WOMEN'S HEALTH: HEREDITARY CANCER GENETICS AND CANCER PREVENTION

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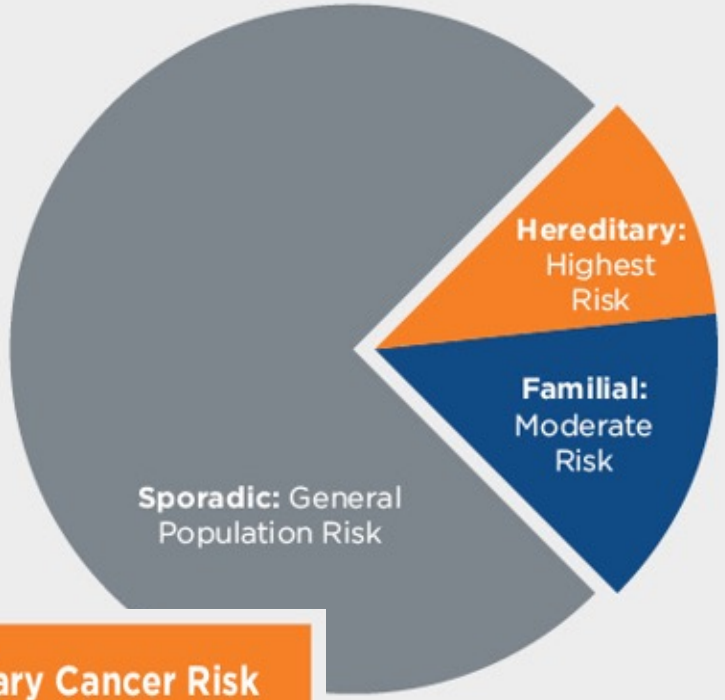
DISCLOSURES

- Member of Myriad Genetics speakers bureau

OBJECTIVES

- Describe hereditary cancer and how it affects cancer risk
- Explain the prevalence of hereditary cancer
- Identify hereditary cancer mutations
- Understand National Comprehensive Cancer Network Guideline criteria for genetic testing
- Describe elements of pre-genetic test counseling
- Understand post-genetic test follow-up management

CANCER CATEGORIES

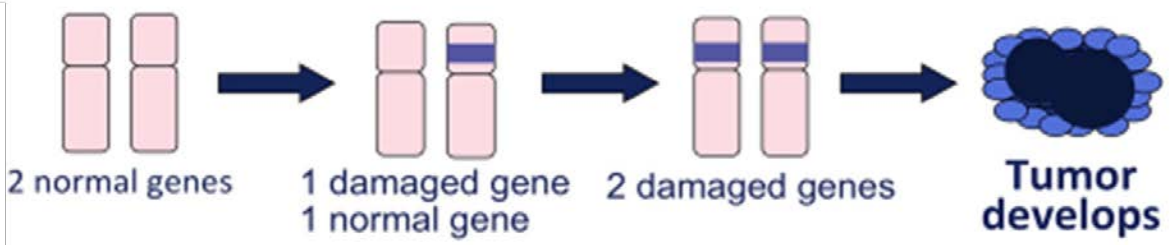


General Population Risk	Familial Cancer Risk	Hereditary Cancer Risk
• Occurs by chance • Negative for a known deleterious mutation in the family	• Likely caused by a combination of genetic and environmental factors	• Occurs when an altered gene is passed down from parent to child • More likely to have relatives with the same or related types of cancer

WHAT IS HEREDITARY CANCER?

