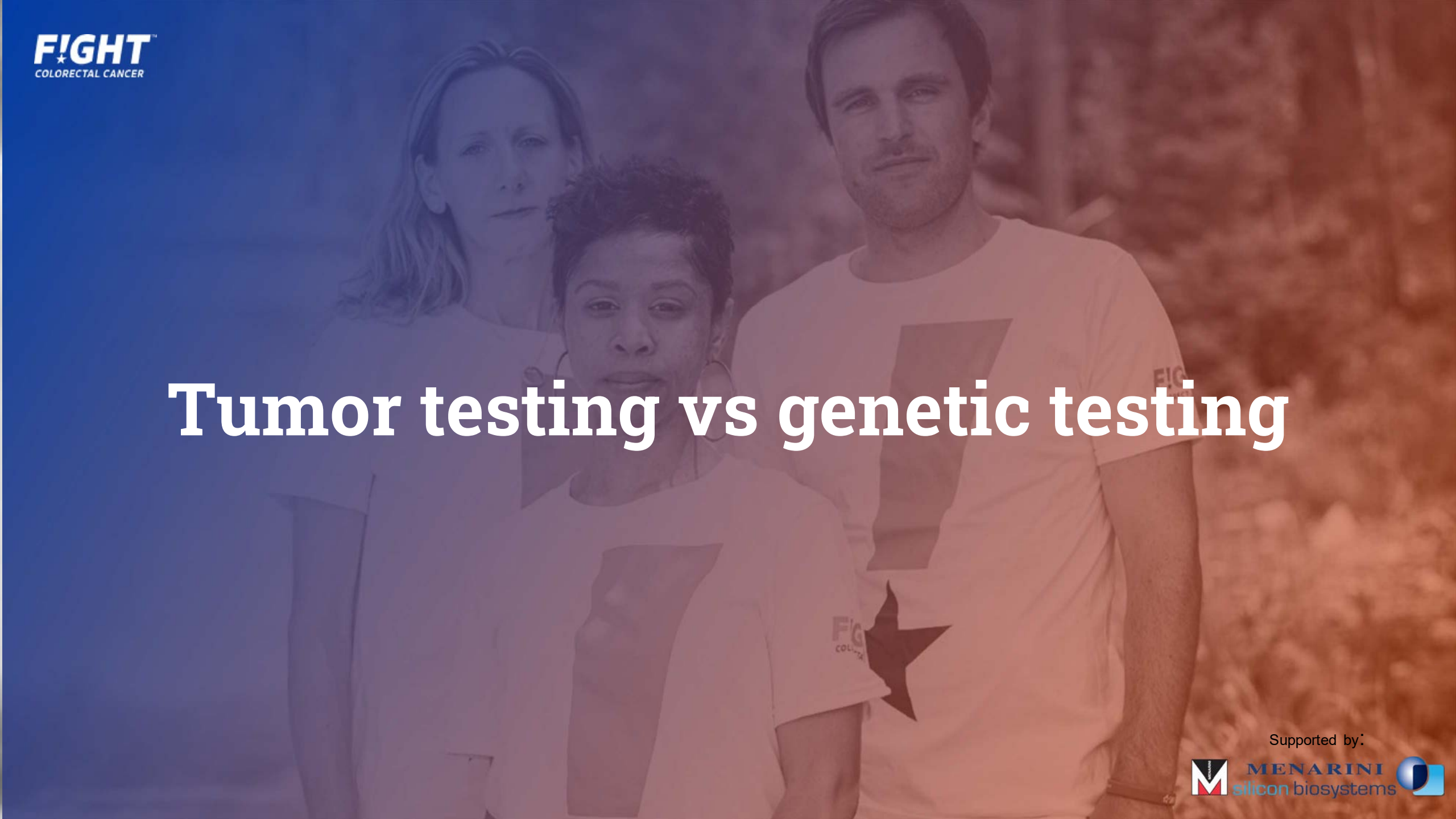
F!GHT™

COLORECTAL CANCER

OUR WEBINAR WILL BEGIN SHORTLY



Tumor testing vs genetic testing

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TODAY'S WEBINAR

01 **QUESTIONS**

Ask a question in the panel on the right side of your screen

02 **WEBINAR ARCHIVE**

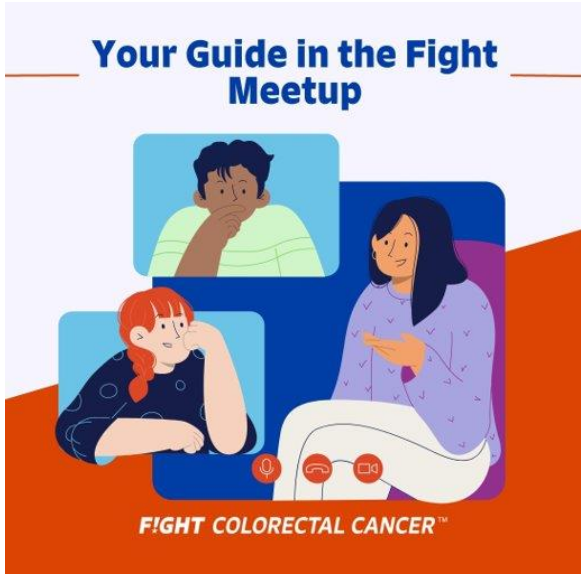
Watch a recording of this webinar on the Fight CRC website. Visit FightCRC.org

03 **TWEET ALONG!**

Follow along on Twitter. Use the hashtag #CRCWebinar

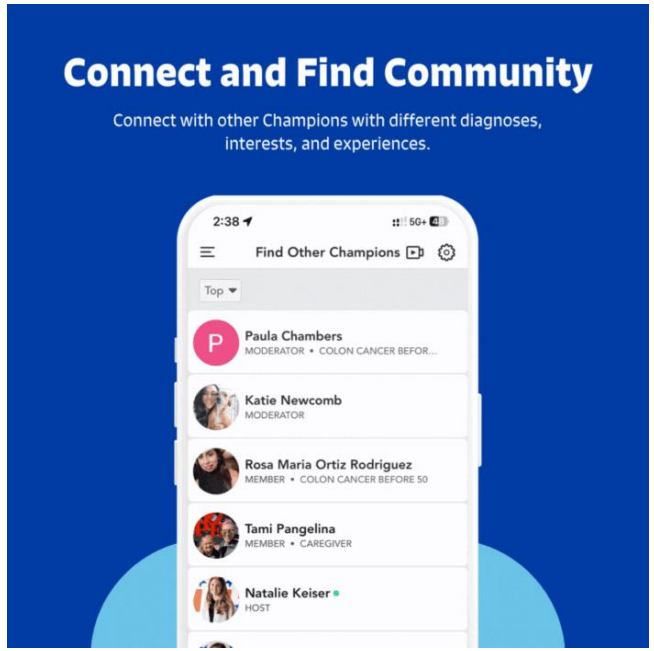
Resources

Fight CRC offers a wide variety of resources for those touched by colorectal cancer. Visit FightCRC.org to view, download, and order the latest resources.



Dedicated virtual meetup spaces

Free Resources



Community of Champions App

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The information and services provided by Fight Colorectal Cancer are for general informational purposes only. The information and services are not intended to be substitutes for professional medical advice, diagnoses or treatment.

If you are ill, or suspect that you are ill, see a doctor immediately. In an emergency, call 911 or go to the nearest emergency room.

Fight Colorectal Cancer never recommends or endorses any specific physicians, products or treatments for any condition.

