

Hereditary Cancer Test

Genes covered and recommended
screening guidelines



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| Gene | Breast | Ovarian | Uterine | Colorectal | Melanoma | Pancreatic | Stomach | Prostate* |
|-----------------|--------|---------|---------|------------|----------|------------|---------|-----------|
| <i>BRCA1</i> | • | • | | | | • | | • |
| <i>BRCA2</i> | • | • | | | • | • | | • |
| <i>MLH1</i> | | • | • | • | | • | • | • |
| <i>MSH2</i> | | • | • | • | | • | • | • |
| <i>MSH6</i> | | • | • | • | | | • | • |
| <i>PMS2</i> *** | | • | • | • | | | | • |
| <i>EPCAM</i> ** | | • | • | • | | • | • | • |
| <i>APC</i> | | | | • | | • | • | |
| <i>MUTYH</i> | | | | • | | | | |
| <i>MITF</i> ** | | | | | • | | | |
| <i>BAP1</i> | | | | | • | | | |
| <i>CDKN2A</i> | | | | | • | • | | |
| <i>CDK4</i> ** | | | | | • | | | |
| <i>TP53</i> | • | • | • | • | • | • | • | • |
| <i>PTEN</i> | • | | • | • | • | | | |
| <i>STK11</i> | • | • | • | • | | • | • | |
| <i>CDH1</i> | • | | | | | | • | |
| <i>BMPR1A</i> | | | | • | | • | • | |
| <i>SMAD4</i> | | | | • | | • | • | |
| <i>GREM1</i> ** | | | | • | | | | |
| <i>POLD1</i> ** | | | | • | | | | |
| <i>POLE</i> ** | | | | • | | | | |
| <i>PALB2</i> | • | • | | | | • | | |
| <i>CHEK2</i> | • | | | • | | | | • |
| <i>ATM</i> | • | | | | | • | | |
| <i>NBN</i> | • | | | | | | | • |
| <i>BARD1</i> | • | | | | | | | |
| <i>BRIP1</i> | • | • | | | | | | |
| <i>RAD51C</i> | | • | | | | | | |
| <i>RAD51D</i> | | • | | | | | | |

* Please note that research and screening guidelines for genes associated with hereditary prostate cancer are still in their early stages. It is part of the Color service to keep you updated if any information related to your results changes.

** Only positions known to impact cancer risk analyzed: *CDK4*: only chr12:g.58145429-58145431 (codon 24) analyzed, *EPCAM*: only large deletions and duplications including 3' end of the gene analyzed, *GREM1*: only duplications in the upstream regulatory region analyzed, *MITF*: only chr3:g.70014091 (including c.952G>A) analyzed, *POLD1*: only chr19:g.50909713 (including c.1433G>A) analyzed, *POLE*: only chr12:g.133250250 (including c.1270C>G) analyzed.

*** *PMS2*: Exons 12-15 not analyzed.

APC

The APC gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary roles of APC are to help control how often a cell divides and how cells move and attach to other cells in the body.

Like most genes, each person has two copies of the APC gene: one inherited from each parent. A mutation in a single copy of the APC gene inherited from either parent is known to cause familial adenomatous polyposis (FAP) or attenuated familial adenomatous polyposis (AFAP). APC mutations are associated with an increased risk of polyposis (a large number of polyps in the gastrointestinal tract) as well as specific cancers (colorectal and others) over a lifetime.

The difference between FAP and AFAP is primarily the clinical symptoms, such as the age at when colorectal polyps first appear and the total number of colon polyps that develop. In general, individuals with FAP develop more polyps, and have higher cancer risks, at earlier ages.

Individuals with FAP and AFAP also have increased risks of other cancers such as brain (medulloblastoma), liver (especially a type called hepatoblastoma that only occurs in children younger than age 5), pancreatic, small bowel (duodenal), stomach, and thyroid. Non-cancerous features of FAP and AFAP can include: osteomas (bone tumors, usually in the skull or jaw bone); desmoid tumors (growths, usually in the abdomen); adrenal gland masses; dental abnormalities (such as extra or missing teeth); skin growths (such as cysts or fibromas); and pigmented regions on the retina of the eye referred to as congenital hypertrophy of the retinal pigment epithelium (CHRPE). These non-cancerous findings are also more common in individuals with FAP compared to AFAP.²

Approximately 20 to 25% of individuals with APC mutations are the first in their family to carry the mutation.^{1,2} This is referred to as a “*de novo*” mutation. Individuals with *de novo* mutations have the same cancer risks as those with an inherited mutation from a parent, and have a 50% chance of passing the mutation on to their children.

