SEER issued the RRSS QC Epath project to address the following objectives:

- Validate the KRAS values in SEER to determine if instances of KRAS testing were missed
- Determine drivers of variation in testing, particularly among Stage IV cases for whom testing is recommended
- Evaluate E-Path as a source of KRAS information

RRSS Study – Inclusion Criteria

- Invasive, microscopically confirmed CRC with ICD-O-3 codes in the following list:
  - C180, C182-189 (colon, excluding Appendix C181)
  - C199 (rectosigmoid junction)
  - C209 (rectum)
- Diagnosed in 2011, 2012 or first 6 months of 2013
- Histologic types included in the Colon & Rectal Cancer Collaborative Stage (CS) Schema v0204
- Cases diagnosed at autopsy or by death certificate were excluded

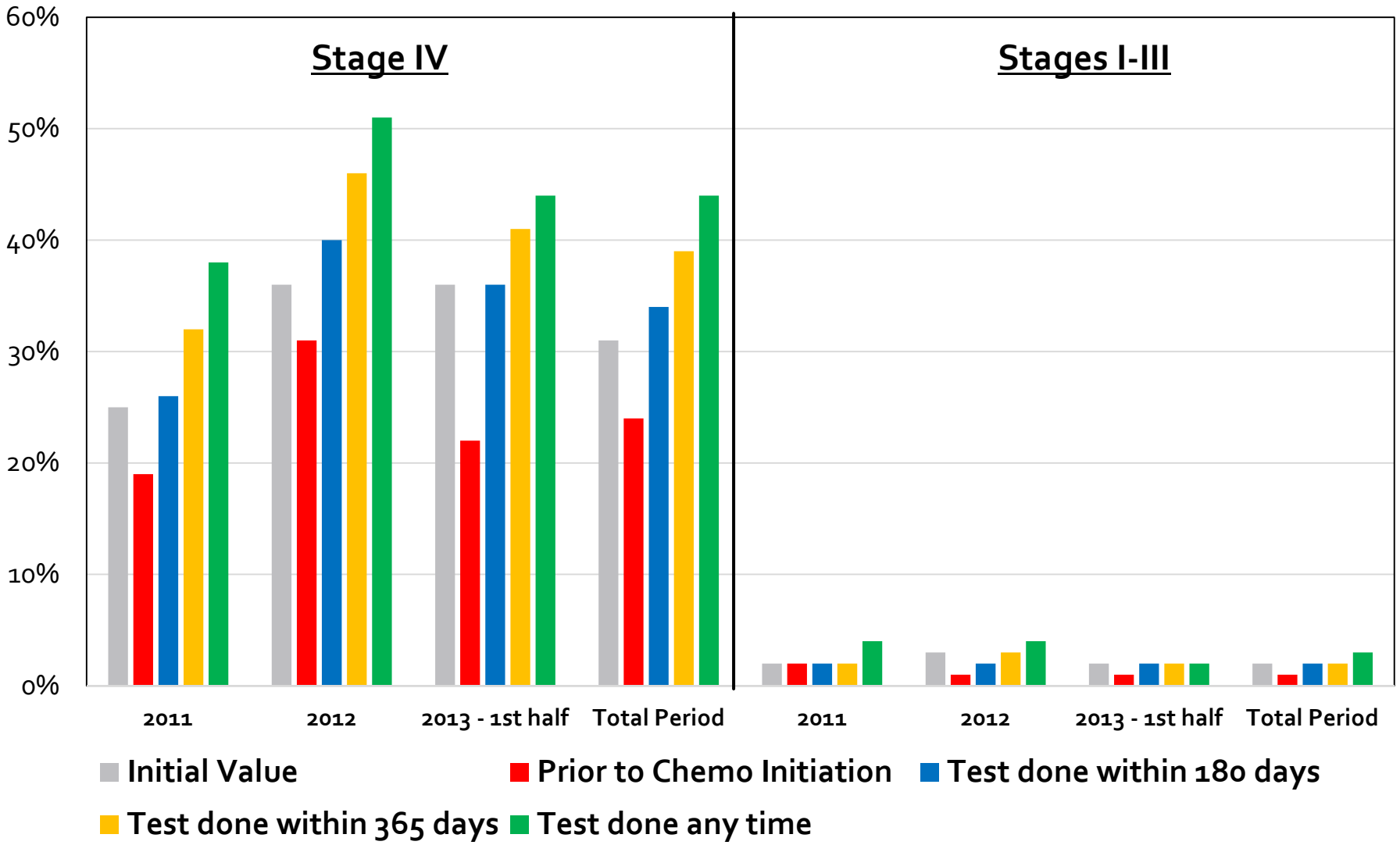
Iowa Analysis & Findings


Total eligible colorectal cancer cases:
N= 2857
Stage 4 cases:
N=541
Stage 1-3 cases:
N=2230
Unstaged cases:
N=86
Manually Reviewed:
N=541
E-Path Only Reviewed:
N=1015
Manually Reviewed:
N=87
No Review:
N=1128
E-Path Only Reviewed:
N=44
No Review:
N=42
Path (+)
N=513
Path (-)
N=28
Path (+)
N=1096
Path (-)
N=6
EPath (+)
N=274
Paper Only
N=239
EPath (+)
N=1071
Paper Only
N=25

Percentage of colorectal cancer cases with KRAS testing by stage & timing of KRAS test

-Total Stage IV cases (N=541); By year: 2011 (N=228); 2012 (N=216); 2013-1st half (N=97)

-Total Stages I-III cases (N=2230); By year: 2011 (N=924); 2012 (N=874); 2013-1st half (N=432)



