University of Michigan Health System

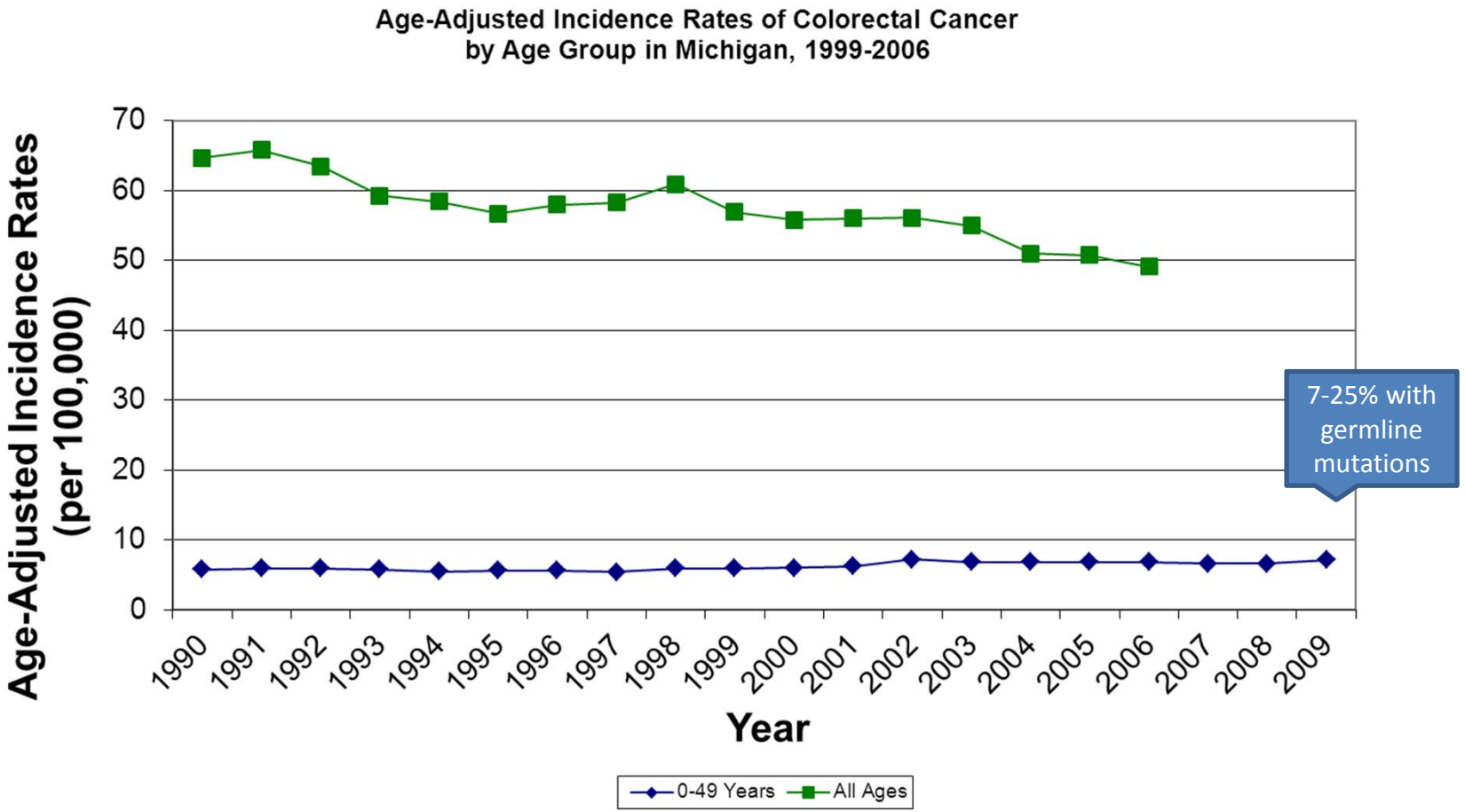
Hereditary GI Cancers: Chemoprevention and Risk Assessment

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Objectives

- Review role for chemoprevention in management of individuals with hereditary CRC
  - Open clinical trials
- Review pilot data for utility of risk assessment tools for identifying patients at increased risk for CRC

CRC in Michigan



“Red Flags” for Hereditary CRC

- Family History
  - Multiple cancers (CRC, endometrial, ovarian, breast, thyroid)

