Precision Medicine in the Real-World: The Impact of the Genetic Testing Evolution in Metastatic Colorectal Cancer

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Background

The emergence of anti-epidermal growth factor receptor (EGFR)-targeted antibodies has made metastatic CRC (mCRC) a model for the evolution and success of precision medicine. Exon 2 KRAS mutations (codons 12/13) are negative predictive biomarkers for EGFR-targeted therapy for mCRC and represent limited testing for these mutations. Subsequent data showed other RAS mutations (KRAS exons 3/4, NRAS exons 2/3/4 and BRAF) were also negative predictors for response, leading to recommendations for extended testing to be performed.

Objective

The objective of this study was to describe the degree of limited or non-limited testing, predictors of non-limited testing, and the rate of targeted therapy initiation in a national sample of patients with incident mCRC.

Methods

Study Design: Retrospective cohort

Data Source: Medical and pharmacy claims, and enrollment information between 8/1/2011 and 6/30/2017 from Humana's Research Database

Inclusion Criteria:

- Age 19-89 years with newly diagnosed mCRC between 8/1/2012 and 12/31/2016
  - Colon or rectal cancer diagnosis on ≥2 medical claims within 60 days during the identification period
  - ≥2 non-diagnostic claims for metastatic disease separated by 30 days during the identification period
- Medicare Advantage enrollment with a pharmacy benefit (MAPD)
- Continuous enrollment for 12 months pre- and 6 months post-index date (first metastatic disease claim in identification period), with at least 30 days minimum post-index enrollment
- Claims evidence of CRC-related genetic testing, classified as:
  - Limited KRAS testing
  - Non-limited testing: included any patient with extended RAS testing (KRAS additional codons and/or NRAS) and/or BRAF testing; in most cases limited KRAS testing was also performed

Exclusion Criteria:

- BRAF testing alone with a diagnosis of skin cancer in the pre-index period
- Died or initiated hospice within the first 30 days after the index date
- Hospice initiation during the pre-index period
- ≥2 codes for metastatic disease greater than 30 days apart in the pre-index period

Outcomes and Statistical Analyses:

- Patient and clinician characteristics were described by type of genetic testing.
- Multivariable logistic regression models were used to assess possible predictors of limited versus non-limited testing.
- Treatment was identified according to NCCN guideline recommendations and classified as a) anti-EGFR at any point during the post-index period, or b) other anticancer treatment.

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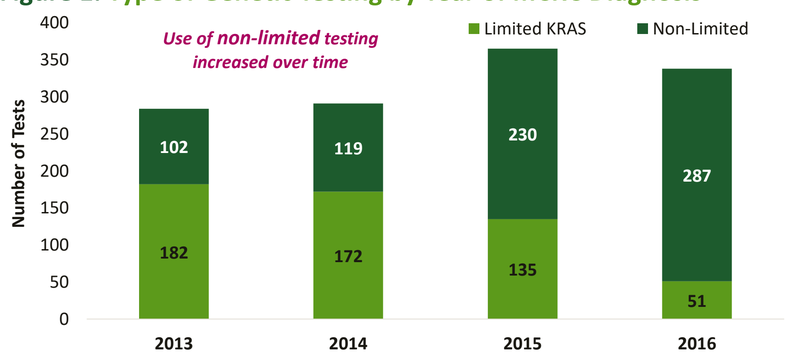
Results

Table 1. Demographic and Clinical Characteristics

Measure	Limited KRAS n=564	Non-Limited n=754	P-value
Age in years, mean ± SD	72.2 ± 7	72.1 ± 8	0.93
Female, n (%)	253 (44.9)	341 (45.2)	0.90
DCCI score, mean ± SD	3.3 ± 3	3.3 ± 3	0.99
Other primary cancer types, n (%)			
Digestive organs and peritoneum	6 (1.1)	13 (1.7)	0.32
Respiratory and intrathoracic organs	19 (3.4)	28 (3.7)	0.74
Bone, connective tissue, and breast	18 (3.2)	27 (3.6)	0.70
Genitourinary organs	16 (2.8)	52 (6.9)	<0.001
Lymphatic and hematopoietic tissue	11 (2.0)	14 (1.9)	0.90
Malignant neoplasm of the skin	9 (1.6)	11 (1.5)	0.84
Other and unspecified sites	<10 (NA)	12 (1.6)	0.15
Other pre-index mCRC treatment, n (%)			
Colon/rectal surgery	112 (19.9)	149 (19.8)	0.97
Radiation	30 (5.3)	42 (5.6)	0.84
Pre-index total healthcare costs, median [IQR]	$1,024 [$413-$2,935]	$1,083 [$401-$3,231]	0.34
Laboratory type, n (%)			
Independent	360 (63.8)	504 (66.8)	0.70
Hospital	157 (27.8)	192 (25.5)	
University	21 (3.7)	28 (3.7)	
Other/unknown	26 (4.6)	30 (4)	
Site of first chemotherapy treatment, n (%)			
Hospital outpatient	170 (35.6)	227 (40.5)	0.03
Physician office	224 (47.0)	230 (41.0)	
Patient's home	47 (9.9)	42 (7.5)	
Other/unknown	36 (7.5)	62 (11.1)	
Clinician region, n (%)			
Northeast	19 (3.4)	10 (1.3)	0.003
Midwest	139 (24.6)	205 (27.2)	
South	358 (63.5)	441 (58.5)	
West	48 (8.5)	98 (13.0)	

