Learning objectives:

At the conclusion of this presentation, learners will:

- Understand the increased cancer risks in IBD patients.
- Integrate screening recommendations into practice, including education of patients about prevention.
- Incorporate quality improvement process measures related to cancer screening.
Prevention of Cancer in the Inflammatory Bowel Disease Patient

- Disease-related
  - Colorectal
- Therapy-related
  - Skin
  - Lymphoma
  - Cervical
  - Anal

- Understand risk factors
- Educate patients
- Incorporate general screening recommendations
- There are no prospective prevention trials
- Consider risks in context of disease progression risk

Colorectal Cancer in IBD
Cumulative Risk of Colorectal Cancer in IBD Referral Center v. Population Based Studies

- 9 recent population-based studies
- 323,536 person-years
- Standardized Incidence Ratio equal for CD, UC and IBD combined

1.7 (95% CI, 1.3-2.1)

Updated Risk Factors for Dysplasia and Colorectal Cancer in Ulcerative Colitis

- Longer duration of disease
- Greater extent of colonic involvement
- Increased inflammatory activity
- Family history of CRC
- Primary sclerosing cholangitis
- Younger age of diagnosis
- Backwash ileitis
- Mass/stricture
- Prior dysplasia
- Pseudopolyps
- Male gender
Current Guidelines for Cancer Prevention in UC and Crohn’s Colitis are Similar (and out of date...)

- Start at 8-10 years (except PSC)
- Intervals vary
- Biopsies at 10 cm intervals (at least 33)
- Chromoendoscopy not recommended as standard of care, but acknowledged as superior to random biopsies.
- HGD $\rightarrow$ colectomy
- Polypoid lesions completely removed $\rightarrow$ vigilant follow-up
- Unresectable/carpet lesions $\rightarrow$ surgery


Low Yield of Random Biopsies in Colitis Surveillance
Most Dysplasia is Visible with White Light

- **Random biopsies**\(^1\):
  - N=167 patients, 466 surveillance colonoscopies
  - 24 of 11,772 random biopsies detected neoplasia (0.2% per-biopsy yield)
  - ~1 in 500 random biopsies

- **Visible dysplasia**\(^2,3\):
  - Per lesion sensitivity: 61.6%-77.3%
  - Per patient sensitivity: 78.3%-89.3%

The terms “DALM” and “ALM” are being replaced by:
- “polypoid”
- “non-polyloid”
- “flat”
- “invisible” dysplasia

**Approach to the Visible Dysplastic Lesion in IBD**

- **Dysplastic Lesion**
  - **Endoscopic appearance**
    - Flat
    - Visible/raised
  - **Grade?**
    - High
    - Low
  - **Multifocal?**
    - Yes
    - No
- **Colectomy**
- **Complete endoscopic resection**
- **Colonoscopy ≤6 months and follow-up**

**What is the utility of enhanced visualization?**

Chromoendoscopy is Highly Sensitive and Specific for Dysplasia in UC

- Meta-analysis of 6 randomized controlled trials comparing dye-spray to white light/conventional colonoscopy
- Methylene blue or indigo carmine

Challenges to Chromoendoscopy in IBD

- Perception of time consuming and expensive (time plus supplies)
- Unclear if it changes outcomes (cancer or mortality)
- Many patients don’t “qualify” for it due to poor prep or too much inflammation
- No consensus on its use in our field
- No defined training pathway or competency requirement
- Comparison to newer high definition scopes not completed
Narrow Band Imaging is not Superior to Conventional Colonoscopy for Dysplasia Detection in UC

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>NBI</th>
<th>WLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dekker et al. (2007)</td>
<td>Tandem</td>
<td>42</td>
<td>8/11(^a) (73%)</td>
<td>7/11(^a) (64%)</td>
</tr>
<tr>
<td>Van den Broek et al. (2011)</td>
<td>Tandem</td>
<td>48</td>
<td>8/11(^a) (73%)</td>
<td>9/11(^a) (82%)</td>
</tr>
<tr>
<td>Ignjatovic et al. (2012)</td>
<td>Parallel group</td>
<td>112</td>
<td>5/56(^b) (9%)</td>
<td>5/56(^b) (9%)</td>
</tr>
</tbody>
</table>

NBI Narrow band imaging; WLE; White light endoscopy.
\(^a\)Proportion of total dysplastic lesions detected overall; \(^b\)Proportion of patients with at least one dysplastic lesion.

