Disclaimers

• I am a member of the Advisory Board of the Mississippi Cancer Registry and the Medical/Research Advisor to the Mississippi Partnership for Comprehensive Cancer Control Executive Board; these are uncompensated voluntary appointments.

• I am the recipient of a Patient-Centered Outcomes Research Institute (PCORI) Program Award (EA-1148-UMC).

• Otherwise, I have no conflicts of interest to disclose.

• The statements and views expressed in this presentation are my own and may not reflect the opinions of the University of Mississippi Medical Center or any other organization with which I am associated.
Why focus on colorectal cancer?

- CRC is highly preventable & declining in most states.
- CRC is 2\textsuperscript{nd} most common cancer in men + women.  
  - 1 in 20 lifetime probability of CRC.
- CRC is 2\textsuperscript{nd} leading cause of cancer death in men + women.
- CRC treatment costs are 2\textsuperscript{nd} highest of all cancer sites.
- CRC screens are net cost-\textbf{SAVING}. 
Sequence of development from polyp to cancer

Take-home lesson:

CRC cancer biology explains why prevention is highly effective, but atypical CRC cancer biology may shed light on future progress
A generalized (Vogelstein) model of CRC development & progression

- Adenoma is precursor to CRC, rarely occurs in individuals under 49, adenomas & CRC more prevalent later in life.
- In the 6th, 7th, and 8th decades of life the prevalence of adenomas increases.
- The dwell time of an early to advanced adenoma ~2-5 years.
- Similarly, the dwell time of an advanced adenoma to early cancer ~2-5 years.
IMPORTANT UNANSWERED QUESTION: Do all CRCs follow the generalized model of progression, or are some lesions “primed” to metastasize at earlier stages?

Epidemiology of colorectal cancer

Take-home lesson:
Dynamic changes in CRC epidemiology reflect changing landscape of disparately-distributed positive & negative risk factors
Colorectal Cancer Incidence and Mortality Rates, United States.

- 135,430 newly diagnosed CRC cases (U.S., 2017, projected)
- 40.7 per 100,000 (U.S., 2009-2013, age-adjusted incidence)
- 50,260 deaths from CRC (U.S., 2017, projected)
- 14.8 per 100,000 (U.S., 2010-2014, age-adjusted mortality)

Regional differences in CRC mortality rates may reflect decreasing & increasing trends

- Decreasing CRC mortality rates in Midwest & Northeast best explained by increasing CRC screening rates.

- Increasing CRC rates (esp. in Mississippi River Delta) may involve other risk factors (e.g., “nutrition transition”).
Population-based disparities have significant adverse effect on overall CRC mortality rates in U.S.

Colorectal Cancer Incidence (2009-2013) and Mortality (2010-2014) Rates by Race/Ethnicity and Sex, United States

Increased incidence of colorectal cancer in people younger than 50

Take-home lesson:
Causes of recent trends are unknown, but an immediate response requires attention to symptoms to avoid delays in diagnosis
Colorectal Cancer Incidence and Mortality Trends by Age and Sex, United States, 1975-2014.

- NOTE: Ordinate scales on graphs are not equal; magnitude of CRC incidence & mortality very different in age groups shown.
- Greatest decrease in CRC incidence & mortality in population age ≥ 65y
- Significant decrease in CRC mortality in 50-64 y.o.
- Significant increase in CRC incidence in 20 – 49 y.o. since 2000

Annual percent change in age-specific rectal cancer incidence rates in the United States, 1974–2013

**Increasing trends in 20-54 y.o.**

- 20-29 y
  - 1974-2013 APC = 3.2% 
  - 1974-1980 APC = 3.9% 
  - 1980-2013 APC = 3.3%

**Decreasing trends in age ≥ 55 y.o.**

- 55-59 y
  - 1974-2013 APC = 0.4%
  - 1968-1980 APC = 2.2%
  - 1980-2013 APC = 5.3%

- 60-64 y
  - 1974-1986 APC = 0.5
  - 1966-1980 APC = 3.0%
  - 1994-1997 APC = 2.9
  - 1980-2013 APC = 0.5%

- 65-69 y
  - 1974-1993 APC = 0.8%
  - 1969-1980 APC = 3.8%
  - 1994-1997 APC = 2.9
  - 1980-2013 APC = 3.5%

- 70-74 y
  - 1974-1993 APC = 0.2%
  - 1969-1980 APC = 3.8%
  - 1994-1997 APC = 2.9
  - 1980-2013 APC = 2.3%

- 75-79 y
  - 1974-1980 APC = 0.4%
  - 1968-2004 APC = 2.2%
  - 2004-2013 APC = 5.4%

**NOTE:** Tremendous variation in ordinate scales

Annual percent change in age-specific colon cancer incidence rates in the United States, 1974–2013

Increasing trends in 20-49 y.o.