How common are mutations in the APC gene?

Mutations in the APC gene are rare—found in approximately 3 in 10,000 individuals in a study of the United Kingdom population.³ APC mutations account for <1% of all colorectal cancers.¹

¹ Jaspersion KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. *Gastro*. 2010 Jun;138(6):2044-58.

² Bisgaard ML, Fenger K, Bulow S, Niebuhr E, Mohr J. Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. *Hum Mutat*. 1994;3:121–5.

³ Burn J, Chapman P, Delhanty J et al. The UK Northern region genetic register for familial adenomatous polyposis coli: use of age of onset, congenital hypertrophy of the retinal pigment epithelium, and DNA markers in risk calculations. *Journal of Medical Genetics*. 1991;28(5):289-296.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *APC* gene, her chances of developing colorectal and other cancers, including brain (especially medulloblastoma), pancreatic, small bowel (especially in the duodenum), stomach, and thyroid cancer, as well as non-cancerous growths called desmoid tumors, are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 80 | Average US woman ^{4,5} | With <i>APC</i> mutation ^{1,6,7,8,9,10} |
|-------------------------|---------------------------------|--|
| Colorectal | 2.7% | 70-100% |
| Brain (medulloblastoma) | <1% | Elevated |
| Desmoid tumors | <0.1% | Elevated |
| Pancreatic | <1% | 1.7% |
| Small bowel (duodenal) | <1% | Elevated |
| Stomach | <1% | Elevated |
| Thyroid | 1.7% | 2.1% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

⁴ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

⁵ Bhandari S, Sinha A, Clark SK. Evaluation of management of desmoids tumours associated with familial adenomatous polyposis in Dutch patients. *Br J Cancer*. 2011;104(7):1236.

⁶ Burt RW, et al. Genetic testing and phenotype in a large kindred with attenuated familial adenomatous polyposis. *Gastro*. 2004 Aug;127(2):444-51.

⁷ Attard TM, Giglio P, Koppula S, Snyder C, Lynch HT. Brain tumors in individuals with familial adenomatous polyposis: a cancer registry experience and pooled case report analysis. *Cancer*. 2007;109(4):761-6.

⁸ Sturt NJ, Gallagher MC, Bassett P, et al. Evidence for genetic predisposition to desmoid tumours in familial adenomatous polyposis independent of the germline *APC* mutation. *Gut*. 2004;53(12):1832-6.

⁹ Giardiello FM, Offerhaus GJ, Lee DH, et al. Increased risk of thyroid and pancreatic carcinoma in familial adenomatous polyposis. *Gut*. 1993;34(10):1394-6.

¹⁰ Bülow S, Björk J, Christensen IJ, et al. Duodenal adenomatosis in familial adenomatous polyposis. *Gut*. 2004;53(3):381-6.

Men

If a man has a mutation in the *APC* gene, his chances of developing colorectal and other cancers, including brain (especially medulloblastoma), pancreatic, small bowel (especially in the duodenum), stomach, and thyroid cancer, as well as non-cancerous growths called desmoid tumors, are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 80 | Average US man ^{4,5} | With <i>APC</i> mutation ^{1,6,7,8,9,10} |
|-------------------------|-------------------------------|--|
| Colorectal | 3.3% | 70-100% |
| Brain (medulloblastoma) | <1% | Elevated |
| Desmoid tumors | <0.1 | Elevated |
| Pancreatic | 1.1% | 1.7% |
| Small bowel (duodenal) | <1% | Elevated |
| Stomach | <1% | Elevated |
| Thyroid | <1% | 2.1% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Additional information

Not all *APC* mutations have the same impact on cancer risk.

A specific mutation in the *APC* gene, called I1307K, is not associated with FAP or AFAP, but is linked to a slightly increased risk to develop colorectal cancer. Research on this specific gene mutation is ongoing. Studies have shown approximately 5-10% of all people of Ashkenazi Jewish descent carry this mutation, and the current colorectal cancer risk estimate for *APC* I1307K is based on studies in this specific population.^{11,12}

¹¹ Rozen P, Shomrat R, Strul H, et al. Prevalence of the I1307K *APC* gene variant in Israeli Jews of differing ethnic origin and risk for colorectal cancer. *Gastro*. January 1999;116(1):54-7.

¹² Boursi B, Sella T, Liberman E, et al. The *APC* p.I1307K polymorphism is a significant risk factor for CRC in average risk Ashkenazi Jews. *Eur J Cancer*. November 2013;49(17):3680-5.