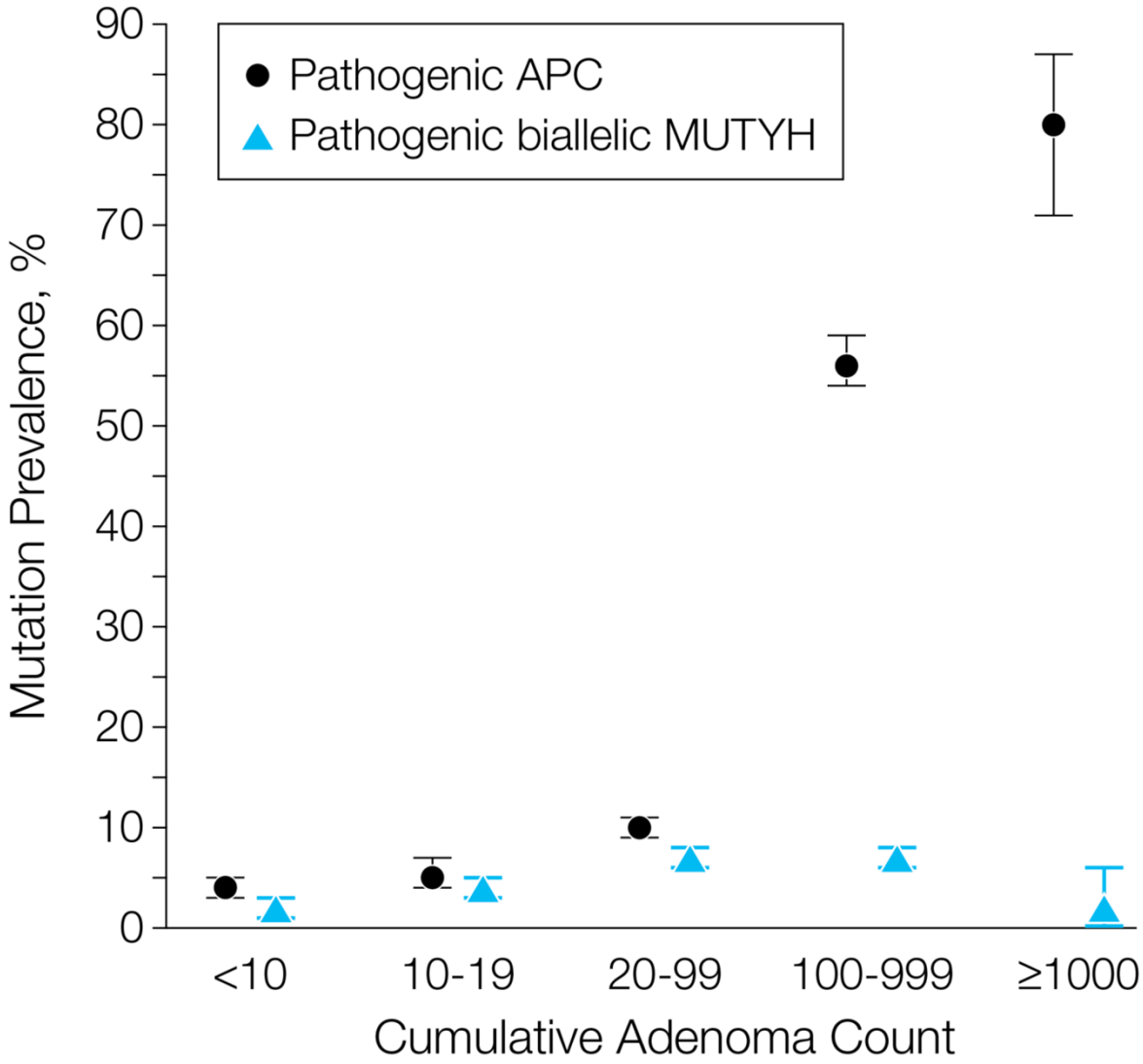
- Personal history
  - Young CRC (age<50)
  - Multiple primary cancers
  - CRCs arising after colonoscopy (interval cancers)

  - Multiple polyps
    - Adenomas: ≥10-20
    - Hamartomas: ≥3-5
    - Sessile Serrated: Multiple (>20), >5 large in proximal colon
    - Mixed polyp types (eg, ganglioneuromas)

Approaches to Genetic Risk Assessment

- Universal tumor testing of CRCs (and endometrial cancers) for Mismatch Repair
- Family History—How to implement in clinical settings?
- Personal history (cancers, polyps)

Prevalence of Germline Mutations in Patients with "Multiple" Adenomas



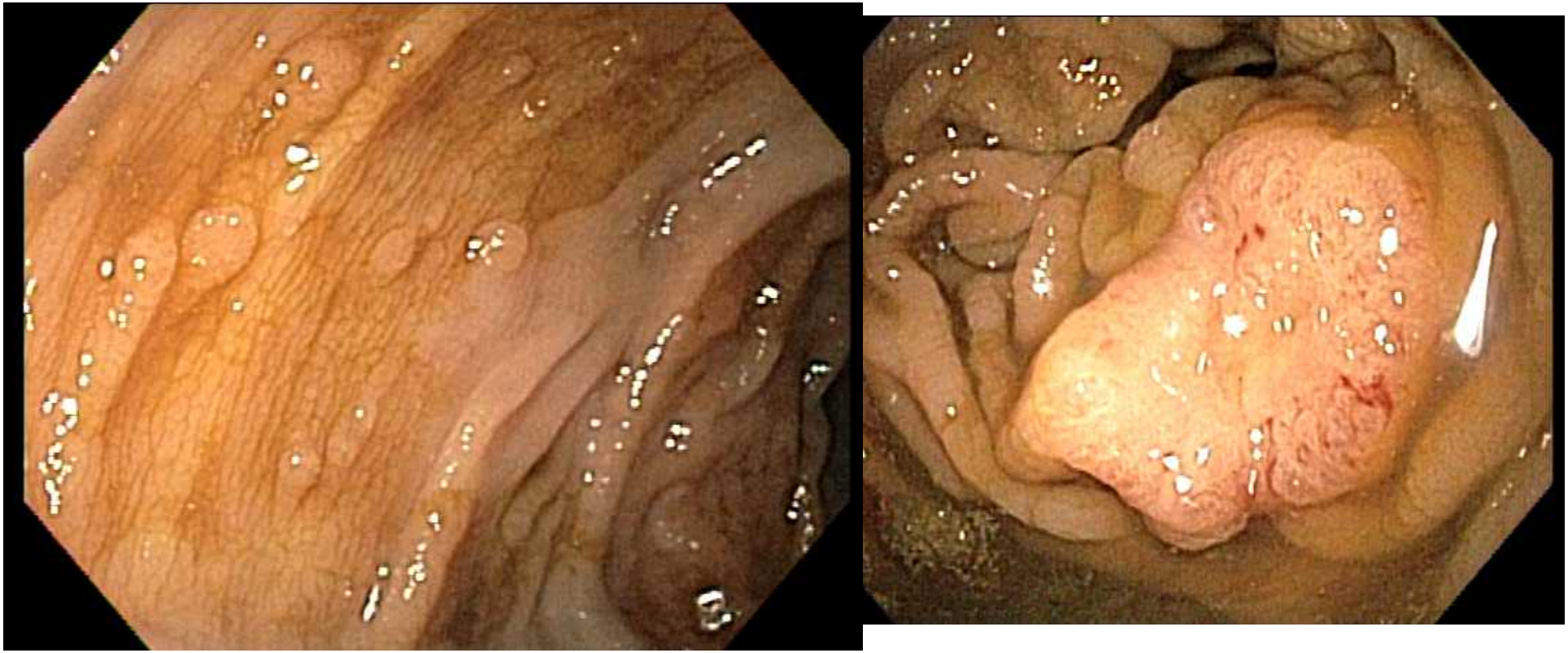
Grover S. JAMA. 2012;308(5):485-492.

