KRAS Biomarker Testing & Treatment among Colorectal Cancer Patients

Results from CDC Comparative Effectiveness Research Project

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First presented by Adriana Rico at NAACCR 2015
Acknowledgements
KRAS Analytic Team

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• Dee West, PhD
Outline

- **Background**
  - NPCR Comparative Effectiveness Research (CER) Project
  - $KRAS$ test/recommendations

- **Results**
  - $KRAS$ testing results
  - Treatment by $KRAS$ testing results

- **Comparison to previous KRAS studies**
2009 Institute of Medicine Report

Initial National Priorities for Comparative Effectiveness

- Set priorities for questions to be addressed by Comparative Effectiveness Research (CER)
- Supported by American Recovery and Reinvestment Act
Cancer Registries and CER Priorities

- Addressing CER questions through central cancer registries
  - Population-based surveillance already established
  - Enhance cancer registry infrastructure
  - Collect add’l biomarker/treatment data

- CDC’s National Program of Cancer Registries
  - Enhanced data collection for 2011 cases
  - Focus on breast, colon, rectum, and CML
  - CER Project* – May 2010 to September 2013

Specialized Registries (AK, CA*, CO, FL*, ID, LA, NC, NH, RI, TX)
IOM Comparative Effectiveness Research

IOM Priority Question on Biomarkers:

- “Compare the effectiveness of genetic and biomarker testing and usual care in preventing and treating breast, colorectal, prostate, lung, and ovarian cancer, and possibly other clinical conditions for which promising biomarkers exist.”

CDC/NPCR Comparative Effectiveness Research question:

- Are colon and rectum (colorectal) cancer patients tested for KRAS
  - If tested, are the results used appropriately to determine treatment?
  - If not tested, what patient characteristics influenced no KRAS testing?

First time NPCR collecting KRAS testing info/treatment agent
**KRAS Test**

- **KRAS test for stage IV colorectal cancer patients**
- **KRAS results determine treatment options using anti-Epidermal Growth Factor Receptor (anti-EGFR)**
  - Cetuximab (Erbitux – FDA approved 2004*)
  - Panitumumab (Vectibix – FDA approved 2006*)

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Recommendation on KRAS Testing

- National Comprehensive Cancer Network (NCCN)*
  - 2009 – Updated guidelines
  - All stage IV colorectal cancer (CRC) patients should be tested for KRAS upon diagnosis and before treatment

Study Population

Total stage IV, CER colorectal cases (N=4,626)

- Histology cases (n=93)
- Missing KRAS test (n=6)

Total stage IV, CER colorectal cases (N=4,527)

- All unknown, other race (n=147)
- Transsexual, unknown sex (n=3)
- Died w/in 2 months or missing info (n=769)

*Total stage IV, CER colorectal cases analyzed (N=3,608)
KRAS Testing Results

- Total 2011 colorectal stage IV cases analyzed (N=3,608)
- Total 2011 tested stage IV cases with documented KRAS test (N=992)*

Not tested
2,616 (73%)

Tested
n=992
(27%)

Mutated
n=422
(44%)

Normal
n=534
(56%)

n=36 test ordered, but results not in chart

*Note: The total tested cases (N=992) is lower than the total analyzed cases (N=3,608) due to the exclusion of cases with no documented test results.
Characteristics of Stage IV Colorectal Cancer Patients with Documented KRAS Testing - NPCR/CER States, 2011 (n=3,608)

Chi-square tests:
- Age at dx (older age)
- Race/ethnicity (Black non-Hispanics/Hispanics)
- State of dx (CA, LA, TX, and FL)
- Insurance status (public)
- Education by census tract (low)
- Sex
- % of people below poverty level
- Rural/urban by census tract
- Comorbidities

No significant differences

Red denotes less likely to receive KRAS test
Characteristics of Stage IV Colorectal Cancer Patients with Documented KRAS Testing - NPCRCER States, 2011 (n=3,608)

Multivariate logistic regression:
- Age at dx
- Race/ethnicity
- State of dx
- Insurance status
- Education by census tract
- Sex
- % of people below poverty level
- Rural/urban by census tract
- Comorbidities

