Genomics Applications in Gastrointestinal Cancers: from Screening to Therapy

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DISCLOSURE:

NO COMMERCIAL CONFLICT
Cancer is a leading cause of death worldwide: an estimated 9.6 million deaths (2018)

The most common cancers are:

- Lung - 2.09 million cases
- Breast - 2.09 million cases
- Colorectal - 1.80 million cases
- Prostate - 1.28 million cases
- Skin cancer non-melanoma - 1.04 million cases
- Stomach - 1.03 million cases

The most common causes of cancer death are cancers of:

- Lung - 1.76 million deaths
- Colorectal - 862 000 deaths
- Stomach - 783 000 deaths
- Liver - 782 000 deaths
- Breast - 627 000 deaths

https://www.who.int/news-room/fact-sheets/detail/cancer
Five-year cancer survival rates in the USA

Average five-year survival rates from common cancer types in the United States, shown as the rate over the period 1970-77 [●] and over the period 2007-2013 [●].

This five-year interval indicates the percentage of people who live longer than five years following diagnosis.

Based on data by Journal of the National Cancer Institute; Surveillance, Epidemiology and End Results Program.

The data visualization is available at OurWorldinData.org. There you find research and more visualizations on this topic.

Licensed under CC-BY-SA by the authors Hannah Ritchie and Max Roser.

https://ourworldindata.org/cancer#cancer-over-the-long-run
Cancer Survival

Screening/Early Detection

Therapy
SCREENING FOR COLORECTAL CANCER

Stool Fecal Immunohistochemical Test (Stool FIT)

1. Ensure that your name is on the bottle.
2. Write the date on the bottle.
3. Unfold the tissue paper & place it on top of the water in the toilet bowl.
4. Deposit stool on top of collection (tissue) paper.
5. Open the cap of the bottle by twisting & lifting.
6. Collect a stool sample by scraping the stick on stool until only the grooved part of the stick is covered with stool.

Colonoscopy

- Colon polyt
- Adenoma
- Colorectal cancer

MediciNet
SCREENING FOR COLORECTAL CANCER

1. Ensure that your name is on the bottle.
2. Write the date on the bottle.
3. Unfold the tissue paper & place it on top of the water in the toilet bowl.
4. Deposit stool on top of collection (tissue) paper.
5. Open the cap of the bottle by twisting & lifting.
6. Collect a stool sample by scraping the stick on stool until only the grooved part of the stick is covered with stool.

Stool FIT

Stool DNA
### Test performance: sDNA vs FIT

<table>
<thead>
<tr>
<th></th>
<th>Colonoscopy</th>
<th>mt-sDNA test</th>
<th>FIT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall CRC sensitivity</td>
<td>65 (0.7%)</td>
<td>60 (92.3%)</td>
<td>48 (73.8%)</td>
<td></td>
</tr>
<tr>
<td>Overall CRC specificity</td>
<td>86.6%</td>
<td></td>
<td>94.9%</td>
<td></td>
</tr>
<tr>
<td>Proximal CRC sensitivity</td>
<td>90.0%</td>
<td>66.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal CRC sensitivity</td>
<td>94.3%</td>
<td>80.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall AAP sensitivity</td>
<td>757 (7.6%)</td>
<td>321 (42.4%)</td>
<td>180 (23.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serrated polyps &gt;1 cm</td>
<td></td>
<td>42.4%</td>
<td>5.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proximal AAP sensitivity</td>
<td></td>
<td>33.0%</td>
<td>15.5%</td>
<td></td>
</tr>
<tr>
<td>Distal AAP sensitivity</td>
<td></td>
<td>54.6%</td>
<td>34.8%</td>
<td></td>
</tr>
<tr>
<td>$n$ needed to detect one CRC</td>
<td>154 persons</td>
<td>166 persons</td>
<td>208 persons</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AAP, adenoma of advanced pathology ($\geq$1 cm, villous or adenocarcinoma component); CRC, colorectal cancer; FIT, fecal immunochemical testing; mt-sDNA, multitarget stool DNA.

