# Multidisciplinary Clinic for High-Risk GI Cancers

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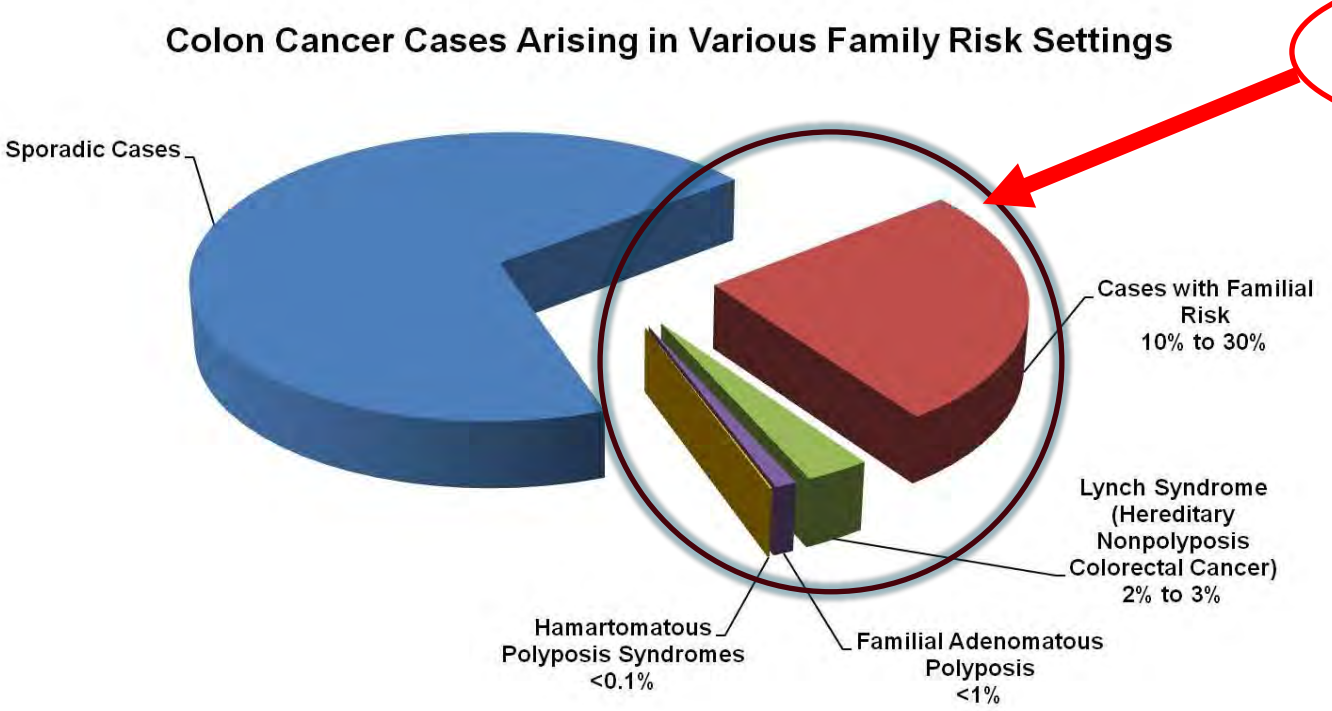
# Disclosures

We do not have actual or potential conflicts of interest in relation to this presentation

# Agenda

- Review GI Cancer Risks
- Introduce Cancer Risk and Prevention Multidisciplinary Clinic
- Case Discussions

# Identifying Those at High Risk




**Who should we be thinking about**

- Young onset colon cancer
- Family history
- Universal testing & follow-up
- Cumulative colonic adenomas
- Hamartomatous polyps
- Numerous/large serrated polyps

Burt, R. *Gastroenterology* 2000. 119, 3: 837-853
Kupfer & Burke. *Am J Gastro* 2020. 115(1): 1-4

# Young Onset Colon Cancer (YOCRC)

2022 ACG Syeed et al.
Evaluate the rate of referral to genetic counseling
Uptake and outcome of germline testing in YOCRC patients

Table 1. Demographics, Referral to and Uptake of Genetic Counseling and Testing and Outcome of Genetic Testing

| Number of patients with YOCRC<br>Demographics | 793<br>N (%) | Mean (SD) |
|---|---|---|
| Age | | 41.9 (6.8) |
| Sex | | |
| Male | 457 (57.6) | |
| Female | 336 (42.4) | |
| Race | | |
| White | 684 (86.3) | |
| Black | 72 (9.1) | |
| Other | 37 (4.7) | |
| Family History of CRC | | |
| Yes | 280 (40.2) | |
| No | 417 (59.8) | |
| Referral for Genetic Counseling | 445 (56.1) | |
| Attended Genetic Counseling | 390 (87.6) | |
| Underwent Genetic Testing | 376 (96.4) | |
| • Pathogenic Variant Detected | 77 (20.5) | |
| • Variant of Uncertain Significance Detected | 88 (23.4) | |
| • No Variant Detected | 211 (56.1) | |