1. Cases found to have known KRAS values after re-review (any stage) who had any pathology report available (hard copy or E-Path, includes molecular reports)
2. Cases found to have known KRAS values after re-review (any stage) who had an E-Path report available

	1. Pathology Report (Any)			2. E-Path Report Only		
KRAS SSF based on re-review of cases	KRAS info in Path Report	KRAS info not in Path Report	Total	KRAS info in E-Path Report	KRAS info not in E-Path report	Total
2011 Cases						
Known KRAS Value	107 (92%)	9 (8%)	116 (100%)	63 (100%)	0 (0%)	63 (100%)
2012 Cases						
Known KRAS Value	122 (88%)	17 (12%)	139 (100%)	67 (99%)	1 (1%)	68 (100%)
2013 (1st half) Cases						
Known KRAS Value	48 (100%)	0 (0%)	48 (100%)	31 (100%)	0 (0%)	31 (100%)

Number and percent of colorectal cancer cases (any stage) who had E-Path reports available and MSI or BRAF testing information identified from E-Path reports

	MSI Test Done	BRAF Test Done	Total Cases with E-Path
Year			
2011	25 (4.6%)	14 (2.6%)	543
2012	27 (5.0%)	17 (3.1%)	541
2013 (1st half)	21 (6.8%)	6 (2.0%)	308
Total study period	73 (5.2%)	37 (2.7%)	1,392
Stage			
I	0 (0%)	1 (0.3%)	339
II	6 (1.8%)	6 (1.8%)	336
III	14 (3.3%)	11 (2.6%)	420
IV	53 (17.9%)	19 (6.4%)	297

Logistic Regression Model Predicting KRAS Testing among Stage IV Cases (no time restrictions on the testing)

Characteristic	Odds Ratio	95% Wald Confidence Limits	
Age <50 vs 75+	4.96	2.70	9.11
50-64 vs 75+	3.60	2.28	5.70
65-74 vs 75+	1.83	1.09	3.06
Major Teaching Affiliation (Yes vs. No)	1.50	1.02	2.22

Louisiana Analysis & Findings

Table 2. Louisiana Documentation of KRAS Testing After Re-Review of Stage IV cases 2011-2013*,
E-path report available (Epath+) vs. no E-path available (Epath-)

	KRAS TESTED EPATH+ (N=219)				KRAS TESTED EPATH- (N=59)		
KRAS tested based on re-review of cases	KRAS info in Paper path	KRAS info in Epath	KRAS info other+	Total	KRAS info in Paper path	KRAS info other+	Total
2011 Cases	1 (92.2%)	49 (61.3%)	30 (37.5%)	80	1 (3.1%)	31 (96.9%)	32
2012 Cases	0	64 (65.3%)	34(34.7%)	98	1 (3.9%)	25 (96.2%)	26
2013 Cases (1st half)	0	31 (75.6%)	10 (24.4%)	41	0	1 (100%)	1

*first 6 months only for 2013
+KRAS information documented in NAACCR abstract text/only coded in SSF9

Table 3. Distribution Louisiana Colorectal cancer cases (any stage) with MSI or BRAF testing information in E-path 2011-2013*

	MMR Test frequencies (MSI and IHC) **	BRAF test frequencies	Total Cases with E-Path
Year			
2011	107 (7.9%)	21 (1.6%)	1353
2012	235 (18.0%)	36 (2.8%)	1302
2013 (1st half)	48 (27.7%)	12 (6.9%)	173
Stage			
I	87 (12.6%)	7 (1.0%)	689
II	106 (14.6%)	19 (2.6%)	725
III	142 (18.2%)	22 (2.8%)	781
IV	55 (8.9%)	21 (3.3%)	633
Total study period	390 (13.8%)	69 (2.4%)	2828

*first 6 months only for 2013

**tests for mutations in mismatch repair genes includes immunohistochemistry and microsatellite instability testing

Table 4. Factors Associated with KRAS Testing in Louisiana Stage IV Colorectal Cases in Multivariate Logistic Regression Model (within 6 months of dx) 2011-2013*

	Characteristic	Odds Ratio	95% Confidence Interval	
Age	Age <50 vs Age 75+	3.1	1.4	5.6
	Age 50-64 vs Age 75+	3.7	2.2	6.1
	Age 65-74 vs Age 75+	2.0	1.2	3.2
Insurance	Medicaid Only vs. Private Insurance	.40	.23	.69
	Medicare vs. Private Insurance	.40	.20	.80
Treatment Facility Type	Teaching Hospital vs. Public Hospital	.36	.23	.57

*first 6 months only for 2013

Table 5. Louisiana Stage IV indicators for not KRAS testing (within 6 months of dx) 2011-2013 (1st half)*

Reasons for LA Stage IV CRC cases (N=764)** not KRAS tested	#	%
Contraindicated	45	6%
Hospice/Palliative care	121	16%
KRAS ordered, no results	15	2%
Refused treatment	27	4%
Expired soon after dx	88	12%
Unknown/ not enough information	468	61%

*first 6 months only for 2013

**764 of the 1042 Stage IV cases were not KRAS tested. 278 Stage IV cases were found to be KRAS tested after re-review.

Overall Conclusions

Conclusions

- KRAS testing was missed primarily when performed well after diagnosis and/or abstraction date
- Addition of a test date would help to understand treatment patterns and determine consistent coding criteria
- E-Path appears to be a promising source of capturing KRAS values, but do not catch all instances of testing (other sources remain important)
  - E-Path addenda must be included as this is often where KRAS testing is documented
  - Note that some facilities may have developed separate 'Molecular Reports' that may not be included in E-Path (e.g., UIHC, Mayo)