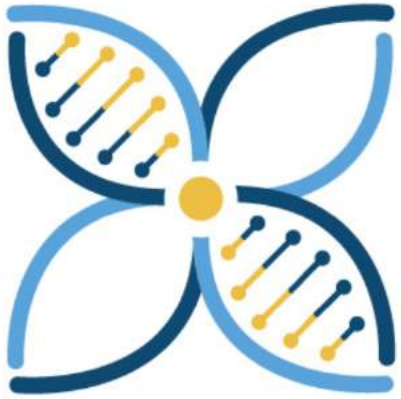


bloom syndrome association

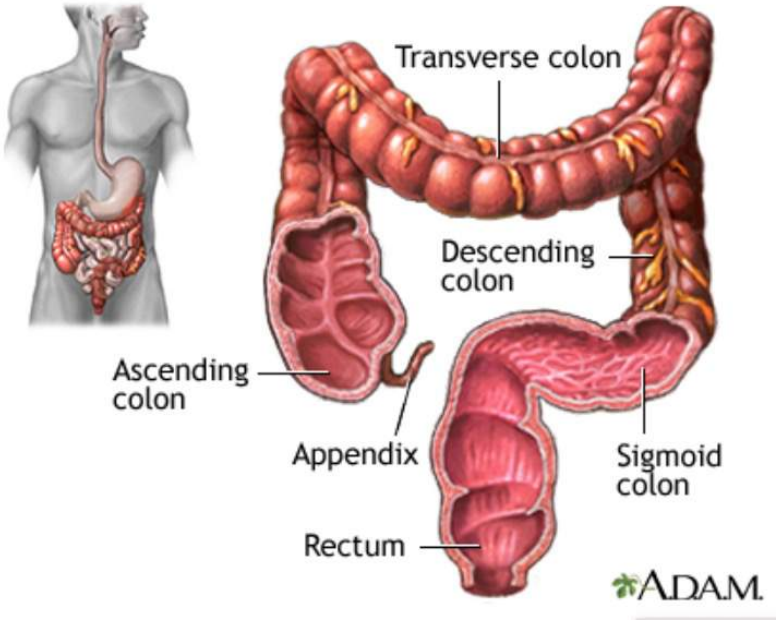
Developing a Bloom syndrome biobank

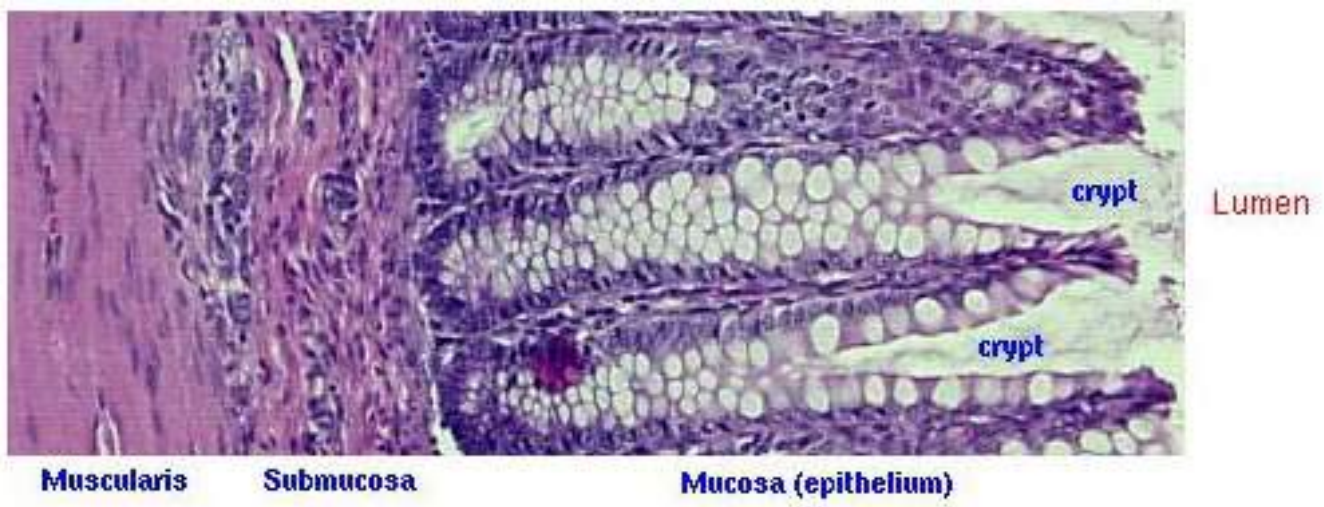
Bloom syndrome webinar

Nathan Ellis

August 22, 2023

Anatomy and function of the large bowel





ANATOMY

Length – 1.5 m (150 cm)
Circumference – 6.5 cm