Risk Stratification of Dysplasia in Colitis
Guide to Follow-up and Colectomy Recommendations

Pt/disease-related factors:
• PSC
• Family history of CRC
• Duration
• Degree of inflammation over time and on last exam
• Male v Female

Dysplasia-related factors:
• GRADE:
  – IND vs. LGD vs. HGD
• MORPHOLOGY:
  – Flat vs. Polypoid
  – “Invisible” vs. raised
• FIELD EFFECT/SYNCHRONICITY:
  – Unifocal vs. multifocal
• LONGITUDINAL FOLLOW-UP?
  – Dysplasia on a single exam vs. metachronous lesions on serial exams

STAY TUNED: International Consensus Meeting on Colorectal Neoplasia in IBD, March 2014, San Francisco

What are the risks of cancer related to the therapies in IBD?
Skin Cancer and therapy for IBD

Risk of Skin Cancers in IBD patients and Therapy Exposure

- Retrospective cohort and nested case-control studies using administrative data from the LifeLink Health Plan Claims Database
- 1997-2009
- N=108,579 patients with IBD, matched to 4 individuals without IBD

<table>
<thead>
<tr>
<th>Medication*</th>
<th>Melanoma</th>
<th>NMSC</th>
<th>Melanoma</th>
<th>NMSC</th>
<th>Melanoma</th>
<th>NMSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any use 5-ASA</td>
<td>1.06 (0.77-1.45)</td>
<td>0.99 (0.92-1.08)</td>
<td>0.98 (0.63-1.53)</td>
<td>1.01 (0.90-1.13)</td>
<td>1.22 (0.76-1.96)</td>
<td>0.99 (0.89-1.11)</td>
</tr>
<tr>
<td>Biologic</td>
<td>1.88 (1.08-3.39)</td>
<td>1.14 (0.95-1.36)</td>
<td>1.94 (1.03-3.68)</td>
<td>1.16 (0.95-1.41)</td>
<td>1.73 (0.53-5.63)</td>
<td>1.06 (0.62-1.84)</td>
</tr>
<tr>
<td>Thiouine</td>
<td>1.10 (0.72-1.67)</td>
<td>1.05 (1.00-2.05)</td>
<td>0.92 (0.53-1.59)</td>
<td>1.99 (1.73-2.27)</td>
<td>1.31 (0.66-2.60)</td>
<td>1.63 (1.38-1.94)</td>
</tr>
</tbody>
</table>

**Risk of Melanoma in IBD patients**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Melanoma</th>
<th>Total IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernstein 2001</td>
<td>1.09</td>
<td>0.50</td>
<td>2.38</td>
<td>7</td>
<td>5,529</td>
</tr>
<tr>
<td>Ekborn 1991</td>
<td>0.70</td>
<td>0.25</td>
<td>1.95</td>
<td>4</td>
<td>4,776</td>
</tr>
<tr>
<td>Jess 2004</td>
<td>2.03</td>
<td>0.45</td>
<td>9.16</td>
<td>3</td>
<td>374</td>
</tr>
<tr>
<td>Winther 2004</td>
<td>1.74</td>
<td>0.89</td>
<td>3.41</td>
<td>9</td>
<td>1,161</td>
</tr>
<tr>
<td>Karien 1999</td>
<td>1.20</td>
<td>0.44</td>
<td>3.24</td>
<td>4</td>
<td>1,547</td>
</tr>
<tr>
<td>Persson 1994</td>
<td>1.21</td>
<td>0.27</td>
<td>5.45</td>
<td>3</td>
<td>1,231</td>
</tr>
<tr>
<td>Long 2012</td>
<td>1.29</td>
<td>1.09</td>
<td>1.63</td>
<td>28</td>
<td>108,579</td>
</tr>
<tr>
<td>Mellemkjær 1995</td>
<td>1.20</td>
<td>0.54</td>
<td>3.68</td>
<td>5.95</td>
<td>5,546</td>
</tr>
<tr>
<td>Poppin-Bisvalet 2012</td>
<td>0.64</td>
<td>0.24</td>
<td>1.70</td>
<td>4.26</td>
<td>19,488</td>
</tr>
<tr>
<td>Yager 2012</td>
<td>2.31</td>
<td>1.19</td>
<td>4.50</td>
<td>8.06</td>
<td>839</td>
</tr>
<tr>
<td>Greenstein 1986</td>
<td>5.41</td>
<td>2.08</td>
<td>14.07</td>
<td>4.44</td>
<td>1,961</td>
</tr>
<tr>
<td>Hemminki 2009</td>
<td>1.23</td>
<td>0.95</td>
<td>1.69</td>
<td>22.91</td>
<td>61</td>
</tr>
</tbody>
</table>

