**Case**

- 62 yo M with a history of prostate cancer at 58, presents for surveillance colonoscopy

<table>
<thead>
<tr>
<th>Colonoscopy Date</th>
<th>Endoscopic Result</th>
<th>Histologic Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>“Many” small polyps throughout</td>
<td>Tubular Adenomas</td>
</tr>
<tr>
<td>2009</td>
<td>Six 10-20mm polyps in right colon</td>
<td>Tubular Adenomas and one TVA w/ HGD</td>
</tr>
<tr>
<td>2009</td>
<td>One 20mm polyp in AC</td>
<td>Tubular Adenomas</td>
</tr>
<tr>
<td></td>
<td>Seven small polyps throughout</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>Four 2-5mm polyps in right colon</td>
<td>Tubular Adenomas</td>
</tr>
<tr>
<td>2011</td>
<td>Seven small polyps throughout</td>
<td>Tubular Adenomas</td>
</tr>
<tr>
<td>2015</td>
<td>Seventeen 2-15mm polyps throughout</td>
<td>Tubular Adenomas</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>42+ Precancerous Polyps</td>
<td></td>
</tr>
</tbody>
</table>
Case

Healthy, BMI 23, only on ASA81

– Tobacco: 1/2 pack of cigarettes per day for ~40 years
– Other exposures: Grew up in Pittsburgh which was “heavily polluted”

Family History:
– No children
– One sister, 73: ?Uterine cancer at 43
– One brother, died at 24 of complications from diabetes
If \( \geq 20 \) cumulative adenomatous polyps -> **Genetic counseling and testing for specific hereditary colorectal cancer (CRC) syndromes**

Guidelines also recommend consideration of genetic evaluation in individuals with 10-19 cumulative adenomas

- Especially if suggestive family history (FHx) or associated extra-intestinal manifestations of hereditary syndromes**

*Additional testing at discretion of Provider

**Personal history of desmoid tumor, hepatoblastoma, papillary thyroid cancer, CHRPE

Provenzale, et al. NCCN Guidelines, 2018
Case

Referred and seen in Hereditary Cancer Clinic
• Genetic testing for known hereditary CRC syndromes were negative

Diagnosis: Colonic Polyposis of Unknown Etiology (CPUE)
• “These results are uninformative and do not lower the risk for cancer in the patient or in family members”
Outline: Colonic Polyposis of Unknown Etiology

- Colorectal cancer (CRC) as a genetic disease
- Definition of Colonic Polyposis of Unknown Etiology (CPUE)
- Significance
- Epidemiology
- Original research
- Future clinical impact
**CRC Epidemiology**

**Lifetime CRC Risk**
- 4.6% of men (1 in 22)
- 4.2% of women (1 in 24)

**CRC incidence has decreased since initiation of screening:**
- 60.5 cases (per 100,000) in 1976 to 40.7 in 2013
- Mortality rate drop >50% from 1976

**Other contributing factors:**
- Tobacco use has decreased
- Diet has changed
- Aspirin is more widely used
- More effective treatments

95% of CRC are adenocarcinomas, which arise from pre-cancerous polyps are termed “adenomas”

- Adenomas transform to CRC over 1-2 decades, mostly after age 60

Screening for CRC is unique: it seeks early detection AND prevention

CRC as a Genetic Disease: Adenoma to Carcinoma Sequence

Only two studies have investigated individuals with \( \geq 10 \) but \(< 50\) adenomas, and found FAP or MAP germline mutations in \(< 10\%\).

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genes</th>
<th>Clinical features</th>
<th>Lifetime CRC risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial adenomatous polyposis</td>
<td><em>APC</em></td>
<td>Adenomas, thyroid cancer, desmoid tumors, duodenal adenomas, mandibular osteomas, and congenital hypertrophic pigmentary lesions of the retina</td>
<td>100%(^\text{13})</td>
</tr>
<tr>
<td>MYH-associated polyposis</td>
<td><em>MUTYH</em> (biallelic)</td>
<td>Adenomas, thyroid cancer, colorectal cancer</td>
<td>43%-100%(^\text{14})</td>
</tr>
</tbody>
</table>
Polyposis: CPUE

Colonic polyposis of unknown etiology (CPUE):
- Cumulative lifetime adenomas counts of ≥10-20
- Negative testing for hereditary CRC syndromes

National Cooperative Studies Program (CSP)
VA RESEARCH PROGRAMS

Under Secretary for Health

Chief Research & Development Officer

Office of Research and Development (ORD)

Biomedical Laboratory R&D Service
Clinical Science R&D Service
Cooperative Studies Program
Health Services R&D Service
Rehabilitation R&D Service