Surface area – 995 cm^2

15 million crypts
2000 cells/crypt
12-18 stem cells each crypt

Slightly different numbers for the small intestine

FUNCTIONS

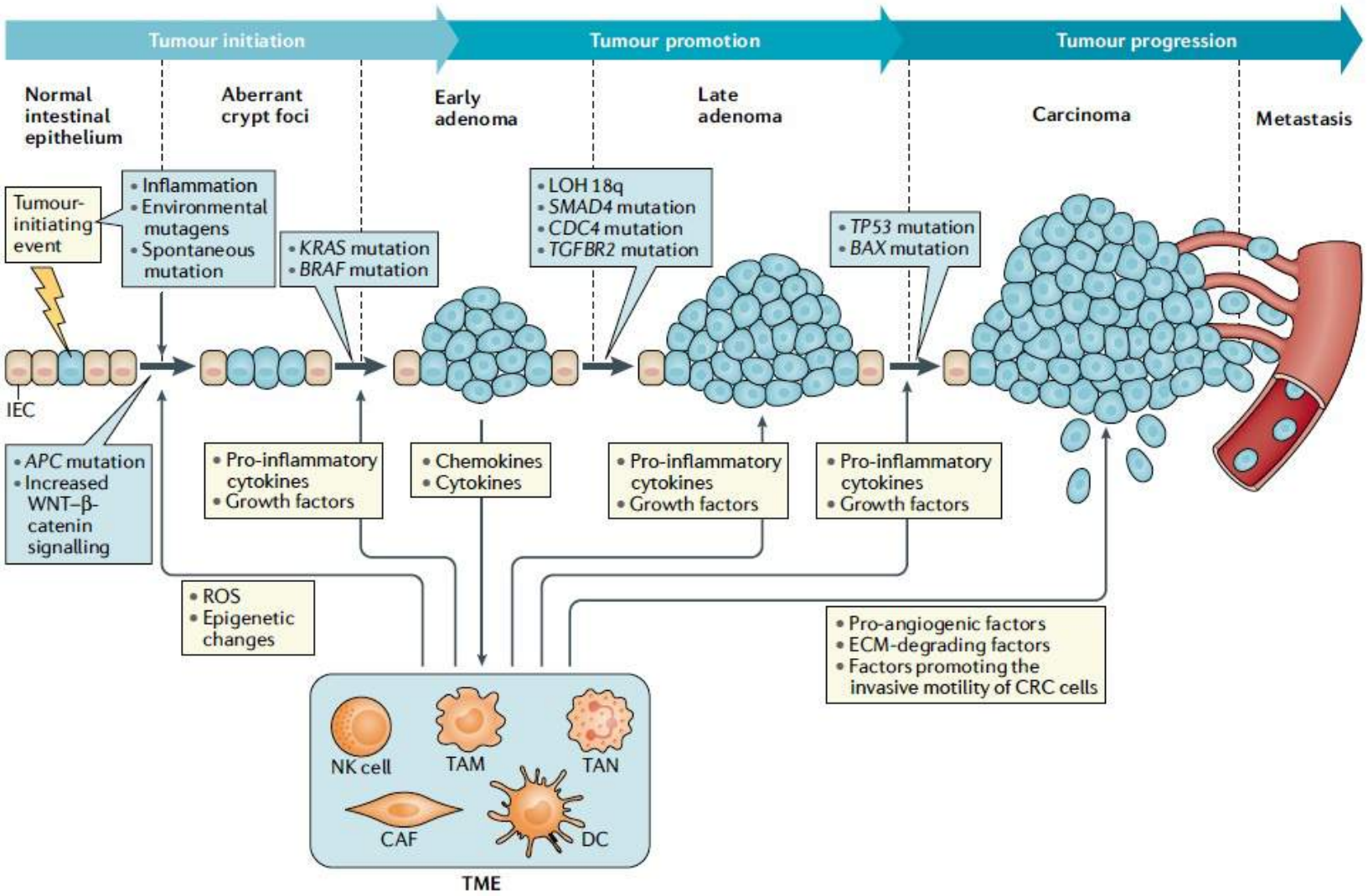
Water and bile resorption
Fecal mass consolidation
Barrier
Peristalsis
Highly vascularized
Mesenteric lymph nodes
Pathogen surveillance; defense against pathogens
Microbiota

