It Takes a Village
Implementing Tumor Screening for Lynch Syndrome (LS)

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Division of Population Sciences
Moffitt Cancer Center
Deborah Cragun has documented that she has no financial relationships to disclose or conflicts of interest to resolve.
• Doing routine colorectal cancer (CRC) screening for Lynch syndrome (LS)?
  - Running smoothly?
  - Could improve patient follow-through?
  - Other concerns or challenges?

• Setting up CRC screening for LS?
  - Difficulty getting stakeholders on board?
  - Cost concerns?
  - Questions about issues of consent?
  - Other logistical concerns?
• Doing routine **endometrial cancer (EC)** screening for LS?
  - Running smoothly?
  - Could improve patient follow-through?
  - Other concerns or challenges?

• **Setting up EC** screening for LS?
  - Difficulty getting stakeholders on board?
  - Cost concerns?
  - Logistical questions?
TIPS: Tumor screening Implementation Planning Strategy

http://www.lynchscreening.net/tips-tumor-screening-implementation-planning-strategy
Agenda

- **Making the Case for Tumor Screening**
  - Impact on patient outcomes

- Planning and Implementation

- Quality Assurance
Mary’s uncle died at age 68 from colon cancer.

Mary’s cousin died at age 68 from endometrial cancer.

Mary, age 62, was diagnosed with stage 1 colon cancer.

Sara, age 35, was diagnosed with stage 4 colon cancer.

Chloe is a child.
Imagine if...

Mary's cousin
hysterectomy at age 58

Mary
stage 1 colon cancer at age 52

Sara
first polyps removed at age 25

Chloe
Increased Cancer Risks with Lynch Syndrome

The diagram compares the cancer risks for colorectal, endometrial, and ovarian cancers between Lynch Syndrome and the general population.

- **Lynch Syndrome**
  - Colorectal: 70%
  - Endometrial: 60%
  - Ovarian: 10%

- **General Population**
  - Colorectal: 0%
  - Endometrial: 0%
  - Ovarian: 0%
# Lynch Syndrome Diagnosis: Opportunities for Cancer Prevention & Early Detection

| Colonoscopy (every 1-2 years) | • Lowers CRC risks \(^1,^2\)  
|                             | • Finds CRC at earlier stage \(^1,^3\)  
|                             | • Improves survival \(^1,^2,^4-^6\)  
|                             | • Survival = among those with and without LS \(^6\)  
| Surgical prevention options | • Hysterectomy \(^7\)  
|                             | • Salpingo-ophorectomy \(^7\)  

## Lynch Syndrome Diagnosis:
**Important for Patients with CRC**

| Future cancer screening | • Ongoing colonoscopy every 1-2 years ¹  
| | • Screen for other Lynch-related cancers ¹ |
| Treatment options | • Chance of second CRC within 10 years after subtotal (3.4%) vs. partial colectomy (15.7%) ²  
| | • May influence choice of chemotherapy ³ |
| Prognosis | • MSI-High predicts better patient outcomes ³ |
| Surgical prevention options | • Hysterectomy ⁴  
| | • Salpingo-oophorectomy ⁴ |


Lynch Syndrome Diagnosis: Important for Patients with EC

| Future cancer screening | • Colonoscopy every 1-2 years \(^1\)  
• Screen for other Lynch-related cancers \(^1\) |
|-------------------------|------------------------------------------------|
| Treatment or prevention options | • Hysterectomy \(^2\)  
• Salpingo-oophorectomy \(^3\)  
• May influence benefits of adjuvant treatment \(^4\) |
| Prognosis? | • Young women (<40-50 y) MMR deficiency poorer prognostic indicators and lower survival \(^2,5,6\)  
• MMR deficiency in a subset improved survival after adjuvant radiotherapy \(^4\)  
• MSI status lacks prognostic value endometrioid EC \(^7\) |


Agenda

• **Making the Case for Tumor Screening**
  – Impact on patient outcomes
  – *Supporting guidelines*

• Planning and Implementation

• Quality Assurance
Summary of Recommendations: The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found sufficient evidence to recommend offering genetic testing for Lynch syndrome to individuals with newly diagnosed colorectal cancer to reduce morbidity and mortality in relatives.
“Increase the proportion of persons with newly diagnosed colorectal cancer who receive genetic testing to identify Lynch syndrome…”
Public Health Screening

• Population has **NOT** sought medical attention due to symptoms

• Identify those at high risk to offer diagnostic testing

• Typically to benefit individuals being screened

All CRC patients or CRC patients diagnosed at age <70 and those > 70 who meet Bethesda guidelines
Multi-society Task Force Recommendation

All CRC patients **or** CRC patients diagnosed at age <70 and those > 70 who meet Bethesda guidelines
SGO Clinical Practice Statement (2014)

Summary: All women who are diagnosed with endometrial cancer should undergo systematic clinical screening for Lynch syndrome (review of personal and family history) and/or molecular screening.