Grant Huang, PhD--Director
Cooperative Studies Program

Aims to advance health care of Veterans through collaborative research studies while also providing solutions to national healthcare problems

• Conducts large, innovative multicenter clinical trials and epidemiological studies
Cooperative Studies Program

CSP
Central Office
Washington, DC

5 clinical trial coordinating centers (CSPCC)
- Boston, MA
- Hines, IL
- Palo Alto, CA
- Perry Point, MD
- West Haven, CT

6 epidemiological centers (CSPEC)
- Boston, MA
- Durham, NC
- Seattle, WA
- West Haven, CT
- Little Rock, AR
- Palo Alto, CA

Clinical Research Pharmacy Coordinating Center (CRPCC)
- Albuquerque, NM
  - Site Monitoring, Auditing, and Resource Team (SMART)

Network of Dedicated Enrollment Sites (NODES)
Focus areas of CSP studies

- PTSD
- Lung and prostate cancer
- Diabetes
- Hernia repair
- Cardiac bypass surgery
- Acute renal failure
- Schizophrenia and bipolar illness
- Colorectal cancer screening
- Hepatitis C Virus
- Ischemic stroke
- Gulf War veterans
- Vietnam-era veterans
Durham Cooperative Studies Program Epidemiology Center (CSPEC)
Established in 1997, CSPEC-Durham is currently one of six CSPECs nationwide within the Office of Research & Development.

Part of the Veterans Affairs Medical Center in Durham, NC

Closely affiliated with the VA Center for Health Services Research & Development (HSR&D) in Durham, NC.
Enhance VA health care delivery by promoting **VA-based population research** and converting results into a format that VA providers and administrators can apply to **improve patient care**

**Our Goals:**

- Investigate the determinants of disease in Veterans, including molecular, genetic, and biologic components
- Investigate the sources of disparities in the delivery and outcomes of medical care through VA-based population research
- Provide training opportunities in epidemiology to MD and PhD investigators through mentored research
CSP #380 Screening Colonoscopy Cohort
CSP #380 Overview

Screening colonoscopies performed in 3,121 asymptomatic Veterans aged 50-75 from 1994-1997 across 13 VA centers

Data collected:
- Demographics, medical history, medications
- Lifestyle factors: diet, tobacco and alcohol use, and physical activity
- Family history of CRC

Clinical outcomes available over at least 10 years of follow up

Lieberman, et al. NEJM 2000
Characteristics of CSP #380 Cohort

- Average age is 63
- 96.8% were male
- 83.6% were white
- 14% had a family history of CRC

Table 1. Characteristics of the 3121 Patients.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>62.9±0.13</td>
</tr>
<tr>
<td>Mean ±SE</td>
<td></td>
</tr>
<tr>
<td>50–59 yr — no. (%)</td>
<td>1044 (33.5)</td>
</tr>
<tr>
<td>60–69 yr — no. (%)</td>
<td>1481 (47.5)</td>
</tr>
<tr>
<td>&gt;69 yr — no. (%)</td>
<td>596 (19.1)</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td></td>
</tr>
<tr>
<td>Race — no. (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2609 (83.6)</td>
</tr>
<tr>
<td>Other</td>
<td>512 (16.4)</td>
</tr>
<tr>
<td>Family history of colorectal cancer — no./total no. (%)*</td>
<td>434/3121 (13.9)</td>
</tr>
<tr>
<td>Final study population</td>
<td>462/5617 (8.2)</td>
</tr>
<tr>
<td>All patients randomly selected from clinic lists</td>
<td></td>
</tr>
<tr>
<td>Recruitment method — no. (%)</td>
<td></td>
</tr>
<tr>
<td>Random selection from clinic lists</td>
<td>1524 (48.8)</td>
</tr>
<tr>
<td>Sigmoidoscopy referral</td>
<td>1404 (45.0)</td>
</tr>
<tr>
<td>Advertisement for patients with family history*</td>
<td>193 (6.2)</td>
</tr>
</tbody>
</table>

*A family history of colorectal cancer was defined as one or more affected first-degree relatives.