Referral to GC higher in:
Younger (40y vs 43y)
FH (70% vs 53%)

1 in 5 had a pathologic variant detected

If a referral is made, the majority of patients will attend GC and testing
A care pathway to include referral to multidisciplinary clinic with GC can help mitigate the potential impact of under-referral

# Polyposis Syndromes
# Colorectal Cancer Risk

**Numerous genes to consider**
**Risk is heterogeneous**
**Cancer risk extends beyond the colon**

**Table 5. Cumulative risks of colorectal cancer in hereditary colorectal cancer syndromes**

| Syndrome | Gene | Risk | Average age of diagnosis (years) |
|---|---|---|---|
| Sporadic cancer | | 4.8% | 69 |
| Lynch syndrome | *MLH1/MSH2* | M: 27–74%<br>F: 22–61% | 27–60 |
| | *MSH6* | M: 22–69%<br>F: 10–30%<br>M/F: 12% | 50–63 |
| | *PMS2* | M: 20%<br>F: 15% | 47–66 |
| Familial adenomatous polyposis (FAP) | *APC* | 100% | 38–41 |
| Attenuated FAP | *APC* | 69% | 54–58 |
| *MUTYH*-associated polyposis | *MUTYH* | 43–100% | 48–50 |
| Juvenile polyposis | *SMAD4*<br>*BMPR1A* | 38–68% | 34–44 |
| Peutz–Jeghers syndrome | *STK11* | 39% | 42–46 |
| Cowden syndrome | *PTEN* | 9–16% | 44–48 |
| Serrated polyposis syndrome | Not known | ~>50% | 48 |

**Table 7. Cumulative risks of extracolorectal cancer in hereditary colorectal cancer syndromes**

| Cancer site | General population risk[a] | Syndrome risk | Average age of diagnosis (years) |
|---|---|---|---|
| *Familial adenomatous polyposis(FAP)* | | | |
| Small bowel (duodenum/periampullary) | <1% | 3–10% | 44<br>50–52[b] |
| Stomach | <1% | <1% | 49 |
| Pancreas | 1.5% | 1.7% | 50[b] |
| Thyroid | 1.1% | 2% | 25–33 |
| Liver (hepatoblastoma) | <1% | 1–2% | Most often occurs in the first 5 years of life |
| Brain/central nervous system | <1% | 1–2% | 15–21 |
| *Attenuated FAP* | | | |
| Small bowel (duodenum/periampullary) | <1% | 4–12% | 60 |
| Thyroid | 1.1% | 1–2% | 26 |
| *MUTYH-associated polyposis* | | | |
| Small bowel (duodenum) | <1% | 4% | 61 [b] |
| Stomach | <1% | 1% | 38 [b] |

Syngal et al. Am J Gastro. 2015; 110:223-262

| Syndrome Mutation | % lifetime risk | Screening/Surveillance interval | Initiation Age |
|---|---|---|---|
| Familial Adenomatous Polyposis (FAP) APC | 100% | High-quality colonoscopy **every 12m.** Surgical referral. Surveillance after colectomy | **10-15 y** |
| Attenuated FAP APC | 69% | High quality colonoscopy **every 1-2 years** (low adenoma burden) Surgical referral (high adenoma burden) | **Late teens** |
| MUTYH-associate Polyposis (MAP) MUTYH | 43-100% | High quality colonoscopy **every 1-2 years** (low adenoma burden) Surgical referral (high adenoma burden) | **No later than 25-30 y** |
| Peutz-Jeghers Syndrome STK11 / LKB1 | Up to 50% | High-quality colonoscopy **every 2–3 y.*** If no polyps, then resume at age 18 y. | **~8-10 y** |
| Juvenile Polyposis Syndrome SMAD4/ BMPR1A | Up to 50% | High-quality colonoscopy with polypectomy: If polyps are found, repeat **every 2–3 y.*** | **~18 y** |
| CHEK2 | 5-10% | High quality colonoscopy screening **every 5 y.** | **40 y **** |
| Cowden PTEN | 9-16% | High quality colonoscopy **every 2 y.** | **15 y** |

* Shorter intervals may be indicated based on polyp size, number, and pathology
** OR 10 y prior to age of first-degree relative's CRC diagnosis when indicated

Greidinger et al. JCO Precision Oncology 2020 :4, 551-556
NCCN Guidelines Version 1.2023
Syngal et al. Am J Gastro. 2015; 110:223-262