CELL BIOLOGY

Differentiated cells types:
Stem cells
Colonocyte or enterocyte (absorptive)
Paneth (secretory; small intestine only)
Goblet (secretory)
Enteroendocrine (secretory)
Tuft (secretory)
M cell (immuno-regulatory)
Stroma – fibroblasts, smooth muscle, endothelial, and neuronal

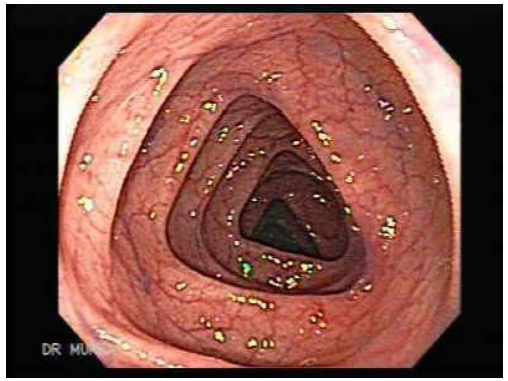
Colorectal Cancer

- Colorectal cancer (CRC) is the third most diagnosed cancer and third leading cause of cancer-related death in the US.
- Expected 153,020 new CRC cases in 2023 in the US, predicted 52,550 CRC-related deaths.
- CRC incidence is declining in older individuals (>65 years of age)
- CRC increases from 11% in 1995 to 20% in 2019 in persons under 50 years of age

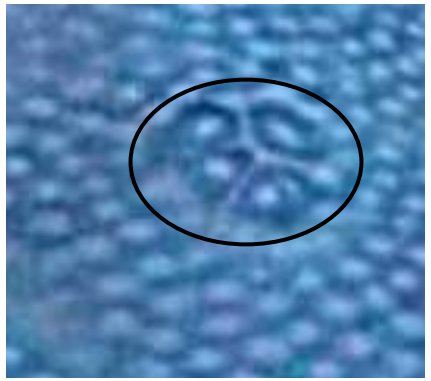


Vogelstein and Fearon, 1990; Siegel, 2023; Schmitt, 2021

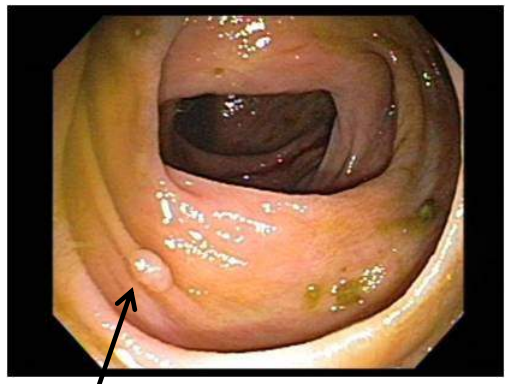
Through the endoscope lens



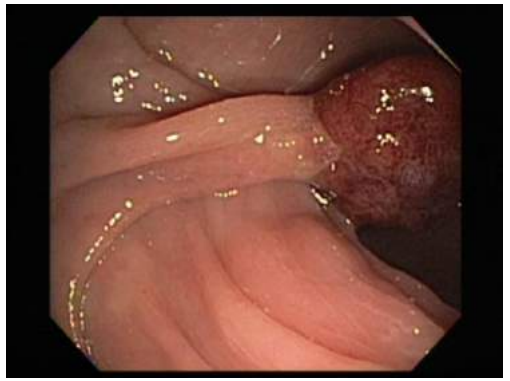
“clean colon”