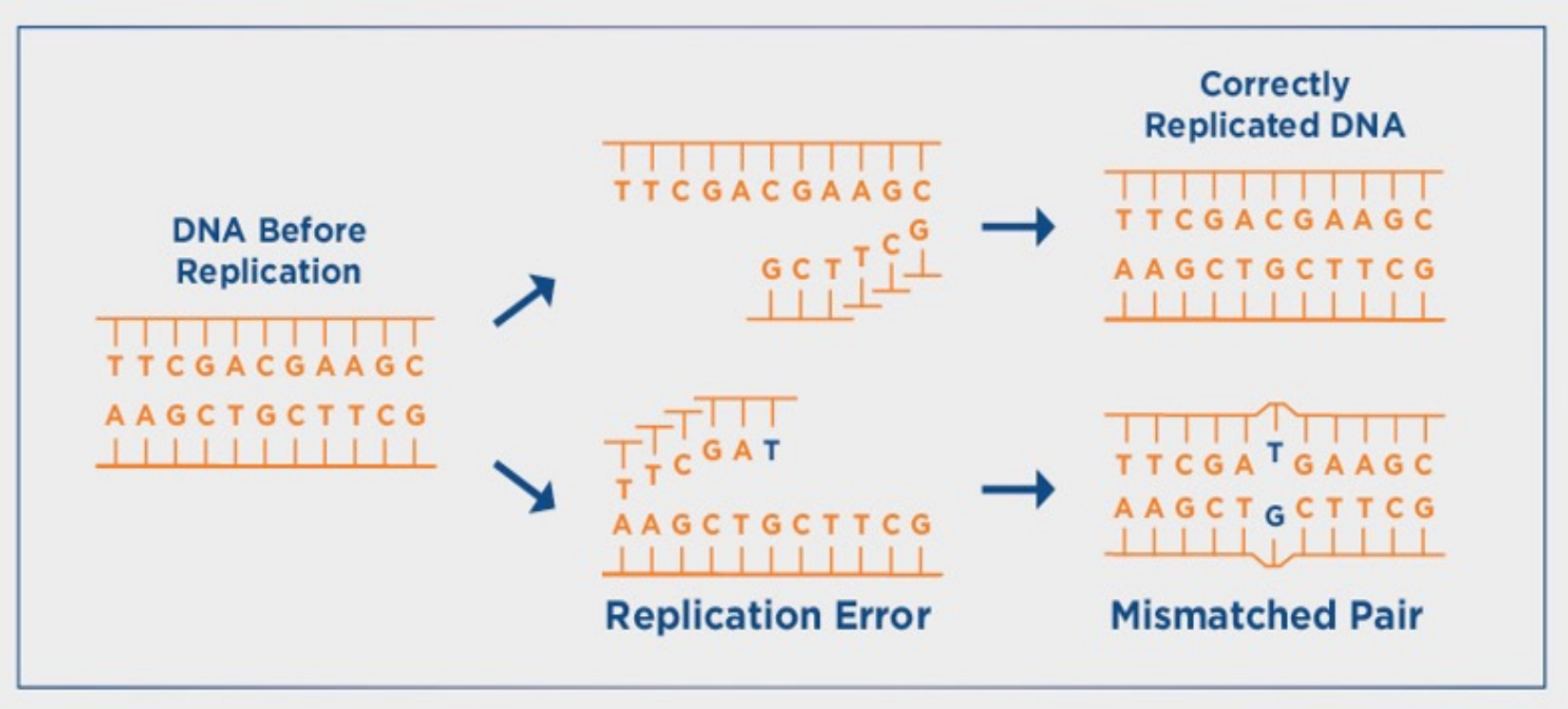
- Mutation or alteration in a person's DNA
- High risk of cancer
- Passed from parent to child
- Autosomal dominant inheritance

TUMOR SUPPRESSOR GENES



In hereditary cancer, one damaged gene is inherited.