Screening guidelines (FAP and AFAP)

These screening guidelines are for individuals with FAP or AFAP who have a mutation in the APC gene. Because management of FAP and AFAP is complex, evaluation and follow-up by a team of specialists is recommended. Your healthcare provider may use these guidelines to help create a customized screening plan for you.¹³

Women and Men

Colorectal (FAP):¹⁴

- **Starting at age 10-15:** Colonoscopy (preferred) or flexible sigmoidoscopy every year.
- **Starting at age 18 or depending on number of polyps:** NCCN recommends colectomy (surgical removal of the colon).
- **Following colectomy:** Speak to your provider about recommended follow up, which may include surveillance with endoscopy, and medications to reduce the risks of polyps and cancer.

Colorectal (AFAP):¹⁴

- **In late teens:** Colonoscopy every 2-3 years until polyps are found. After polyps are found, colonoscopy every 1-2 years.
- **Depending on age and number of polyps:** NCCN recommends colectomy (surgical removal of the colon).
- **Following colectomy:** Speak to your provider about recommended follow up, which may include surveillance with endoscopy, and medications to reduce the risk of polyps and cancer.

Brain (medulloblastoma) (FAP, AFAP):¹⁴

- **Ongoing:** Physical examination every year.

Desmoid tumors (FAP):¹⁴

- **Ongoing:** Abdominal palpation every year.
- **With family history or symptoms of desmoid tumors:** Your provider may discuss abdominal MRI or CT 1-3 years after colectomy and then every 5-10 years.

Pancreatic (FAP, AFAP):

- Currently, there are no pancreatic cancer screening guidelines specific to APC mutation carriers. Your provider may discuss screening or referral to a specialist.

Small bowel (duodenal and other sections) (FAP, AFAP):¹⁴

¹³ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal V.3.2017. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed April 2, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

¹⁴ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. *NCCN Guidelines Version 3.2017*. Available at www.nccn.org. Published October 2017.

- **Starting at age 20-25 years, or earlier if colectomy before age 20:** Upper endoscopy (including complete visualization of ampulla of Vater). Frequency of the endoscopy depends on the number and size of polyps identified.

Stomach (FAP, AFAP):¹⁴

- **Starting at age 20-25 years:** Examine stomach at the time of upper endoscopy.
- Surgery may be recommended based on findings of biopsy.

Thyroid (FAP, AFAP):¹⁴

- **Starting in late teenage years:** Thyroid examination every year. Your provider may discuss a thyroid ultrasound every year.

Screening guidelines (APC I1307K)

These screening guidelines are for individuals who have an APC I1307K mutation. Your healthcare provider may use these guidelines to help create a customized screening plan for you.¹³

Women and Men

Colorectal¹⁴

- **Beginning at age 40 or 10 years younger than the earliest diagnosis of colorectal cancer in a parent, sibling, or child (whichever is earlier):** Colonoscopy every 5 years.
- These recommendations may change if you have polyps, colorectal cancer, inflammatory bowel disease (IBD), or family history of colorectal cancer.

Useful resources

Colon Cancer Alliance

An organization dedicated to colon cancer prevention, funding colon cancer research and providing support to patients.

www.ccalliance.org

Hereditary Colon Cancer Foundation

A nonprofit organization serving the hereditary colorectal cancer community.

www.hcctakesguts.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions

www.kintalk.org

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ATM

The *ATM* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *ATM* is coordinating a response to damaged DNA so it can be repaired by other genes, including *BRCA1*, *NBN*, *TP53*, and *CHEK2*.

Like most genes, each person has two copies of the *ATM* gene: one inherited from each parent. A mutation in a single copy of the *ATM* gene inherited from either parent is known to increase risk of specific cancers (breast, pancreatic, prostate, and possibly others) over a lifetime.

Some studies have suggested that individuals with *ATM* mutations have a higher sensitivity to ionizing radiation, such as that used in treating cancer. More research is needed to clarify these risks further. We recommend discussing this with your provider.

In very rare cases, a person can inherit two *ATM* mutations, one from each parent. This causes a condition called ataxia-telangiectasia, which is associated with increased risk for childhood cancers, as well as impairments of the nervous and immune systems.

How common are mutations in the *ATM* gene?

Mutations in the *ATM* gene are rare—found in approximately 0.5-1% of people of Caucasian ancestry.¹ Studies to establish how common *ATM* mutations are in other populations are ongoing.