FIGHT COLORECTAL CANCER

TODAY'S PRESENTERS

Heather Hampel, MS, CGC

Fight CRC Medical Advisory Board Member
Genetic Counselor and Researcher
Associate Director, Division of Clinical Cancer Genomics
Professor, Department of Medical Oncology & Therapeutics Research

Al Benson III, MD, FACP, FACC, FASCO

Fight CRC Medical Advisory Board Member
Professor of Medicine
Associate Director for Cooperative Groups
Robert H Lurie Comprehensive Cancer Center of Northwestern University

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Cancer Genetic Counseling & Testing

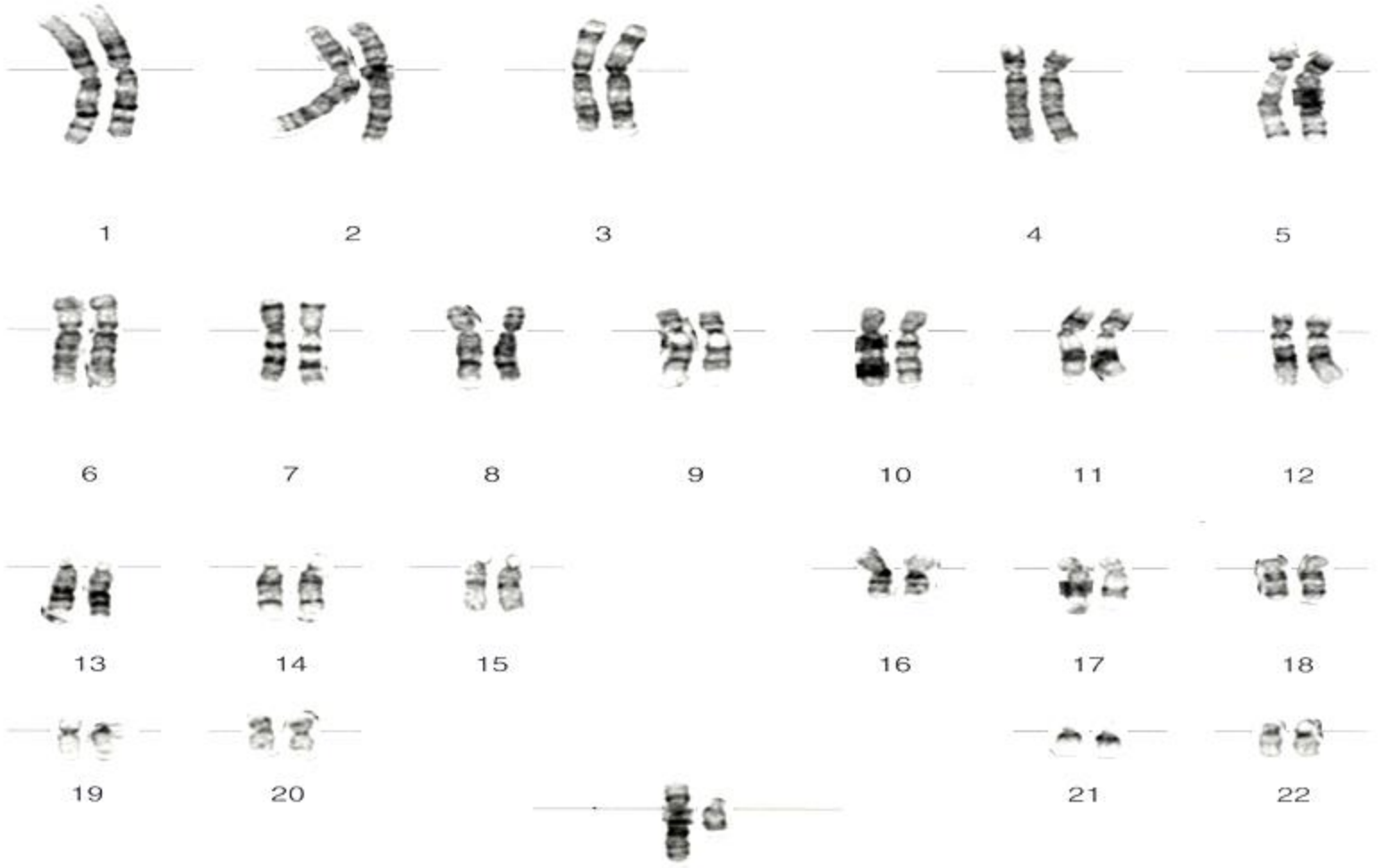
Heather Hampel, MS, LGC

Associate Director, Division of Human Genetics

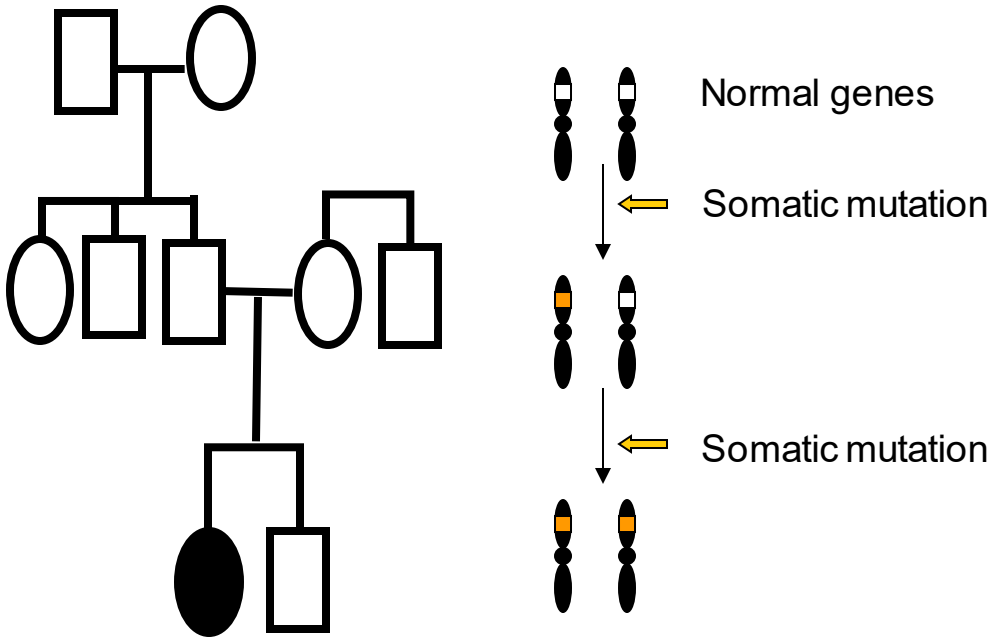
Professor, Department of Internal Medicine