$n = 9,989$ persons; there were 90 sites.
# Modeling of the effect of screening strategies

<table>
<thead>
<tr>
<th>CRC screening strategy</th>
<th>Decrease in CRC incidence (%)</th>
<th>Decrease in CRC mortality (%)</th>
<th>Quality-adjusted life-years (QALY) gained</th>
<th>Cost-effectiveness ratios ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No screening</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>$0</td>
</tr>
<tr>
<td>Colonoscopy every 10 years</td>
<td>65</td>
<td>73</td>
<td>0.1330</td>
<td>—</td>
</tr>
<tr>
<td>mt-sDNA annually</td>
<td>63</td>
<td>72</td>
<td>0.1290</td>
<td>$20,178</td>
</tr>
<tr>
<td>mt-sDNA every 3 years</td>
<td>57</td>
<td>67</td>
<td>0.1160</td>
<td>$11,313</td>
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<tr>
<td>mt-sDNA every 5 years</td>
<td>52</td>
<td>62</td>
<td>0.1050</td>
<td>$7,388</td>
</tr>
</tbody>
</table>

Abbreviations: CRC, colorectal cancer; mt-sDNA, multitarget stool DNA.

*aCost used for the mt-sDNA was $600 per test, and colonoscopy was $1,500 per test.*
Cancer Survival

- Screening/Early Detection
- Therapy
- Predictive/Prognostic Markers
Prognostic Markers in Early Colorectal Cancer - MSI

<table>
<thead>
<tr>
<th>Variable and Disease Setting</th>
<th>No. of Patients</th>
<th>End Point</th>
<th>HR</th>
<th>95% CI</th>
<th>Data Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI v MSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II untreated</td>
<td>307</td>
<td>TTR</td>
<td>0.35*</td>
<td>0.15 to 0.80</td>
<td>Meta-analysis (ACCE[N]t)30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS</td>
<td>0.37*</td>
<td>0.17 to 0.81</td>
<td></td>
</tr>
<tr>
<td>Stage II treated and untreated</td>
<td>1,913</td>
<td>RFS</td>
<td>0.53*</td>
<td>0.40 to 0.70</td>
<td>Clinical trial (QUASAR)21</td>
</tr>
<tr>
<td>Stage II and III treated</td>
<td>1,796</td>
<td>TTR</td>
<td>0.48</td>
<td>0.33 to 0.70</td>
<td>Clinical trial (NSABP C-07/C-08)31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS</td>
<td>0.64</td>
<td>0.46 to 0.89</td>
<td></td>
</tr>
<tr>
<td>Stage II and III treated</td>
<td>1,404</td>
<td>RFS</td>
<td>0.49</td>
<td>0.34 to 0.69</td>
<td>Clinical trial (PETACC-3)32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS</td>
<td>0.47</td>
<td>0.31 to 0.72</td>
<td></td>
</tr>
<tr>
<td>Stage III treated</td>
<td>2,723</td>
<td>TTR</td>
<td>0.82*</td>
<td>0.67 to 0.99</td>
<td>Meta-analysis (ACCE[N]t)30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS</td>
<td>0.81*</td>
<td>0.67 to 0.99</td>
<td></td>
</tr>
<tr>
<td>MSI v MSS (left side)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III treated</td>
<td>2,480</td>
<td>DFS</td>
<td>1.28</td>
<td>0.75 to 2.20</td>
<td>Clinical trial (N0147)43</td>
</tr>
<tr>
<td>891</td>
<td></td>
<td>DFS</td>
<td>1.58</td>
<td>0.72 to 3.46</td>
<td>Clinical trial (CALGB89803)40</td>
</tr>
<tr>
<td>MSI v MSS (right side)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III treated</td>
<td>2,480</td>
<td>DFS</td>
<td>0.73</td>
<td>0.55 to 0.96</td>
<td>Clinical trial (N0147)43</td>
</tr>
<tr>
<td>891</td>
<td></td>
<td>DFS</td>
<td>0.59</td>
<td>0.41 to 0.86</td>
<td>Clinical trial (CALGB89803)40</td>
</tr>
</tbody>
</table>