¹ Swift M, Morrell D, Cromartie E, Chamberlin AR, Skolnick MH, Bishop DT. The incidence and gene frequency of ataxia-telangiectasia in the United States. *Am J Hum Genet.* 1986;39(5):573-83.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *ATM* gene, her chances of developing breast and pancreatic cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 70 | Average US woman ² | With <i>ATM</i> mutation ^{3,4} |
|------------------|-------------------------------|---|
| Breast | 7.2% | Elevated (up to 21%) |
| Pancreatic | <1% | Elevated ⁵ |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Men

If a man has a mutation in the *ATM* gene, his chances of developing pancreatic and prostate cancer are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 70 | Average US man ² | With <i>ATM</i> mutation ^{5,6,7} |
|------------------|-----------------------------|---|
| Pancreatic | <1% | Elevated |
| Prostate | 5.9% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

² Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

³ Easton DF, Pharoah PD, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. *N Engl J Med*. 2015;372(23):2243-57.

⁴ Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol*. 2016;13(9):581-8.

⁵ Roberts NJ, Jiao Y, Yu J, et al. *ATM* mutations in patients with hereditary pancreatic cancer. *Cancer Discov*. 2012;2(1):41-6.

⁶ Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. *N Engl J Med*. 2016;375(5):443-53.

⁷ Na R, Zheng SL, Han M, et al. Germline Mutations in *ATM* and *BRCA1/2* Distinguish Risk for Lethal and Indolent Prostate Cancer and are Associated with Early Age at Death. *Eur Urol*. 2017;71(5):740-747.

Screening guidelines

These screening guidelines are for individuals with a mutation in the *ATM* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.⁸

Women

Breast:^{9,10}

- **Starting at age 25:** Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider.
- **Between ages 25-39:** Breast exam, risk assessment, and risk reduction counseling by your provider every 1-3 years.
- **Starting at age 40 or 5-10 years prior to the earliest diagnosis of breast cancer in your family (whichever is earlier):** Breast exam, risk assessment, and risk reduction counseling by your provider and mammogram every year. Your provider may discuss screening with tomosynthesis (3D mammogram) and breast MRI with contrast every year.
- Your provider may discuss the option of having a risk-reducing bilateral mastectomy (the surgical removal of both breasts) based on family history.

Pancreatic:¹¹

- Currently, there are no pancreatic cancer screening guidelines from the NCCN specific to *ATM* mutation carriers. Your provider may discuss screening or referral to a specialist.

Men

Pancreatic:¹¹

- Currently, there are no pancreatic cancer screening guidelines from the NCCN specific to *ATM* mutation carriers. Your provider may discuss screening or referral to a specialist.

Prostate:

- Currently, there are no prostate cancer screening guidelines from the NCCN specific to *ATM* mutation carriers. Your provider may discuss screening or referral to a specialist.

⁸ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V.1.2018 and Breast Cancer Screening and Diagnosis V.2.2018. © National Comprehensive Cancer Network, Inc 2018. All rights reserved. Accessed May 23, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

⁹ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. *NCCN Guidelines Version 1.2018*. Available at www.nccn.org. Published October 2017.

¹⁰ National Comprehensive Cancer Network. Breast Cancer Screening and Diagnosis. *NCCN Guidelines Version 2.2018*. Available at www.nccn.org. Published May 2018.

¹¹ Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*. 2013;62(3):339-47.

Useful resources

FORCE

Providing support, education, research, and resources for survivors and people at increased risk of cancer due to an inherited mutation or family history of cancer.

www.facingourrisk.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions.

www.kintalk.org

Susan G. Komen

Dedicated to reducing deaths from breast cancer by funding breast cancer research, ensuring access to care through community programs worldwide and supporting public health policies that help people facing breast cancer.

www.komen.org/

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BAP1

The *BAP1* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary roles of *BAP1* are to assist in the repair of damaged DNA and to regulate cell growth and division.

Like most genes, each person has two copies of the *BAP1* gene: one inherited from each parent. A mutation in a single copy of the *BAP1* gene inherited from either parent is known to increase risks of specific cancers (melanoma of the eye and skin, kidney, and lung, specifically a type called mesothelioma) as well as non-cancerous skin growths called melanocytic BAP1-mutated atypical intradermal tumors (MBAITs), over a lifetime.

Certain factors can greatly increase risk of melanoma, including a person's geographical region, ethnicity and sun exposure. For example, melanoma is 20 times more common in Caucasians than it is in African Americans.¹ The risk of kidney cancer also varies depending on whether a person has a history of smoking cigarettes or exposure to certain substances and chemicals.² The risk of lung cancer (specifically a type called mesothelioma) is impacted by exposure to asbestos and other harmful substances.³

How common are mutations in the *BAP1* gene?