hhampel@coh.org: Twitter @HHampel1

Normal Male Karyotype

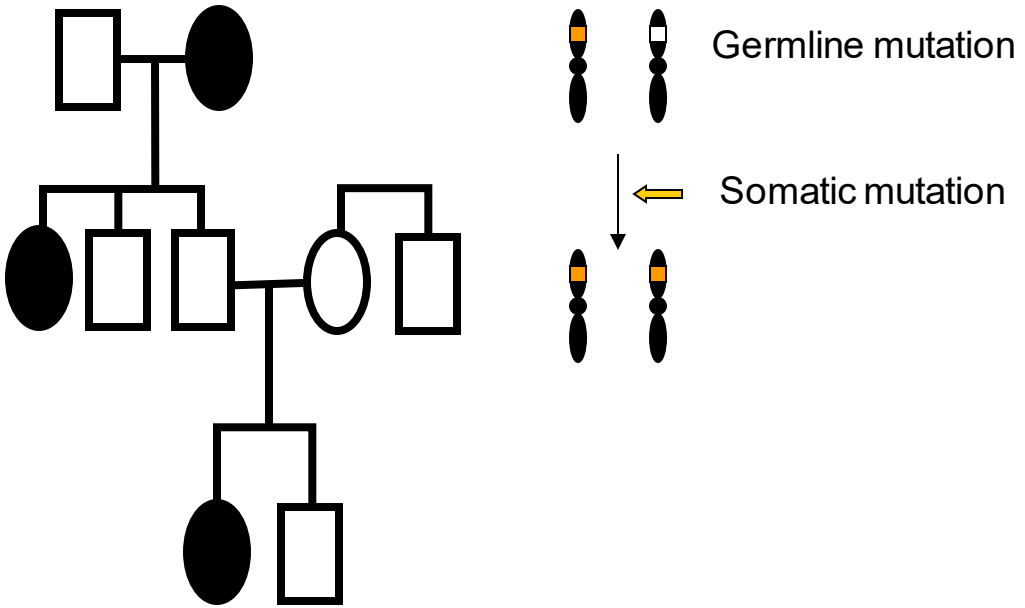


Sporadic



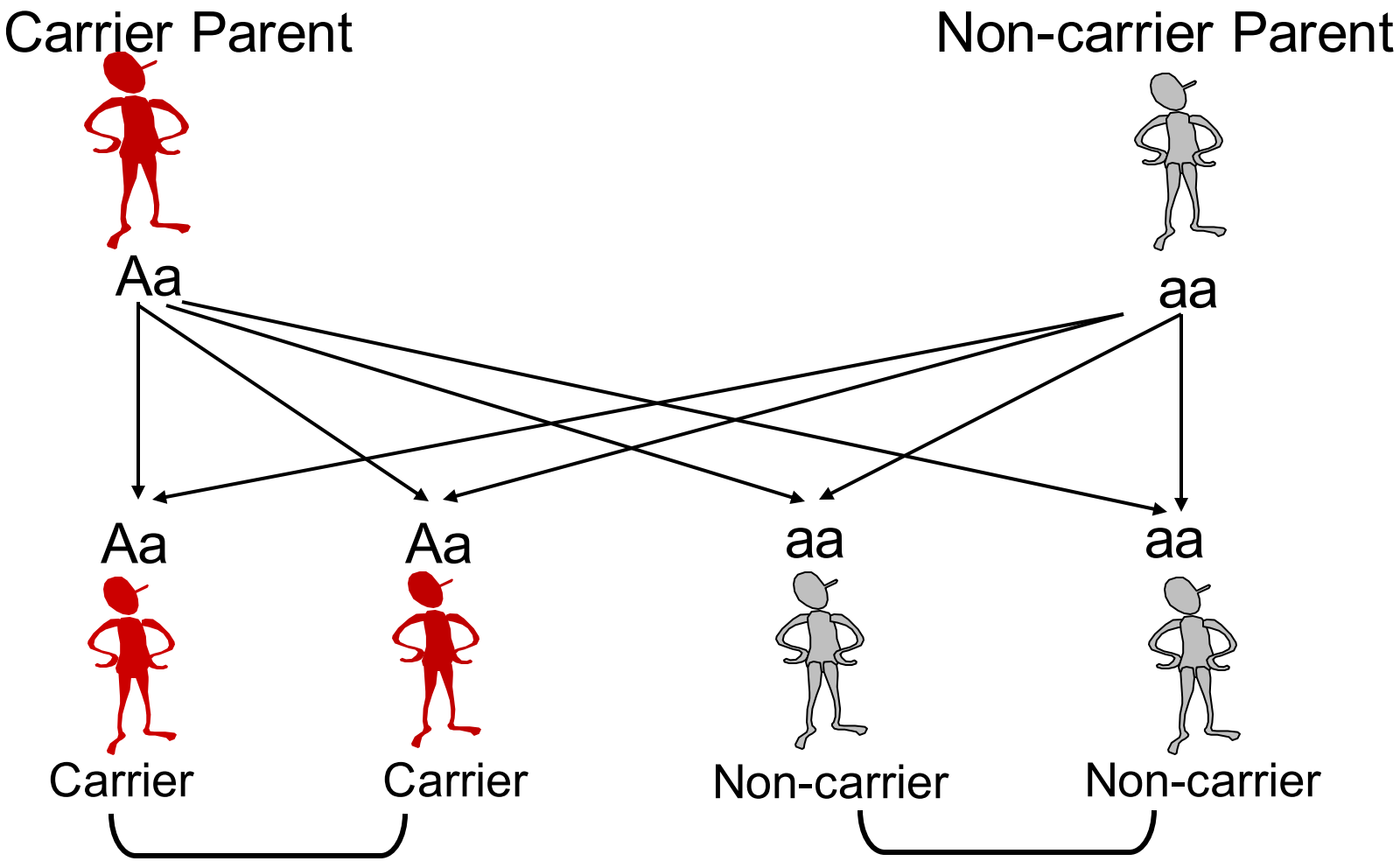
- Later age at onset (60s or 70s)
- Little or no family history of cancer
- Single or unilateral tumors

Inherited

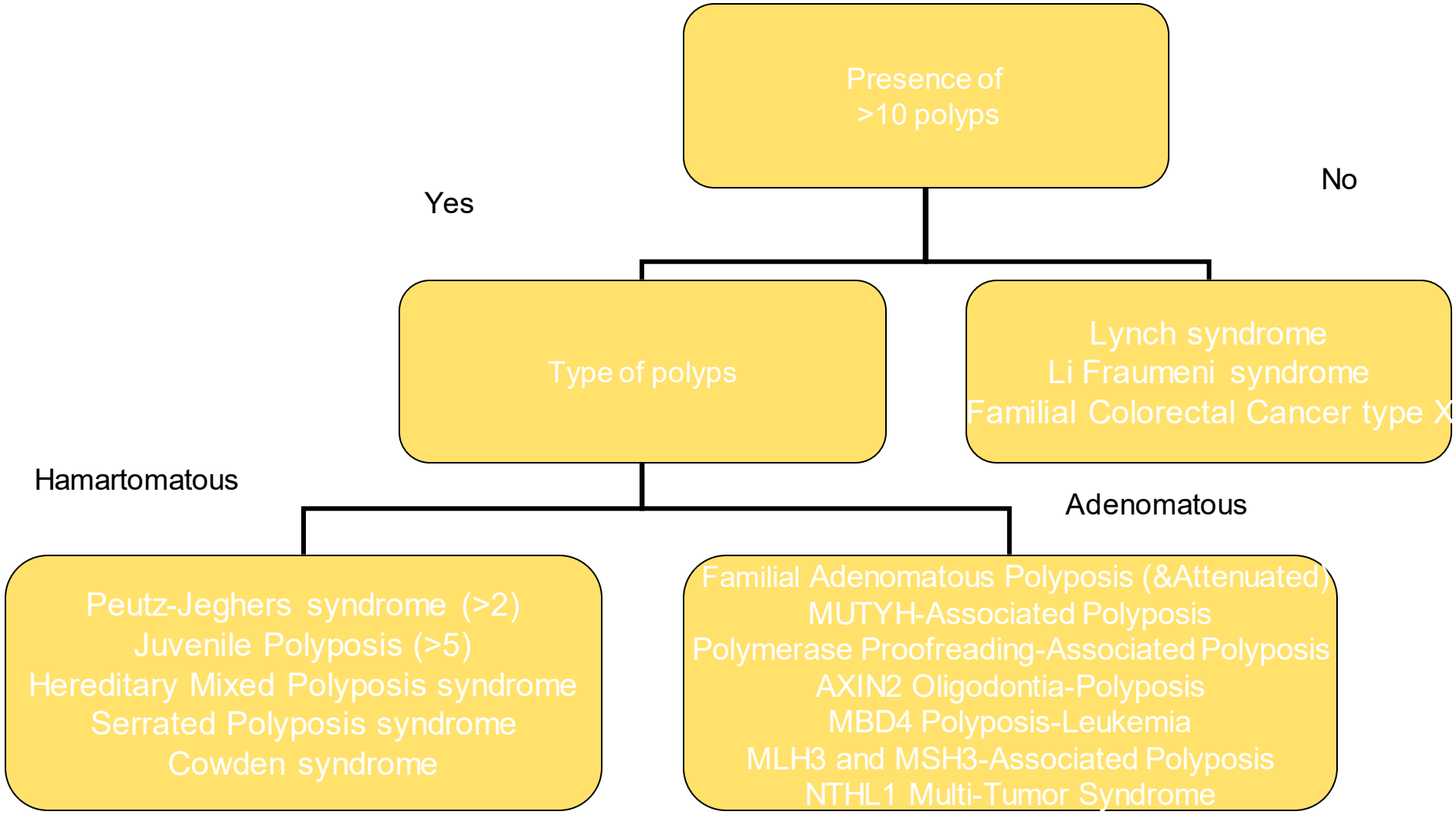


- Early age at onset (<50)
- Multiple generations with cancer
- Bilateral or multiple primary cancers
- Clustering of certain cancers (i.e. colon/uterine)

