Incident Testing for Lynch Syndrome in Colorectal Cancer Under 50 in British Columbia

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Background

- Lynch syndrome (HNPCC) is the most common form of inherited colorectal cancer
  - 2-5% of all colorectal cancers
  - High life-time risk of colon and other cancers

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General population risk</th>
<th>HNPCC risk</th>
<th>Mean age of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>6%</td>
<td>80%</td>
<td>44 yrs</td>
</tr>
<tr>
<td>Endometrial</td>
<td>3%</td>
<td>20-60%</td>
<td>46 yrs</td>
</tr>
<tr>
<td>Stomach</td>
<td>~1%</td>
<td>10-19%</td>
<td>56 yrs</td>
</tr>
<tr>
<td>Ovary</td>
<td>2-3%</td>
<td>10-12%</td>
<td>42 yrs</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>2-7%</td>
<td>not reported</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>4-5%</td>
<td>~55 yrs</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>1-4%</td>
<td>49 yrs</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>&lt;1%</td>
<td>1-3%</td>
<td>~50 yrs</td>
</tr>
</tbody>
</table>

Adapted from Genereviews
Background

- Underlying mutations in DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6 and PMS2

- Microsatellite instability (MSI) in up to 90% of Lynch colorectal tumors

- Intensive cancer screening and prophylactic surgery shown to reduce incidence and mortality of colorectal cancer and endometrial cancer

- Optimal method of identifying individuals with Lynch syndrome is currently under debate
Background

• Genetic counselling and testing for Lynch syndrome have been available on a clinical basis
  ▫ Amsterdam I or II or revised Bethesda criteria

• Previous work has shown:
  ▫ Overall yield of Lynch mutations differs based on ascertainment method
    • Colorectal cancer <50 years of age was 14% (Hampel et al. 2008)
    • Clinic based approach at BCCA (including individuals with and without cancer) is 3.4% (Cremin et al. 2009)

• Evaluation of Genomic Applications in Practice and Prevention Working Group recommended removal of family history from consideration as a preliminary test in newly diagnosed colorectal cancer (Palomaki et al. 2009)
Clinical Criteria - Amsterdam

• Amsterdam I
  1. $\geq 3$ relatives with colorectal cancer (CRC) plus
  2. One affected patient should be a first degree relative of the other two
  3. $\geq 2$ successive generations affected
  4. At least one case of CRC dx $< 50$
  5. FAP excluded
  6. Pathology confirmation

• Amsterdam II
  1. $\geq 3$ relatives with Lynch-associated cancers plus
  2. One affected patient should be a first degree relative of the other two
  3. $\geq 2$ successive generations affected
  4. One or more cases of CRC dx $< 50$
  5. FAP excluded
  6. Pathology confirmation
Clinical Criteria - Bethesda and HCP

**Revised Bethesda**
1. CRC dx <50
2. Synchronous, metachronous CRC or other Lynch-associated tumor
3. CRC <60 with tumor infiltrating lymphocytes, crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation or medullary growth pattern
4. CRC dx in patients with ≥1 first degree relative with Lynch-associated tumor with ≥1 dx <50
5. CRC dx in patient with ≥2 first or second degree relatives with Lynch-associated tumor regardless of age

**HCP**
1. Carrier testing
2. Isolated CRC ≤40
3. ≥2 HNPCC primaries, one being colon, one dx ≤50
4. Amsterdam I
5. 2 first degree relatives with HNPCC-related cancers, one being colon, both dx ≤50
6. ≥3 HNPCC-related cancers, one being colon, one dx ≤50 and more than one generation affected
7. Isolated case CRC ≤50 with MSI-H result
Lynch syndrome identification in BC

- In BC a combination approach to identify patients at increased risk for Lynch syndrome has been used since June 2008

- Patients identified in two ways:
  - Clinic-based: Referral to the HCP due to personal and/or family history of colorectal and other Lynch-related cancers
  - Incident-case based: MSI analysis in patients ≤50 diagnosed with colorectal cancer.
Referral to BCCA vs. HCP

• **Referral to BCCA includes referral for**
  - Oncological consult and care
  - Cancer drug therapy
  - Radiation therapy
  - MSI, IHC, Germline mutation testing
  - Referral to HCP

• **Referral to HCP**
  - Appointment with a Geneticist/ Genetic Counsellor due to personal or family cancer history that might indicate an inherited gene mutation
  - Further investigation for Lynch syndrome
Hypothesis

Direct referral for MSI analysis on incident colorectal cancer (CRC) \( \leq 50 \) will generate a different rate of ascertainment of Lynch syndrome than referrals based on Amsterdam and revised Bethesda guidelines.
What is MSI?

- Microsatellite instability (MSI) refers to difference between the size of microsatellites in DNA from tumor tissue compared to normal tissue from the same person.

- A panel of five mononucleotide and dinucleotide markers recommended by National Cancer Institute in 1998 is used in assessing MSI.
  - BCCA lab currently uses a panel of 7 markers.