# Lynch ≠ Lynch ≠ Lynch

| Site | Estimated Average Age of Presentation | Cumulative Risk for Dx Through Lifetime for Gen Pop | Cumulative Risk for Diagnosis Through Age 80 years | | | |
|---|---|---|---|---|---|---|
| | | | MLH1 | MSH2 EPCAM | MSH6 | PMS2 |
| Colorectal | 44 years | 4.2% | 46%-61% | 33-52% | 10%-44% | 8.7%-20% |

**Risk of colorectal cancer by age 70 in Lynch Syndrome**

| Gene mutation carriers | Risk | Average age of diagnosis (years) |
|---|---|---|
| Sporadic colorectal cancer | 5.5% | 69 |
| *MLH1* and *MSH2* | 22-74% | 27-46 |
| *MSH6* | 10-22% | 54-63 |
| *PMS2* | 15-20% | 47-66 |

Lodewijk et al. Surg Clin North Am. 2015 Oct; 95(5)
NCCN Guidelines Version 1.2023 Lynch Syndrome

# Lynch Syndrome: Risk of extracolonic cancer by age 70

| Cancer | Risk general population | Risk in LS | Average age of diagnosis (years) |
|---|---|---|---|
| Endometrium | 2.7% | | 65 |
| *MLH1/MSH2* | | 14-54% | 48-62 |
| *MSH6* | | 17-71% | 54-57 |
| *PMS2* | | 15% | 49 |
| Stomach | <1% | 0.2-13% | 49-55 |
| Ovary | 1.6% | 4-20% | 43-45 |
| Breast | 12.4% | 5-18% | 52 |
| Prostate | 16.2% | 9-30% | 59-60 |
| Urinary tract | <1% | 0.2-25% | 52-60 |
| Small bowel | <1% | 0.4-12% | 46-49 |
| Pancreas | 1.5% | 0.4-4.0% | 63-65 |
| Hepatobiliary tract | <1% | 0.02-4% | 54-57 |
| Brain/central nervous system | <1% | 1-4% | 50 |
| Sebaceous neoplasm | <1% | 1-9% | n/a |

Lodewijk et al. Surg Clin North Am. 2015 Oct; 95(5)

# Cancer Risk and Prevention Multidisciplinary Clinic

## Welcome to the Cancer Risk and Prevention Clinic

### The first of its kind in Nebraska

This comprehensive clinic is designed to care for individuals who have an increased risk of all types of cancer due to family history, medical and genetic factors, and/or lifestyle influences. Our team – who are specially trained in cancer genetics – includes providers from medical oncology, surgical oncology, gynecology, gastroenterology, endocrinology, urology, dermatology, radiology and genetics.

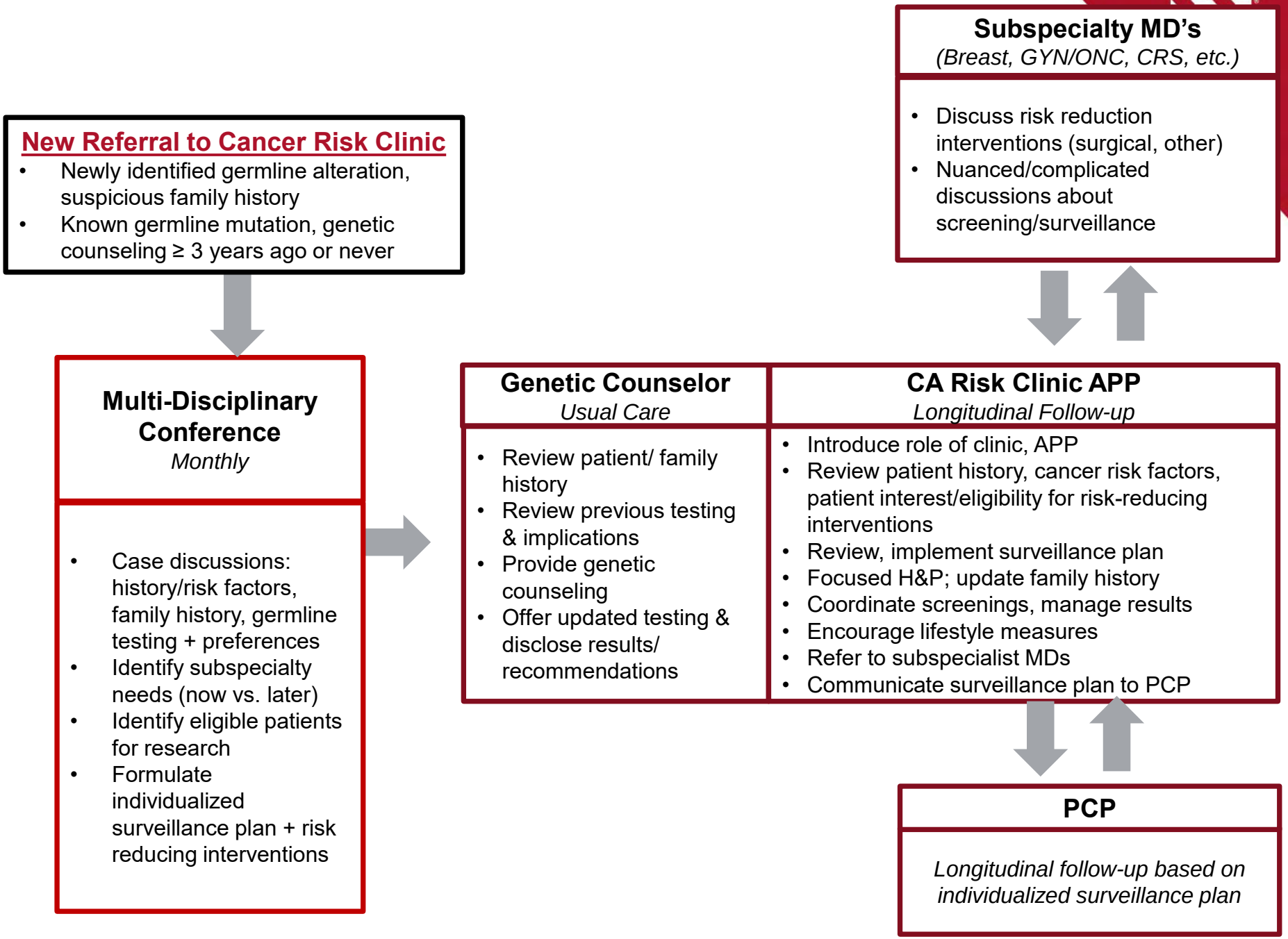
We are here for you and your loved ones.