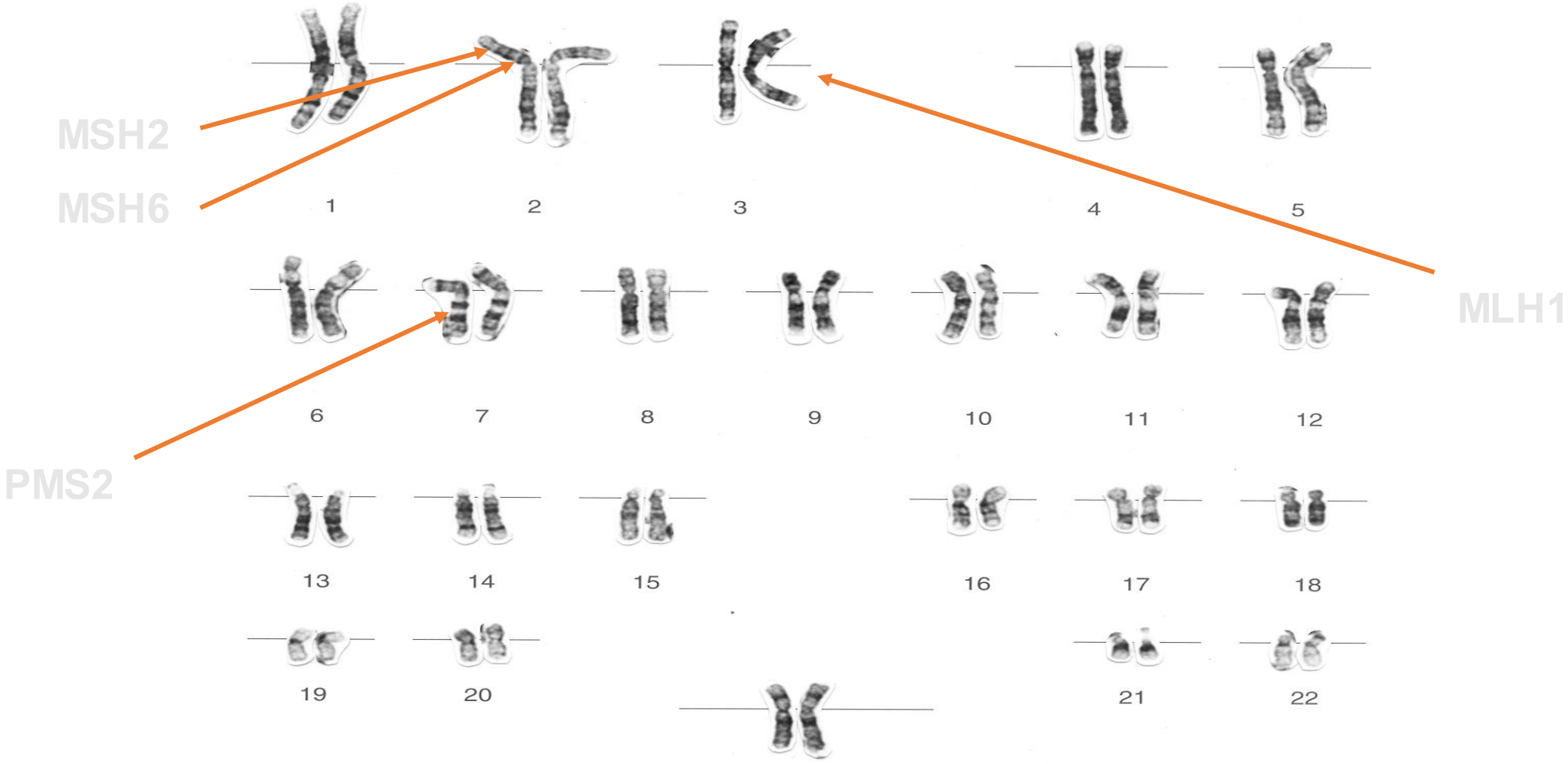
Autosomal Dominant Inheritance



Flowchart for Hereditary Colon Cancer Differential Diagnosis

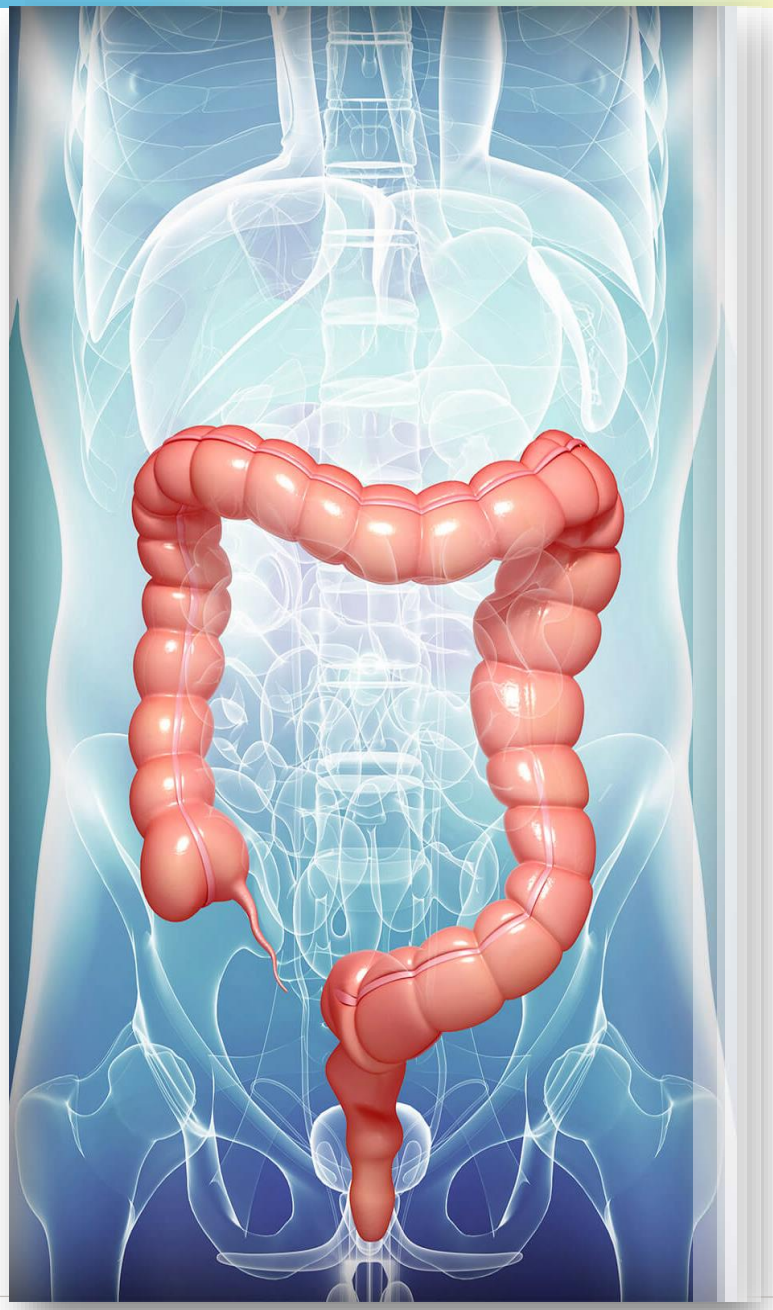


Lynch Syndrome



Lynch Syndrome

- Over 1.2 million individuals in the United States have Lynch syndrome
- Inherited condition that causes high risks for colorectal cancer, endometrial cancer, and other cancers
- Preventable cancers with early and more frequent screening
- 95% of affected individuals do not know they have Lynch syndrome