Aberrant crypt focus



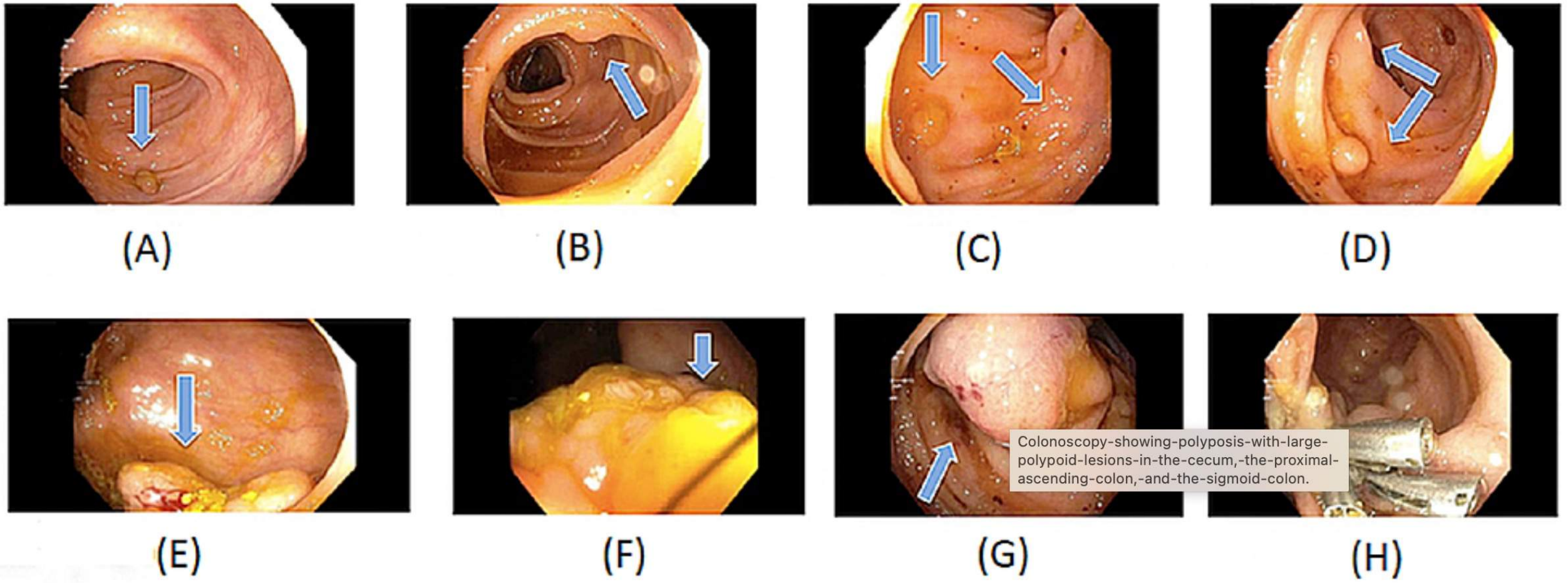
Early adenoma



Advanced adenoma

Colorectal cancer

Attenuated polyposis

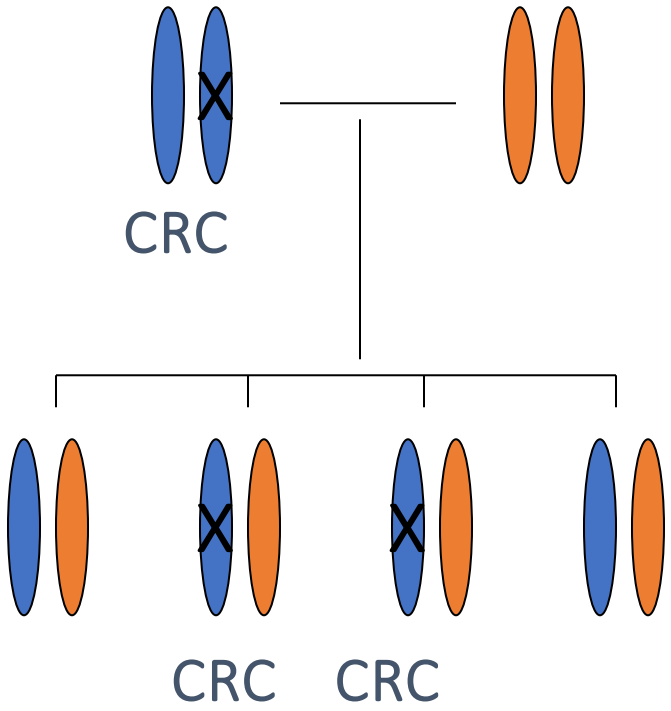


Cureus-–Springer Nature Group article; Bhesania et al.

Inheritance patterns of CRC syndromes

Autosomal dominant

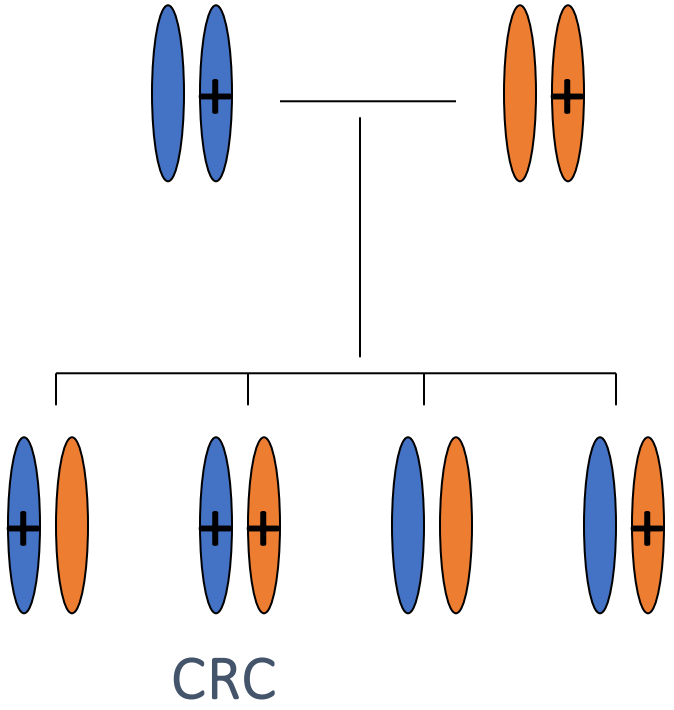
(FAP, AFAP, PPAP, Lynch Syndrome, Hamartomtatous polyposis)