### Our services include:

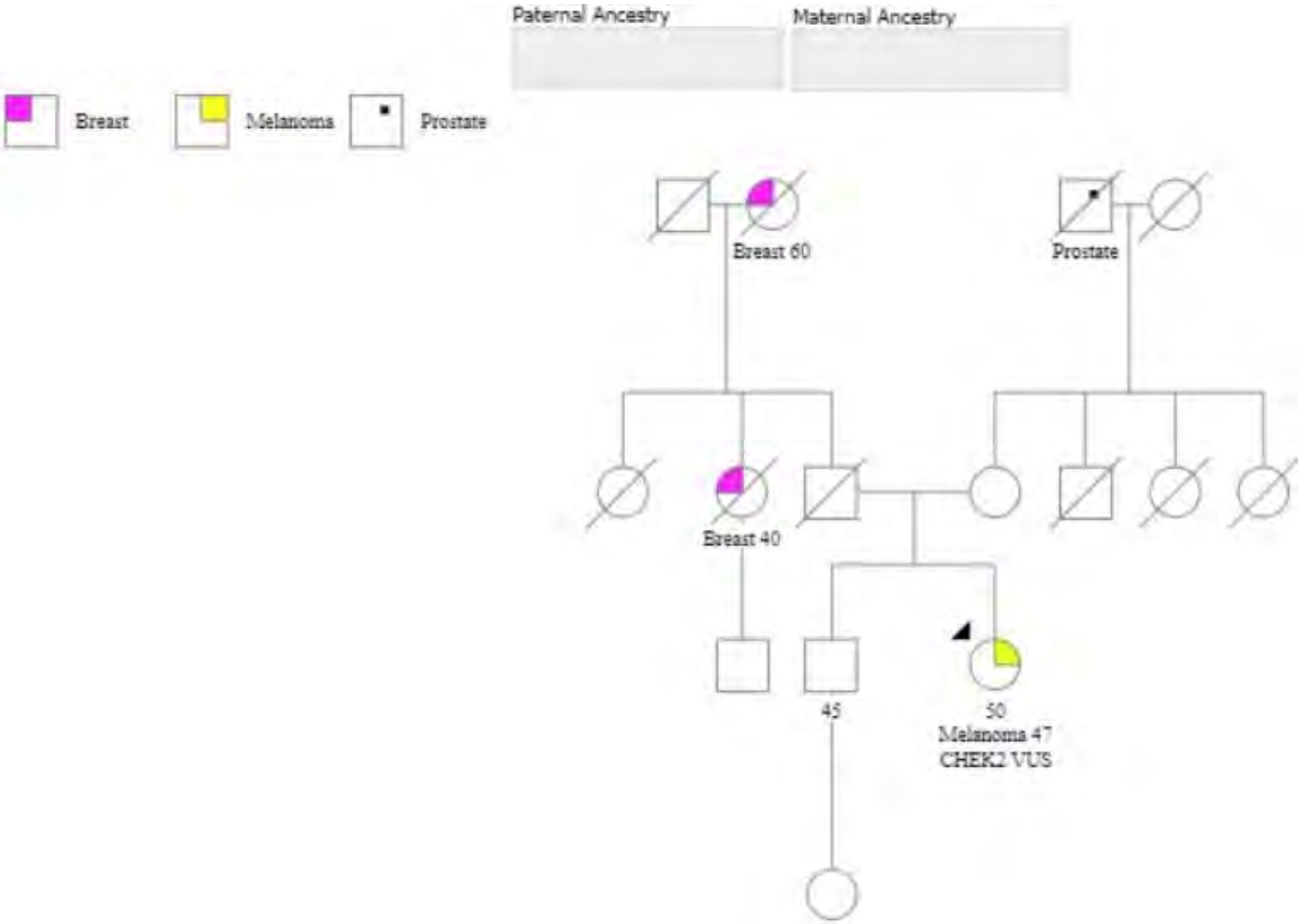
- Access to clinical trials in prevention
- Comprehensive risk assessment
- Genetic counseling and testing
- Patient education
- Physician referral services
- Prevention measures
- Psychological services
- Screenings (mammogram, MRI, colonoscopy, blood tests, etc.)