- **MSI-high** - ≥30% of the markers show instability.
- **MSI-low** - <30% of the markers show instability.
- **MSI-stable** - 0% of the markers show instability.
Data Set

• Cases of colorectal cancer ≤50 diagnosed between June 1, 2008 – August 30, 2009 referred to the BC Cancer Agency*

• 169 cases
  ▫ 60 (36%) referred to HCP
  ▫ 91 female
  ▫ 78 male

*An additional 103 non-referred cases were identified from the BC Cancer Registry but are not included in this preliminary report
Data request specifications

Some demographic and clinicopathologic information:

- Date of birth
- Date of death
- Sex
- Age at diagnosis
- Tumor site
- TNM stage and grade classification
- Health authority at time of diagnosis
- Referral status to HCP
Age Distribution (n=169)
Median age at diagnosis - 46
Sex Distribution (n=169)

- **HCP group (n=60)**
  - Male, 21, 35%
  - Female, 39, 65%

- **Incident group (n=109)**
  - Male, 57, 52%
  - Female, 52, 48%

p=0.037
Health authority distribution at time of diagnosis (n=169)

<table>
<thead>
<tr>
<th>Health Authority</th>
<th>HCP group (n=60)</th>
<th>Incident group (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancouver Coastal</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>Vancouver Island</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Fraser Valley</td>
<td>23</td>
<td>46</td>
</tr>
<tr>
<td>Southern Interior</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Northern and Other</td>
<td>12</td>
<td>5</td>
</tr>
</tbody>
</table>

p=0.035
Tumor site distribution (n=169)
Tumor surgical grade (n=169)
Tumor surgical stage (n=169)

\[ p = 0.049 \]
Patient distribution by Clinical criteria

<table>
<thead>
<tr>
<th>Clinical criteria met</th>
<th>Number of patients (n=176)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revised Bethesda</td>
<td>169</td>
</tr>
<tr>
<td>Amsterdam I</td>
<td>2</td>
</tr>
<tr>
<td>Amsterdam II</td>
<td>4</td>
</tr>
<tr>
<td>HCP</td>
<td>72</td>
</tr>
<tr>
<td>Family history not taken or incomplete</td>
<td>24</td>
</tr>
<tr>
<td>Adopted</td>
<td>6</td>
</tr>
</tbody>
</table>

Each patient may qualify for one or more criteria
Patients diagnosed at 50 were considered to fulfill Revised Bethesda criteria
Patient distribution by clinical criteria (n=169)

HCP group (n=60)

- 1,2; 1,3; 1,4; 1,5: 35%
- 1 alone: 65%

Incident group (n=109)

- 1,2; 1,3; 1,4; 1,5: 15%
- 1 alone: 85%

p=0.003
MSI analysis in patient population (n=146)

HCP group (n=37)

- MSI analysis performed: 43%
- MSI analysis not performed: 57%

Incident group (n=109)

- MSI analysis performed: 26%
- MSI analysis not performed: 74%

\[ p = 0.001 \]
23 patients did not have genetic counselling

<table>
<thead>
<tr>
<th>Reason</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient deceased</td>
<td>2</td>
</tr>
<tr>
<td>Patient did not wish to attend appointment</td>
<td>1</td>
</tr>
<tr>
<td>No appointment offered - personal or family history not suggestive of Lynch syndrome</td>
<td>7</td>
</tr>
<tr>
<td>No appointment offered - Patient referred to Oncologist for MSI analysis</td>
<td>1</td>
</tr>
<tr>
<td>Personal or family history or genetic testing suggestive of other cancer syndrome (FAP, HBOC, NHL)</td>
<td>3</td>
</tr>
<tr>
<td>Patient awaiting appointment</td>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
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## MSI utilization rate and results

<table>
<thead>
<tr>
<th></th>
<th>HCP group (n=37)</th>
<th>Incident group (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI utilization rate</td>
<td>25/37 = 67%</td>
<td>28/109 = 26%</td>
</tr>
<tr>
<td>MSI-H rate</td>
<td>48%</td>
<td>18%</td>
</tr>
</tbody>
</table>

- 37 of the 60 patients in the HCP group received genetic counselling
- MSI analysis was offered to 25 of 37 patients in the HCP group
- Overall 53 patients underwent MSI analysis
- 32% of patients receiving MSI analysis showed microsatellite instability
MSI analysis in HCP group (n=37)

- MSI analysis performed, 25
- Patient declined testing, 1
- Genetic testing for other genetic syndrome undertaken, 2
- IHC analysis performed without MSI analysis, 1
- Genetic testing in other family member not suggestive of Lynch syndrome, 1
- Family mutation known, 5
- Colon pathology, 1
MSI analysis results in HCP and Incident groups

<table>
<thead>
<tr>
<th></th>
<th>MSS</th>
<th>MSI-L</th>
<th>MSI-H</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCP group (n=25)</strong></td>
<td>13</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td><strong>Incident group (n=28)</strong></td>
<td>23</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
IHC analysis based on MSI results (n=17)
Germline mutation analysis results (n=6)

HCP group (n=5)