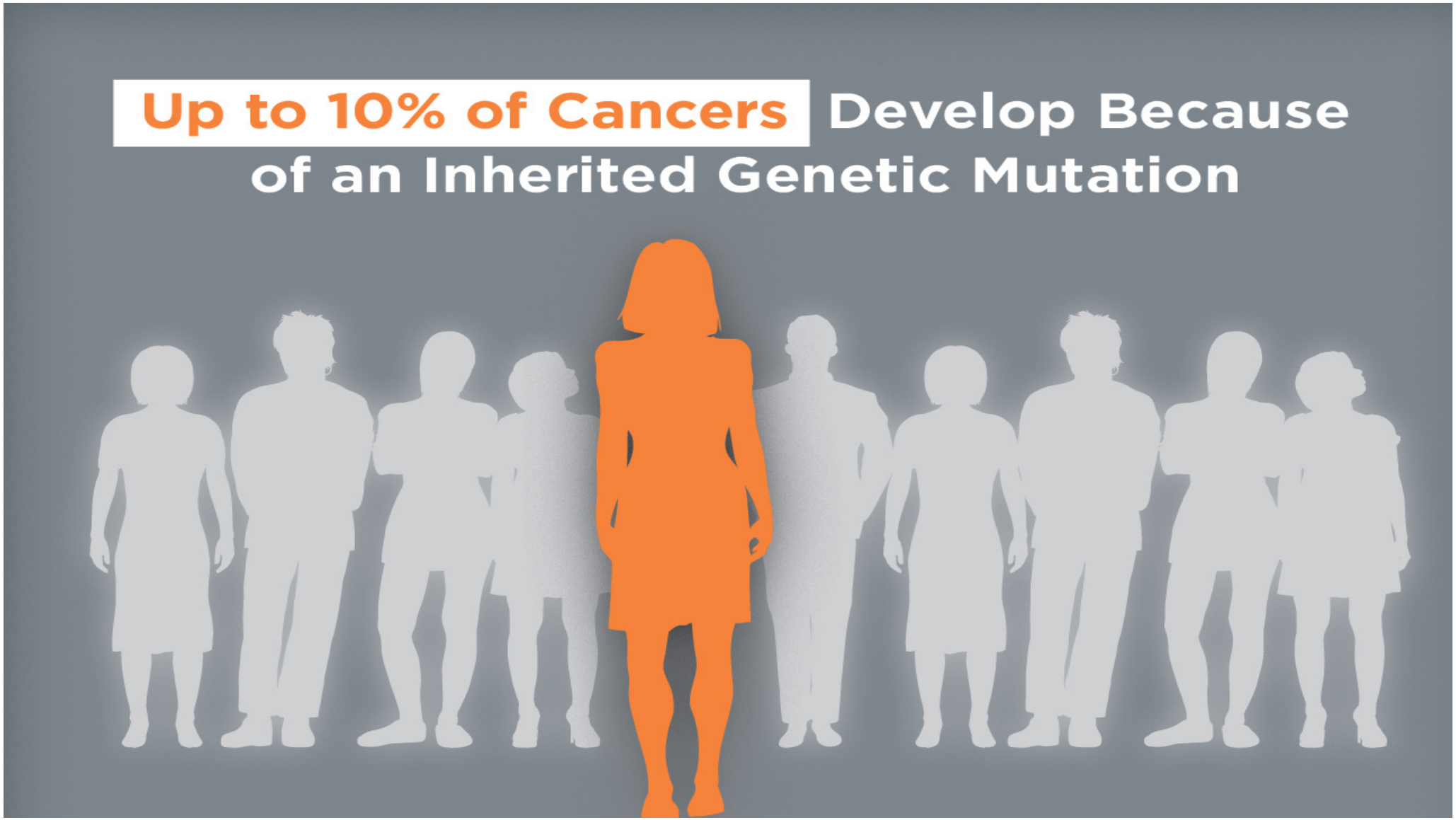
MISMATCH REPAIR GENES



ANNUAL INCIDENCE OF HEREDITARY CANCER

Site	Estimated New Cases 2022	% Hereditary	# Patients with Hereditary Cancer
Breast	300,000	14%	42,000
Ovary	20,000	24%	4,800
Uterus	66,000	9%	5,940
Colorectal	153,000	10%	15,300