Lynch Syndrome Cancer Risks

Cancer Type	MLH1 and MSH2	MSH6	PMS2	General Public
Colon cancer	33%-61%	10%-44%	8.7%-20%	4.2%
Endometrial cancer	21%-57%	16%-49%	13-26%	3.1%
Stomach	0.2%-9%	≤1-7.9%	ND	< 1%
Ovarian	4%-38%	≤1%-13%	1.3-3%	1.3 %

NCCN Guidelines Version 1.2022; Genetic/Familial High-Risk Assessment: Colorectal

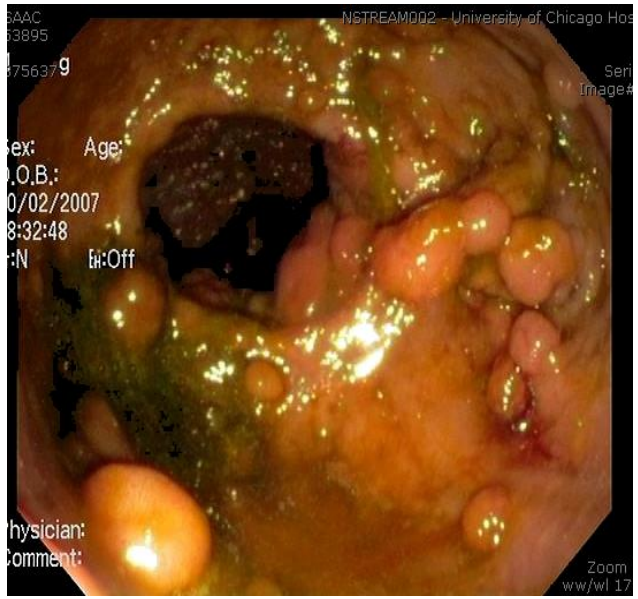
Lynch Syndrome Management

Intervention	Recommendation
Colon Cancer	MLH1 & MSH2: Colonoscopy every 1-2 y beginning at age 20-25 (or 2-5 years younger than earliest diagnosis if <25 MSH6 & PMS2: Colonoscopy every 1-2 y beginning at age 30-35 (or 2-5 years younger than earliest diagnosis if <25
Endometrial Cancer	Education regarding symptoms Consideration of hysterectomy after childbearing Endometrial biopsy every 1-2 y beginning at age 30-35 can be considered
Ovarian Cancer	Education regarding symptoms TVUS and CA-125 surveillance could be considered by no evidence of efficacy BSO can be considered after childbearing
Gastric & Small Bowel Cancer	EGD every 2-4 y starting at age 40

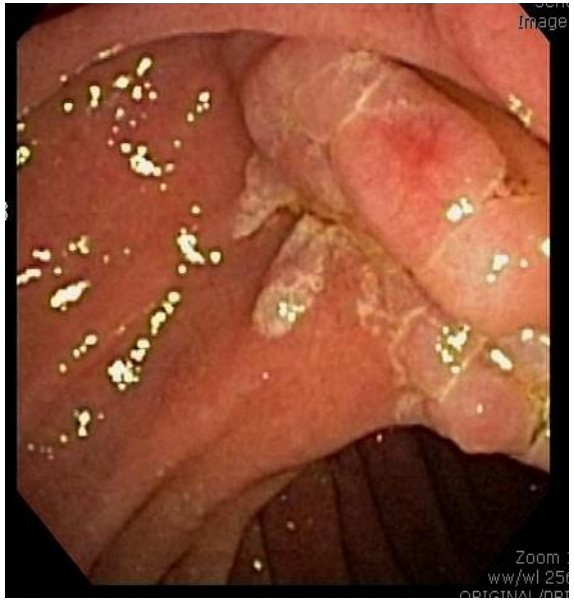
Lynch Syndrome Management

Cancer Type	**Recommendation**
Urothelial cancer	No clear evidence to support. Consider in select individuals with a family history of urothelial cancer and individuals with *MSH2* pathogenic variants (especially males). Annual urinalysis starting at age 30-35
Pancreatic Cancer	Consider pancreatic cancer screening beginning at age 50 or 10 years younger than the earliest dx in family. Annual contrast-enhanced MRI/MRCP and/or EUS with consideration of shorter screening intervals for individuals found to have worrisome abnormalities on screening. Most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any intervention.
Prostate Cancer	General population screening
Breast Cancer	General population screening
Brain Cancer	Annual physical/neurologic examination starting at age 25-30y
Reproductive Risks	Advise about prenatal diagnosis and assisted reproduction including preimplantation genetic testing Advise about risk of rare recessive syndrome called CMMR deficiency if both partners are carriers of pathogenic variants in the same MMR gene

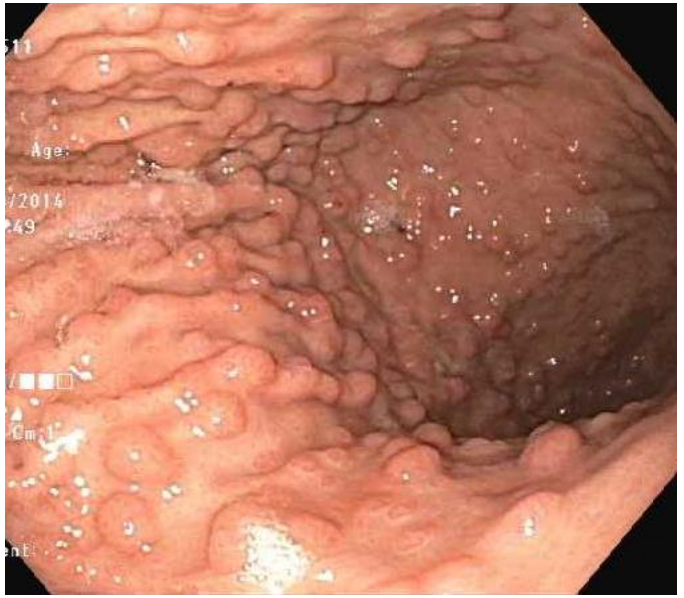
Familial Adenomatous Polyposis (FAP)