Mutations in the *BAP1* gene are rare—the exact frequency is not yet known. Studies to establish the frequency of *BAP1* mutations are ongoing.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *BAP1* gene, her chances of developing melanoma of the eye and skin, kidney, and lung cancer (specifically a type called mesothelioma) are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

¹ What are the risk factors for melanoma skin cancer? American Cancer Society Website.
<http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-risk-factors> Updated February 01, 2016.

² Risk factors for kidney cancer. American Cancer Society website
<https://www.cancer.org/cancer/kidney-cancer/causes-risks-prevention/risk-factors.html>. Updated August, 1, 2017. accessed April 2, 2018.

³ What are the Risk Factors for Malignant Mesothelioma? American Cancer Society website.
<http://www.cancer.org/cancer/malignantmesothelioma/> Updated February 17, 2016. Accessed April 2, 2018.

| Cancer by age 95 | Average US woman ⁴ | With <i>BAP1</i> mutation ^{5,6,7} |
|---------------------|-------------------------------|--|
| Melanoma | 1.7% | Elevated |
| Kidney | 1.2% | Elevated |
| Lung (mesothelioma) | <0.1% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Men

If a man has a mutation in the *BAP1* gene, his chances of developing melanoma of the eye and skin, kidney, and lung cancer (specifically a type called mesothelioma) are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 95 | Average US man ⁴ | With <i>BAP1</i> mutation ^{5,6,7} |
|---------------------|-----------------------------|--|
| Melanoma | 2.7% | Elevated |
| Kidney | 2.1% | Elevated |
| Lung (mesothelioma) | <0.1% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

⁴ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

⁵ Rai K, Pilarski R, Cebulla CM, Abdel-rahman MH. Comprehensive review of *BAP1* tumor predisposition syndrome with report of two new cases. *Clin Genet*. 2016;89(3):285-94.

⁶ Carbone M, Yang H, Pass HI, Krausz T, Testa JR, Gaudino G. *BAP1* and cancer. *Nat Rev Cancer*. 2013;13(3):153-9.

⁷ Popova T, Hebert L, Jacquemin V, et al. Germline *BAP1* mutations predispose to renal cell carcinomas. *Am J Hum Genet*. 2013;92(6):974-80.

Screening guidelines

There are no published screening guidelines specific to individuals with *BAP1* mutations. Below are guidelines for individuals who have the same risk of melanoma as the average US individual. Speak with your healthcare provider about additional recommendations to reduce the risk of melanoma. Your healthcare provider may use these guidelines to help create a customized screening plan for you.

Women and Men

Melanoma:⁸

- Your healthcare provider may discuss skin exams and eye exams to screen for melanoma.
- To reduce the chance of developing melanoma, the American Cancer Society recommends limiting exposure to UV light by avoiding excess sun exposure, wearing a hat, sunglasses and long protective clothing, applying sunscreen with SPF of 30 or higher and avoiding tanning beds and sun lamps.
- Any new, unusual, or changing moles should be reported to your provider or dermatologist.

Kidney:

- Currently, there are no kidney cancer screening guidelines specific to *BAP1* mutation carriers. Your provider may discuss screening or referral to a specialist.

Lung (specifically a type called mesothelioma):

- Currently, there are no lung cancer screening guidelines specific to *BAP1* mutation carriers. Your provider may discuss screening or referral to a specialist.

Useful resources

American Melanoma Foundation

An organization supporting melanoma research, and providing advocacy and public awareness of melanoma.

www.melanomafoundation.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions.

www.kintalk.org

Version 1.1, last updated June 8, 2018

⁸ Skin Cancer Prevention and Early Detection. The American Cancer Society website. <https://www.cancer.org/cancer/skin-cancer/prevention-and-early-detection.html>. Updated March 19, 2017. Accessed April 2, 2018.

BARD1

The *BARD1* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *BARD1* is to stabilize and assist the *BRCA1* gene in repairing damaged DNA before a cell divides.

Like most genes, each person has two copies of the *BARD1* gene: one inherited from each parent. A mutation in a single copy of the *BARD1* gene inherited from either parent is known to increase risk of specific cancers (breast) over a lifetime.

How common are mutations in the *BARD1* gene?