**Decreased** | **Increased**

**Recommendations for Melanoma and NMSC**

- Education of patients and physicians related to risk factors
  - Fair skin pigmentation
  - Overall UV exposure
  - Thiopurines (NMSC) predominantly
  - Personal or family history of melanoma

- Primary protection:
  - Sun avoidance
  - Sun protection via sunscreen or sun-protective clothing

- Secondary prevention:
  - Yearly dermatology screening of patients on immunosuppressives

---

2. Skin Cancer screening. (<http://www.cancer.gov/cancertopics/pdq/screening/skin/HealthProfessional/page2>)
Lymphoma and therapy for IBD

Risk of lymphoproliferative disorders in inflammatory bowel disease: CESAME cohort

- 19,486 patients with median f/u 35 months
- 22 non-Hodgkin, 1 Hodgkin
- EBV positive in most
- Incidence rates (95% CI):
  - Current thiopurines: 0.90/1000 (0.50-1.49)
  - Newer thiopurines: 0.26/1000 (0.10-0.57)
  - Previous thiopurines: 0.20/1000 (0.02-0.72)

- Hazard ratio any vs. no thiopurine exposure:
  - 5.28 (95% CI 2.01-13.9)

### Risk of Lymphoma Returns to Normal After Stopping Thiopurines

- 36,891 VA patients with UC with a median follow up of 6.7 years and a median age of 60 years at inclusion
  - 4,734 patients using thiopurines; median duration of exposure: 0.97 years
- 142 confirmed lymphoma cases

![Graph showing incidence rates](image)

VA, Veterans Affairs

### Meta-analysis of lymphoma rate associated with anti-TNF agents

- 8905 patients representing 20,602 patient-years
- 13 Non-Hodgkin lymphomas (mean age 52, 62% male)
- 10/13 exposed to immunomodulators (IM), 2/13 not reported

<table>
<thead>
<tr>
<th></th>
<th>NHL rate per 10,000</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEER all ages</td>
<td>1.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IM alone</td>
<td>3.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-TNF vs. SEER</td>
<td>6.1</td>
<td>3.23</td>
<td>1.5-6.9</td>
</tr>
<tr>
<td>Anti-TNF vs. IM alone</td>
<td>6.1</td>
<td>1.7</td>
<td>0.5-7.1</td>
</tr>
</tbody>
</table>


*Not significantly different*
Lymphoproliferative disorders with thiopurines and anti-TNFs

- FDA Administration Adverse Event Reporting System
- Data from 2003-2010

Lymphoma Risk Recommendations

- Understand risk factors: primarily thiopurine exposure and not anti-TNF therapy
  - Routine EBV testing not recommended at this time
- Accurate discussion of risk stratification and choice of therapies
- Consideration of non-thiopurine approaches (e.g. methotrexate)
- Evolving approach may involve discontinuation or de-escalation with some therapies to modify risk, but this is not defined yet
### Cervical cancer studies in IBD