# Multidisciplinary Conference Team

- Medical Oncology
- Cancer Genetics
- Radiology
- Breast Surgical Oncology
- Gynecologic Oncology
- Gastroenterology
- Endocrinology
- Urology
- Dermatology


New Referral to Cancer Risk Clinic
• Newly identified germline alteration, suspicious family history
• Known germline mutation, genetic counseling ≥ 3 years ago or never
Multi-Disciplinary Conference
Monthly
• Case discussions: history/risk factors, family history, germline testing + preferences
• Identify subspecialty needs (now vs. later)
• Identify eligible patients for research
• Formulate individualized surveillance plan + risk reducing interventions
Genetic Counselor
Usual Care
• Review patient/ family history
• Review previous testing & implications
• Provide genetic counseling
• Offer updated testing & disclose results/ recommendations
CA Risk Clinic APP
Longitudinal Follow-up
• Introduce role of clinic, APP
• Review patient history, cancer risk factors, patient interest/eligibility for risk-reducing interventions
• Review, implement surveillance plan
• Focused H&P; update family history
• Coordinate screenings, manage results
• Encourage lifestyle measures
• Refer to subspecialist MDs
• Communicate surveillance plan to PCP
Subspecialty MD's
(Breast, GYN/ONC, CRS, etc.)
• Discuss risk reduction interventions (surgical, other)
• Nuanced/complicated discussions about screening/surveillance
PCP
Longitudinal follow-up based on individualized surveillance plan

# Case 1


Paternal Ancestry
Maternal Ancestry
Breast
Melanoma
Prostate
Breast 60
Prostate
Breast 40
45
50
Melanoma 47
CHEK2 VUS

# Reclassified Test Result

## CHEK2 Likely Pathogenic

**Reason for testing**
Diagnostic test for a personal and family history of disease

**Test performed**
Sequence analysis and deletion/duplication testing of the 46 genes listed in the Genes Analyzed section.

- Invitae Common Hereditary Cancers Panel

This report supersedes RQ490619 (10.01.2018) and updates the interpretation of the below variant(s).

- The change in variant classification was made as a result of re-review of the evidence in light of new variant interpretation guidelines and/or new information.
- Please note that the design of the report has changed from the original report and some of the content may have moved.

Updated Interpretations

| GENE | VARIANT | ZYGOSITY | PRIOR VARIANT CLASSIFICATION | NEW VARIANT CLASSIFICATION |
|---|---|---|---|---|
| CHEK2 | c.846+4_846+7del (Intronic) | heterozygous | Uncertain Significance | Likely Pathogenic |

**RESULT: POSITIVE**

**One Likely Pathogenic variant identified in CHEK2. CHEK2 is associated with autosomal dominant predisposition to hereditary cancers.**

| GENE | VARIANT | ZYGOSITY | VARIANT CLASSIFICATION |
|---|---|---|---|
| CHEK2 | c.846+4_846+7del (Intronic) | heterozygous | Likely Pathogenic |

**About this test**
This diagnostic test evaluates 46 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

# Test Result 2018

## CHEK2 VUS

**Test Performed**
Sequence analysis and deletion/duplication testing of the 46 genes listed in the results section below.
- Invitae Common Hereditary Cancers Panel

**Reason for Testing**
Family history

### Summary

Variant of Uncertain Significance identified in CHEK2.