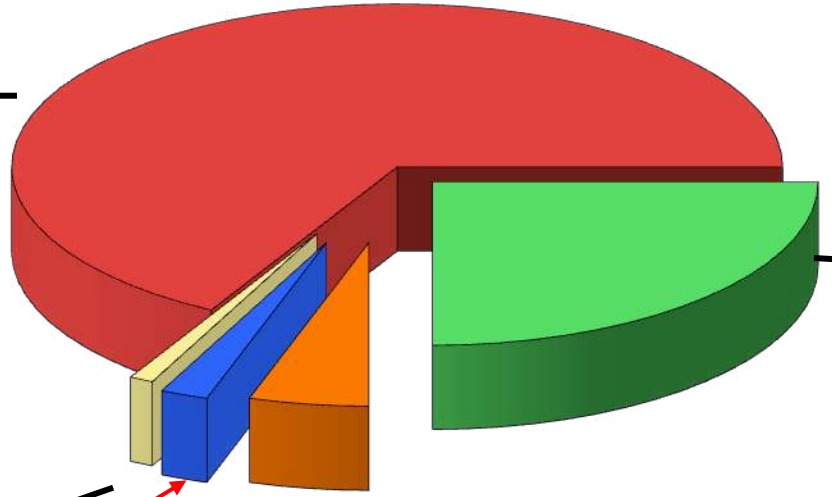
Autosomal recessive

(MAP, *NTHL-1, MSH3*)

Bloom syndrome is here



Hereditary Susceptibility to CRC



Sporadic
(65%–85%)

Familial
(15%–20%)

Hamartomatous
polyposis (<0.1%)

Adenomatous polyposis
(FAP, AFAP, MAP, PPAP)
(2%)

Hereditary non-polyposis
colorectal cancer-including
Lynch syndrome- (≈3%)
MLH1, MSH2, MSH6, PMS2