Molecular screening is the preferred strategy when resources are available.

Agenda

• **Making the Case for Tumor Screening**
  – Impact on patient outcomes
  – Supporting guidelines
  – **Cost-effectiveness**

• Planning and Implementation

• Quality Assurance
Cost Evaluations (CRC tumor screening)

- **Studies agree screening age <70 is cost effective** (U.S. healthcare)\(^1,2\)
- **Screening all is cost effective**\(^1\) or costs may be acceptable (U.S. healthcare)\(^2\)
- **UTS is cost effective** (private healthcare system)\(^3\)
- **Results and conclusions vary due to differences in:**
  - Screening protocols (and associated costs)
  - Societal value judgment ($50,000 per life-year saved)
  - **Number of at-risk relatives tested**
  - Other assumptions

http://www.lynchscreening.net/development/setinel-research-references/cost-effectiveness-of-universal-screening/
Cost Evaluations (EC tumor screening)

- No consensus on cost effectiveness

- Resnick study\(^1\)
  - Gene sequencing all under age 60 least effective and more costly among 4 strategies that were compared
  - IHC for all most cost effective among 4 strategies

- Kwon study\(^2\)
  - Universal EC tumor testing is NOT cost effective
  - IHC for all with family history of 1 first degree relative with LS-related cancer (any age) is cost-effective; identifies more cases than age criteria alone with fewer needing IHC\(^2\)


Billing and Reimbursement

- Cost effective ≠ cost neutral

- Billing\(^1\)
  - included in DRG (related to inpatient surgery)
  - biopsy screening independently billed

- Many genetic professionals not aware of how billing works\(^1\)

- Reimbursement issues rare\(^1\)
  (except perhaps endometrial tumor screening)

\(^1\)Cragun (2014) *Genet Med* and unpublished interview data
Case for Routine CRC Tumor Screening

- LS is common: ~3% of CRC patients
- Identifies more LS patients\textsuperscript{1-4}
- Reduce morbidity and mortality
- Recommended by several professional organizations
- Cost effective
- Meets public health screening program criteria
- Becoming standard of care

\textsuperscript{1} Morrison (2011) \textit{Scand J Gastroenterol}; \textsuperscript{2} Tranø (2010) \textit{Br J Cancer}; \textsuperscript{3} Mills (2014) \textit{Am J Surg Pathol}; \textsuperscript{4} Ryan (2011) \textit{Cancer}
Case for Routine EC Tumor Screening

• LS is common: ~2-6% of endometrial cancer patients\textsuperscript{1,2}
• Identifies more LS patients\textsuperscript{2-4}
• Reduce morbidity and mortality
• Supported by Society of Gynecologic Oncology (SGO)
• Cost effective?
• Other institutions are doing it!

\textsuperscript{1} Ferguson (2014) \textit{Cancer}; \textsuperscript{2} Hampel (2006 & 2007) \textit{Cancer Res};
\textsuperscript{3} Garg (2009) \textit{Am J Surg Pathol}; \textsuperscript{3} Mills (2014) \textit{Am J Surg Pathol}
Agenda

• Making the Case for Tumor Screening
  – Impact on patient outcomes
  – Supporting guidelines
  – Cost-effectiveness

• Planning and Implementation
  – Identify and engage stakeholders

• Quality Assurance
Stakeholders

• Surgery
• Pathology
• Oncology
• Gastroenterology
• Genetics
• Gynecology*
• Patients
• Families
• Administrators
How to Engage Stakeholders

• Make the case
• Hold a conference
• Tumor Board
• Elicit barriers
• Find champions
• Include key players in planning

It is wise to persuade people to do things and make them think it was their own idea.

—Nelson Mandela
Agenda

• Making the Case for Tumor Screening
  – Impact on patient outcomes
  – Supporting guidelines
  – Cost-effectiveness

• Planning and Implementation
  – Identify and engage stakeholders
  – Screening protocol

• Quality Assurance
## Who to Screen?

<table>
<thead>
<tr>
<th>Universal tumor screening (UTS)</th>
<th>Criterion-based Screening (CBS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximizes # of cases identified</strong></td>
<td>Better than no screening (BUT misses ~25-70% likely LS) (^1)(^-)(^4)</td>
</tr>
<tr>
<td><strong>Easier to automate</strong></td>
<td>Harder to automate (time spent determining if criteria met; easier to miss cases)</td>
</tr>
<tr>
<td><strong>More expensive (still may argue it is cost effective)</strong></td>
<td><strong>Less costly</strong></td>
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### Who to screen?

