Universal Screening for Lynch Syndrome

St. Vincent/Ameripath protocol proposal
Lynch syndrome (HNPCC)

- 1/35 individuals with colorectal cancer has Lynch syndrome
- Over half individuals are >50 at time of first dxs CRC
- Autosomal dominant
- Associated with mutation in one of 4 mismatch repair genes
  - Results in microsatellite instability
Lynch syndrome

Lifetime cancer risks:

– Colorectal 50-80%
– Endometrial 20-60%
– Gastric 13-19%
– Ovarian 9-12%
– Urinary tract 12%
– Pancreas 4%
– Small bowel 1-4%
– Biliary tract 2%
– Brain/CNS 1-3%
Features of Colon Cancer Associated with Lynch Syndrome

- Right-sided
- Proximal
- Mucinous, signet ring cell
- Microsatellite instability present
- Accelerated time between adenomas and tumor
- Increased survival
IHC screening

- Antibodies stain for presence or absence of MLH1, MSH2, MSH6 and PMS2 proteins
- Indicates which gene likely to be mutated
- Quick, inexpensive
- Available in-house
- Can be performed on biopsy specimen
- Correlates well with Lynch syndrome
  - ~97% Lynch will have abnormal IHC
Why determine which CRC cases have Lynch syndrome (LS)?

- All MSI-H CRC patients have a better prognosis
- MSI-H CRC patients MAY need different treatment in future
- LS patients at high risk for second primary cancers (CRC and others)
- LS patients have at-risk relatives who could benefit from genetic testing
Lynch Syndrome Implications for Patient

- 16-30% chance of second primary CRC in the 10 years after their first diagnosis
- NCCN guidelines differ for CRC patients with LS and without LS
  - With LS, colonoscopy every 1-2 years for life
  - Without LS, colonoscopy 1 yr after dx, repeat in 2-3 yrs, then every 3-5 years based on findings
- Management also changes due to the risk for other cancers
Lynch Syndrome Implications for Family

- 6 relatives tested on average per proband identified with LS
- 50% with LS need increased cancer surveillance
  - Compliance with surveillance is good (96% for CRC and 97% for Gyn)
  - Cancer risk ratio of relatives with LS compared to relatives without LS is 5.8
  - No significant difference in cancer mortality (RR, 2.28) or overall death rates (RR, 1.26)
- 50% without LS can follow the ACS guidelines
Columbus-area HNPCC study (1999-2005)

Colorectal cancer
Total accrued (n=1600)
Testing completed (n=1566)

MSI positive (high & low)
n=307 (19.6%)

MSI negative
n=1259 (80.4%)

Sequence
Immunohistochemistry
Methylation of MLH1 promoter

Deleterious mutation
n=44* (2.8%)
*2 had MSI- tumors

Variant of uncertain significance
n=55 (3.5%)

Polymorphism or no mutation
n=209 (13.4%)

OSU Universal screening experience:

44 CRC probands with deleterious mutations:

- Age at diagnosis – 51.4 (range 23-87)
- 50% diagnosed over age 50
- 25% did not meet either Amsterdam or Bethesda criteria

Hampel et al. NEJM 2005;352:1851-60.
EGAPP

(Evaluation of Genomic Applications in Practice and Prevention)

– Established in 2005 to assess evidence regarding the validity & utility of rapidly emerging genetic tests for clinical practice.

– Independent, multidisciplinary panel prioritizes and selects tests, reviews CDC-commissioned evidence reports, finds gaps, and provides guidance.
EGAPP Recommendations

- Moderate certainty that testing patients with CRC for LS and then testing their relatives would provide moderate population benefit.
- Adequate evidence to conclude that the analytic sensitivity and specificity of the preliminary and diagnostic tests were high.
- Adequate evidence to describe the clinical sensitivity and specificity of three preliminary tests and four testing strategies.
- Adequate evidence for testing uptake, compliance with surveillance, relatives approachable, harms associated with f/u and effectiveness of routine cx supporting the use of genetic testing strategies to reduce morbidity and mortality in relatives with LS.
- No one test strategy was clearly superior.
- Inadequate evidence that screening for LS will reduce EC morbidity or mortality

Cost effectiveness study

- **Strategy 1**
  - IHC testing for 4 MMR genes
  - MLH1 protein absent
  - Other proteins absent
  - All present, LS not likely
  - BRAF mutation testing
    - Positive LS not likely
    - Negative
  - MMR gene sequencing / rearrangement testing. Order based on IHC test results

- **Strategy 2**
  - IHC testing for 4 MMR genes
  - One or more proteins absent
  - All present, LS not likely
  - MMR gene sequencing / rearrangement testing. Order based on IHC test results

- **Strategy 3**
  - MSI testing
  - MSI-high
  - MSI-stable, LS not likely
  - MMR gene sequencing / rearrangement testing. Order based on costs and prevalence.