Lieberman, et al. NEJM 2000
CSP #380 Impact

- First large study using colonoscopy as a screening test
- Results informed Congress about the benefits of screening colonoscopy, leading to Medicare coverage in 2001
- Subsequent publications informed the 2006 and 2012 U.S. Multisociety Task Force Guidelines on CRC screening and follow up
CSP #380 Biorepository (n=815 participants)

Specimen Types:
- DNA from blood samples
- Serum lymphocytes
- Frozen normal rectal tissues
- Frozen polyp tissues
- Formalin-fixed polyp tissues
- Bouin’s fixed polyp samples
- DNA from tissue samples

Important Features:
- Includes baseline and serially biopsied specimens
- Linked with demographics, and clinical and survival outcomes through at least 10 years
- Includes participants with no adenomas, small adenomas, advanced adenomas, multiple adenomas, and CRC
Colonic Polyposis of Unknown Etiology (CPUE)
Polyposis: What We Know So Far

Risk for future high-risk lesions if 5+ adenomas on initial colonoscopy: 24%
• vs 8% if no adenomas

Similarly, >10 adenomas at baseline: 27%
• vs 11% if 3-10 adenomas

Polyposis: What We Need to Know

There are limited data regarding:

- The frequency of individuals with ≥10 cumulative adenomas encountered during routine CRC screening and surveillance
- Whether they are truly a distinct higher-risk population
Individuals with ≥10 *cumulative* adenomas (ie, CPUE) were at much higher risk for **CRC: OR 10.2** (95% CI 3.9-23.2)
Importance of CPUE

Individuals with ≥10 *cumulative* adenomas (ie, CPUE) were at much higher risk for **CRC: OR 10.2** (95% CI 3.9-23.2)

FACT:

Colorectal cancer is the 2nd leading cause of cancer death among men & women combined.

Sullivan, et al. DDW Abstract 2017
Clinical Epidemiology

• 6.5% participants had ≥10 cumulative adenomas over 10.5 yrs

Figure 1. Risk of Developing ≥10 cumulative adenomas.
Clinical Epidemiology

CPUE incidence will certainly increase:
- Efforts to increase CRC screening uptake
- Increased Adenoma Detection Rates (ADRs)
- Improved quality metrics
- Improved endoscopic technology

Can we use known CRC risk factors to better understand the etiology of CPUE?

Same risk factors for recurrent adenomas as for CRC:
- Obesity
- Diet: Red meat, lack of fiber
- Smoking
- Diabetes
- Family history

We found that those with ≥10 cumulative adenomas lacked an obvious cluster of identifiable clinical CRC risk factors.

Therefore, we hypothesize that underlying genetic variations are likely associated with this high-risk phenotype.
Current genetic testing guidelines for high cumulative adenoma counts are based on limited data:

- Known genetic CRC syndromes present in only small fraction of cases
- Study populations were referred for genetic testing, so high likelihood of selection bias

To refine current CRC genetic screening guidelines, we need to:

- Better understand the genetic profiles of these patients
- Monitor the impact of these recommendations in the general population

Grover, et al. JAMA 2012
Ongoing work are beginning to identify additional genes associated with CPUE:

– Rare but highly penetrant genes POLE, POLD1, NTHL1, AXIN1/2
– Low-level mutations isolated to colonic tissue (mosaicism)

The proportion of those with an “unknown” etiology will likely diminish

If an individual has positive genetic testing, NCCN has guidelines for the follow up of those with specific mutations
Genetic Epidemiology

What is the role of specific single nucleotide polymorphism (SNP) testing?

Can we determine if the SNPs known associated with CRC are also found in individuals with CPUE?

Table 2: CRC-risk SNPs Associated with Multiple Adenomas

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>OR</th>
<th>P</th>
<th>Associated Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs10936599</td>
<td>TERC</td>
<td>1.13</td>
<td>0.007</td>
<td>Multiple Adenomas</td>
</tr>
<tr>
<td>rs6983267</td>
<td>MYC</td>
<td>1.20</td>
<td>2.68x10^-6</td>
<td>Multiple Adenomas</td>
</tr>
<tr>
<td>rs10795668</td>
<td>None</td>
<td>1.13</td>
<td>0.004</td>
<td>Multiple Adenomas</td>
</tr>
<tr>
<td>rs3802842</td>
<td>POU2AF1</td>
<td>1.22</td>
<td>1.74x10^-6</td>
<td>Multiple Adenomas</td>
</tr>
<tr>
<td>rs4444235</td>
<td>BMP4</td>
<td>1.15</td>
<td>0.001</td>
<td>Multiple Adenomas</td>
</tr>
<tr>
<td>rs1957636</td>
<td>BMP4</td>
<td>1.10</td>
<td>0.012</td>
<td>Multiple Adenomas</td>
</tr>
<tr>
<td>rs4939827</td>
<td>SMAD7</td>
<td>1.18</td>
<td>1.17x10^-5</td>
<td>Multiple Adenomas</td>
</tr>
<tr>
<td>rs961253</td>
<td>BMP2</td>
<td>1.18</td>
<td>4.42x10^-5</td>
<td>Multiple Adenomas</td>
</tr>
<tr>
<td>rs3802842</td>
<td>C11orf93</td>
<td>1.6</td>
<td>2x10^-5</td>
<td>&gt;10 Adenomas</td>
</tr>
<tr>
<td>rs4779584</td>
<td>SCG5, GREM1, FMN1, CRAC1</td>
<td>1.5</td>
<td>0.001</td>
<td>&gt;10 Adenomas</td>
</tr>
</tbody>
</table>
Role of SNP Testing