Impact of Genetic Diagnosis on Management

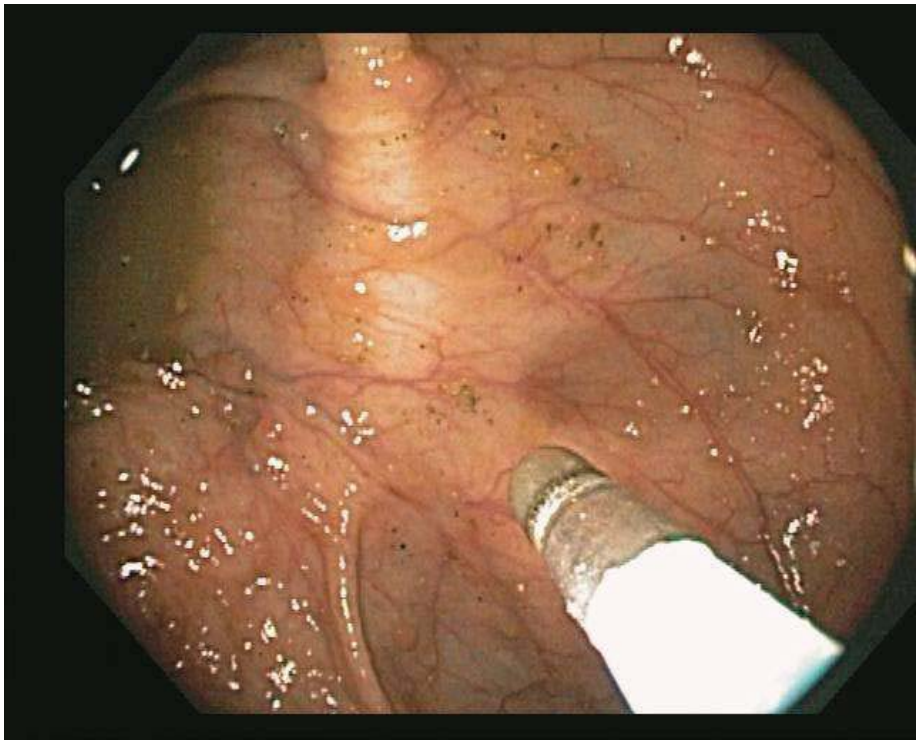
- Endoscopic surveillance
  - Types of exams (colonoscopy +/- EGD)
  - Interval (q 6 months to 2 years depending on polyp burden)
- Type of Surgery
  - Segmental colectomy
  - Subtotal Colectomy
  - Total Colectomy
    - Ileorectal anastomosis
    - Ileoanal anastomosis (J pouch)

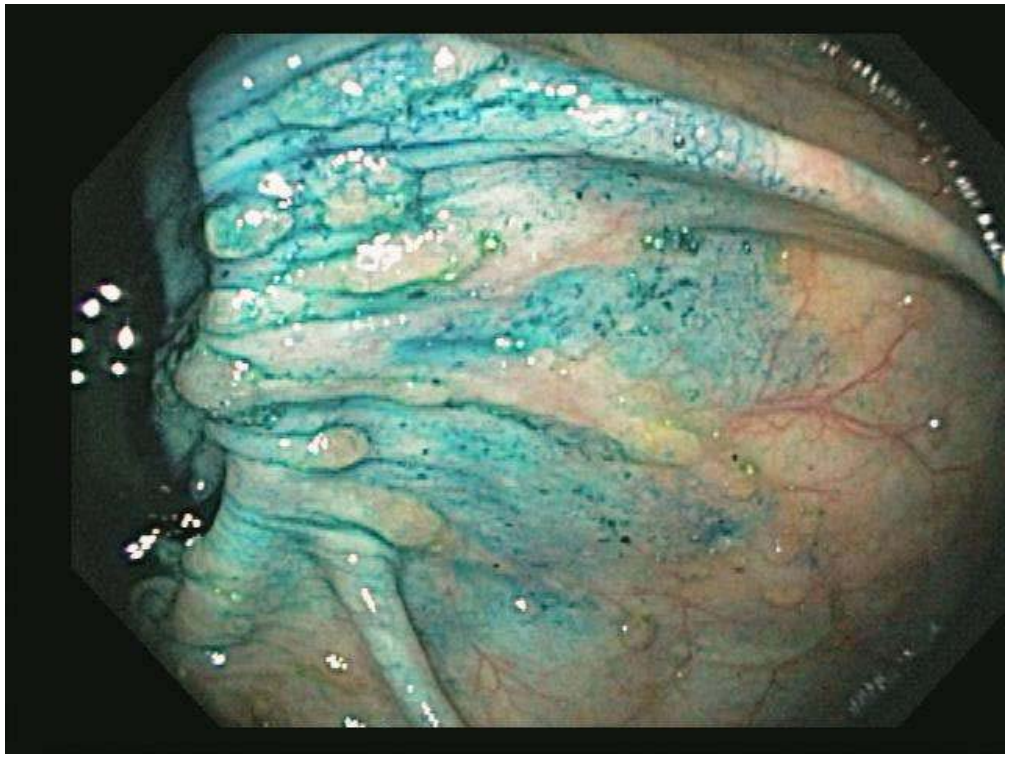
Cancers After Colectomy--FAP

Rectal Remnant (IRA)