American Cancer Society, 2023


Up to 10% of Cancers Develop Because of an Inherited Genetic Mutation

1 OUT OF 4 PATIENTS QUALIFY FOR GENETIC TESTING

DeFrancesco et al., 2018

ONLY 20% OF PATIENTS WHO QUALIFY FOR GENETIC TESTING HAVE UNDERGONE TESTING

Childers, 2017

MULTI-GENE PANEL GENETIC TESTING IS RECOMMENDED FOR THOSE WHO MEET CRITERIA

Daly et al., 2023

CRITERIA FOR TESTING

- Individuals with a blood relative with a known hereditary cancer gene mutation
- Personal or family history in a 1st or 2nd degree relative:
  - Breast cancer age 50 or younger
  - 3 or more breast cancers on the same side of the family
  - Male breast cancer at any age
  - Breast cancer at any age and Ashkenazi Jewish ancestry

Daly et al., 2023

CRITERIA FOR TESTING

- Personal or family history in a 1st or 2nd degree relative of ovarian cancer at any age
- Personal or family history in a 1st degree relative of pancreatic cancer at any age
- Personal or family history in a 1st degree relative with metastatic prostate cancer
- Personal or family history in a 1st degree relative of colorectal or endometrial cancer at age 50 or younger

Daly et al., 2023

Hereditary Cancer Syndromes

- **Hereditary Breast/ Ovarian Cancer**
  BRCA1, BRCA2
- **Lynch Syndrome**
  MLH1, MSH2, MSH6, PMS2, EPCAM

- Hereditary Breast
  PALB2, CHEK2, ATM
- Li-Fraumeni
  TP53
- Peutz-Jeghers
  STK11
- *PTEN* Hamartoma Tumor Syndrome (PHTS)
  PTEN
- Hereditary Diffuse Gastric Cancer (HDGC)
  CDH1

HEREDITARY BREAST AND OVARIAN CANCER SYNDROME: BRCA1

- 87% risk of breast cancer in women and 1.2% in men to age 70
- 20% risk of second breast cancer in women within 5 years
- 63% risk of ovarian cancer in women to age 70
- 16% risk of prostate cancer in men to age 70
- Elevated risk of pancreatic cancer

Daly et al., 2023
Myriad Genetics, 2022

HEREDITARY BREAST AND OVARIAN CANCER SYNDROME: BRCA2

- 84% risk of breast cancer in women and 6.8% in men to age 70
- 12% risk of second breast cancer in women within 5 years of primary diagnosis
- 27% risk of ovarian cancer in women to age 70
- 20% risk of prostate cancer in men to age 70
- 7% or higher pancreatic cancer risk with family history
- Elevated risk of melanoma

Daly et al., 2023
Myriad Genetics, 2022

MANAGEMENT: HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

- Breast self-awareness starting at age 18
- Clinical breast exam every 6-12 months starting at age 21
- Annual breast MRI with contrast starting at age 25
- Annual Mammogram starting at age 30
- Risk-reducing bilateral mastectomy: individualized, usually age 35-45

Daly et al., 2023
Myriad Genetics, 2022

MANAGEMENT: HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

- Annual transvaginal ultrasound and CA-125 ages 30-35
- Risk-reducing bilateral salpingo-oophorectomy age 35-40 or upon completion of childbearing
- Family history of pancreatic cancer: endoscopic ultrasonography or MRI/MRCP of the pancreas annually starting at age 50, or 10 years younger than diagnosis of family member
- BRCA 2: annual whole body skin and eye exams
- Risk-Reducing medications

Daly et al., 2023
Myriad Genetics, 2022

HEREDITARY BREAST CANCER: PALB2

- 53% risk of breast cancer in women and 1% in men to age 80
- 5% risk of ovarian cancer to age 80
- 3% risk of pancreatic cancer to age 80