Bloom is in here

Polyposis

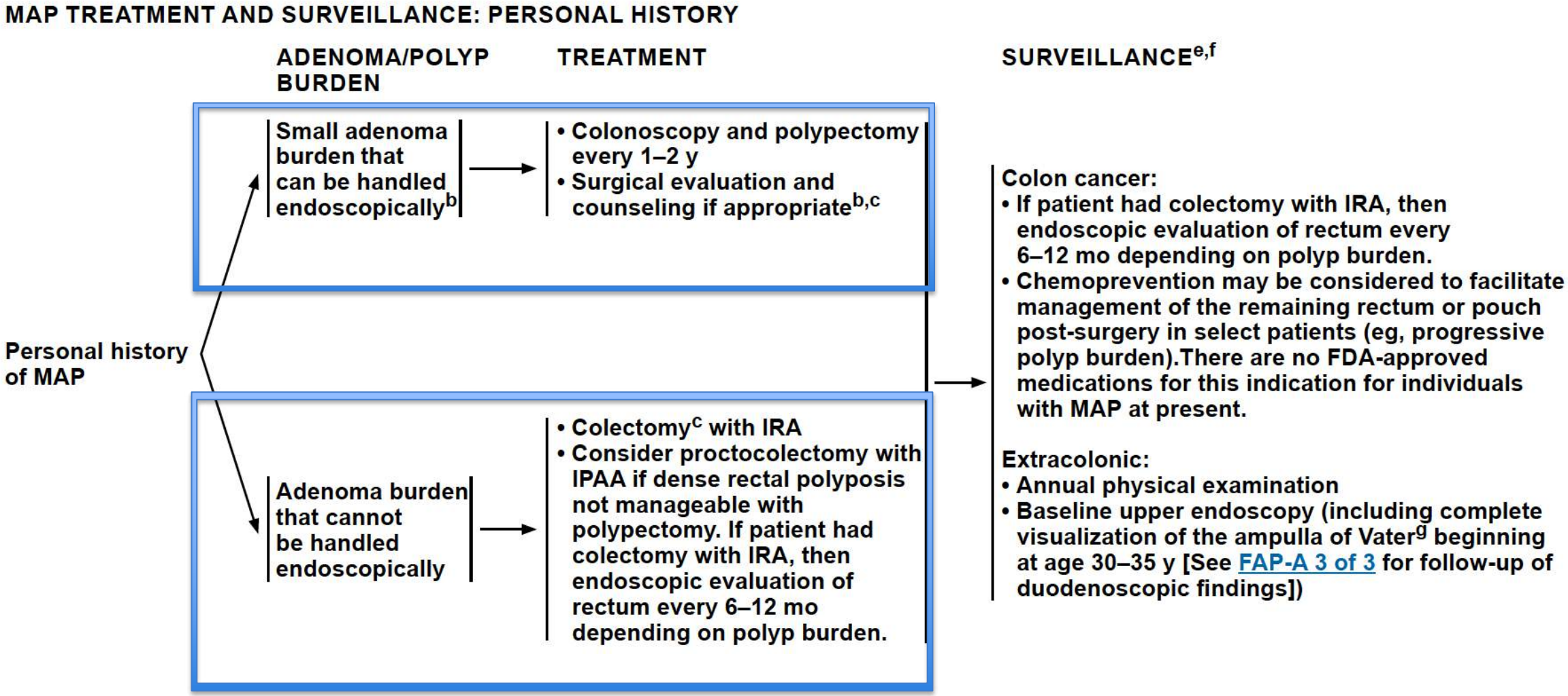
Non-Polyposis

TABLE 1 Recommendations for surveillance and treatment of people with BSyn

Clinical condition	Screening/prevention recommendations	Treatment recommendations
Leukemia	• Awareness of symptoms of leukemia, such as pallor, abnormal bleeding, petechiae, fatigue, and unintentional weight loss	*For all cancers:* There is a possibility of increased risk for secondary cancers after chemotherapy/radiation. MRI and ultrasonography are preferred over CT scans, PET scans, and other radiography procedures. Chemotherapy should be adapted; BSR patients have typically tolerated 50% or below the normal regimen dosage. Ionizing radiation or alkylating agents (busulfan, melphalan, or cyclophosphamide) are not recommended.
Lymphoma	• Awareness of symptoms, such as enlarged lymph nodes, unexplained fevers, night sweats, fatigue, unintentional weight loss • Whole body MRI scanning every 1–2 years, starting at age 12–13	
Colorectal Cancer	• Annual colonoscopy and FIT every 6 months, starting at age 10–12 years	
Breast Cancer	• Annual breast MRI scans, starting at age 18	
Skin Cancer	• Reduce excessive exposure to sunlight • Cover exposed skin • Use a broad-spectrum sunscreen with SPF of 30 with application twice daily and every 2–3 hr if outdoors	
Wilms Tumor	• Awareness of symptoms, such as hematuria and a painless abdominal mass • Abdominal ultrasound every 3 months, starting at diagnosis to age 8	