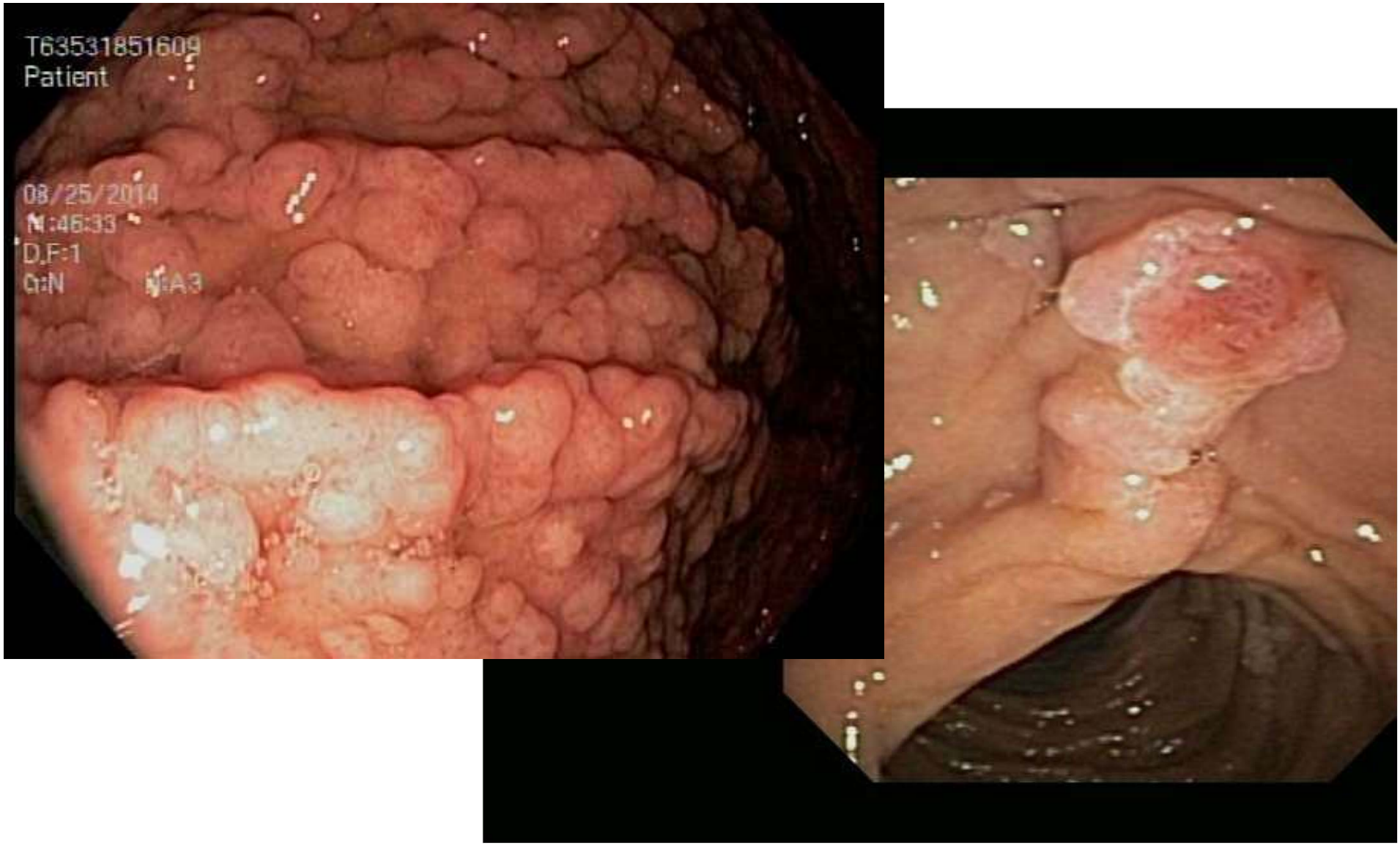
Defining Colonic Polyp Burden: Chromoendoscopy