Colorectal polyps*



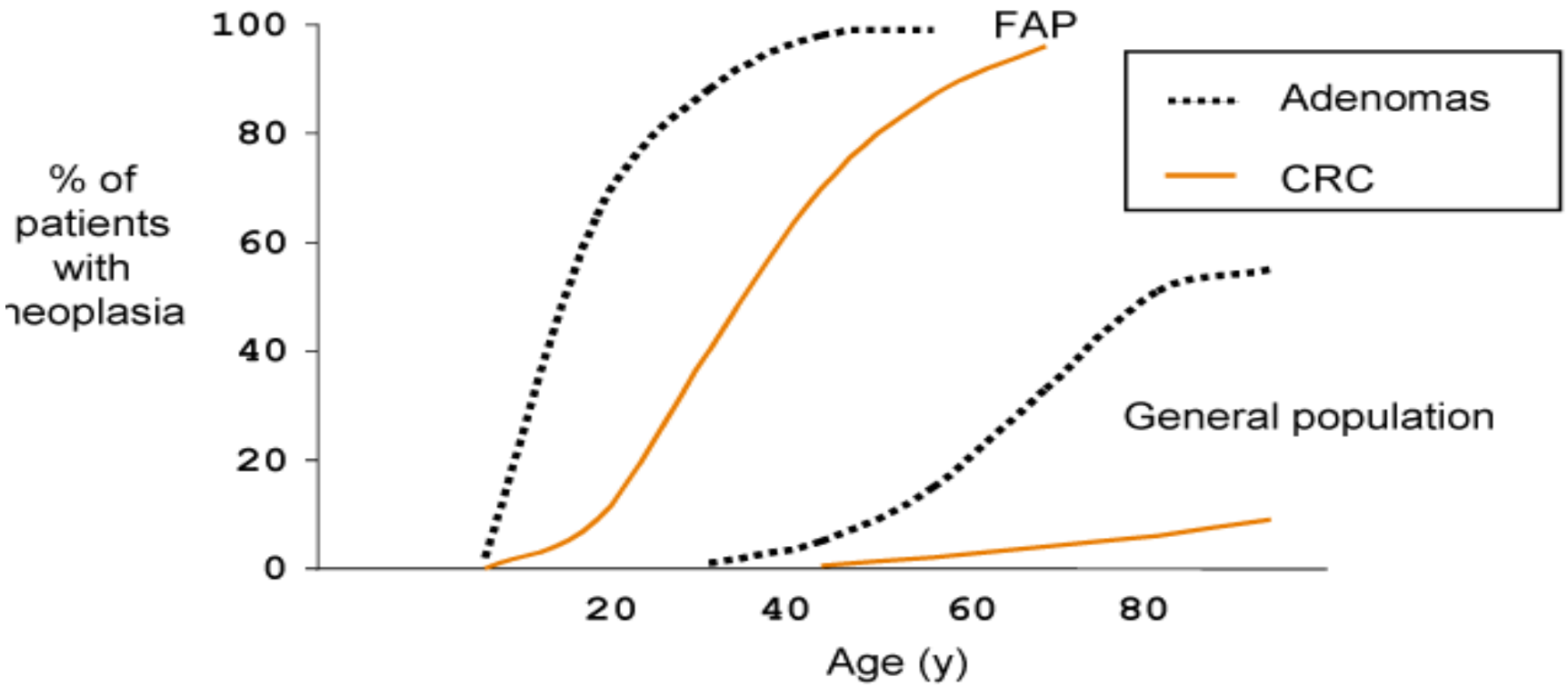
Duodenal polyp*



Gastric fundic gland polyps

* Malignant potential

FAP: Age and Development of Adenomas and CRC



Adapted with permission from the American Gastroenterological Association, Clinical Teaching Project Unit, Colorectal Neoplasia II: Genetics and Prevention.

ASCO®

FAP: Extraintestinal Features

Benign lesions	Malignant lesions
Congenital hypertrophy of the retinal pigmented epithelium (CHRPE) (70-80%)	Papillary thyroid cancer (2-3%)
Epidermoid cysts (50%)	Brain tumor (<1%)
Osteoma (50-90%)	Hepatoblastoma (1%)
Desmoid tumor (10-15%)	Gastric (0.6%)
Supernumerary teeth (11-27%)	
Adrenal gland adenomas (7-13%)	

Adapted from Vasen HFA et al *Gut* 2008

FAP: Genetics

- *APC* gene
  - 100% of individuals with a mutation develop GI polyps
- Autosomal dominant inheritance
  - ~30% de novo mutations
  - Somatic mosaicism has been described (testing blood or saliva is negative but testing multiple colon polyps is positive)
- > 800 *APC* mutations described
- Most mutations result in truncated APC protein
- Genotype-phenotype correlations
- Testing should always include MGPT of all known polyposis genes due to overlapping phenotype

FAP: Management

- Genetic testing for those with clinical FAP and family members of FAP
- ?Testing in children <5 years
    - Hepatoblastoma screening
- Sigmoidoscopy/colonoscopy starting age 10-12
- Appropriately timed colectomy
    - Subtotal colectomy with ileorectal anastomosis
    - Total proctectomy w/ ileo-pouch-anal anastomosis
- Upper endoscopy with side-viewing exam every 1-5 years depending on polyp burden
    - Spigelman classification
- Annual thyroid ultrasound

Vasen HFA et al *Gut* 2008

MUTYH-Associated Polyposis (MAP)

- Oligopolyposis (30-100 adenomas)
  - Accounts for 40% of AFAP mutation negative
- **Autosomal recessive**
- Mixed polyposis
  - adenomas, sessile serrated polyps and hyperplastic polyps
- 93-fold excess risk of CRC in biallelic carriers
- CRC not necessarily associated with polyps
- Controversial: Slight Increase in risk of CRC for heterozygous carriers (carrier rate in US is 1:100)

Genetic Testing Results – 1,058 Colorectal Cancer Patients

- 9.9% had a pathogenic mutation in one of 25 cancer genes
- 3.1% had Lynch syndrome
- 7% had non-Lynch syndrome gene mutations including:
  - 2.2% had mutations high-penetrance genes (5 *APC*, 3 biallelic *MUTYH*, 11 *BRCA1/2*, 2 *PALB2*, 1 *CDKN2A* and 1 *TP53*)
  - 3.6% had mutations in moderate-penetrance CRC risk genes (19 *MUTYH* heterozygotes, 17 *APC* I1307K, and 2 *CHEK2*)
- Age at dx, family history of CRC, nor personal history of other cancers significantly predicted the presence of mutations in non-Lynch syndrome genes

Yurgelun M, et al. J Clin Oncol. 2017;35:1086-95.

Take Home Messages

- Major Risk Factors:
  - Early age of diagnosis (under age 50)
  - More than one cancer in same patient
  - Three cases total of the same or related cancers on one side of the family
  - >10 colon polyps
- Genetic Testing Can Be Helpful for 3 Reasons:
  - Could affect cancer treatment
    - Immunotherapy for Lynch syndrome mutations
  - Can help determine if individual is at increased risk for cancer and needs intensive cancer surveillance and prevention
  - Can help determine which family members are at risk for cancer so they can get intensive cancer surveillance and prevention

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Biomarker (or tumor) testing

Biomarkers can include proteins made in response to the cancer, or changes (mutations) in the DNA of cancer cells. Biomarkers are derived from tumor cells or DNA in the bloodstream.

While biomarkers may involve changes in the DNA of your cells, getting your biomarkers tested *is not* the same as having your genetics tested.

Genetic testing looks for mutations inherited from your biological parents that may predispose you to certain cancers. Biomarker testing looks specifically at your tumor cells to determine their characteristics.

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Who needs biomarker testing?

All colorectal cancer patients need their biomarkers tested. However, not all patients will need the same testing performed.

The biomarkers that your physician decides to test for are determined by the type of cancer you have and the stage that you are diagnosed at.

Biomarker testing is standard of care.

All CRC patients should be tested for their mismatch repair status, known as MSI-H or dMMR.

Stage 0 & Stage I	Your tumor needs to be tested for MSI-H/dMMR. You need your CEA checked. If your stage I cancer recurs, you need to be tested for biomarkers for metastatic disease.
Stage II	Your tumor needs to be tested for MSI-H/dMMR. You need your CEA checked. Ask your doctor if there is a role for ctDNA testing. If your stage II cancer recurs, you need to be tested for biomarkers for metastatic disease.
Stage III	Your tumor needs to be tested for MSI-H/dMMR. You need your CEA checked. Ask your doctor if there is a role for ctDNA testing. If your stage III cancer recurs, you need to be tested for biomarkers for metastatic disease.
Stage IV / Metastatic Disease	Your tumor needs to be tested for MSI-H/dMMR. You need to know which side your tumor formed (Right or Left). You need your CEA checked. Ask your doctor if there is a role for ctDNA testing. Your tumor needs to be tested for genetic alterations, including KRAS, NRAS, and BRAF mutations, HER2 amplification, and NTRK fusions.

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What do your biomarkers mean?