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<tbody>
<tr>
<td><strong>Maximizes # cases identified</strong></td>
<td>May miss 30-60% of cases(^1,2,3,4,5,6) (criteria based on less stringent family history may work better) (^4,6,7)</td>
</tr>
<tr>
<td><strong>Easier to automate</strong></td>
<td>More difficult (^4,8)</td>
</tr>
<tr>
<td><strong>More expensive</strong></td>
<td>Less costly</td>
</tr>
<tr>
<td><strong>Medicare may not reimburse (germline or methylation testing)</strong></td>
<td><strong>Reduces Medicare challenges</strong> (if follow Medicare guidelines)</td>
</tr>
</tbody>
</table>

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Consent for Tumor Screening?

• Ethics committees determined consent is NOT needed
• Most centers do not get consent for screening
• Several provide patient information
• Some include general statement in the pre-op consent form

http://www.lynchscreening.net/implementation/consent/
Primary Methods of Screening

IHC

MLH1 and PMS2 are absent

MSI

Arrows show additional alleles with varying numbers of repeats
## Which Primary Screening Method?

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<thead>
<tr>
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<th>IHC</th>
<th>MSI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effective- 92% sensitivity</strong></td>
<td>Effective- 93% sensitivity</td>
<td></td>
</tr>
<tr>
<td>(IF labs have experience)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Available at most centers</strong></td>
<td>Available less often</td>
<td></td>
</tr>
<tr>
<td><strong>Less reliable in small samples</strong></td>
<td>Requires little tissue</td>
<td></td>
</tr>
<tr>
<td><strong>Lower cost?</strong></td>
<td>Lower cost?</td>
<td>Higher cost?</td>
</tr>
<tr>
<td>(guides which genes to test, but may change with panel testing)</td>
<td>(some centers reflex to IHC; some use both IHC and MSI)</td>
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## Which Primary Screening Method?

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<th>IHC</th>
<th>MSI</th>
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<tr>
<td><strong>More likely to detect resulting from MSH6 mutations</strong>&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>May miss cases resulting from MSH6 mutations&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Available at most centers</strong></td>
<td>Available less often</td>
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<sup>1</sup>Garg (2009) J Clin Pathol;  
<sup>2</sup>Hampel (2006) Cancer Res
Additional testing on subset of tumors

- **Evidence of MMR deficiency or MSI**
  
  *~20% of unselected CRC tumors*
  
  *~20-30% of EC tumors*\(^1\)\(^-\)\(^5\) (31-45% depending on criteria)\(^6\)\(^-\)\(^9\)

  *Many of these do not have LS*

- **Additional reflex testing can improve efficiency:**\(^10\)\(^-\)\(^13\)
  
  - Subset of MSI-high tumors or those with absent MLH1/PMS2
  
  - Refer only those without BRAF or methylation
  
  - Reduces number who require counseling & germline testing

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## BRAF vs. promoter methylation testing?

<table>
<thead>
<tr>
<th>BRAF V600E</th>
<th>Promoter methylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>More widely available</td>
<td>May need to send out</td>
</tr>
<tr>
<td>Detects ~2/3 of CRC tumors with promoter methylation</td>
<td>Eliminates more patients who do not have LS, but could exclude some LS cases&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Less cost efficient&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>More cost effective&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Few endometrial tumors have BRAF mutations&lt;sup&gt;3,4,5&lt;/sup&gt;</td>
<td>Methylation recommended for endometrial tumors</td>
</tr>
</tbody>
</table>

## Biopsies vs. Surgical Resections?

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>Tumor Resections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IHC highly concordant when staining is conclusive</strong>&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Surgical decision-making</td>
<td>Obtained after surgery</td>
</tr>
<tr>
<td><strong>IHC may be easier</strong>&lt;sup&gt;2&lt;/sup&gt; (Higher intensity, more uniform stain)</td>
<td>IHC may be more difficult</td>
</tr>
<tr>
<td><strong>Rectal tumors</strong>&lt;sup&gt;3&lt;/sup&gt; (IHC more reliable before neoadjuvant treatment)</td>
<td>Neoadjuvant treatment may weaken IHC staining intensity&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>May increase loss to follow-up</td>
<td>May be easier to track patients</td>
</tr>
<tr>
<td>Screening could be done twice (biopsy and resection)</td>
<td>Less likely to be done twice</td>
</tr>
</tbody>
</table>

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Agenda

• Making the Case for Tumor Screening
  – Impact on patient outcomes
  – Supporting guidelines
  – Cost-effectiveness

• Planning and Implementation
  – Engage stakeholders
  – Screening protocol
  – Results follow-up