No significant differences

Red denotes less likely to receive KRAS test
### Multivariate logistic regression of demographics associated with **KRAS** testing

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Age</em> (per 5-year increase)</em>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below 70 years</td>
<td>0.92</td>
<td>0.88</td>
<td>(0.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>70 years and older</td>
<td>0.76</td>
<td>0.69</td>
<td>(0.84)</td>
<td></td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, Non-Hispanic</td>
<td>1.00</td>
<td></td>
<td></td>
<td>0.0837</td>
</tr>
<tr>
<td>Black, Non-Hispanic</td>
<td>0.77</td>
<td>0.61</td>
<td>(0.97)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.89</td>
<td>0.70</td>
<td>(1.12)</td>
<td></td>
</tr>
<tr>
<td><strong>State of Dx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>1.00</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AK</td>
<td>1.68</td>
<td>0.71</td>
<td>(3.96)</td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td>0.70</td>
<td>0.47</td>
<td>(1.06)</td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td>1.98</td>
<td>1.45</td>
<td>(2.70)</td>
<td></td>
</tr>
<tr>
<td>FL</td>
<td>1.19</td>
<td>0.93</td>
<td>(1.52)</td>
<td></td>
</tr>
<tr>
<td>ID</td>
<td>1.97</td>
<td>1.31</td>
<td>(2.97)</td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td>0.93</td>
<td>0.69</td>
<td>(1.25)</td>
<td></td>
</tr>
<tr>
<td>NH</td>
<td>2.98</td>
<td>1.84</td>
<td>(4.81)</td>
<td></td>
</tr>
<tr>
<td>NC</td>
<td>1.79</td>
<td>1.42</td>
<td>(2.26)</td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>2.72</td>
<td>1.52</td>
<td>(4.85)</td>
<td></td>
</tr>
</tbody>
</table>
FLOFOX was most common regimen

Bevacizumab used often

24 patients received anti-EGFR (cetuximab or panitumumab)

First line treatment available (n=844)
Receipt of anti-EGFR\(^*\) by KRAS result among patients with known testing results and known treatment

<table>
<thead>
<tr>
<th>EGFR inhibitor treatment</th>
<th>Normal (Wild type)</th>
<th>Abnormal (mutated)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>YES</strong> (received cetuximab or panitumumab)</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td><strong>NO</strong></td>
<td>330</td>
<td>303</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>354</td>
<td>303</td>
</tr>
</tbody>
</table>

- Of 354 patients with documented normal KRAS, 24 (6.8%) received anti-EGFR as first line treatment

\(^*\)First year of diagnosis
First Line Treatment among Stage IV CRC patients without a documented KRAS

- KRAS Not Tested (n=2,616)
  - 1,644 known treatment
  - 755 “no chemo”
  - 204 chemo status unk.
  - 13 discrepancies exc.

- Similar to patients tested for KRAS in regard to use of FOLFOX and Bevacizumab

- 13 patients received anti-EGFR without a documented KRAS test!