Modified from Diesntmann et al, 2015
Prognostic Markers in Early Colorectal Cancer - BRAF

<table>
<thead>
<tr>
<th>Variable and Disease Setting</th>
<th>No. of Patients</th>
<th>End Point</th>
<th>HR</th>
<th>95% CI</th>
<th>Data Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II and III treated and untreated</td>
<td>1,584</td>
<td>RR</td>
<td>0.84*</td>
<td>0.57 to 1.23</td>
<td>Clinical trial (QUASAR)⁷¹</td>
</tr>
<tr>
<td>Stage II and III treated</td>
<td>2,226</td>
<td>TTR</td>
<td>1.02</td>
<td>0.82 to 1.28</td>
<td>Clinical trial (NSABP C-07/C-08)³¹</td>
</tr>
<tr>
<td>Stage II and III treated</td>
<td>1,423</td>
<td>OS</td>
<td>1.46</td>
<td>1.20 to 1.79</td>
<td>Clinical trial (PETACC-3)³⁶</td>
</tr>
<tr>
<td>Stage II and III treated</td>
<td>201</td>
<td>SAR</td>
<td>2.31</td>
<td>1.83 to 2.95</td>
<td>Clinical trial (PETACC-3)³⁶</td>
</tr>
<tr>
<td>Stage III treated</td>
<td>506</td>
<td>OS</td>
<td>1.66*</td>
<td>1.05 to 2.63</td>
<td>Clinical trial (CALGB80803)⁴¹</td>
</tr>
<tr>
<td>BRAF mut v wt (MSI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IV treated and untreated</td>
<td>193</td>
<td>CCSS</td>
<td>1.90</td>
<td>0.79 to 4.57</td>
<td>Prospective cohort²⁸</td>
</tr>
<tr>
<td>Stage III treated</td>
<td>304</td>
<td>OS</td>
<td>1.44</td>
<td>0.91 to 2.30</td>
<td>Clinical trial (N0147)⁶³</td>
</tr>
<tr>
<td>Stage II and III treated</td>
<td>201</td>
<td>DFS</td>
<td>1.58</td>
<td>1.00 to 1.84</td>
<td>Clinical trial (NSABP C-07/C-08)³¹</td>
</tr>
<tr>
<td>BRAF mut v wt (MSS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IV treated and untreated</td>
<td>1,060</td>
<td>CCSS</td>
<td>1.60</td>
<td>1.12 to 2.28</td>
<td>Prospective cohort²⁸</td>
</tr>
<tr>
<td>Stage III treated</td>
<td>2,176</td>
<td>DFS</td>
<td>1.32</td>
<td>1.01 to 1.73</td>
<td>Clinical trial (N0147)⁶³</td>
</tr>
<tr>
<td>Stage II and III treated</td>
<td>1,534</td>
<td>OS</td>
<td>1.58*</td>
<td>1.22 to 2.03</td>
<td>Clinical trial (PETACC-3)³⁶</td>
</tr>
<tr>
<td>Stage II and III treated</td>
<td>1,054</td>
<td>OS</td>
<td>2.82*</td>
<td>1.58 to 4.30</td>
<td>Clinical trial (PETACC-3)³⁶</td>
</tr>
<tr>
<td>BRAF mut v wt (MSS, left sided)</td>
<td>607</td>
<td>RFS</td>
<td>3.57*</td>
<td>2.02 to 6.31</td>
<td>Clinical trial (PETACC-3)³⁶</td>
</tr>
<tr>
<td>Stage II and III treated</td>
<td>607</td>
<td>OS</td>
<td>6.41*</td>
<td>3.57 to 11.52</td>
<td>Clinical trial (PETACC-3)³⁶</td>
</tr>
</tbody>
</table>

Modified from Diesntmann et al, 2015
## Prognostic Markers in Early Colorectal Cancer - KRAS