Decreasing trends in age ≥ 55 y.o.

NOTE: Tremendous variation in ordinate scales

Genetics and colorectal cancer

Take-home lesson:
Genetic factors can identify young high-risk individuals and may be useful in treatment decisions
### Genes with predisposing mutations to inherited colorectal cancer syndromes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Hereditary syndrome</th>
<th>Age of onset (years)</th>
<th>Pathway/biological function*</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>FAP, AFAP</td>
<td>34–43</td>
<td>Wnt signalling pathway</td>
</tr>
<tr>
<td>MUTYH</td>
<td>MAP</td>
<td>48–56</td>
<td>Base excision repair</td>
</tr>
<tr>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>Lynch syndrome</td>
<td>44–56</td>
<td>Mismatch repair</td>
</tr>
<tr>
<td>PTEN</td>
<td>Cowden syndrome (includes BRR syndrome)</td>
<td>&lt;50 (BRR paediatric onset)</td>
<td>Negative regulator of metabolic signalling</td>
</tr>
<tr>
<td>STK11</td>
<td>PJS</td>
<td>65</td>
<td>Tumour suppressor</td>
</tr>
<tr>
<td>GREM1,15q13 locus</td>
<td>HMPS</td>
<td>48</td>
<td>TGFβ/BMP signalling pathway</td>
</tr>
<tr>
<td>BMPR1A</td>
<td>HMPS, juvenile polyposis syndrome</td>
<td>48, 42</td>
<td>TGFβ/BMP signalling pathway</td>
</tr>
<tr>
<td>MADH4/SMAD4</td>
<td>Juvenile polyposis syndrome</td>
<td>42</td>
<td>TGFβ/BMP signalling pathway</td>
</tr>
<tr>
<td>POLE, POLD1</td>
<td>Oligopolyposis or polymerase proofreading associated polyposis</td>
<td>23–80</td>
<td>DNA repair</td>
</tr>
</tbody>
</table>

Genetic architecture of known colorectal cancer genetic susceptibility loci

Epigenomics:
- Chromosomal Instability (CIN) Pathway
- CpG Island Methylator Phenotype (CIMP) Pathway
- MicroSatellite Instability (MSI) Pathway
- Effect of microenvironment (including gut microbiome) on epigenomics & phenotype

Risk factors associated with colorectal cancer

Take-home lesson:
CRC risk factors include intrinsic, behavioral, environmental and socio-economic factors.
## Factors increasing risk for CRC

<table>
<thead>
<tr>
<th>Intrinsic (Most Non-Modifiable)</th>
<th>Environmental / Socio-economic</th>
<th>Behavioral (Modifiable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Community-level poverty</td>
<td>Non-compliant with screening recommendations</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Lack of Insurance</td>
<td>Red meat consumption</td>
</tr>
<tr>
<td>Family History</td>
<td>Lack of Access to Medical Care</td>
<td>Processed meat consumption</td>
</tr>
<tr>
<td>History of Polyps</td>
<td></td>
<td>Low vegetable, low fiber diets</td>
</tr>
<tr>
<td>History of Inflammatory Bowel Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central Obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific Genetic Conditions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Trends in Average Yearly Age-, Race-, and Sex-Adjusted Colorectal Cancer Mortality Rates, Separated into Tertiles of High, Middle, and Low Socioeconomic Status at the County Level, 1968–2008.