CSP #380 biorepository: Tested known CRC-risk SNPS for associations with higher cumulative adenoma counts

Three CRC-risk SNPs were significantly associated with ≥10 cumulative adenomas

- Risk allele ORs of 2.09, 2.30, and 1.94
Role of SNP Testing

While each SNP has small effect size, the combination of multiple genetic variants may work synergistically to promote CPUE phenotype.

Higher number of known adenoma-risk SNPs per individual was associated with increased adenoma counts:

- Weighted OR 1.6 (p=0.03), per each additional risk allele
• Evaluate prevalence of underlying genetic CRC syndromes beyond those recommended for testing by current guidelines

• Evaluate potential CRC gene-environment interactions on diet, smoking, NSAID use, etc

• A longitudinal tissue biorepository will soon be available to analyze individual phenotypic and genotypic changes over time:
  • Characterize varying progression pathways in adenomas
  • Clarify tumorigenesis pathways in different polyp subtypes
Future Directions

Ultimately, this work will serve as the basis for investigations to test novel precancerous:

- **Risk prediction tools**
  - Surveillance intervals
  - Age to start screening

- **Screening modalities**
  - Blood and stool biomarker testing for adenomas in development

- **Therapeutic targets**:
  - Pre-cancer vaccines or other chemopreventive agents

Stoffel, et al. Gastro 2018
Jeon, et al. Gastro 2018
Weigl, et al. Gastro 2018
Myint, et al. Cell Death Dis 2018
Future Directions

The PreCancer Atlas (PCA)
Sudhir Srivastava,¹,* Sharmistha Ghosh,¹ Jacob Kagan,¹ and Richard Mazurchuk¹
¹Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA

Benefits of a PreCancer Atlas

- Identify people at risk
- Define biological characteristics
- Detect early disease
- Adapt new technology
- Improve imaging
- Develop interventions

https://cancergenome.nih.gov/
Current Clinical Strategies

CPUE is a high-risk phenotype strongly associated with CRC

CPUE incidence will likely increase

The clinical and genetic etiology not yet fully elucidated

• So what are current, and potential, management strategies?
Current Management

Shortened surveillance intervals based on adenoma counts:

– 1–2 small (<10 mm) tubular adenomas: 5–10 Years
– 3–10 tubular adenomas: 3 Years
– >10 adenomas: <3 Years

Furthermore, if 3+ adenomas were present on a colonoscopy in the past, shortened intervals may also be recommended.

But, we need more data on the long-term incidence of CRC in individuals with CPUE to determine the best management.
Current Management

Although lacking rigorous data, emphasizing a healthy lifestyle is certainly important

Pharmacologic chemoprevention?

- RCT: Aspirin effective at reducing recurrent adenomas (RR 0.78)
- RCT: Metformin effective at reducing recurrent adenomas (RR 0.60)

Hull, et al. Lancet 2018
Case: CPUE

Final recommendations:

• “No further genetic testing at this time, unless new clinical information becomes available”

• “He should continue to have colonoscopies at the interval recommended by his physicians”
Avoid the temptation of making premature health care decisions based on DNA analysis

- Mis-diagnosis
- Incidental findings
- Non-actionable findings
- Increased costs
- Patient and family anxiety
- Hasty knee-jerk clinical reactions

Know the current guidelines!
‘I’m Permanently Damaged.’ Woman Sues After She Says Doctors Unnecessarily Removed Her Breasts and Uterus

- Doctors misinterpreted a line in the results, which said that there were ‘variants of uncertain significance’ associated with a specific hereditary cancer syndrome
Summary of Key Points

• CPUE incidence will likely increase, which has a strong epidemiologic association with CRC
• Current genetic testing guidelines are lacking data
• Management strategies remain undefined, including utility of increased surveillance over the long term
• Emerging genomic work in those with CPUE may lead to:
  – Risk stratification tools to help guide CRC screening
  – CRC screening modalities using pre-cancer genomic biomarkers
  – Treatment modalities based on new targets in tumorigenesis pathways
Thank you!

Questions or Comments?