Sample **Biomarker Report**

Colon adenocarcinoma (CRC)

PATIENT	PHYSICIAN	SPECIMEN
Colon adenocarcinoma (CRC)		

Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
KRAS wildtype (codons 12 & 13)	Erbitux® (Cetuximab)
KRAS/NRAS wildtype (codons 12, 13, 59, 61, 117, & 146 in exons 2, 3, & 4)	Vectibix® (Panitumumab)
Tumor Mutational Burden (TMB) ≥10 Muts/Mb	Keytruda® (Pembrolizumab)

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite status MSI-High §
Tumor Mutational Burden 47 Muts/Mb §
ASXL1 G646fs*12
ATR I774fs*5
BCOR E623*
BCORL1 P1681fs*20
BRCA2 T3033fs*29
CREBBP R1446C
CTNNB1 R449C
CUL3 R733*
ERBB3 V104M
HNF1A P291fs*51
MAP2K1 (MEK1) K57N
MLH1 Q445*
MLH1 E663D
MLL2 A2205fs*59
MLL2 P648fs*283
MSH3 K383fs*32
MSH6 R361H
MSH6 F1088fs*5
PDGFRB V823I
SPEN A2251fs*102
SPEN R806fs*14
SPEN I1052fs*40

Biomarkers can tell you a lot about your cancer.

Some biomarkers can tell you what specific subset of a given cancer that you have (diagnostic).

Some biomarkers can help you guess about the estimated course of the cancer if it goes without treatment (prognostic).

Some biomarkers can predict how your tumor will or will not respond to certain treatments (predictive).

Results of biomarker testing will be laid out in a report, similar to the one on the left.

Biomarker testing is an evolving field. Not all changes or mutations detected by biomarker testing will be actionable.

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What do your biomarkers mean?

There are many different biomarkers that have been studied in relation to colorectal cancer.

Some are more common than others, and not all biomarkers need to be tested for in every situation.

For instance, some biomarkers will only be tested for in stage IV (metastatic) disease.

The most common (and most studied) biomarkers in CRC are shown at the right.

Visit fightcolorectalcancer.org for more information about specific biomarkers.

- **MSI-H/dMMR**
- **Sidedness**
- **KRAS**
- **NRAS**
- **BRAF**
- **HER2**
- **EGFR**
- **CEA**
- **TRK Fusions**
- **DPD**
- **ctDNA**
- **PD-L1 Pathway**
- **WNT Pathway**
- **Tumor Mutational Burden (TMB)**
- **RET**
- **VEGF**
- **CTC**

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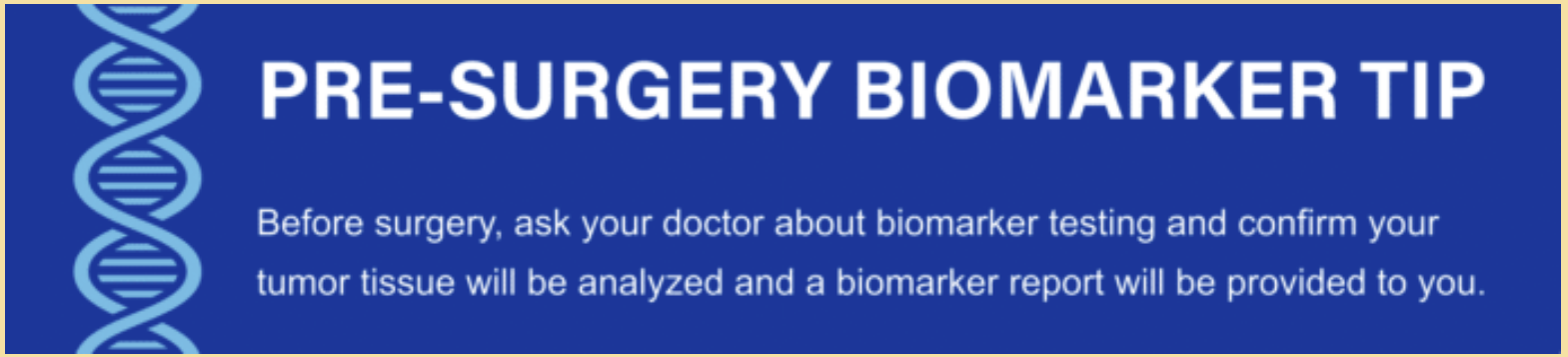
How do I know if my biomarkers have been tested?

You need to have a discussion with your care team to determine if biomarker testing has been ordered or will be performed and when results will be available. Some results may take 2-4 weeks to receive.

If you know your biomarkers have been tested, but are unsure of the results, make sure to discuss this with your physician so you can better understand your treatment plan.



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How does biomarker testing work?

There are multiple biomarker tests available that can be run on either your tumor or your blood. Tests may look for only one biomarker, or they may look for many.

- Single biomarker tests look at a single gene
- Multigene/panel tests look at multiple genes
- Whole-exome sequencing looks at all protein coding regions of genes in your cancer's genome
- Whole-genome sequencing (next generation or NGS) looks at all the DNA in your cancer. This allows for multiple genes to be tested at the same time.
- Tumor mutational burden looks at the total number of genetic changes in your cancer

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How is biomarker testing performed?

There are two ways in which biomarker testing is performed:

- Tumor biopsy
- Liquid biopsy

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Tumor biopsy

A tumor biopsy is a surgical procedure in which a piece of your tumor is removed, and then examined by a pathologist to determine, among other things, the relevant biomarkers present in your cancer.

Tumor biopsies may be "incisional", where only a sample of the tumor tissue is removed for evaluation, or "excisional", where the entire tumor is removed, and tissue is taken for evaluation afterwards.

A biopsy may also be performed using "fine needle aspiration" (FNA), in which a thin needle is used to collect a sample of tissue from the tumor.

Tumor tissue should be stored by the lab, so biomarker testing can be performed in the future, if needed.

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Liquid biopsy

A liquid biopsy is different from a traditional tumor biopsy in that it is performed using blood acquired from a blood draw.

Liquid biopsies are primarily looking for two things: circulating tumor DNA (ctDNA), which are segments of cell free DNA released by tumor cells, and circulating tumor cells (CTCs), which are whole tumor cells that are circulating in the bloodstream.

ctDNA is more commonly utilized than CTCs.

ctDNA and CTC are different, but complimentary tests.

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What are circulating tumor cells (CTCs)?

- They may be single or groups of **whole, intact** cancer cells that are shed by a tumor, circulating in the patient's bloodstream.
- They can be detected and counted by testing following a simple blood draw.
- CTCs are whole cancer cells. As such, they may provide a more complete picture of a tumor's characteristics than just ctDNA alone.
- CTCs in colorectal cancer can be used to detect certain important biomarkers that can impact a patient's treatment.
- Changes in CTC counts throughout treatment can also serve as a predictive indicator for a patient's prognosis.
- Not all tumors necessarily shed CTCs, so CTC testing can be used in addition to ctDNA testing to get a better picture of a patient's condition.
- There is currently one CTC test approved for use in metastatic colorectal cancer.

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What is circulating tumor DNA (ctDNA)?

- Circulating tumor DNA is cell-free DNA shed by dying or damaged tumor cells. Cell-free means that these are bits of DNA that are circulating freely in the bloodstream without the other parts of the tumor cell.

- Like CTCs, ctDNA is detected using a blood sample obtained by a simple blood draw.

- ctDNA may be used to detect certain biomarkers, but this depends on the type of test being used.

- ctDNA may also offer prognostic information throughout the course of a patient's treatment.

- There are several ctDNA tests approved for use in colorectal cancer.

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CTC and ctDNA tests

- Both CTC and ctDNA tests are performed in your doctor's office. A blood sample will be taken, and then sent to a lab for analysis. Analysis time will differ based on the specific test that is chosen.

- Your sample will be analyzed by the lab, and a report will be provided to your physician, who will discuss the results with you and what they mean for your treatment.

- In addition to informing your biomarker status, both CTC and ctDNA tests can provide a wealth of additional information, such as prognostic information, tumor mutational burden, minimal residual disease, and insight into treatment options.