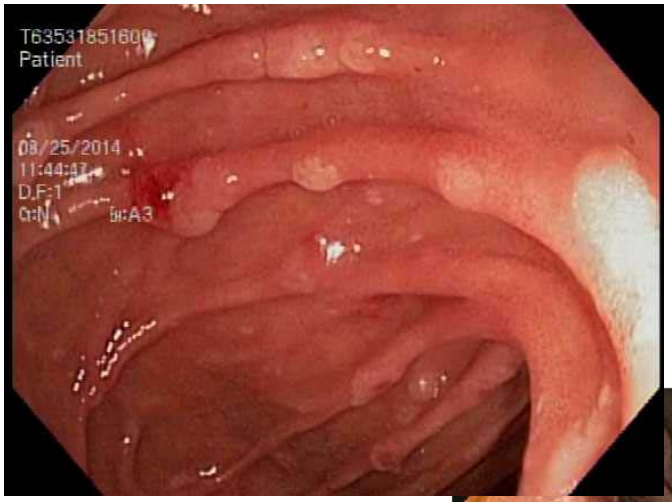
>100 polyps

Upper GI Polyps in FAP

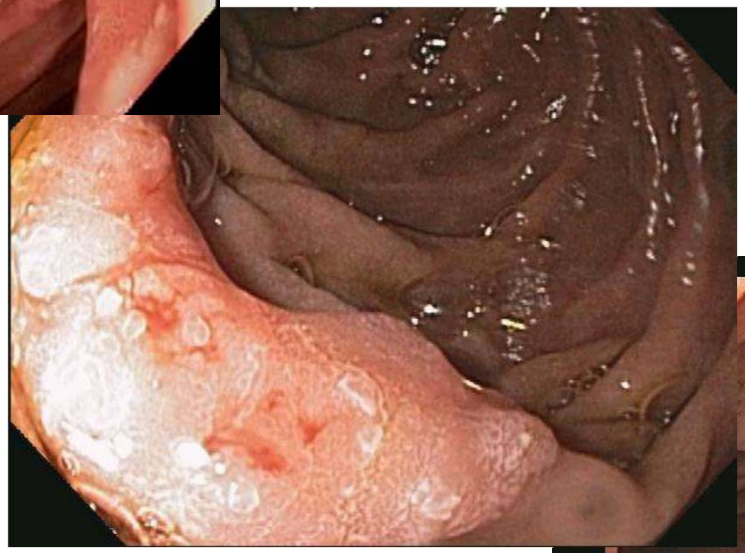


FAP Duodenal Adenomas: Spiegelman Stage

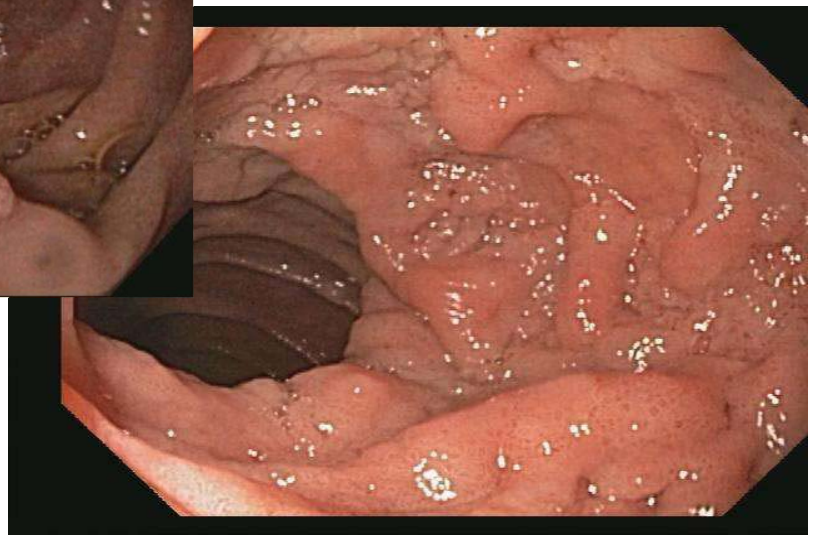
Stage I-II



Stage III



Stage IV



Management of Polyposis

- Endoscopic polypectomy
- Surgical Resection
  - Duodenal resection
  - Pancreatoduodenectomy (Whipple)
- Chemoprevention
  - Sulindac (clinoril), cox-2 inhibitors
  - clinical trials

Eflornithine(DFMO)

- Inhibitor of ornithine decarboxylase (polyamine syntehsis pathway)
- Reduces intestinal polyps in APC min mouse model
- Human Phase III clinical trial demonstrated reduced incidence of sporadic adenomas

A Double-Blind, Randomized Phase III Trial of the Safety and Efficacy of CPP-1X/Sulindac Compared with CPP-1X, Sulindac as Single Agents in Patients with Familial Adenomatous Polyposis

- Industry-sponsored, multicenter study (USA, Europe)
- Randomized Trial Double-Blinded
  - 150 mg Sulindac + Placebo
  - 750 mg DFMO + Placebo
  - 150 mg Sulindac + 750 mg DFMO
- Eligibility Criteria
  - FAP (APC+) and ≥ 18 yrs
  - Disease at one or more sites:
    1. Intact colon (pre-colectomy)
    2. Rectal/Pouch Polyposis
    3. Duodenal Polyposis, Spiegelman 3 or 4

    2-Year Trial
    Endpoints—Surgery, Cancer, Excision of advanced adenoma

Aspirin for Chemoprevention in Hereditary CRC

- FAP—CAPP1 Trial, ASA 600mg qd (RCT)
  - Non-significant reduction in polyp number and size
- Lynch Syndrome—CAPP2, ASA 600mg qd
  - RCT 841 randomized
  - No reduction in risk for neoplasia during 30 month follow up
  - Long-term, 63% reduction in CRC incidence among aspirin users (difference of 16 cancers)

J. Burn Familial Cancer 2013

Chemoprevention for Lynch Syndrome

- "There are data suggesting aspirin may decrease CRC risk in Lynch Syndrome, however the data are not sufficiently robust to make a recommendation for standard use."
  - NCCN 2014

- Clinical Trials?

A Phase Ib Biomarker Trial of Naproxen in Patients at Risk for DNA Mismatch Repair Deficient Colorectal Cancer

- NCI-sponsored
  - MD Anderson (lead), Dana-Farber, University of Michigan
- Randomized, placebo-controlled trial
  - 440 mg Naproxen
  - 220 mg Naproxen
  - Placebo
- Eligibility Criteria
  - Lynch Syndrome (mutation positive) and age ≥ 18

6 month trial—Biomarker endpoint

Preventing Cancers: Early Identification of Patients at risk for Hereditary CRC

- Family History Assessment
- Online Risk Models
  - MMRPro, PREMM1,2,6
- How to integrate risk assessment in clinical settings?