Daly et al., 2023
Myriad Genetics, 2022

HEREDITARY BREAST CANCER: CHEK2

- 31% risk of breast cancer in women and 1% in men to age 80
- Possible elevated risk colorectal cancer

Daly et al., 2023
Myriad Genetics, 2022

HEREDITARY BREAST CANCER: ATM

- 52% risk of breast cancer in women to age 80
- 44% risk of prostate cancer in men to age 80
- 5% risk of pancreatic cancer to age 80

Daly et al., 2023
Myriad Genetics, 2022

MANAGEMENT: HEREDITARY BREAST CANCER

- Breast self-awareness starting at age 18
- Clinical breast exam every 6-12 months starting at age 21
- Annual mammogram and breast MRI with contrast starting at age 30-40
- Risk-reducing medications or bilateral mastectomy: individualized

Daly et al., 2023
Myriad Genetics, 2022

MANAGEMENT: HEREDITARY BREAST CANCER

- No specific ovarian cancer risk-reduction recommendations
- PALB2/ATM: Family history of pancreatic cancer: endoscopic ultrasonography or MRI/MRCP of the pancreas annually starting at age 50, or 10 years younger than diagnosis of family member
- ATM: Consider annual digital rectal exam and Prostate Specific Antigen starting at age 40

Daly et al., 2023
Myriad Genetics, 2022

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER: LYNCH SYNDROME: MLH1

- 58% risk of colorectal cancer to age 70
- 54% risk of endometrial cancer in women to age 70
- 20% risk of ovarian cancer in women to age 70
- Elevated risk of gastric, small bowel, urothelial, skin, pancreatic, brain, and hepatobiliary cancers

Gupta et al., 2023
Myriad Genetics, 2022

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER: LYNCH SYNDROME: MSH2

- 51% risk of colorectal cancer to age 70
- 53% risk of endometrial cancer in women to age 70
- 24% risk of ovarian cancer in women to age 70
- Elevated risk of gastric, small bowel, urothelial, skin, pancreatic, brain, prostate, and hepatobiliary cancers

Gupta et al, 2023
Myriad Genetics, 2022

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER LYNCH SYNDROME: MSH6

- 30% risk of colorectal cancer to age 70
- 71% risk of endometrial cancer in women to age 70
- Elevated risk of urothelial, ovarian, gastric, small bowel, pancreatic, central nervous system, hepatobiliary, and sebaceous cancers

Gupta et al, 2023
Myriad Genetics, 2022

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER LYNCH SYNDROME: PMS2

- 20% risk of colorectal cancer to age 70
- 26% risk of endometrial cancer in women to age 70
- Elevated risk of ovarian, gastric, small bowel, urothelial, pancreatic, brain, hepatobiliary, and skin tumor cancers

Gupta et al, 2023
Myriad Genetics, 2022

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER LYNCH SYNDROME: EPCAM

- 51% risk of colorectal cancer to age 70
- 53% risk of endometrial cancer in women to age 70
- 24% risk of ovarian cancer in women to age 70
- Elevated risk of gastric, small bowel, urothelial, skin, pancreatic, brain, prostate, and hepatobiliary cancers

Gupta et al, 2023
Myriad Genetics, 2022

MANAGEMENT: LYNCH SYNDROME

- Colonoscopy every 1-2 years starting at age 20-25
- Education to seek attention for ovarian cancer symptoms
- Annual transvaginal ultrasound and CA-125 age 30-35
- Bilateral salpingo-oophorectomy: consider after completion of childbearing
- Risk reducing medications

Gupta et al, 2023
Myriad Genetics, 2022

MANAGEMENT: LYNCH SYNDROME

- Consider testing and treatment of H. Pylori infection
- Consider upper endoscopy every 3-5 starting at age 40
- Consider annual urinalysis starting at age 30-35
- Consider whole body skin exams every 1-2 years