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX alone</td>
<td>191</td>
<td>11.62</td>
</tr>
<tr>
<td>FOLFIRI alone</td>
<td>17</td>
<td>1.03</td>
</tr>
<tr>
<td>CapeOx alone</td>
<td>45</td>
<td>2.74</td>
</tr>
<tr>
<td>FOLFOXIRI alone</td>
<td>5</td>
<td>0.3</td>
</tr>
<tr>
<td>Oxaliplatin + Irinotecan</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td>Fluorouracil alone</td>
<td>74</td>
<td>4.5</td>
</tr>
<tr>
<td>Capecitabine alone</td>
<td>99</td>
<td>6.02</td>
</tr>
<tr>
<td>Oxaliplatin alone</td>
<td>81</td>
<td>4.93</td>
</tr>
<tr>
<td>Irinotecan alone</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td>FOLFOX + bevacizumab</td>
<td>325</td>
<td>19.77</td>
</tr>
<tr>
<td>FOLFIRI + bevacizumab</td>
<td>41</td>
<td>2.49</td>
</tr>
<tr>
<td>CapeOx + bevacizumab</td>
<td>50</td>
<td>3.04</td>
</tr>
<tr>
<td>FOLFOXIRI + bevacizumab</td>
<td>14</td>
<td>0.85</td>
</tr>
<tr>
<td>Fluorouracil + bevacizumab</td>
<td>27</td>
<td>1.64</td>
</tr>
<tr>
<td>Capecitabine + bevacizumab</td>
<td>12</td>
<td>0.73</td>
</tr>
<tr>
<td>FOLFOX + cetuximab</td>
<td>7</td>
<td>0.43</td>
</tr>
<tr>
<td>FOLFIRI + cetuximab</td>
<td>3</td>
<td>0.18</td>
</tr>
<tr>
<td>FOLFOX + panitumumab</td>
<td>1</td>
<td>0.06</td>
</tr>
<tr>
<td>Cetuximab alone</td>
<td>2</td>
<td>0.12</td>
</tr>
<tr>
<td>Other single agent</td>
<td>34</td>
<td>2.07</td>
</tr>
<tr>
<td>Any other multiple agents</td>
<td>126</td>
<td>7.66</td>
</tr>
<tr>
<td>Unknown chemo agent</td>
<td>488</td>
<td>29.68</td>
</tr>
<tr>
<td>Total</td>
<td>1,644</td>
<td></td>
</tr>
</tbody>
</table>
Summary of Findings

- 27% received a documented KRAS test
- 73% did not receive a KRAS test
  - Older age was associated with less testing
  - Black, non-Hispanics received less testing than Whites
  - Geographic differences in testing
- Most cases received FOLFOX + bevacizumab as first-line treatment
- Overall, 37 cases received anti-EGFR
  - 13 cases (35%) received anti-EGFR but no KRAS test
Strengths & Limitations

**Strength:** Population-based registry study capturing 27.3% of U.S.,
- 25% of African Americans and
- 44% of Hispanics in U.S.

**Limitations:**
- Did we capture all KRAS testing? If not documented, not captured.
- Numbers to determine impact of anti-EGFR treatment are small.
- Date of test is not captured.
- Data collection was limited to first year of diagnosis.
- Testing beyond first year is unknown.
- Resource intensive.
Comparison to other KRAS studies
Charlton et al., Am J Clinical Onc, 2015

- SEER (Population-based)
- Percentages of documented KRAS among Stage IV colorectal cancer patients are similar
  - SEER registries (2010) 23%
  - NPCR CER registries (2011) 27%

- Differences in KRAS testing by age and geographic sites found in both population-based studies
  - Findings on rural/urban varied
Comparison to other KRAS studies
Webster et al., CEBP 2013.

- Seven integrated health care systems
- Review of EMR with multiple years of data
- 1,188 patients with Stage IV colorectal cancer
  - Diagnosis years 2004-2009
  - 36% received KRAS, 22% received EGFR inhibitors
Conclusions

- Despite recommendations for KRAS testing in metastatic colorectal cancer, only one in four patients had KRAS testing documented in first year since diagnosis.

- Among those with KRAS performed and a normal (wild type) result (i.e., eligible for treatment with anti-EGFR), 15% with known treatment received cetuximab or panitumumab as first-line therapy.

- Our findings may support that KRAS testing and targeted therapy are:
  - Being reserved for progression or recurrence, or
  - Being underutilized

- Outcome studies will be very important to compare survival among those who received early anti-EGFR to those who did not.

With additional funding, we demonstrated ability of NPCR to collect biomarkers and treatment to address CER priorities
This cancer specific CER dataset is available through National Center for Health Statistics Research Data Centers (RDC) which allow researchers access to restricted data.

Detailed treatment and biomarker data for 2011 cases collected from ten geographically diverse registries
- Breast,
- Colon and rectal
- Chronic myeloid leukemia cases

For more information
- Contact: Dr. Loria Pollack for more information (lop5@cdc.gov)
Thank you.

Comments? Questions?

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