DCCI, Deyo Charlson Comorbidity Index; mCRC, metastatic colorectal cancer

Figure 1. Type of Genetic Testing by Year of mCRC Diagnosis



mCRC, metastatic colorectal cancer; p <0.001 across all years; partial year of data for 2012 not shown

Table 2. Potential Predictors of Non-Limited Testing*

Predictor	Odds Ratio	95% Confidence Interval	P-value
Age	0.99	0.97, 1.01	0.48
Female	0.96	0.73, 1.26	0.78
DCCI score	0.99	0.94, 1.05	0.69
Primary genitourinary cancer diagnosis	2.0	0.96, 4.16	0.07
Pre-index colon/rectal surgery	1.09	0.72, 1.65	0.68
Pre-index radiation	1.18	0.65, 2.14	0.58
Pre-index total healthcare costs	1.06	0.93, 1.21	0.37
Laboratory type (ref: independent)			
Hospital	0.81	0.6, 1.11	0.64
University	0.82	0.39, 1.74	0.83
Other/unknown[a]	0.88	0.46, 1.69	0.99
Site of care (ref: physician office)			
Hospital outpatient	1.18	0.87, 1.6	0.46
Other/unknown	1.12	0.76, 1.65	0.87
Clinician located in Southern United States	1.31	0.99, 1.74	0.06
Year of mCRC diagnosis (ref: 2012)			
2013	0.94	0.43, 2.08	<0.001
2014	1.15	0.52, 2.53	<0.001
2015	2.84	1.3, 6.2	0.01
2016	9.79	4.35, 22.07	<0.001

*In patients who received any type of anticancer treatment during the study period.
DCCI, Deyo Charlson Comorbidity Index; mCRC, metastatic colorectal cancer

Only year of metastatic colorectal cancer diagnosis was significantly associated with receipt of non-limited genetic testing.

Table 3. Treatment Patterns by Type of Genetic Testing*

All patients with evidence of genetic testing	Limited KRAS (n=564)	Non-Limited (n=754)	P-value
Treatment choices, n (%)			
No mCRC-related therapy	87 (15.4)	193 (25.6)	<0.001
EGFRi therapy	63 (11.2)	43 (5.7)	<0.001
Anticancer therapy without EGFRi therapy	414 (73.4)	518 (68.7)	0.06
Subset of patients with evidence of EGFRi therapy	**Limited KRAS (n=63)**	**Non-Limited (n=43)**	**P-value**
EGFRi therapy parameters, median [IQR]			
Days of EGFRi therapy	53 [14-12]	72 [28-112]	0.31
Days from testing to targeted therapy initiation	47 [28-88]	38 [25-72]	0.19

*Unadjusted analyses
mCRC, metastatic colorectal cancer; EGFRi, epidermal growth factor receptor inhibitor

Compared with patients who received limited testing, those who received non-limited testing were less likely to subsequently undergo EGFRi therapy.

Limitations

- The study was subject to claims-related limitations such as missing or incorrect data.
- Genetic test results were not available in claims, making it impossible to investigate whether testing was used to guide treatment or if treatment choices were made in accordance with clinical guidelines.
- Results may not be generalizable to non-Medicare populations or those with healthcare coverage from other payers.

Conclusions

- This real-world analysis revealed increasing use of genetic testing, and particularly non-limited testing, over time.
- Treatment patterns suggest that therapy choice was influenced by genetic testing.
- As precision medicine evolves, understanding delays in adoption of genetic testing, and generating real-world evidence regarding its use and effectiveness, is crucial.

References

1. NCCN. NCCN Guidelines©. 2017; https://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed November 26, 2017.
2. Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. Arch Pathol Lab Med. 2017;141(5):625-657.

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