### Clinical Summary

- A Variant of Uncertain Significance, c.846+4_846+7delAGTA (Intronic), was identified in CHEK2.
  - The CHEK2 gene is associated with an increased risk for autosomal dominant breast, colon, thyroid and prostate cancers (PMID: 15492928, 18759107, 21807500, 21876083, 25431674).
  - The clinical significance of this variant is uncertain at this time. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
  - This variant is not eligible for complimentary family studies as part of our VUS Resolution Program because the results are unlikely to assist Invitae in reclassifying this particular variant. However, if desired, testing for this variant in other family members can be ordered at a reduced cost through the Family Variant Testing Program. Details on our VUS Resolution and Family Variant Testing Programs can be found at www.invitae.com.
- These results should be interpreted within the context of additional laboratory results, family history, and clinical findings. Genetic counseling is recommended to discuss the implications of this result. For access to a network of genetic providers, please contact Invitae at clientservices@invitae.com, or visit www.nsgc.org or tagc.med.sc.edu/professional_organizations.asp.

### Complete Results

| Gene | Variant | Zygosity | Variant Classification |
|---|---|---|---|
| CHEK2 | c.846+4_846+7delAGTA (Intronic) | heterozygous | Uncertain Significance |

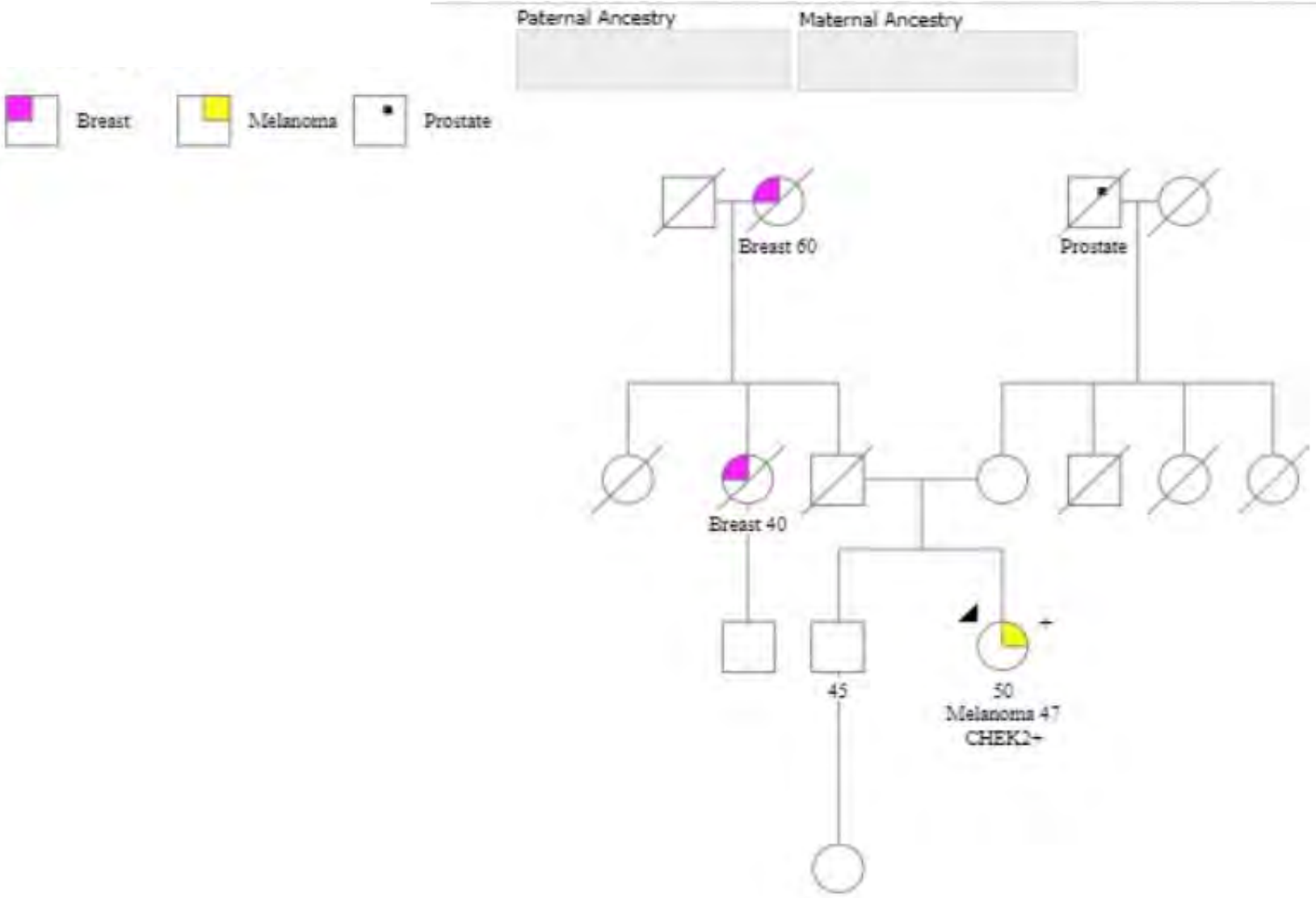
The following genes were evaluated for sequence changes and exonic deletions/duplications:
APC, ATM, AXIN2, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A (p14ARF), CDKN2A (p16INK4a), CHEK2, CTNNA1, DICER1, EPCAM*, GREM1*, KIT, MEN1, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, PALB2, PDGFRA, PMS2, POLD1, POLE, PTEN, RAD50, RAD51C, RAD51D, SDHB, SDHC, SDHD, SMAD4, SMARCA4, STK11, TP53, TSC1, TSC2, VHL