<table>
<thead>
<tr>
<th>Variable and Disease Setting</th>
<th>No. of Patients</th>
<th>End Point</th>
<th>HR</th>
<th>95% CI</th>
<th>Data Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS mut v wt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stago II and III treated and untreated</td>
<td>1,583</td>
<td>RR</td>
<td>1.40*</td>
<td>1.12 to 1.74</td>
<td>Clinical trial (QUASAR)</td>
</tr>
<tr>
<td>Stago II and III treated</td>
<td>2,081</td>
<td>TTR</td>
<td>1.12</td>
<td>0.94 to 1.32</td>
<td>Clinical trial (NSABP C-07-C-03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS</td>
<td>1.09</td>
<td>0.92 to 1.29</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SAR</td>
<td>1.11</td>
<td>0.92 to 1.34</td>
<td></td>
</tr>
<tr>
<td>KRAS mut v wt (right side)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stago III treated</td>
<td>614</td>
<td>TTR</td>
<td>1.29</td>
<td>0.9 to 1.64</td>
<td>Clinical trial (PETACC-8)</td>
</tr>
<tr>
<td>Stago III treated</td>
<td>1,369</td>
<td>DFS</td>
<td>1.27</td>
<td>1.03 to 1.57</td>
<td>Clinical trial (N0147)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS</td>
<td>1.25</td>
<td>0.97 to 1.60</td>
<td></td>
</tr>
<tr>
<td>KRAS codon 13 mut v wt (BRAF wt)</td>
<td>1,075</td>
<td>CCSS</td>
<td>0.86</td>
<td>0.58 to 1.27</td>
<td>Prospective cohort</td>
</tr>
<tr>
<td>Stago I-IV treated and untreated</td>
<td>2,478</td>
<td>OS</td>
<td>0.96</td>
<td>0.71 to 1.30</td>
<td></td>
</tr>
<tr>
<td>Stago III treated</td>
<td>1,043</td>
<td>DFS</td>
<td>1.36</td>
<td>1.04 to 1.77</td>
<td>Clinical trial (N0147)</td>
</tr>
<tr>
<td>KRAS codon 12 mut v wt (BRAF wt)</td>
<td>1,075</td>
<td>TTR</td>
<td>1.59</td>
<td>1.00 to 2.56</td>
<td>Clinical trial (PETACC-8)</td>
</tr>
<tr>
<td>Stago I-IV treated and untreated</td>
<td>2,478</td>
<td>CCSS</td>
<td>1.30</td>
<td>1.02 to 1.67</td>
<td>Prospective cohort</td>
</tr>
<tr>
<td>Stago III treated</td>
<td>1,043</td>
<td>DFS</td>
<td>1.52</td>
<td>1.28 to 1.80</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACCENT, Adjuvant Colon Cancer Endpoints; CALGB, Cancer and Leukemia Group B; CCSS, colon cancer-specific survival; DFS, disease-free survival; HR, hazard ratio; LVI, lymphovascular invasion; MSI, microsatellite instability high; MSS, microsatellite stable, mut, mutant; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; PETACC, Pan-European Trials in Alimentary Tract Cancer; PNI, perineural invasion; QUASAR, Quick and Simple and Reliable; RFS, relapse-free survival; RR, recurrence risk; SAR, survival after relapse; TTR, time to recurrence; wt, wild type.
*Univariable analysis.
Cancer Survival

Screening/Early Detection

Therapy
CANCER DRUGS

1975
1980
1985
1990
1995
2000
2005
2010
2015
2020

5-Fluorouracil
Irinotecan
Oxaliplatin
Capecitabine

Cancer as a Genomic Disease -> Precision Medicine

- **ColoRectal Cancer**
  - **RAS/RAF**\textsuperscript{mut}
  - **PIK3CA and RAS/RAF**\textsuperscript{mut}
  - **Cetuximab, panitumimab**

- **GIST Tumor**
  - **KIT Gene Mutation**
  - **Imatinib**

- **Lung Cancer**
  - **EGFR Mutation**
  - **Erlotinib, gefitinib**

- **Breast Cancer**
  - **ERBB2 Amplification**
  - **Lapatinib, trastuzumab**
### Anti-EGFR treatment – Kras/Nras status