Mutations in the *BARD1* gene are rare—the exact frequency is not yet known. Studies to establish the frequency of *BARD1* mutations are ongoing.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *BARD1* gene, her chance of developing breast cancer is greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 80 | Average US woman ¹ | With <i>BARD1</i> mutation ^{2,3} |
|------------------|-------------------------------|---|
| Breast | 10% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Men

If a man has a mutation in the *BARD1* gene, his chance of developing cancer is not known to be increased.

Additional information

Research on the *BARD1* gene is ongoing, especially research related to its impact on ovarian cancer risk.

Screening guidelines

There are no published screening guidelines specific to women with *BARD1* mutations. Below are guidelines for women who have the same breast cancer risk as the average US woman. However, your healthcare provider may recommend additional screening and risk reduction options, such as earlier and more frequent screening, screening with breast MRI, and medications to reduce the risk of breast cancer. Your healthcare provider may use these guidelines to help create a customized screening plan for you.⁴

¹ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

² De brakeleer S, De grève J, Loris R, et al. Cancer predisposing missense and protein truncating BARD1 mutations in non-BRCA1 or BRCA2 breast cancer families. *Hum Mutat.* 2010;31(3):E1175-85.

³ Couch FJ, Hart SN, Sharma P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. *J Clin Oncol.* 2015;33(4):304-11.

⁴ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer Screening and Diagnosis V.2.2018. © National Comprehensive Cancer Network, Inc 2018. All rights reserved. Accessed May 23, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Women**Breast:**⁵

- **Starting at age 25:** Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider.
- **Between ages 25-39:** Breast exam, risk assessment, and risk reduction counseling by your provider every 1-3 years.
- **Starting at age 40:** Breast exam, risk assessment, and risk reduction counseling by your provider and mammogram every year. Your provider may discuss screening with tomosynthesis.

Useful resources**FORCE**

Providing support, education, research, and resources for survivors and people at increased risk of cancer due to an inherited mutation or family history of cancer.

www.facingourrisk.org

Bright Pink

Focused on the prevention and early detection of breast and ovarian cancer in young women, while providing support for high-risk individuals.

www.brightpink.org

Susan G. Komen

Dedicated to reducing deaths from breast cancer by funding breast cancer research, ensuring access to care through community programs worldwide and supporting public health policies that help people facing breast cancer.

www.komen.org/

Version 1.1, last updated June 8, 2018

⁵ National Comprehensive Cancer Network. Breast Cancer Screening and Diagnosis. *NCCN Guidelines Version 2.2018*. Available at www.nccn.org. Published May 2018.

BMPR1A

The *BMPR1A* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *BMPR1A* is to help regulate the stability and growth of cells in the gastrointestinal tract.

Like most genes, each person has two copies of the *BMPR1A* gene, one inherited from each parent. A mutation in a single copy of the *BMPR1A* gene inherited from either parent causes juvenile polyposis syndrome (JPS), which is associated with gastrointestinal polyps, especially a type of polyp called juvenile polyps, and is also known to increase the risks of specific cancers (colorectal, stomach, pancreatic, and small bowel) over a lifetime.

Approximately 25% of individuals with JPS are the first in their family to carry the mutation.¹ This is referred to as a “*de novo*” mutation. Individuals with *de novo* mutations have the same cancer risks as those with an inherited mutation from a parent, and have a 50% chance of passing the mutation on to their children.

How common are mutations in the *BMPR1A* gene?

Mutations in the *BMPR1A* gene are rare—but approximately 20-25% of individuals with JPS have a mutation in *BMPR1A*.²

¹ Larsen Haidle J, Howe JR. 2015 December 3. Juvenile Polyposis Syndrome. In: GeneReviews® (database online). Copyright, University of Washington, Seattle. 1993-2016. Available at <http://www.ncbi.nlm.nih.gov/books/NBK1469/>. April 21, 2016.

² Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. *Ann Surg Oncol*. 1998;5(8):751-6.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *BMPR1A* gene, her chances of developing colorectal, stomach, pancreatic, and small bowel (especially in the duodenum) cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 80 | Average US woman ³ | With <i>BMPR1A</i> mutation ^{2,4} |
|------------------------|-------------------------------|--|
| Colorectal | 2.7% | 39% |
| Stomach | <1% | Elevated (21%) |
| Pancreatic | <1% | Elevated |
| Small Bowel (Duodenal) | <1% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Men

If a man has a mutation in the *BMPR1A* gene, his chances of developing colorectal, stomach, pancreatic, and small bowel (especially in the duodenum) cancer are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 80 | Average US man ³ | With <i>BMPR1A</i> mutation ^{2,4} |
|------------------------|-----------------------------|--|
| Colorectal | 3.3% | 39% |
| Stomach | <1% | Elevated (21%) |
| Pancreatic | 1.1% | Elevated |
| Small Bowel (Duodenal) | <1% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

³ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

⁴ Brosens LA, Van hattem A, Hyland LM, et al. Risk of colorectal cancer in juvenile polyposis. *Gut*. 2007;56(7):965-7.