The following genes were evaluated for sequence changes only:
HOXB13*, NTHL1*, SDHA

Results are negative unless otherwise indicated

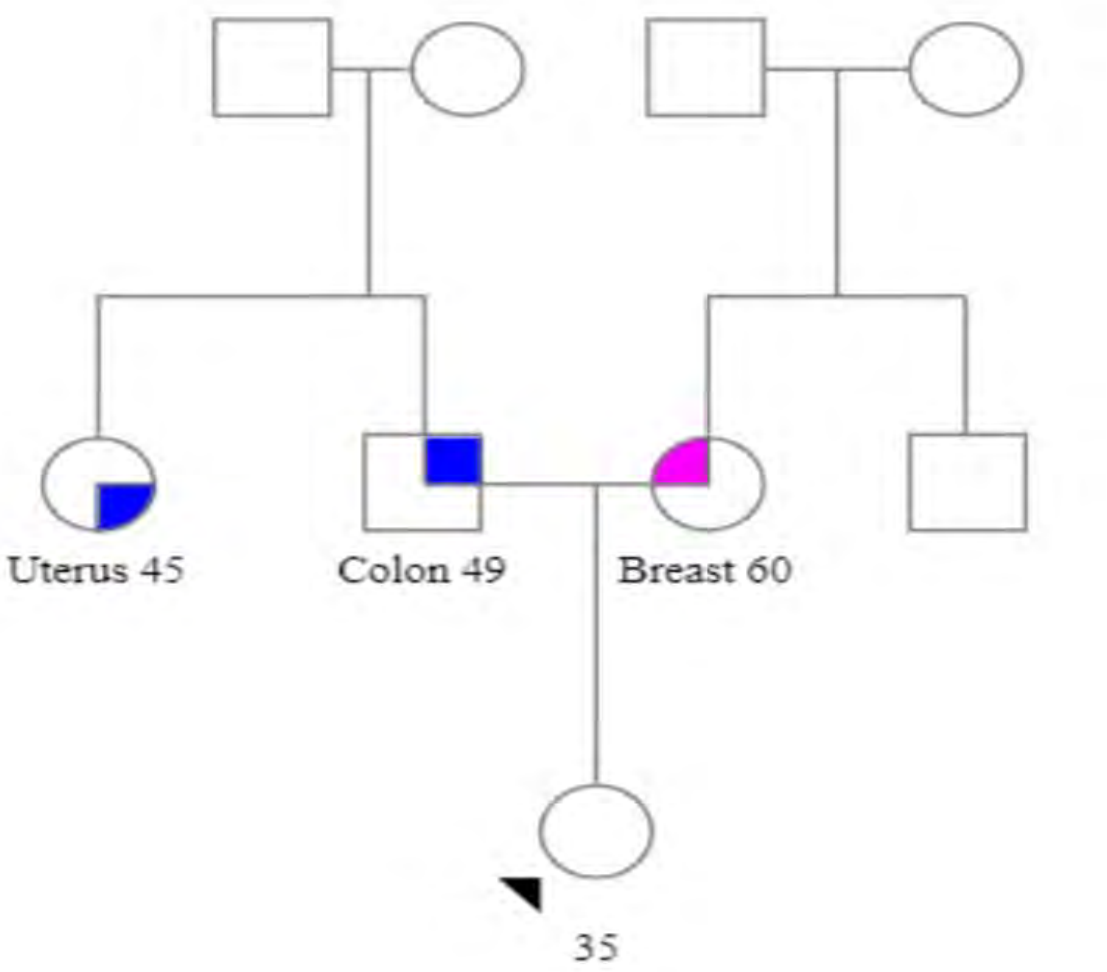
Benign and Likely Benign variants are not included in this report but are available upon request. An asterisk (*) indicates that this gene has a limitation. Please see the Limitations section for details.