Gupta et al, 2023
Myriad Genetics, 2022

LI-FRAUMENI SYNDROME: TP53

- 7%-20% not inherited from a parent, de novo mutation
  - 95% overall cancer risk in males to age 70
  - 100% overall cancer risk in females to age 70
  - 50% risk of second primary cancer within 10 years of first diagnosis
  - 85% risk of breast cancer in females to age 70- majority before age 45

Daly et al., 2023
Myriad Genetics, 2022

MANAGEMENT: LI-FRAUMENI SYNDROME

- Provide education about overall symptoms of cancer
- Female breast self-awareness starting at age 18
- Clinical breast exam every 6-12 months starting at age 20
- Annual breast MRI starting at age 20
- Annual mammogram starting at age 30

Daly et al., 2023
Myriad Genetics, 2022

MANAGEMENT: LI-FRAUMENI SYNDROME

- Consider risk-reducing bilateral mastectomy: individualized
- Comprehensive physical and neurological exam every 3-4 months from birth to age 18 and every 6-12 months from age 18
- Whole body MRI annually from birth
- Abdominal and pelvic ultrasound every 3-4 months from birth to age 18 and annually from age 18

Daly et al., 2023
Myriad Genetics, 2022

HAMARTOMA TUMOR SYNDROME: PTEN

- 89% overall cancer risk to age 70
- 85% risk of breast cancer to age 70
- 28% risk of endometrial cancer to age 70
- 38% risk of thyroid cancer to age 70
- 16% risk of colorectal cancer to age 70
- 34% risk of renal cancer to age 70
- 6% risk of melanoma to age 70

Daly et al., 2023
Myriad Genetics, 2022

MANAGEMENT: HAMARTOMA TUMOR SYNDROME

- Provide education about overall symptoms of cancer
- Annual comprehensive physical exam with particular attention to thyroid starting at age 18
- Breast self-awareness starting at age 18
- Clinical breast exam every 6-12 months starting at age 25
- Annual mammogram starting at age 30

Daly et al., 2023
Myriad Genetics, 2022

MANAGEMENT: HAMARTOMA TUMOR SYNDROME

- Risk-reducing bilateral mastectomy: individualized
- Education to seek attention for symptoms of endometrial cancer
- Transvaginal ultrasound: consider in postmenopausal women
- Endometrial biopsy: every 1-2 years starting at age 35
- Hysterectomy: consider after childbearing complete

Daly et al., 2023
Myriad Genetics, 2022

MANAGEMENT: HAMARTOMA TUMOR SYNDROME

- Annual thyroid ultrasound starting at age 7
- Colonoscopy every 5 years starting at age 35 or 5-10 years younger than earliest family member diagnosis
- Renal ultrasound every 1-2 years starting at age 40
- Annual whole-body skin exam

Daly et al., 2023
Myriad Genetics, 2022

PEUTZ-JEGHERS SYNDROME: STK11

- 39% risk of colorectal cancer to age 70
- 36% risk of pancreatic cancer to age 70
- 54% risk of breast cancer to age 70
- 29% risk of gastric cancer to age 70
- 13% risk of small bowel cancer to age 70
- 21% risk of ovarian cancer to age 70
- 9% risk of endometrial cancer to age 70
- 10% risk of cervical cancer to age 70
- 17% risk of lung cancer to age 70
- Elevated risk of testicular cancer

Daly et al., 2023
Myriad Genetics, 2022

MANAGEMENT PEUTZ-JEGHERS SYNDROME

- Colonoscopy: baseline at age 8-10, then every 2-3 years from age 18
- MRCP or endoscopic ultrasound of pancreas annually starting at age 30
- Breast self-awareness starting at age 18
- Clinical breast exam every 6 months starting at age 30
- Annual mammogram starting at age 30