Cunniff et al. American Journal of Medical Genetics, 2018

MUTYH-associated polyposis (MAP): treatment and surveillance



Xavier Llor, Yale School of Medicine

NCCN guidelines v.2, 2022

Penn Medicine

the orphan disease center

**********NOTICE OF AWARD **********

BLOOM SYNDROME GRANT PROGRAM

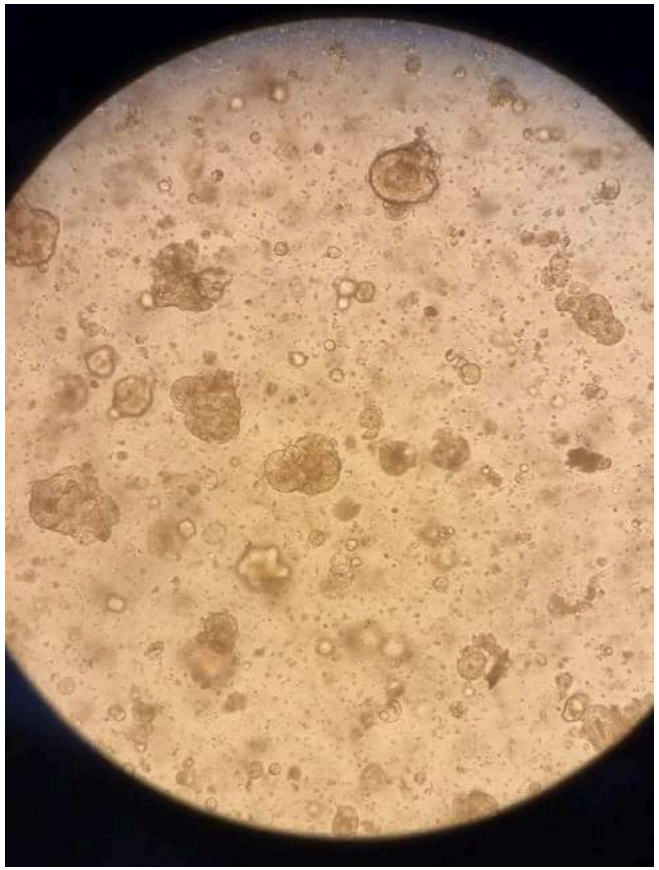
Issue Date: July 27, 2022

Orphan Disease Center
University of Pennsylvania
TRL, Suite 1200
125 S. 31st Street
Philadelphia, PA 19104

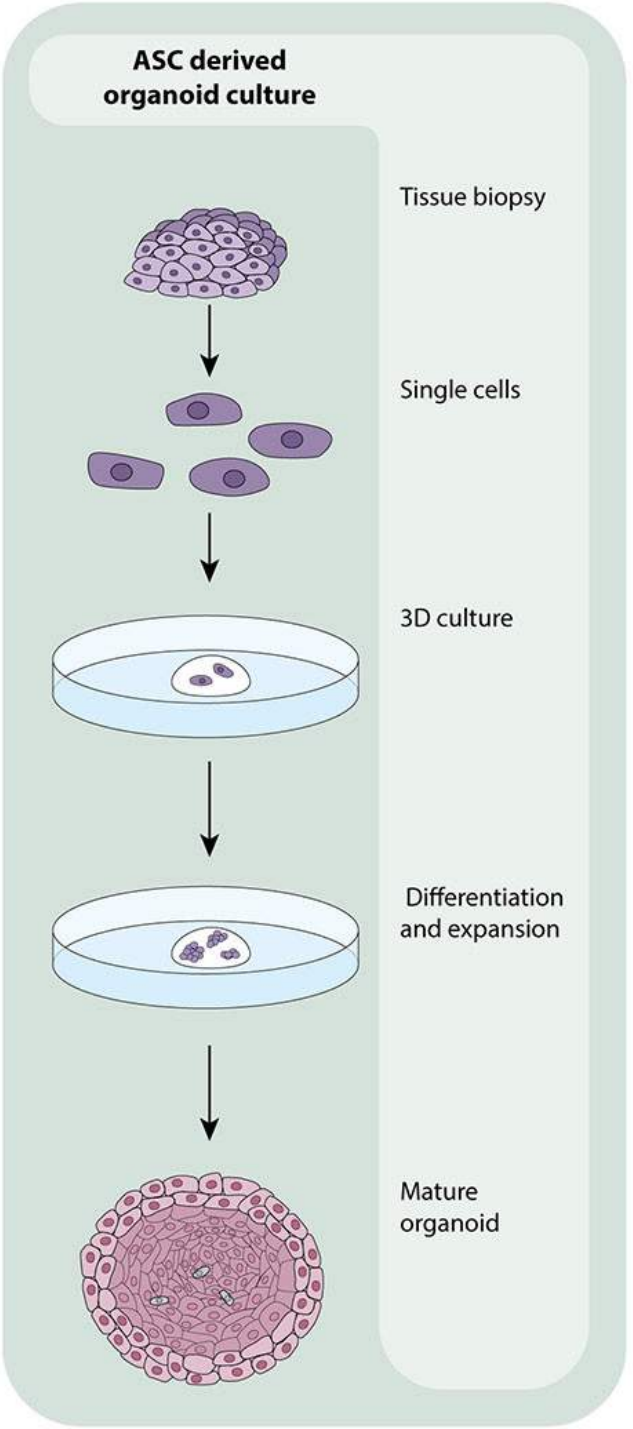
****

Pilot Award Number: **BLOOM-22-001-01**
Principal Investigator: **Nathan Ellis**
Project Title: **Development of Normal and Tumor Organoids from Bloom Syndrome to Evaluate Responses to Pharmacological and Genetic Perturbations**