<table>
<thead>
<tr>
<th>Study</th>
<th>RAS status</th>
<th>$n$</th>
<th>Treatment</th>
<th>RR</th>
<th>$p$ value*</th>
<th>PFS</th>
<th>$p$ value*</th>
<th>OS</th>
<th>$p$ value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB/SWOG 80405</td>
<td>KRAS wt exon 2</td>
<td>559</td>
<td>(FOLFOX or FOLFIRI)/bevacizumab</td>
<td>NA</td>
<td>NA</td>
<td>10.84</td>
<td>0.55</td>
<td>29.0</td>
<td>0.34</td>
</tr>
<tr>
<td>ESMO [2014],</td>
<td>RAS wt at all loci</td>
<td>578</td>
<td>(FOLFOX or FOLFIRI)/cetuximab</td>
<td>NA</td>
<td>NA</td>
<td>10.45</td>
<td>0.45</td>
<td>29.9</td>
<td>0.45</td>
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<tr>
<td>Lenz et al. [2014],</td>
<td></td>
<td>256</td>
<td>(FOLFOX or FOLFIRI)/bevacizumab</td>
<td>53.6</td>
<td>0.01</td>
<td>10.45</td>
<td>0.56</td>
<td>31.2</td>
<td>0.40</td>
</tr>
<tr>
<td>Venook et al. [2014]</td>
<td></td>
<td>270</td>
<td>(FOLFOX or FOLFIRI)/cetuximab</td>
<td>68.6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>32.0</td>
<td>0.40</td>
</tr>
<tr>
<td>European consortium</td>
<td>KRAS mut exon 2, 3,</td>
<td>253</td>
<td>Chemotherapy/cetuximab</td>
<td>6.7</td>
<td>&lt;0.0001</td>
<td>2.8</td>
<td>&lt;0.0001</td>
<td>7.4</td>
<td>&lt;0.0001</td>
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<tr>
<td>De Roock et al. [2010]</td>
<td>4,</td>
<td>352</td>
<td>Chemotherapy/cetuximab</td>
<td>35.8</td>
<td>0.013</td>
<td>5.5</td>
<td>0.055</td>
<td>11.5</td>
<td>0.051</td>
</tr>
<tr>
<td>NRAS mut exon 2, 3, 4</td>
<td></td>
<td>13</td>
<td>Chemotherapy/cetuximab</td>
<td>7.7</td>
<td>0.013</td>
<td>3.5</td>
<td>0.055</td>
<td>8.8</td>
<td>0.051</td>
</tr>
<tr>
<td>NRAS wt exon 2, 3, 4</td>
<td></td>
<td>289</td>
<td>Chemotherapy/cetuximab</td>
<td>38.1</td>
<td>0.013</td>
<td>6.5</td>
<td>0.055</td>
<td>11.5</td>
<td>0.051</td>
</tr>
<tr>
<td>OPUS</td>
<td>KRAS wt exon 2</td>
<td>82</td>
<td>FOLFOX4/cetuximab</td>
<td>57</td>
<td>0.0027</td>
<td>8.3</td>
<td>0.0064</td>
<td>22.8</td>
<td>0.39</td>
</tr>
<tr>
<td>Bokemeyer et al. [2011]</td>
<td></td>
<td>97</td>
<td>FOLFOX4</td>
<td>34</td>
<td>0.0290</td>
<td>7.2</td>
<td>0.015</td>
<td>13.4</td>
<td>0.20</td>
</tr>
<tr>
<td>Tejpar et al. [2014]</td>
<td>KRAS mut exon 2</td>
<td>77</td>
<td>FOLFOX4/cetuximab</td>
<td>34</td>
<td>0.0290</td>
<td>5.5</td>
<td>0.015</td>
<td>13.4</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>59</td>
<td>FOLFOX4</td>
<td>53</td>
<td>0.057</td>
<td>8.3</td>
<td>0.0064</td>
<td>17.5</td>
<td>0.41</td>
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<td>KRAS mut exon 3, 4</td>
<td>17</td>
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<td>0.11</td>
<td>7.4</td>
<td>0.018</td>
<td>13.4</td>
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<td>4</td>
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<td>36.1</td>
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<td>7.2</td>
<td>0.56</td>
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Tran et al, 2015
# Anti-EGFR treatment – Braf status