Daly et al., 2023
Myriad Genetics, 2022

MANAGEMENT PEUTZ-JEGHERS SYNDROME

- Upper endoscopy: baseline at age 8-10, then every 2-3 years from age 18
- Small bowel CT or MRI: baseline at age 8-10, then every 2-3 years from age 18
- Physical exam for precocious puberty annually starting at age 8
- Pelvic exam and pap smear annually beginning at age 18-20
- Testicular exam and observance for feminizing changes annually starting at age 10
- Education about avoidance/cessation of smoking

Daly et al., 2023
Myriad Genetics, 2022

HEREDITARY DIFFUSE GASTRIC CANCER SYNDROME: CDH1

- 83% risk of diffuse gastric cancer to age 80
- 52% risk of breast cancer in women to age 70

Daly et al., 2023
Myriad Genetics, 2022

MANAGEMENT: HEREDITARY DIFFUSE GASTRIC CANCER SYNDROME

- Gastrectomy after baseline endoscopy: age 18-40
- Surveillance with endoscopy and biopsy every 6-12 months for those delaying gastrectomy
- Test for and treat H. Pylori
- Breast self-awareness starting at age 18

Daly et al., 2023
Myriad Genetics, 2022

MANAGEMENT: HEREDITARY DIFFUSE GASTRIC CANCER SYNDROME

- Annual clinical breast exam starting at age 25
- Annual mammogram starting at age 30
- Annual breast MRI starting at age 30
- Consider bilateral risk-reducing mastectomy between ages 30-60

Daly et al., 2023
Myriad Genetics, 2022

HEREDITARY CANCER RISK ASSESSMENT

- Personal cancer history
  - Type, histology/pathology
  - Age at diagnosis
  - Any previous genetic testing and results

Daly et al., 2023

HEREDITARY CANCER RISK ASSESSMENT

- Family history:
  - Previous genetic testing and results of family members
  - Cancer diagnosis in first-, second-, and third-degree relatives on each side of the family
  - Type of cancer
  - Age at diagnosis
  - Ethnicity (specifically Ashkenazi Jewish ancestry)

Daly et al., 2023

PRETEST COUNSELING

- Educate the patient on inheritance patterns: 50%
- Prepare for possible outcomes: positive, negative, and variants of uncertain clinical significance
- Obtain informed consent and document it in the patient's medical record
- Discuss the plan for results disclosure
- Educate patient that enhanced screening, risk-reducing medications and surgery available if mutation identified

Daly et al., 2023

PRETEST COUNSELING

- Discuss that results may be important to therapeutic decision-making
- Advise about possible inherited cancer risk to relatives
- Discuss the cost of genetic testing
- Provide an overview of current legislation regarding genetic discrimination and the privacy of genetic information

Daly et al., 2023

POST-TEST FOLLOW UP

(Daly et al., 2023)

POSITIVE

- Referral for formal genetic counseling
  - Testing of family members
- Begin early/increased screenings
- Consider risk-reducing medications
- Consider risk-reducing surgeries
- Fertility planning: pre-implantation genetic testing

Daly et al., 2023

HIGH RISK NEGATIVE

- Genetic testing negative for clinically significant mutations
- Lifetime breast cancer risk 20% or greater
- Increased breast cancer screening
  - Breast self-awareness
  - Annual clinical breast exam
  - Start annual mammogram 10 years younger than family member diagnosis, not before age 30 and no later than age 40
  - Start annual breast MRI with contrast 10 years younger than family member diagnosis, no later than 40
  - Individualized consideration of risk-reducing medications

Daly et al., 2023

VARIANTS OF UNCERTAIN CLINICAL SIGNIFICANCE

- Variation in gene
- 90% will be reclassified as benign
- No change in clinical management

Daly et al., 2023

RISK-REDUCING MEDICATIONS: BREAST CANCER

- Consider for women 35 and older with a 5 year breast cancer risk of 3% or greater
- Does not apply to women with previous or current diagnosis of breast cancer
- Selective Estrogen Receptor Modulator
  - Acta as an estrogen antagonist in breast cancer cells preventing tumor growth
- Aromatase Inhibitors- NO FDA-APPROVED INDICATION FOR RISK REDUCTION
  - Lower estrogen levels by preventing aromatase from converting androgen into estrogen