Screening guidelines

These guidelines are for individuals with JPS who have a mutation in the *BMPR1A* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.⁵

Women and Men

Colorectal:⁶

- **Starting around age 15:** Colonoscopy every 2-3 years, or every year if polyps are found.

Stomach:⁶

- **Starting around age 15:** Upper endoscopy every 2-3 years, or every year if polyps are found. If multiple polyps lead to anemia requiring blood transfusion, your provider may discuss surgical removal of the stomach (gastrectomy).

Pancreatic:⁶

- Currently, there are no pancreatic cancer screening guidelines specific to *BMPR1A* mutation carriers. Your provider may discuss screening or referral to a specialist.

Small bowel cancer (duodenal and other sections):⁶

- Currently, there are no small bowel cancer screening guidelines specific to *BMPR1A* mutation carriers. Your provider may discuss screening or referral to a specialist.

⁵ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal. V.3.2017. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed April 2, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

⁶ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. *NCCN Guidelines Version 3.2017*. Available at www.nccn.org. Published October 2017.

Useful resources

Colon Cancer Alliance

An organization dedicated to colon cancer prevention, funding colon cancer research and providing support to patients.

www.ccalliance.org

Hereditary Colon Cancer Foundation

A nonprofit organization serving the hereditary colorectal cancer community.

www.hcctakesguts.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions

www.kintalk.org

Version 1.1, last updated June 8, 2018

BRCA1

The *BRCA1* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *BRCA1* is repairing damaged DNA before a cell divides to make more copies of itself. *BRCA1* works together with other genes such as *BARD1*, *PALB2*, and *BRCA2* to direct the repair of the DNA damage.

Like most genes, each person has two copies of the *BRCA1* gene: one inherited from each parent. A mutation in a single copy of the *BRCA1* gene inherited from either parent is known to increase risk of specific cancers (breast, ovarian, prostate, and pancreatic) over a lifetime.

How common are mutations in the *BRCA1* gene?

Mutations in the *BRCA1* gene are rare—found in approximately 1 in 450 individuals in the general population and 1 in 40 Ashkenazi Jewish individuals.^{1,2}

¹ Prevalence and penetrance of *BRCA1* and *BRCA2* mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. *Br J Cancer*. 2000;83(10):1301-8.

² Moyer VA on behalf of the US Preventive Services Task Force. Risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer in women: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. February 2014;160(4):271-81.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *BRCA1* gene, her chances of developing breast, ovarian and pancreatic cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 80 | Average US woman ³ | With <i>BRCA1</i> mutation ^{4,5,6,7} |
|------------------|-------------------------------|---|
| Breast | 10% | Up to 81% |
| Ovarian | <1% | Up to 68% |
| Pancreatic | <1% | Elevated (3-5%) |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Men

If a man has a mutation in the *BRCA1* gene, his chances of developing male breast, prostate, and pancreatic cancer are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 80 | Average US man ³ | With <i>BRCA1</i> mutation ^{7,8,9,10} |
|------------------|-----------------------------|--|
| Male breast | <0.1% | 1.8% |
| Prostate | 9.7% | Elevated |
| Pancreatic | 1.1% | Elevated (3-6%) |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

³ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

⁴ King MC, Marks JH, Mandell JB, New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in *BRCA1* and *BRCA2*. *Science*. October 2003;302(5645):643-6.

⁵ Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers. *JAMA*. 2017;317(23):2402-2416.

⁶ Mavaddat N, Peock S, Frost D, et al. Cancer risks for *BRCA1* and *BRCA2* mutation carriers: results from prospective analysis of EMBRACE. *J Natl Cancer Inst*. 2013;105(11):812-22.

⁷ Mocci E, Milne RL, Mendez-Villamil EY, et al. Risk of pancreatic cancer in breast cancer families from the breast cancer family registry. *Cancer Epidemiology Biomarkers Prev*. May 2013;22(5):803-11.

⁸ Tai YC, Domchek S, Parmigiani G, Chen S. Breast cancer risk among male *BRCA1* and *BRCA2* mutation carriers. *J Natl Cancer Inst*. December 2007; 99(23):1811-4.