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QUESTION AND ANSWER

Type in your questions on the panel on the right side of your screen

Fight Colorectal Cancer's *Biomarker Brochure*

Our *Biomarker Brochure* outlines information your biomarker report should contain why biomarker testing is so important when looking at your treatment options. No matter what part of the colorectal cancer continuum you are in, it's important to know your tumor's biomarkers.

Download or order this brochure at **fightcrc.org/resources**

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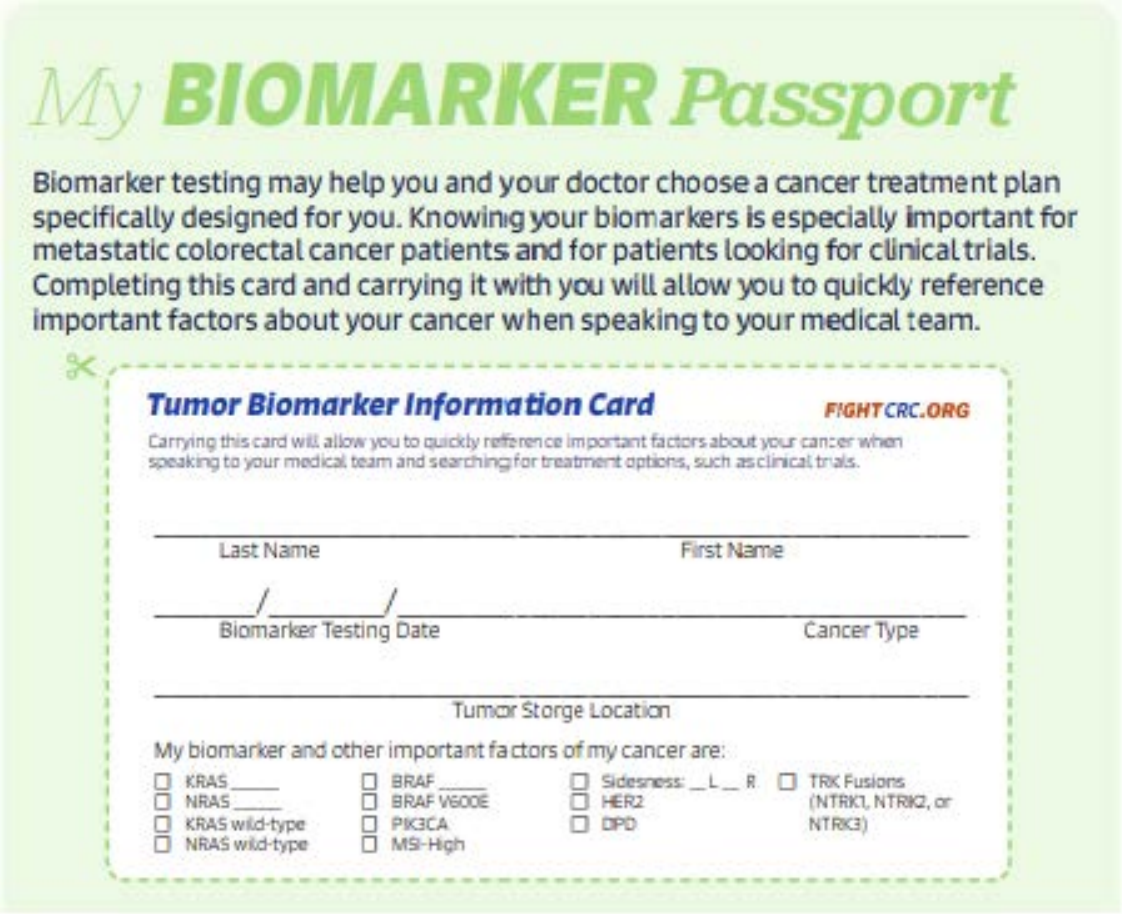
Biomarker Passport



My BIOMARKER Passport

Biomarker testing may help you and your doctor choose a cancer treatment plan specifically designed for you. Knowing your biomarkers is especially important for metastatic colorectal cancer patients and for patients looking for clinical trials. Completing this card and carrying it with you will allow you to quickly reference important factors about your cancer when speaking to your medical team.

Tumor Biomarker Information Card FIGHTCRC.ORG

Carrying this card will allow you to quickly reference important factors about your cancer when speaking to your medical team and searching for treatment options, such as clinical trials.

Last Name First Name

Biomarker Testing Date Cancer Type

Tumor Storge Location

My biomarker and other important factors of my cancer are:

- ☐ KRAS ____
- ☐ NRAS ____
- ☐ KRAS wild-type
- ☐ NRAS wild-type
- ☐ BRAF ____
- ☐ BRAF V600E
- ☐ PIK3CA
- ☐ MSI-High
- ☐ Sidedness: __L __ R
- ☐ HER2
- ☐ DPD
- ☐ TRK Fusions (NTRK1, NTRK2, or NTRK3)

Included in every *Biomarker Brochure* is our handy Biomarker Passport. This perforated card is intended to be removed from the brochure and kept with you. Filling out and keeping this card will allow you to quickly reference important information about your cancer when speaking with your medical team.

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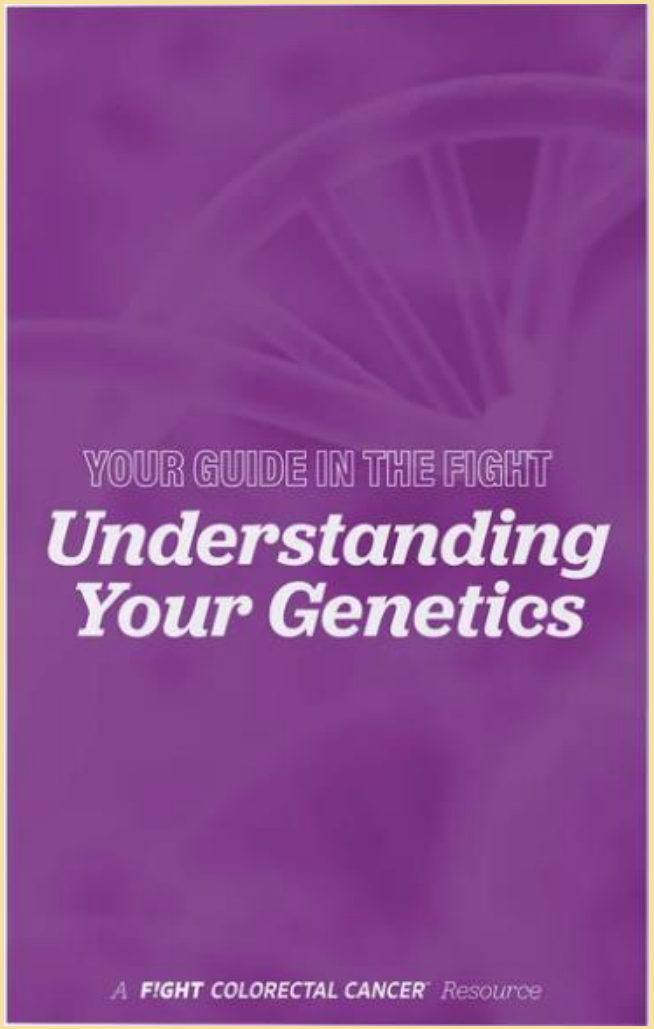
Fight Colorectal Cancer's *Understanding Your Genetics* Brochure



Learn about the impact of genetics and heredity on colorectal cancer with our *Understanding Your Genetics* brochure. An essential resource to help patients understand their risk and options, it covers the emerging field of genetic testing, its efficacy and limitations, and the guidelines for testing.

Download or order this brochure at
fightcrc.org/resources

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Fight Colorectal Cancer Mission

We FIGHT to cure colorectal cancer and serve as relentless champions of hope for all affected by this disease through informed patient support, impactful policy change, and breakthrough research endeavors.

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THANK YOU