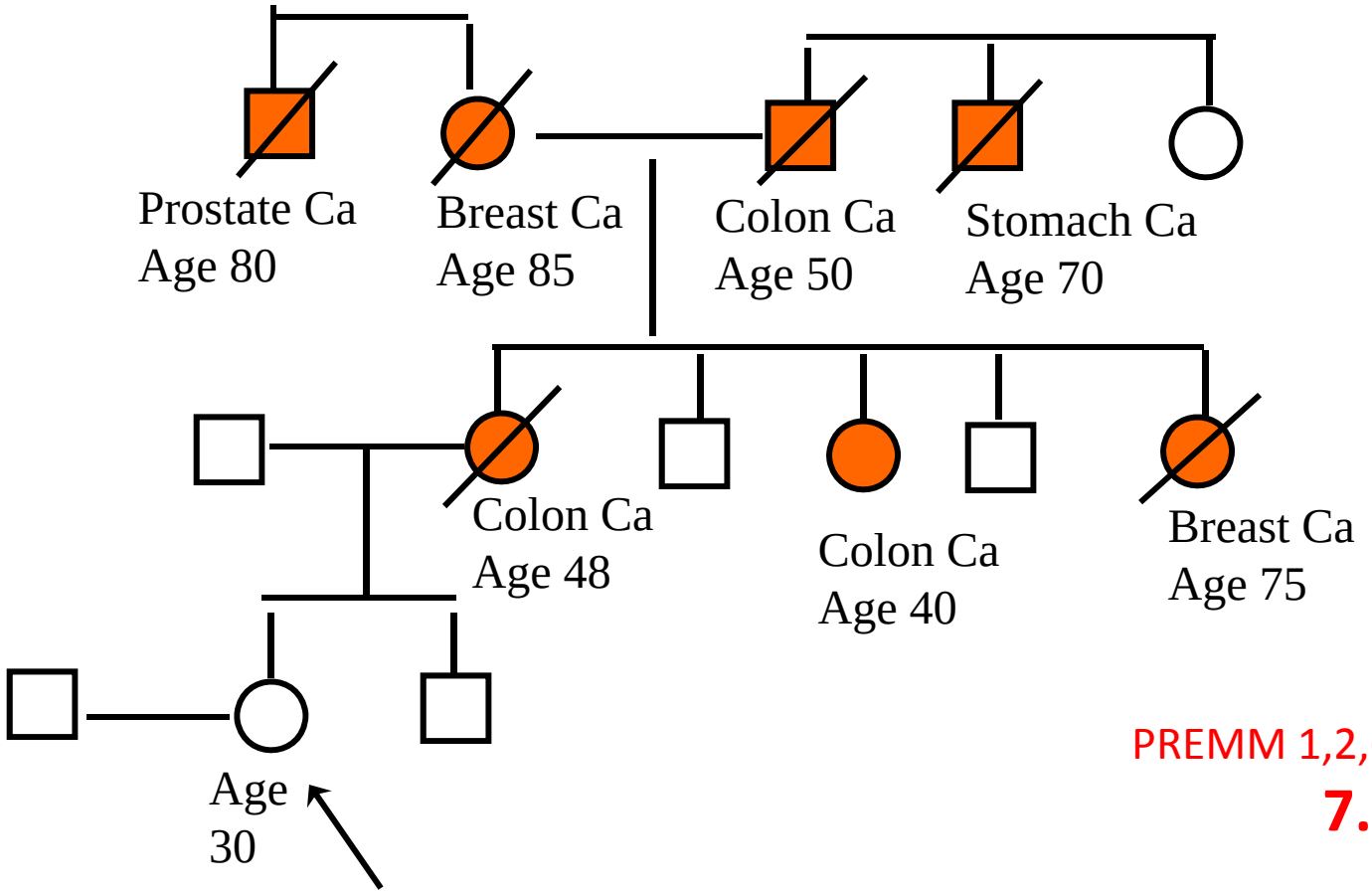
Case

- An asymptomatic 30 year old woman asks when she should start colorectal cancer screening

- Family history is notable for mother who died of CRC at age 48

  - Options:
    - A. Colonoscopy at age 50
    - B. Colonoscopy at age 38, 10 years before age at dx
    - C. Colonoscopy now