Community-level wealth & per-capita income affects resource distribution

Table 4 Incomes within and beyond 30-min drives to colonoscopy facilities

<table>
<thead>
<tr>
<th>Variable</th>
<th>Within 30-min drives</th>
<th>Beyond 30-min drives</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median household income</td>
<td>33,607</td>
<td>33,953</td>
<td>0.597</td>
</tr>
<tr>
<td>Mean household income</td>
<td>46,291</td>
<td>45,279</td>
<td>0.194</td>
</tr>
<tr>
<td>Per capital income</td>
<td>17,797</td>
<td>17,141</td>
<td>0.049</td>
</tr>
</tbody>
</table>

52% of the state (17% of the population) is beyond a 30-minute drive to a colonoscopy facility

Table 5 Incomes within and beyond 30-min drives to gastroenterologists’ primary practice sites

<table>
<thead>
<tr>
<th>Variable</th>
<th>Within 30-min drives</th>
<th>Beyond 30-min drives</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median household income</td>
<td>35,058</td>
<td>33,889</td>
<td>0.279</td>
</tr>
<tr>
<td>Mean household income</td>
<td>47,370</td>
<td>45,572</td>
<td>0.083</td>
</tr>
<tr>
<td>Per capital income</td>
<td>18,334</td>
<td>17,294</td>
<td>0.016</td>
</tr>
</tbody>
</table>

79% of the state (38% of the population) is beyond a 30-minute drive to gastroenterologist
Self-reported colonoscopy rates in Mississippi’s Public Health Districts are strongly correlated with CRC incidence rates and mortality rates.
Dietary risks for colorectal cancer

- Processed meat **INCREASES** CRC risk (WHO Group 1, carcinogenic to humans)
- Red meat **INCREASES** CRC risk (WHO Group 2A, probably carcinogenic to humans)
- Fruits, vegetables and dietary fiber **DECREASE** CRC risk

Screening options

Take-home lesson:
Many choices available for preventive and early-detection screens, which all require colonoscopy for diagnostic confirmation
<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Description</th>
<th>United States Preventive Services Task Force (USPSTF)</th>
<th>American Cancer Society–U.S. Multi-Society Task Force (ACS-USMSTF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal occult blood test (FOBT)* and fecal immunochemical test (FIT)*</td>
<td>Examination of the stool for traces of blood not visible to the naked eye</td>
<td>Recommends high-sensitivity FOBT and FIT annually for ages 50-75</td>
<td>Recommends high-sensitivity FOBT and FIT annually for ages ≥ 50</td>
</tr>
<tr>
<td>Sigmoidoscopy*</td>
<td>Internal examination of the lower part of the large intestine</td>
<td>Recommends every 5 years with high-sensitivity FOBT every 3 years for ages 50-75</td>
<td>Age ≥ 50, every 5 years</td>
</tr>
<tr>
<td>Double-contrast barium enema*</td>
<td>X-ray examination of the colon</td>
<td>--</td>
<td>Age ≥ 50, every 5 years</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Internal examination of the entire large intestine</td>
<td>Recommends every 10 years for ages 50-75</td>
<td>Age ≥ 50, every 10 years</td>
</tr>
<tr>
<td>Computed tomography colonography*</td>
<td>Examination of the colon and rectum using pictures obtained using a computed tomography scanner</td>
<td>Age ≥ 50, every 5 years</td>
<td>Age ≥ 50, every 5 years</td>
</tr>
<tr>
<td>Fecal DNA*</td>
<td>Examination of the stool for traces of colorectal cancer DNA</td>
<td>Age ≥ 50, every 1 or 3 years</td>
<td>Age ≥ 50, every 3 years</td>
</tr>
</tbody>
</table>

*Positive findings require follow-up colonoscopy.
All CRC screens require confirmation via colonoscopy

Flexible fiber optics revolutionized CRC prevention & control in 1973:

“Polypectomy Via the Fiberoptic Colonoscope — Removal of Neoplasms beyond Reach of the Sigmoidoscope”


William I. Wolff, M.D. and Hiromi Shinya, M.D.
Can colonoscopy / polypectomy alone eliminate CRC mortality?

- <10% of all adenomas become cancerous, but

- > 95% of colorectal cancers develop from adenomas.