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<tr>
<th>Study</th>
<th><em>BRAF</em> status exon 15 codon 600</th>
<th>n</th>
<th>Treatment</th>
<th>RR</th>
<th>p value</th>
<th>PFS</th>
<th>p value</th>
<th>OS</th>
<th>p value</th>
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<td>[Cetuximab or panitumumab] ± chemotherapy</td>
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<td></td>
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<td>Chemotherapy/cetuximab</td>
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</tr>
</tbody>
</table>

*All RAS wildtype. $^a$Compared to row immediately below.
Chemo, chemotherapy; EGFR, epidermal growth factor receptor; NA, not available; NR, not reached; mut, mutation; OS, overall survival; PFS, progression-free survival; RR, relative risk; wt, wildtype.
## Anti-EGFR therapy and mutational status

<table>
<thead>
<tr>
<th>MUTATION</th>
<th>Anti-EGFR Therapy</th>
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<tbody>
<tr>
<td>Kras (exons 2, 3, 4)</td>
<td>Not indicated</td>
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<tr>
<td>Nras (exons 2, 3, 4)</td>
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<tr>
<td>Braf (V600E)</td>
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<tr>
<td>PIK3CA</td>
<td>&gt;2-line therapy</td>
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<tr>
<td>All wildtype</td>
<td>indicated</td>
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</tbody>
</table>

Tran et al, 2015
Anti-PD1 Therapy

MSS tumor

- Tumor
- MHC
- PD-L1/PD-L2
- TCR
- PD1
- T cell
- Poor response

MSI-H/dMMR tumor

- Tumor
- mutation
- neoantigen
- Anti-PD-1 antibody
- T cell
- Good response

Modified from Eso et al, 2020
Potential Combinations of Molecularly Targeted Treatments

- **RAS wt 50%**
  - Anti-EGFR antibodies + chemotherapy

- **RAS mut 50%**
  - No targeted therapy

- **BRAF mut 8%**
  - BRAF inhibition + MEK inhibitors

- **HER2+ 5%**
  - anti-HER2 therapy

- **MSI 5%**
  - Anti-PD1 antibodies
Cancer Survival

Screening/Early Detection

Personalized Therapy?
DNA sequencing costs

[Graph showing the decline in cost per raw megabase of DNA sequence (in dollars) from 2000 to 2015. Key points include:
- 2001: IHGSC reports the sequence of the first human genome.
- 2008: First tumor-normal genome sequenced.
- 2011: $10K genome.
- 2013: $1,000 genome?

The graph is divided into two phases:
- Sanger sequencing (2000-2008)

Moore's Law is also depicted, showing the exponential decrease in cost.]
Onco-omics → Precision Cancer Treatment
Personalized Oncogenomics (POG) Project

Whole Genome + Transcriptome Analysis → Inform Treatment Decisions

Project Leaders:
Dr. Janessa Laskin (Medical Oncology, BC Cancer)
Dr. Marco Marra (Director, Genome Sciences Centre, BC Cancer)
Personalized Oncogenomics Project:

- Patients with advanced, incurable cancer; heavily pre-treated & limited / no treatment options. Consider all cancers.
- Determine the feasibility of approach in a tertiary cancer care centre.
  - genomes (tumor, normal) + transcriptome
  - Bottlenecks?
  - Analytic pipelines?
- Can the biopsy and subsequent analyses be completed in a timely fashion?
- What is the frequency of “actionable” results?
POG case – Colorectal Cancer

- 67 year old
- Initially presented in May 2010 Stage III colon cancer
  - T3N1 1/18 nodes positive (0.1 mm tumour deposit)
  - moderately differentiated adenocarcinoma
- Genetic testing:
  - MLH1 deleted / BRAF wild type (IHC)
- Family History:
  - Mother - pancreatic cancer, sister - brain tumor, brother - prostate cancer
  - 11 brothers and sisters
- 2014: metastasis
  - Enrolled to POG in Sept 2014
Pre-treatment PET/CT (Nov 2014)