# Case 1


Paternal Ancestry
Maternal Ancestry
Breast
Melanoma
Prostate
Breast 60
Prostate
Breast 40
45
50
Melanoma 47
CHEK2+

# Discussion

# Case 2



# Many At-Risk Patients Are Being Missed With Current Approaches

- >90% of people with pathogenic variants (PV) are unaware of their elevated risk
- ~50% of people with a PV do not have a close relative with cancer
- >70% of people at risk may not meet NCCN criteria
- Racial and socioeconomic disparities

Manchanda R, Patel S, Gordeev VS, et al., JNCI, 2018, p 714

# Colon Cancer Gene Panel Results

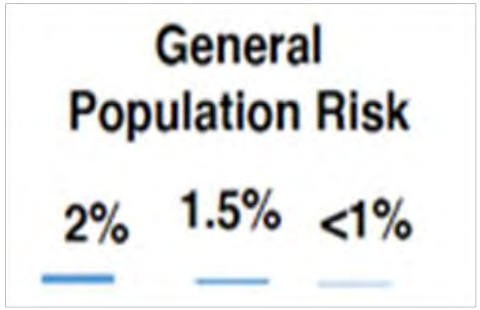
**RESULT: POSITIVE**

**One Pathogenic variant identified in MLH1. MLH1 is associated with autosomal dominant Lynch syndrome and autosomal recessive constitutional mismatch repair deficiency syndrome.**

| GENE | VARIANT | ZYGOSITY | VARIANT CLASSIFICATION |
|---|---|---|---|
| MLH1 | c.454-2A>C (Splice acceptor) | heterozygous | PATHOGENIC |

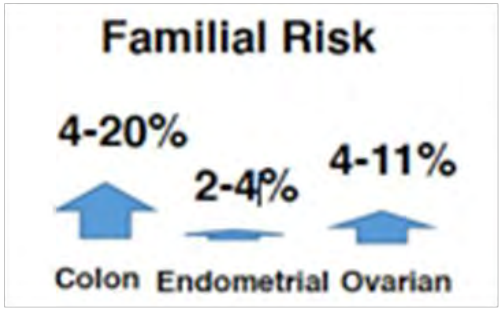
**MLH1**: Lynch syndrome

# Risk Stratified Estimates




**Colon:**
- Begin screening at age 45

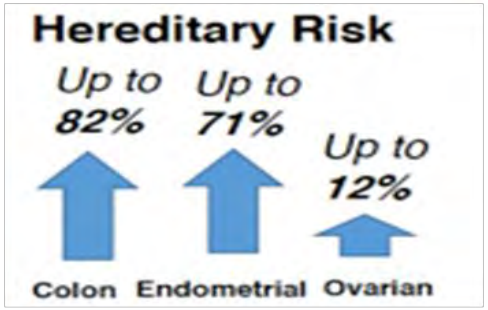
**Endometrial/Ovarian:**
- No published screening guidelines




**Would start at age 39**

**Colon:**
- Colonoscopy 10 years prior to youngest diagnosis in the family

**Endometrial/Ovarian:**
- No published screenin g guidelines




**MLH1 Pathogenic Variant**

**Colon:**
- Colonoscopy every 1-2 years beginning at age 20-25 (or 2-5 years prior to earliest colorectal cancer in the family

**Endometrial/Ovarian:**
- Increased surveillance beginning at age 25-35
- Discuss prophylactic removal of endometrium and/or ovaries

# Discussion

# Risk/Benefit Discussion

Provide information about:

- Cancer Risks
- Screening Services
- Genetic Testing

| Risks | Benefits |
| --- | --- |
| - Overtreatment<br>- False positives (anxiety)<br>- False negatives<br>- Cost | - Detect precursors to cancer (polyps)<br>- Downstaging and less treatment<br>- Improving morbidity and mortality |

# Why patients benefit

Multidisciplinary clinic addresses

- Genetic counseling
- Genetic testing
- Recommendations beyond the GI tract

High risk patients are at risk for extraintestinal malignancies

- Personalized plan

Improved outcomes

Improved patient satisfaction

# Resources

- Li-Fraumeni Syndrome Association www.lfsassociation.org
- Living Li-Fraumeni Syndrome www.livinglfs.org or 1-844-537-2255
- Hereditary Cancer Foundation www.hereditarycancer.org/
- FORCE (Facing Our Risk of Cancer Empowered), 866-288-7475 or www.facingourrisk.org
- Bright Pink, www.brightpink.org
- Alive and Kickin' www.aliveandkickin.org
- Lynch Syndrome International https://lynchcancers.com/
- No Stomach for Cancer www.nostomachforcancer.org/
- Pheo Para Alliance www.pheopara.org
- VHL Alliance www.vhl.org
- Aim at Melanoma Foundation - www.aimatmelanoma.org
- Melanoma Genetics Consortium - www.genomel.org
- Information about GINA (Genetic Information Non-Discrimination Act) Law: https://www.genome.gov/about-genomics/policy-issues/Genetic-Discrimination
- The National Pancreas Foundation - https://pancreasfoundation.org/
- National Society of Genetic Counselor - www.nsgc.org
- Find a genetic counselor - www.findageneticcouselor.com