- **Strategy 4**
## Cost-effectiveness Results

**Table 1** Outcomes and costs associated with Lynch syndrome testing strategies among newly diagnosed patients with colorectal cancer (CRC) and testing and surveillance for CRC among their first degree relatives

<table>
<thead>
<tr>
<th>Universal offer of testing of all newly diagnosed patients with CRC</th>
<th>Strategy for detecting Lynch syndrome in newly diagnosed patients with colorectal cancer&lt;sup&gt;a&lt;/sup&gt;</th>
<th>IHC, (BRAF) testing and then sequencing (Strategy 1)</th>
<th>IHC testing and then sequencing (Strategy 2)</th>
<th>MSI testing and then sequencing (Strategy 3)</th>
<th>Genetic sequencing for all four genes (Strategy 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of newly diagnosed patients with CRC with Lynch syndrome detected</td>
<td>2,469</td>
<td>2,477</td>
<td>2,540</td>
<td>2,982</td>
<td></td>
</tr>
<tr>
<td>No. of relatives approached</td>
<td>9,895</td>
<td>9,930</td>
<td>10,225</td>
<td>12,788</td>
<td></td>
</tr>
<tr>
<td>No. of relatives tested for Lynch syndrome</td>
<td>4,888</td>
<td>4,905</td>
<td>5,051</td>
<td>6,317</td>
<td></td>
</tr>
<tr>
<td>No. of relatives with Lynch syndrome detected</td>
<td>2,197</td>
<td>2,205</td>
<td>2,261</td>
<td>2,654</td>
<td></td>
</tr>
<tr>
<td>Life-years saved among relatives</td>
<td>2,346</td>
<td>2,353</td>
<td>2,413</td>
<td>2,833</td>
<td></td>
</tr>
<tr>
<td>Costs of detecting Lynch syndrome in newly diagnosed patients with CRC&lt;sup&gt;b&lt;/sup&gt;</td>
<td>$43,492</td>
<td>$45,442</td>
<td>$90,493</td>
<td>$391,479</td>
<td></td>
</tr>
<tr>
<td>Costs of detecting Lynch syndrome in relatives&lt;sup&gt;b&lt;/sup&gt;</td>
<td>$3,014</td>
<td>$3,024</td>
<td>$3,114</td>
<td>$3,895</td>
<td></td>
</tr>
<tr>
<td>Costs of surveillance and treatment for CRC&lt;sup&gt;b&lt;/sup&gt;</td>
<td>$36,112</td>
<td>$36,233</td>
<td>$37,209</td>
<td>$44,597</td>
<td></td>
</tr>
<tr>
<td>Total costs&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>$82,617</td>
<td>$84,699</td>
<td>$130,817</td>
<td>$439,971</td>
<td></td>
</tr>
</tbody>
</table>
## Incremental Cost-Effectiveness Ratios per LYS compared to no testing at all

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Medicare rates</th>
<th>List prices from labs</th>
<th>12 relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC, BRAF testing &amp; sequencing</td>
<td>$22,552</td>
<td>$30,331</td>
<td>$12,332</td>
</tr>
<tr>
<td>IHC testing &amp; sequencing</td>
<td>$23,321</td>
<td>$30,740</td>
<td>$12,663</td>
</tr>
<tr>
<td>MSI testing &amp; sequencing</td>
<td>$41,511</td>
<td>$49,272</td>
<td>$20,470</td>
</tr>
<tr>
<td>Genetic sequencing for 4 genes</td>
<td>$142,289</td>
<td>$200,037</td>
<td>$63,773</td>
</tr>
</tbody>
</table>
Cost-Effectiveness Evaluation

- Universal screening detects nearly twice as many cases of LS as targeting younger patients
- Strategy 1 is the most cost effective strategy
- Cost-effectiveness ratio of universal screening is $\leq 25,000$ per life-year saved relative to no testing
- ICER comparable with other preventive services (colonoscopy every 10 years has ICER of $25,000$)
Screening protocol at Ameripath Indiana

Colorectal cancer < 70
IHC testing

- All proteins present (negative IHC results)
- Absence of MSH2, MSH6 and/or PMS2

- Absence of MLH1
  - BRAF + Hyper-Methylation negative
  - BRAF + Hyper-Methylation positive

- Indeterminate IHC on another tumor
- MSI and/or IHC

CRC < 45 and/or Suspicious family history
CRC > 45 and no Family history

Referral to Genetics and/or Genetic Testing

STOP

- MSI-H
- MSI-L or MSS
- Suspicious family history
Timeline of Ameripath Indiana Screening for Lynch Syndrome

Ameripath CAD, FL MLH1/MSH2
Mayo 4MMR / 9MSI
Mayo Ameripath, CT
Ameripath Indy 4 MMR SL/Nichols Inst MSI-PCR

2004 2005 2006 2007
Revised Bethesda Criteria <=50 yo Morphology
Passive- recommending to clinicians

2008 2009 2010
<= 60 yo Morphology
<= 70 yo Morphology
### Ameripath Indiana Screening For Lynch Syndrome

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>total</th>
</tr>
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<tbody>
<tr>
<td>Screened</td>
<td>40 (11%)</td>
<td>68 (20%)</td>
<td>54 (22%)</td>
<td><strong>162</strong></td>
</tr>
<tr>
<td>Total</td>
<td>350</td>
<td>333</td>
<td>245</td>
<td><strong>928</strong></td>
</tr>
</tbody>
</table>

- **MMR intact**: 145
- **MSH2/6 def**: 6
- **MLH1/PMS2 def**: 26
- **PMS2 def**: 2
- **MMR+MSI-H**: 1
- **21% abnormal**: 34 cases

- **Total cases**: 76 M, 62 M, 60 F, 54 M, 47 F, 40 F
# Cancer Genetics Program

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>Total cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14</td>
<td>7</td>
<td>6</td>
<td>27</td>
</tr>
</tbody>
</table>

- At least 12 of these had not had IHC performed prior to appointment
- Most referred by oncology
- Missing at least 44% abnormal IHCs identified on screening
Proposal

• Abnormal IHC result gets faxed to Cancer Genetics Risk Assessment program
• GC will review case and request additional testing (hypermethylation/BRAF or MSI, eg) directly from pathology as needed
• In appropriate cases, GCs will fax referral form to ordering MD
• If MD agrees with referral, then will sign and fax back for us to contact patient for appointment
  – MD will need to alert patient as to need for appointment
www.stvincent.org
Medical education
Distance learning
Lynch symposium