METASTASIS
PI3K-Akt not highly deregulated

**Mismatch-repair defective**
- LoF [2]: MLH1, MLH3
- LoF [2]: MSH3, MSH6
- LoF [1]: ATM
- VUS [2]: FANCM
- DNA Repair: POLN, MLH3, MSH3, MSH6

**PI3K-Akt Pathway**
- PIK3CA
- PIK3R1
- PTEN
- [LoF]
- [GoF]
- [20%]
- [60%]
- mTOR
- FOXO1
- Invasion and Metastasis
- Gene regulation

**Gene regulation**
- FOS
- JUN
- [98%]
- [100%]
- AP1 complex

**Gene regulation**
- [GoF]: gain of function
- [LoF]: loss of function
- VUS: uncertain sig.
- hom: homozygous
- het: heterozygous
- sc: subclonal
- [%]: high percentile
- [%]: low percentile
- [HomD]: homozygous del

**WNT Pathway**
- GSK3A
- APC
- WNT
- [95%]
- [4%]
- TCF
- CTTNB1

**HHog Pathway**
- DHH
- FZD
- PTCH1
- SMO
- GLI
- [70%]
- [51%]
- [27%]
- [75%]

**Cell Cycle**
- CYCLINS
- E2Fs
- [90%]
- [50-80%]

**DNA Repair**
- POLN
- MLH3
- MSH3
- MSH6

**Survival and Proliferation**
- VUS [1]: CDKN1B
- CDK6
- E2Fs
- [98%]
- [90%]

**Apoptosis**
- BAX
- TP53
- VUS [1]
- VUS [2]
- E2Fs
- [50-80%]

**GoF**
- gain of function

**Loss**
- [LoF]: loss of function

**Copy # relative PLOIDY**
- UP: expression (fold change) up
- Down: expression (fold change) down
- Copy Number Change ('n' # copy change)

**Expression**
- Fold Change: Colon Percentile: COAD

**Fold Change:** Colon Percentile: COAD

**Gene regulation**
- [GoF]: gain of function
- [LoF]: loss of function
- VUS: uncertain sig.
- hom: homozygous
- het: heterozygous
- sc: subclonal
- [%]: high percentile
- [%]: low percentile
- [HomD]: homozygous del

**Driver**
- Tumour Sup.

**Drug Target**
- BCCA Confidential - For Research Purposes Only
Mechanism?

Drug

POG-CRC pathway analysis

http://www.nature.com/ki/journal/v77/n2/fig_tab/ki2009349f2.html
Post-treatment (4 Weeks)
Advances in “omics” and Potential Impact on Cancer Management

**Personalized medicine**
- Prevention
- Precision treatment
- Early intervention strategies

**Drug discovery**
- Efficacy
- Resistance

**Disease mechanisms**
- Origin
- Transition
- Resistance

**Interactions**
- Molecular
- Cellular
- Spatial

**Signatures & new biomarkers**
- Pre-cancer lesions
- Metastatic makers
- Drug resistance makers

**Diagnostics**
- Patient stratification
- Early detective

Modified from Rozenblatt-Rosen et al, Cell 2020
Thank you!
ACKNOWLEDGEMENTS

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Charles Scudamore
Andrew Buckowski
Stephen Chung

Genome Sciences Centre

Sharon Gorski
Gregg Morin
Marco Marra
Steven Jones
Simon Chan

BC Cancer

Margaret Sutcliffe
Lorena Barclay
Nhu Le
Linlea Armstrong
Sharlene Gill
Hagen Kennecke
Howard Lim
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Hye-Lim Ju
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Mahbuba Hasan
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Chaoyang Jin
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Mi Zhao
Annie Chan
Justin Chan
Farnaz Taghizadeh
Shirley Ho
Winnie So
Young Kim

Michael Smith Foundation for Health Research

CIHR IRSC

Canadian Association of Gastroenterology

Cancer Research Society