<table>
<thead>
<tr>
<th></th>
<th>HCP group (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH-1</td>
<td>1</td>
</tr>
<tr>
<td>MSH-2</td>
<td>3</td>
</tr>
<tr>
<td>MSH-6</td>
<td>0</td>
</tr>
<tr>
<td>PMS-2</td>
<td>1</td>
</tr>
</tbody>
</table>
Demographic & clinicopathologic features of CRC in individuals whose tumors showed microsatellite instability (n=17)

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Geographic location at diagnosis</th>
<th>Tumor location</th>
<th>Tumor surgical stage</th>
<th>Tumor surgical grade</th>
<th>Clinical criteria met</th>
<th>MSI results</th>
<th>Genetic testing results</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td>Fraser</td>
<td>RECTUM, NOS</td>
<td>3A</td>
<td>3</td>
<td>RB-1</td>
<td>MSI-L 1/6</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Fraser</td>
<td>SPLENIC FLEXURE OF COLON</td>
<td>2A</td>
<td>2</td>
<td>RB-1, 4; AMS-I</td>
<td>MSI-H 7/7</td>
<td>MLH1</td>
</tr>
<tr>
<td>47</td>
<td>Vancouver Island</td>
<td>ASCENDING COLON</td>
<td>4</td>
<td>9</td>
<td>RB-1</td>
<td>MSI-L-3/7</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>Fraser</td>
<td>CECUM</td>
<td>2A</td>
<td>2</td>
<td>RB-1</td>
<td>MSI-H 7/7</td>
<td>PMS2-biallelic</td>
</tr>
<tr>
<td>43</td>
<td>Fraser</td>
<td>CECUM</td>
<td>2A</td>
<td>2</td>
<td>RB-1</td>
<td>MSI-H 7/7</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>Fraser</td>
<td>APPENDIX</td>
<td>4</td>
<td>1</td>
<td>RB-1</td>
<td>MSI-L 1/6</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>Fraser</td>
<td>APPENDIX</td>
<td>4</td>
<td>1</td>
<td>RB-1</td>
<td>MSI-L 1/6</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>Fraser</td>
<td>SIGMOID COLON</td>
<td>4</td>
<td>1</td>
<td>RB-1</td>
<td>MSI-H 7/7</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>Vancouver Island</td>
<td>RECTUM, NOS</td>
<td>3B</td>
<td>2</td>
<td>RB-1</td>
<td>MSI-L 3/7</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>Northern</td>
<td>RECTUM, NOS</td>
<td>1</td>
<td>2</td>
<td>RB-1</td>
<td>MSI-H 7/7</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>Fraser</td>
<td>CECUM</td>
<td>2A</td>
<td>2</td>
<td>RB-1, 4; AMS-II</td>
<td>MSI-H 7/7</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>Fraser</td>
<td>COLON, NOS</td>
<td>3B</td>
<td>2</td>
<td>RB-1, 4</td>
<td>MSI-H 4/7</td>
<td>MSH2</td>
</tr>
<tr>
<td>49</td>
<td>Fraser</td>
<td>TRANSVERSE COLON</td>
<td>3C</td>
<td>2</td>
<td>RB-1</td>
<td>MSI-L 1/6</td>
<td>MSH2</td>
</tr>
<tr>
<td>38</td>
<td>Vancouver Coastal</td>
<td>TRANSVERSE COLON</td>
<td>3A</td>
<td>2</td>
<td>RB-1, 5</td>
<td>MSI-H 5/5</td>
<td>MSH2</td>
</tr>
<tr>
<td>41</td>
<td>Southern Interior</td>
<td>HEPATIC FLEXURE</td>
<td>3A</td>
<td>RB1</td>
<td></td>
<td>MSI-H 7/7</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>Vancouver Coastal</td>
<td>RECTUM, NOS</td>
<td>3A</td>
<td>RB 1</td>
<td></td>
<td>MSI-L 1/6</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

- Low overall MSI utilization rate especially in the incident group
  - High uptake of MSI testing among those to whom it was offered in the HCP group
- Difficult to make conclusions about effectiveness of MSI testing given low utilization rate
  - 18% microsatellite instability in those having MSI analysis
- Germline mutations identified in HCP group only
Conclusions

• Both approaches have advantages and disadvantages

• Possible reasons for low MSI utilization rate
  ▫ Lack of knowledge about availability and criteria for MSI analysis
  ▫ Perhaps pathologists are better able to utilize MSI

• Further education regarding MSI analysis availability and criteria

• Analysis of data from patients with CRC ≤50 from September 2009-May 2010
Patients diagnosed with CRC ≤50 in BCCA database (June 2008-Aug 2009, n=169)

Referred to HCP (n=60)

Selection for MSI testing by oncologist-Incident patients (n=109)

MSI analysis performed (n=25)

14 MSS

12 MSI-L and MSI-H

7 IHC

3 patients were referred to HCP: 2 MSI-L, 1 MSI-H

MSI analysis performed (n=28)

5 MSI-L and MSI-H

23 MSS

5 IHC

2 IHC

2 IHC
Thank You!