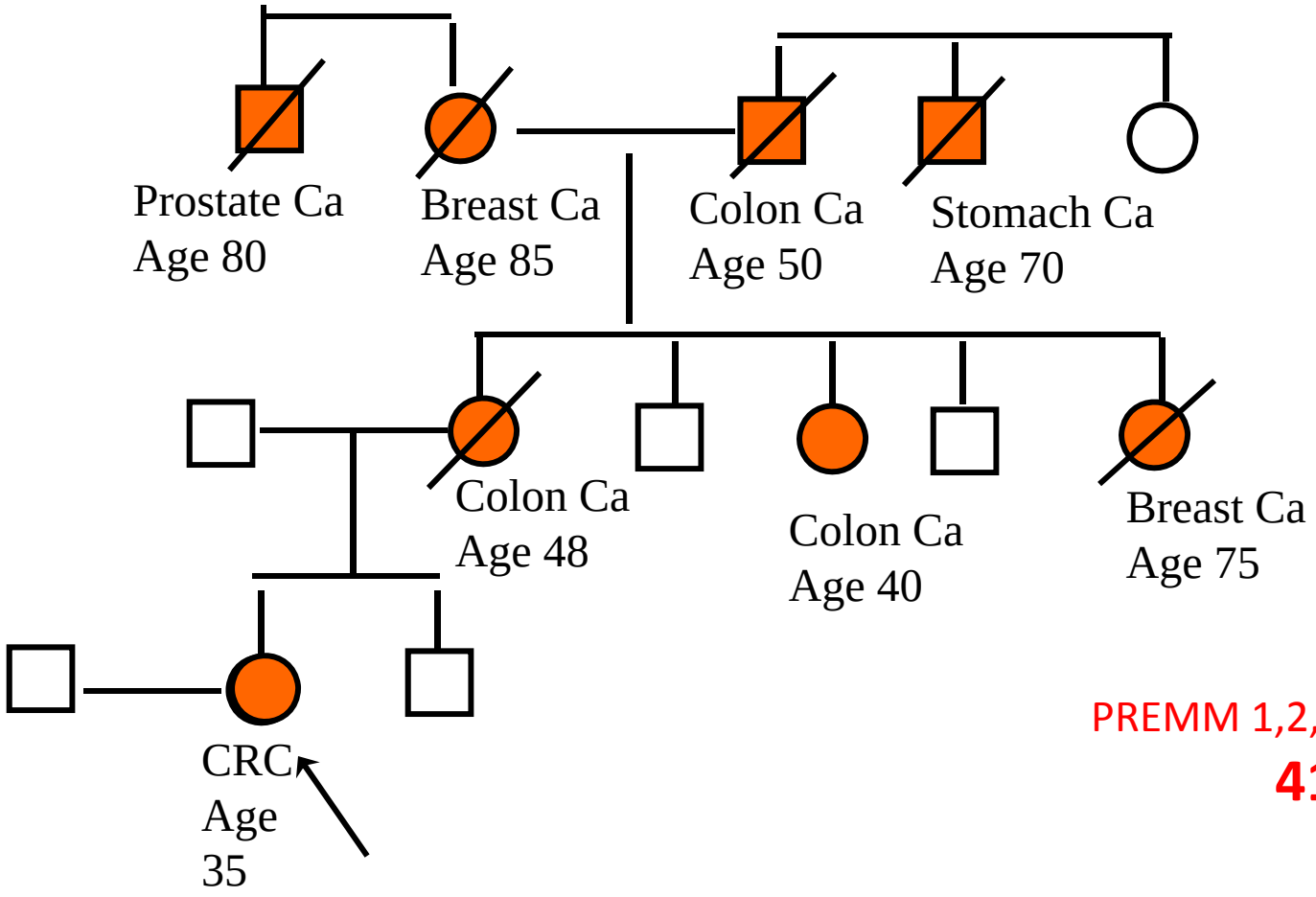
Family History



PREMM 1,2,6 Score:

7.7%

Family History



PREMM 1,2,6 Score:

41%

5 Question Screen

1.	**Do you have a first degree relative (father, mother, siblings, child) with any of the following conditions?** • **Colon or rectal cancer** • **Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts, pancreas, or brain** **If the answer is yes to any of the above, were they diagnosed before age 60?**	**Yes No** **Yes No** **Yes No**
2.	Do you have three or more relatives (this includes grandparents, aunts, uncles, cousins) with a history of colon or rectal cancer?	Yes No
3.	Do you have a first degree relative (father, mother, brother, sister, child) diagnosed with colon polyps before the age of 60?	Yes No
4.	Have you had any of the following conditions diagnosed before age 50? • Colon or Rectal Cancer • Colon or Rectal Polyps • Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts, pancreas, or brain	Yes No Yes No Yes No
5.	Have you had a total of 10 or more colon polyps removed in your lifetime?	Yes No

Adapted from Kastrinos, F, et al., Development and validation of a colon cancer risk assessment tool for patients undergoing colonoscopy. *Am J Gastroenterol*, 2009 June. 104(6):1508-1518.

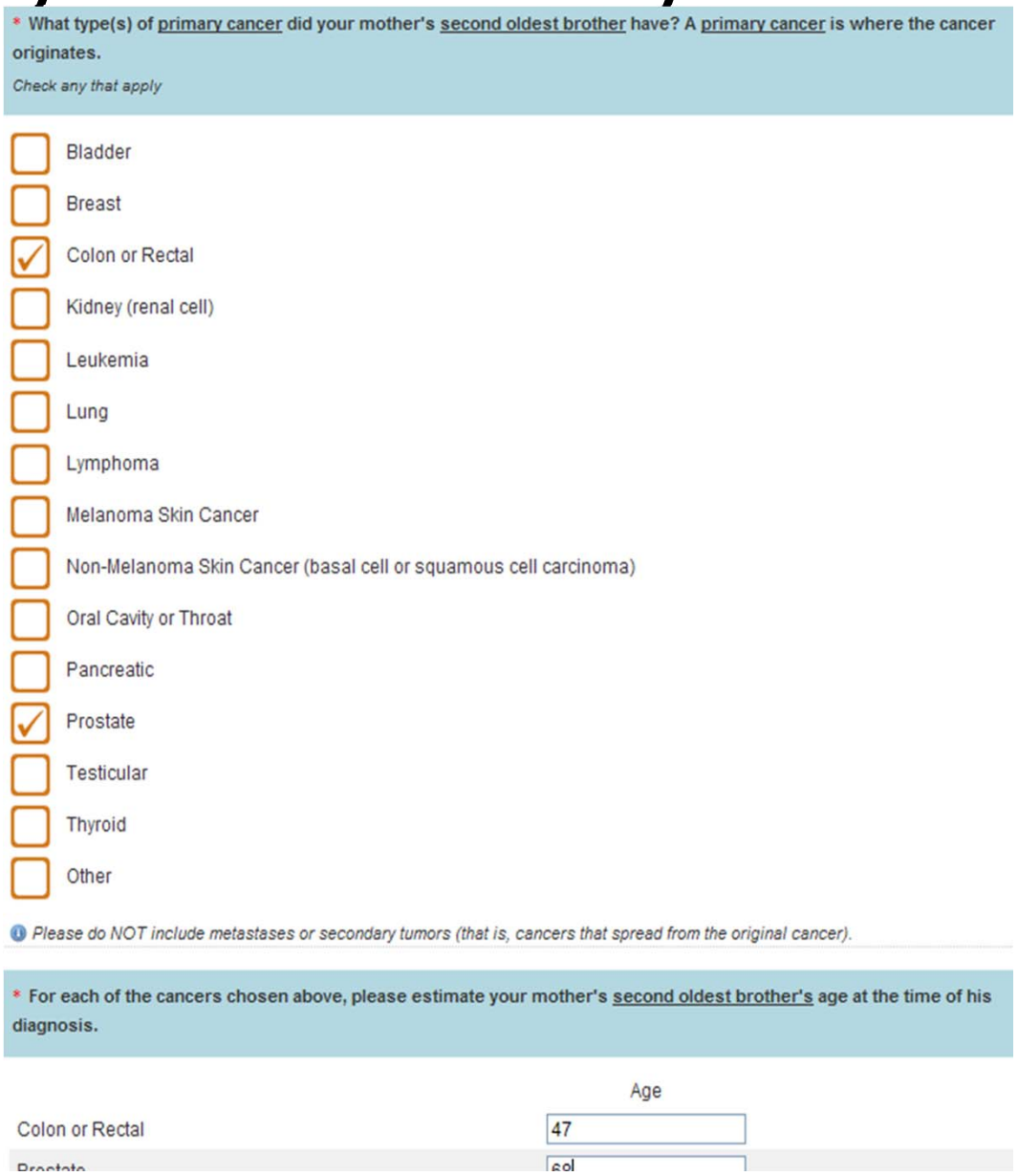
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Web-Based Family Cancer History Tool

