Esophageal Cancer Screening
Esophageal cancer:
One of most lethal cancers in US

16,980
new cases per year

15,590
deaths per year

Urgency to detect esophageal cancer before symptoms develop

98 out of 100 survive 5 years if diagnosed asymptomatic in Stage I

<15 out of 100 survive 5 years if diagnosed after symptoms in Stages I, II, III or IV

Source: SEER 18 2004-2010

Pech et al. Gastroenterology 2014;14:652
Collaborating to detect pancreatic cancer early

- Leveraging long-standing relationship and building on success of Cologuard®
- Significant intellectual property portfolio
- Proprietary know-how and biospecimens
- World leadership in cancer care through early detection
Pancreatic Cancer Screening

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Gastroenterologist, Gatton Professor of Digestive Diseases Research, Mayo Clinic
Opportunities for early detection of esophageal cancer

- Recognizable pre-malignant condition: Barrett’s esophagus
- Effective endoscopic treatment for Barrett’s esophagus and earliest stage esophageal cancer
- Molecular tools offer potential to improve effectiveness of early detection
What is Barrett’s esophagus?

- A premalignant change in lining of lower esophagus
- Linked to gastro-esophageal reflux (GERD), which occurs in 40% of general US population
- Broad prevalence*
  - General population: 3-15%
  - Patients with GERD: 8-25%
- Readily recognized by endoscopy

Progression from Barrett’s esophagus to cancer

- Histological progression
  - Long pre-symptomatic window
  - Barrett’s esophagus \(\rightarrow\) low grade dysplasia
  \(\rightarrow\) high grade dysplasia \(\rightarrow\) cancer

- Increased cancer risk with Barrett’s esophagus 11-50x

- Lifetime cancer risk with Barrett’s esophagus 5-20%

Barrett’s esophagus without dysplasia
Barrett’s esophagus with dysplasia (high grade)
Mucosal cancer
# Current approaches for early detection face multiple challenges

<table>
<thead>
<tr>
<th></th>
<th>Barrett’s Esophagus Screening</th>
<th>Barrett’s Esophagus Dysplasia Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Status</strong></td>
<td>Endoscopy</td>
<td>Guideline recommended periodic surveillance in patients with BE (random biopsies)</td>
</tr>
<tr>
<td><strong>Challenges</strong></td>
<td>Poor adherence</td>
<td>50% miss rate for cancer and focal high grade dysplasia by conventional (every 2cm) random biopsies*</td>
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</table>


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**Barrett’s Esophagus**

Random biopsies frequently miss focal dysplasia

- Focal dysplasia
- Random biopsies

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**Notes:**

- Poor adherence
- 50% miss rate for cancer and focal high grade dysplasia by conventional (every 2cm) random biopsies
Our solution: A clinical application of esophageal brushing

- Evaluate and monitor Barrett’s esophagus
- Endoscopic brushing of Barrett’s segment
- More representative and accurate than random biopsies
- Assay of methylated DNA markers to determine presence of dysplasia or cancer
Using endoscopic brushing to detect Barrett’s esophagus-related dysplasia and cancer

• Addresses clinical need to increase sensitivity

• Potential to improve surveillance outcomes
  – Better cancer prevention by improved dysplasia detection
  – Reduced cancer mortality by improved early stage detection
  – Lower treatment-related morbidity as early detection allows endoscopic Rx

• Health economics are driven by enhanced detection over biopsy alone
Our approach to successful early detection in Barrett’s esophagus

- Identified and secured best-in-class markers
  - Whole methylome discovery
  - On tissue validation, best markers highly discriminant (AUC ~1)*
- Demonstrated feasibility
  - BE dysplasia and early-stage EAC detection from whole esophageal brushing
  - 3-marker panel: sensitivity 81% any dysplasia, 100% early EAC**
- Optimize marker combinations and assay methods
- Validate in clinical case-control study

Source: *Taylor et al. DDW 2015, **Iyer et al. DDW 2015
Mayo Clinic’s prospective esophageal brushing study

Primary Aim
Assess accuracy of methylated DNA markers in esophageal brushings to detect BE-related esophageal cancer and dysplasia

N=300
Normal esophagus (100)

BE without dysplasia (100)

BE with dysplasia: LG, HG, or mucosal EAC (100)

Biospecimens Collected
esophageal brushings, sponge-on-string
Effective endoscopic options to treat and prevent esophageal cancer

- Endoscopic curative removal of early cancer
  - Endoscopic mucosal resection

- Endoscopic ablation
  - Radio frequency
  - Cryotherapy

Source: Images courtesy of Mayo Foundation for Medical Education and Research
Opportunities for early detection in Barrett’s esophagus with new molecular tools

- Endoscopic brushing (near-term)
  - Dysplasia surveillance

- Sponge-on-string (longer-term)
  - Population screening
    - Early studies suggest feasibility*
    - Optimal markers and methods needed
  - Dysplasia surveillance
    - Early studies suggest feasibility
    - Optimal markers and methods needed

Source: Iyer et al. DDW 2014
Paving the way to esophageal cancer screening in patients

• Initiating clinical trial with Mayo Clinic
• Evaluating regulatory pathway
• Building powerful economic story for Medicare and commercial payers
US market opportunity for esophageal cancer early detection

<table>
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<tr>
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<th>Total Number of Patients in Addressable Population Per Year</th>
<th>US Market Opportunity</th>
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<tr>
<td><strong>Dysplasia surveillance</strong>&lt;br&gt;(every 2 years for diagnosed Barrett’s patients)</td>
<td>1M+</td>
<td>$500M+</td>
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