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Setting</th>
<th>IBD cases (CD)</th>
<th>Outcome</th>
<th>Dz</th>
<th>Measure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connell 1994</td>
<td>Cohort registry</td>
<td>Tertiary center</td>
<td>755(450)</td>
<td>Carcinoma</td>
<td>IBD</td>
<td>SIR</td>
<td>4 (2/0.5) (P=0.09)</td>
</tr>
<tr>
<td>Bhatia 2006</td>
<td>Case-control</td>
<td>Tertiary center</td>
<td>116 (64)</td>
<td>Dysplasia</td>
<td>IBD</td>
<td>%</td>
<td>18% vs 5% (P=0.004)</td>
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<td>OR</td>
<td>(1.45 95% CI 0.74-2.84)</td>
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<tr>
<td>Singh 2009</td>
<td>Nested case-control</td>
<td>Population-based</td>
<td>595(292)</td>
<td>Cervical abnormality</td>
<td>IBD</td>
<td>OR</td>
<td>(1.41 95% CI 1.09-1.81)</td>
</tr>
<tr>
<td>Lees 2009</td>
<td>Case-control</td>
<td>Tertiary center</td>
<td>362(184)</td>
<td>Dysplasia on pap smears</td>
<td>IBD</td>
<td>%</td>
<td>(LGD 10.5% vs 7.7% HGD 9.0% vs 6.9% (P = 0.37)</td>
</tr>
<tr>
<td>Rungå 2013 (abstract)</td>
<td>Matched-cohort</td>
<td>Population-based</td>
<td>30,008(9,466)</td>
<td>Dysplasia or cancer</td>
<td>CD</td>
<td>Hazard ratio</td>
<td>(1.51; 95% CI: 1.08-2.13)</td>
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<td></td>
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O/E ratio=Observed-Expected ratio; HR= Hazard ratio; OR=adjusted Odds ratio; LGD=low-grade dysplasia; HGD=high-grade dysplasia. Numbers in bold are significant results.
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O/E ratio=Observed-Expected ratio; HR=Hazard ratio; OR=adjusted Odds ratio; LGD=Low-grade dysplasia; HGD=High-grade dysplasia. Numbers in bold are significant results.

## Cervical Cancer Prevention Recommendations for IBD Patients

- Educate patients of risks associated with cervical cancer:
  - high parity
  - prolonged oral contraceptive use
  - number of sexual partners
  - smoking tobacco
  - Infections with HPV or Chlamydia

- Minimum screening and vaccination recommendations
  - HPV vaccine in males and females under age 26 years

- **Smokers** and patients using any immunosuppressives should undergo annual screening (similar to the transplant population).
Anal Cancer and therapy for IBD

Anal Cancer in IBD

• Rare, usually squamous cell carcinomas
• Risks:
  – HPV
  – long-standing severe anorectal Crohn’s disease\(^1\)
  – HIV + MSM
  – Prior high grade cervical dysplasia
  – Immune suppression in organ transplantation
• Screening recommended in high risk individuals\(^2\)

Anal Cancer Screening Suggestions

- Anal Pap smear
- Exam under anesthesia with biopsies
- Suspect anal cancer in exuberant perianal tissue, persistent ulceration or anorectal pain or bleeding

- **DELAY** in IBD anal cancer diagnosis → Often misdiagnosed as benign stricture.


Other Solid Tumors and therapy for IBD
No Risk of Solid Tumors with anti-TNF Therapy

<table>
<thead>
<tr>
<th>Rheumatoid arthritis</th>
<th>Type of Cancer</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All cancers</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td></td>
<td>All solid tumors</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td></td>
<td>Colon</td>
<td>0.8 (0.3-1.7)</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>1.1 (0.7-1.8)</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
<td>0.9 (0.5-1.3)</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>0.5 (0.1-2.6)</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>2.3 (0.9-5.4)</td>
</tr>
<tr>
<td></td>
<td>Non-melanoma</td>
<td>1.5 (1.2-1.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inflammatory bowel disease</th>
<th>Type of study</th>
<th>Associated risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Population based 651 patients</td>
<td>SIR 0.7 (0.2-1.7)</td>
</tr>
<tr>
<td></td>
<td>Single center 734 patients</td>
<td>OR 0.97 (0.56-1.65)</td>
</tr>
</tbody>
</table>

No clear evidence that anti-TNF is associated with (non-skin) solid tumors

Wolfe, Arthritis and Rheumatism 2007;56:2886.

Summary: Cancer Prevention in IBD

• Colorectal cancer and dysplasia
  – Colonoscopy and dysplasia identification
  – Risk stratification for follow-up and surgery

• Skin cancer
  – Avoidance of excess UV exposure
  – Annual dermatology visits for patients on immunosuppressives

• Lymphoma
  – Selection of patients
  – Consider withdrawal or substitution of thiopurines in appropriate patients

• Cervical cancer
  – HPV vaccination
  – Annual Pap in immune suppressed patients

• Anal cancer
  – Don’t miss it!
  – Early exam under anesthesia and biopsies
Incorporation of cancer prevention into your practice: Consider checklists

http://cornerstoneshealth.org/checklist/