Cancer Organoid Models: current best method to study human cancer



Human colorectal cancer organoids

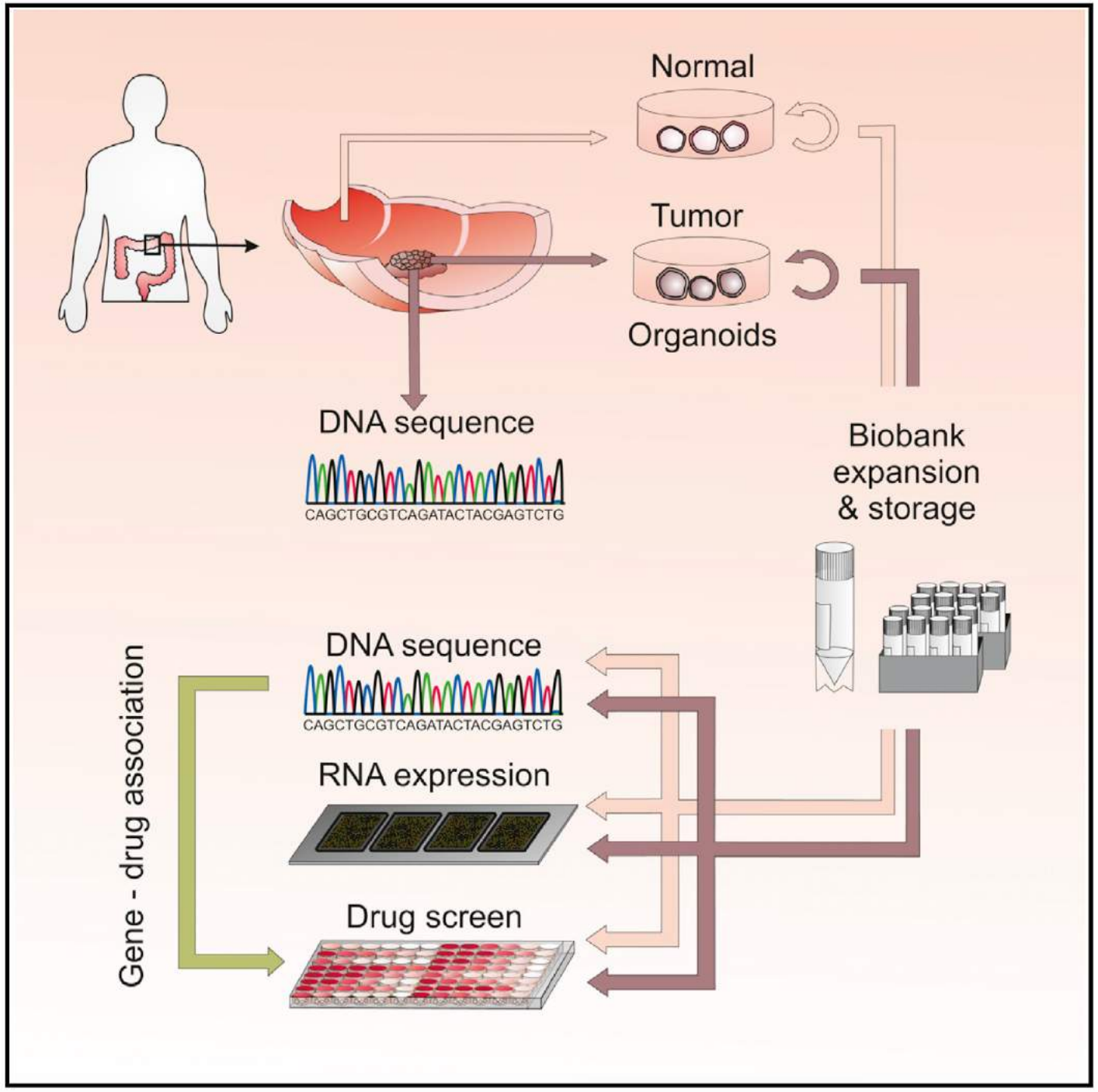


Bloom syndrome organoid biobank

Cancer driver gene somatic mutations

Bulk and single-cell RNA expression profiles

Drug screening platform to identify cancer cell vulnerabilities and host sensitivities



What can you do to help?

- We are making
  - Cancer organoids from any and all types of cancer from surgeries or biopsies
  - Normal tissue organoids from non-involved tissue from surgeries or biopsies
  - Normal and adenoma samples from endoscopies
- To make normal and cancer organoid models, WE NEED FRESH CANCER and NORMAL TISSUES
  - Samples from the GI lab or the surgical suite via pathology must be sent to Ellis lab in Arizona within 24 hours
  - Please alert your surgeon and his team, the BSR, and Nathan. We will coordinate the transport of specimens to the various interested parties
- ORGANOID RESEARCH COULD BE TRANSFORMATIVE FOR TREATING BLOOM CANCERS!

Thank you!!!

2022 Bloom meeting

2008 Bloom meetings

We love you!

Caretaker gene mutations change the mutation rate