Colorectal cancer screening as part of preventive care

Take-home lesson:
Pro-active CRC screening policies can yield maximum benefit to health care system & reduce expensive medical procedures
Why does screening matter?
Because survival is tremendously improved by early-stage diagnosis
(SEER 2005-2011 Data, All Races, Both Sexes)

Percent of Cases by Stage

- Distant (20%)
  - Cancer Has Metastasized
- Localized (39%)
  - Confined to Primary Site
- Regional (36%)
  - Spread to Regional Lymph Nodes
- Unknown (5%)
  - Unstaged

5-Year Relative Survival

- Localized: 90.1%
- Regional: 70.8%
- Distant: 13.1%
- Unstaged: 34.5%
<table>
<thead>
<tr>
<th>Stage</th>
<th>Colon Cancer</th>
<th>Rectal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Surgery only (polypectomy or partial colectomy)</td>
<td>Surgery only (polypectomy, local excision or transanal resection)</td>
</tr>
<tr>
<td>I</td>
<td>Surgery only (polypectomy or partial colectomy with lymph node dissection)</td>
<td>Surgery (above or proctectomy w/ colo-anal anastomosis, other surgical options) Possible radiotherapy if patient not suitable for surgery</td>
</tr>
<tr>
<td>II</td>
<td>Surgery (partial colectomy with lymph node dissection) Possible chemotherapy (typically (5-FU + leucovorin) or capecitibine) Possible radiotherapy</td>
<td>Combination modality (surgery + (neoadjuvant &amp; adjuvant) chemotherapy ± radiation) Chemo options include FOLFOX (Oxaliplatin + 5-FU + leucovorin) or CapeOx (capecitibine + oxaliplatin)</td>
</tr>
<tr>
<td>III</td>
<td>Surgery w/ lymph node dissection + adjuvant chemotherapy (FOLFOX or CapeOx) Possible adjuvant radiotherapy</td>
<td>Combination modality (neoadjuvant chemotherapy + radiation, then surgery + adjuvant/consolidation chemotherapy)</td>
</tr>
<tr>
<td>IV</td>
<td>Systemic chemotherapy (above or FOLFIRI (5-FU + leucovorin + irinotecan) or FOLFOXIRI) ± targeted biologic therapies (e.g., bevacizumab or cetuximab) Possible surgery (diverting colostomy + excise metastases)</td>
<td>Systemic chemotherapy (above or FOLFIRI or FOLFOXIRI) or via hepatic artery infusion) ± targeted biologic therapies + radiation + possible surgery Possible ablation or embolization</td>
</tr>
<tr>
<td>Recurrent</td>
<td>Clinical trials frequently offered Options &amp; treatment goals dictated by local vs. distant recurrence</td>
<td>Clinical trials frequently offered Options &amp; treatment goals dictated by local vs. distant recurrence</td>
</tr>
</tbody>
</table>
In contrast to breast cancer clinical practices, physicians routinely treat CRC based on stage, not subtype.

**Colorectal cancers**

86% of all stage I & II CRCs treated with surgery alone

<table>
<thead>
<tr>
<th>Stage</th>
<th>Polypectomy alone</th>
<th>Colectomy alone</th>
<th>Colectomy + chemo (+/- RT)</th>
<th>Chemo and/or RT</th>
<th>No treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I &amp; II</td>
<td>4</td>
<td>12</td>
<td>1</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>71</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>18</td>
<td>19</td>
<td>50</td>
<td>12</td>
</tr>
</tbody>
</table>

**Breast cancers**

27% of all stage I & II BCs treated with surgery alone

<table>
<thead>
<tr>
<th>Stage</th>
<th>BCS alone</th>
<th>BCS + RT</th>
<th>BCS + RT + chemo</th>
<th>Mastectomy alone</th>
<th>Mastectomy + chemo</th>
<th>Mastectomy + RT</th>
<th>Mastectomy + RT + chemo</th>
<th>No surgical treatment</th>
<th>No treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>16</td>
<td>17</td>
<td>14</td>
<td>14</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Late</td>
<td>10</td>
<td>7</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

What is my challenge to this audience?
Change early-stage CRC treatment paradigms based on molecular subtype.

Currently: “Cut them all”

Next: Which do vs. don’t need consolidation therapy?

Ultimate: Optimize subtype-to-therapy match

86% of all stage I & II CRCs treated with surgery alone

How do we get there from here?
Summary

• CRC cancer biology explains why prevention is highly effective & identifies areas for improvement.
• CRC epidemiology reveals changing landscape of disease.
• CRC in young adults requires attention to symptoms to avoid delays in diagnosis.
• CRC genetic factors can identify young high-risk individuals.
• CRC risk factors include intrinsic, behavioral, environmental and socio-economic factors.
• CRC screening options are varied & require colonoscopy for confirmation.
• CRC screening policies benefit to health care system by reducing expensive medical procedures & saving lives.