Owens, 2019

SELECTIVE ESTROGEN RECEPTOR MODULATORS

- Tamoxifen 20 mg PO daily x 5 years
  - Reduced incidence of invasive breast cancer by 7 per 1,000 over 5 years
  - Risk of VTEs, vasomotor symptoms, endometrial cancer, and cataracts
  - Approved for premenopausal and postmenopausal women

Owens, 2019

SELECTIVE ESTROGEN RECEPTOR MODULATORS

- Raloxifene- 60 mg PO daily x 5 years
  - Reduced incidence of invasive breast cancer by 9 per 1,000 over 5 years
  - Risk of VTEs and vasomotor symptoms
  - Use only in postmenopausal women
  - Discontinue >72 hours before surgery with VTE risk

Owens, 2019

AROMATASE INHIBITORS

- Letrozole, Anastrozole, Exemestane
  - reduced incidence of breast cancer by 16 per 1,000 over 5 years
  - Vasomotor symptoms, gastrointestinal symptoms, musculoskeletal pain
  - Use only in postmenopausal women

Owens, 2019

RISK-REDUCING MEDICATIONS: OVARIAN AND ENDOMETRIAL CANCER

- Combined hormonal contraceptive pills
  - Up to 50% reduction of ovarian and endometrial cancer risk when taken for 5+ consecutive years
  - Follow WHO Medical Eligibility Criteria for Contraceptive Use

Daly et al., 2023
Myriad Genetics, 2022

RISK-REDUCING AGENTS: COLORECTAL CANCER

- Aspirin
  - 600 mg/day for up to 4 years
  - Up to 50% reduction in risk

Daly et al., 2023
Myriad Genetics, 2022

CASE SCENARIO

- 39 year old female
- Personal history
  - Colorectal cancer age 34
- Family history:
  - Mother melanoma age 45
  - Maternal grandmother thyroid cancer age 25
  - Paternal aunt ovarian cancer age 28

CASE SCENARIO

Personal and Family Hx Guided Management

- Routine screenings
- Colonoscopy every 3 years
- Annual skin exam

CASE SCENARIO

- + BRCA1
  - 87% risk of breast cancer
  - Annual Breast MRI starting at 25
  - Annual mammogram starting at age 30
  - CBE every 6-12 months
  - Risk-reducing mastectomy
  - 63% risk of ovarian cancer
  - BSO

CASE SCENARIO

- 40 year old male
- No personal cancer history
- Family history:
  - Mother endometrial age 45
  - Maternal aunt ovarian cancer age 60

CASE SCENARIO

Family Hx Guided Management

- Routine screenings
- Colonoscopy every 10 years staring at age 45

CASE SCENARIO

- + MLH1

- Up to 82% risk of colon cancer
- **Annual** colonoscopy starting at 20-25y
- Up to 11% risk of gastric cancer
- Consider upper endoscopy every 3-5 years

CASE SCENARIO

- 36 year old female
- No personal cancer history
- Family history:
  - Father pancreatic cancer age 51
  - Paternal grandmother melanoma age 45

CASE SCENARIO

Family Hx Guided Management

- Routine screenings
- Annual skin exams

CASE SCENARIO

- + CDH1
  - Up to 83% risk of gastric cancer
  - Risk-reducing gastrectomy age 18-40
  - Up to 52% risk of breast cancer
  - Annual Breast MRI starting at 25
  - Annual mammogram starting at age 30
  - CBE every 6-12 months
  - Risk-reducing mastectomy age 30-60

KEY TAKEAWAYS

- Risk assessment and testing key to identifying genetic mutations
- Reg flags: young, rare, multiple cancers
- Identification of genetic mutations prevents cancer
- Entire family is affected

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