• Quality Assurance
Implementation of Universal Microsatellite Instability and Immunohistochemistry Screening for Diagnosing Lynch Syndrome in a Large Academic Medical Center

Brandie Heald, Thomas Plesec, Xiuli Liu, Rish Pai, Deepa Patil, Jessica Moline, Richard R. Sharp, Carol A. Burke, Matthew F. Kalady, James Church, and Charis Eng

Approach 1: Results sent only to surgeon (32% GC)

Approach 2: Results sent to GC and she e-mailed surgeon regarding referral (64% GC)

Approach 3: GC received results and contacted patient to facilitate follow-up (71% GC)
Comparing universal Lynch syndrome tumor-screening programs to evaluate associations between implementation strategies and patient follow-through

Deborah Cragun, MS, PhD¹, Rita D. DeBate, PhD², Susan T. Vadaparampil, PhD¹, Julie Baldwin, PhD², Heather Hampel, MS³ and Tuya Pal, MD¹

Outcome: Patient follow-through (PF)

- **High-PF** = >40%
- **Medium-PF** = 11-40%
- **Low-PF** = <10%

Conditions: Differences in screening protocol and follow-up procedures
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conditions</th>
</tr>
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<tbody>
<tr>
<td>Patient follow-through</td>
<td>Implementation challenges≥ facilitators</td>
</tr>
<tr>
<td>&gt;85%</td>
<td>X</td>
</tr>
<tr>
<td>71-85%</td>
<td>X</td>
</tr>
<tr>
<td>56-70%</td>
<td>X</td>
</tr>
<tr>
<td>41-55%</td>
<td>X</td>
</tr>
<tr>
<td>41-55%</td>
<td>X</td>
</tr>
<tr>
<td>26-40%</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>11-25%</td>
<td>X</td>
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<tr>
<td>≤10%</td>
<td>X</td>
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High-PF

Medium-PF

Low-PF

Outcome Conditions
Implementation Recommendations

• **Streamline tumor screening procedures**
  – Automate processes
  – Use reflex testing (BRAF / hypermethylation)
  – Eliminate need for referral

• **High involvement of dedicated person(s)**
  – Receive and track screening results
  – Results disclosure & communication
  – Meet patients at follow-up appointment

• **Facilitators to overcome barriers**
  – Communication
  – Education
Negative Screening Results

- Document in chart

- Active tracking of negative results helps identify others at high risk for hereditary cancer

- Some institutions send patient letter (see LSSN website)
Agenda

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• Planning and Implementation
  – Engage stakeholders
  – Screening protocol
  – Results follow-up

• Quality Assurance
  – Tracking outcomes
Importance of Tracking Outcomes

- Track screening (Excel spreadsheet or database)
- Maintain records on how plan was executed and changes made
- Monitor for any negative outcomes
Agenda

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• Quality Assurance
  – Tracking outcomes
  – Reflecting and evaluating
Reflecting and Evaluating

- Reflect on processes regularly (and when personnel change)
- Determine what is and what is not working
- Identify ways to streamline
- Provide stakeholders with feedback
- Notify stakeholders when patients are identified with LS
Agenda

• **Making the Case for Tumor Screening**
  – Impact on patient outcomes
  – Supporting guidelines
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• **Planning and Implementation**
  – Engage stakeholders
  – Screening protocol
  – Results follow-up

• **Quality Assurance**
  – Tracking outcomes
  – Reflecting and evaluating
  – **Overcoming challenges**
Challenges with IHC

- IHC can show high interobserver variation\(^1\)
- IHC can result in focal, weak, unusual staining\(^1,2,3\)
- Need to institute quality control measures
- Indefinite result should be followed by MSI
- IHC can be inaccurate even when performed by experienced pathologists\(^4\)

Challenges with Patient Follow-through

- **Sub-optimal patient follow-through**$^{1,2,3,4}$
  - Overwhelmed with diagnosis/anxiety
  - Perceive low risk or lack of relevance
  - Travel or extra appointments
  - Insurance issues

- **Added work for healthcare providers**
  - Timely incorporation of results
  - Need buy in from all healthcare providers
  - Someone willing to take primary ownership

Potential Ways to Improve Patient Follow-through

- Have providers stress importance of follow-up
- Awareness of funds for germline testing of uninsured
- Follow-up again with patients after treatment
- Send a letter tailored to the patient
- Send a letter reminding treating physician to follow-up
- Reminders during tumor boards
- Put an electronic reminder system in place
Other Challenges

• Questions about challenging cases

• Abnormal tumor screening with no germline mutation

“Ask the Expert”

http://www.lynchscreening.net/implementation/ask-experts/

Ask questions using LSSN listserv (LSSN members only)
Heather Hampel*
Cecelia Bellcross*
Deb Duquette
Kory Jasperson
Sarah Mange