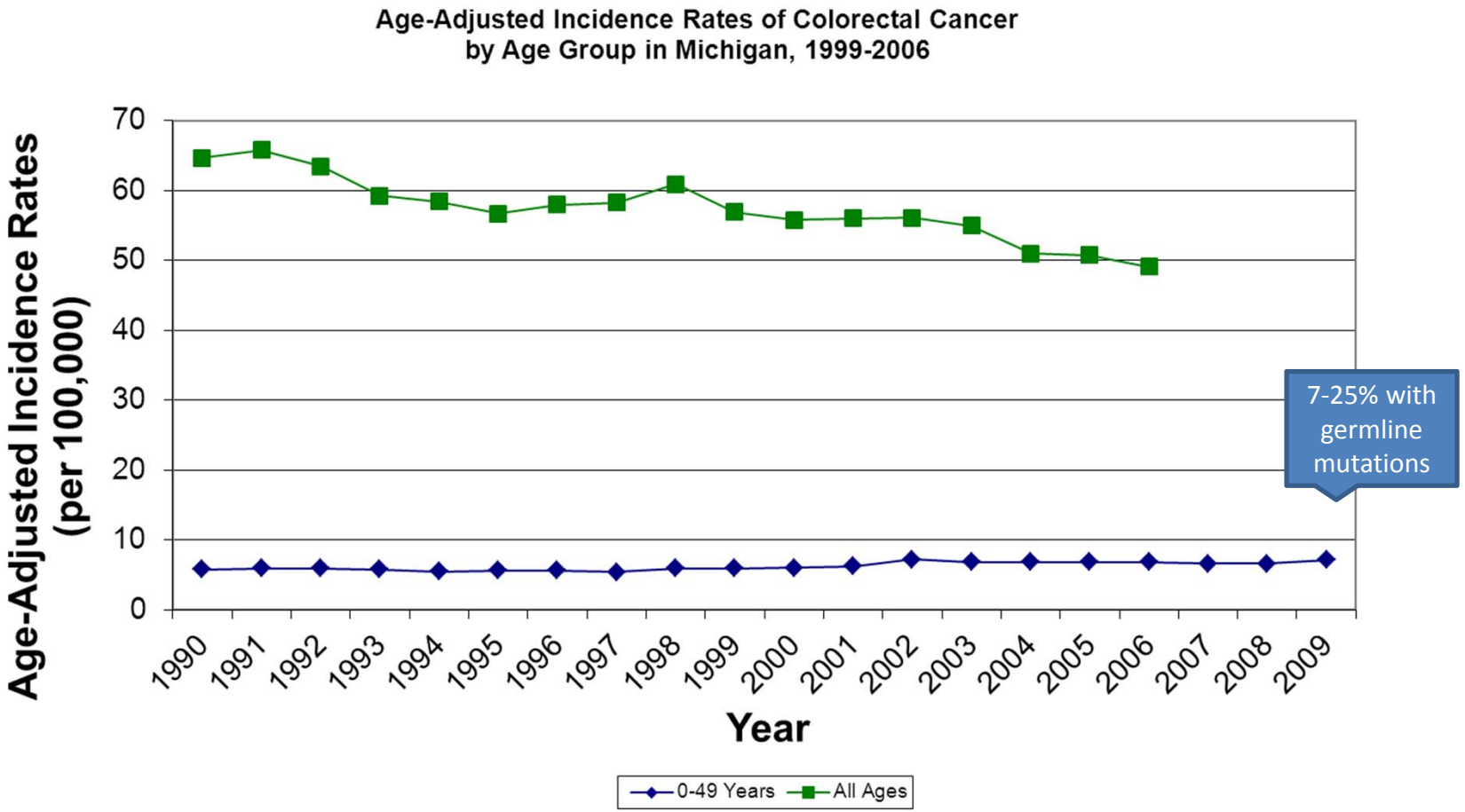
- Elicits cancer type and age at diagnosis in FDR, SDR
- Piloted and validated in Cancer Genetics Clinic
- Roll-out in UMHS outpatient clinics
  - Integrate risk models



Risk Assessment at Colonoscopy

- 800 unselected colonoscopy patients
- 55% were above average risk
  - 7% met criteria for genetic evaluation

CRC in Michigan



Next Steps

Molecular characterization of CRC cases age<50

– Germline and tumor mutation profiling

Systematize Family History Assessments

Primary care (presymptomatic), Cancer Clinics

Chemoprevention

High, Moderate, Average risk populations

Thank You

- Cancer Genetics Clinic, University of Michigan
  - estoffel@med.umich.edu
  - 734-615-9712

Selected References

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