⁹ Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in *BRCA1* or *BRCA2*: a review of the literature. *J Clin Oncol*. February 2004; 22(4):735-42.

¹⁰ Leongamornlert D, Mahmud N, Tymrakiewicz M, et al. Germline *BRCA1* mutations increase prostate cancer risk. *Br J Cancer*. May 2012; 106(10):1697-701.

Additional information

The *BRCA1* gene was the first gene linked to families with hereditary breast and ovarian cancer. The evidence for increased cancer risk associated with mutations this gene was discovered by Dr. Mary-Claire King. Researchers have identified hundreds of different mutations in the *BRCA1* gene that cause an increased risk of cancer since that time.

Screening guidelines

These screening guidelines are for individuals who have a mutation in the *BRCA1* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.¹¹

Women

Breast and ovarian:¹²

- **Starting at age 18:** Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider. Performing regular breast self exams may help increase breast awareness, especially when checked at the end of the menstrual cycle.
- **Starting at age 25:** Breast exam by your provider every 6-12 months.
- **Between ages 25-29 or individualized based on family history:** Breast MRI screening with contrast every year. Your provider may discuss screening with tomosynthesis (3D mammogram) if MRI is unavailable.
- **Between ages 30-75:** Breast MRI screening with contrast and mammogram every year. Your provider may discuss screening with tomosynthesis and may wish to alternate between these two screenings every 6 months.
- **Between ages 35-40, or after you are finished having children:** NCCN recommends a risk-reducing salpingo-oophorectomy (the surgical removal of the ovaries and fallopian tubes) to lower the risk of developing breast and ovarian cancers.
- **After age 75:** Your provider may discuss an individualized management plan with you.
- Your provider may discuss the option of having a risk-reducing bilateral mastectomy (the surgical removal of both breasts).
- Your provider may discuss the use of medications that might reduce the risk of developing breast or ovarian cancer.
- **Starting at age 30-35:** Your provider may discuss circumstances where ovarian cancer screening with transvaginal ultrasound and a blood test for a protein called CA-125 are helpful, but these techniques have not been shown to be effective in detecting early ovarian cancer.

¹¹ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V.1.2018. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed April 2, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

¹² National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. *NCCN Guidelines Version 1.2018*. Available at www.nccn.org. Published October 2017.

Pancreatic:¹²

- Currently, there are no pancreatic cancer screening guidelines specific to *BRCA1* mutation carriers. Your provider may discuss screening or referral to a specialist.

Men

Male breast:¹²

- **Starting at age 35:** Breast self-exam training and education. Breast exam by your provider every year.

Pancreatic:¹²

- Currently, there are no pancreatic cancer screening guidelines specific to *BRCA1* mutation carriers. Your provider may discuss screening or referral to a specialist.

Prostate:¹²

- **Starting at age 45:** Your healthcare provider may discuss prostate cancer screening.

Useful resources

FORCE

Providing support, education, research, and resources for survivors and people at increased risk of cancer due to an inherited mutation or family history of cancer.

www.facingourrisk.org

Bright Pink

Focused on the prevention and early detection of breast and ovarian cancer in young women, while providing support for high-risk individuals.

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Dedicated to reducing deaths from breast cancer by funding breast cancer research, ensuring access to care through community programs worldwide and supporting public health policies that help people facing breast cancer.

www.komen.org

His Breast Cancer

Information about male breast cancer. Here to inform, educate, bring awareness, and teach prevention regarding breast cancer in men.

www.hisbreastcancer.org

Version 1.1, last updated June 8, 2018

BRCA2

The *BRCA2* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *BRCA2* is repairing damaged DNA before a cell divides to make more copies of itself. *BRCA2* works together with other genes, such as *BRCA1*, *PALB2*, and the *RAD51* gene complex to direct the repair of the damage.

Like most genes, each person has two copies of the *BRCA2* gene: one inherited from each parent. A mutation in a single copy of the *BRCA2* gene inherited from either parent is known to increase risk of specific cancers (breast, ovarian, prostate, pancreatic, melanoma) over a lifetime.

In very rare cases, a person can inherit two *BRCA2* mutations, one from each parent. This causes a blood condition called Fanconi anemia, which is associated with bone marrow failure, physical disabilities, and childhood cancers.

How common are mutations in the *BRCA2* gene?

Mutations in the *BRCA2* gene are rare—found in approximately 1 in 1,100 individuals in the general population and 1 in 40 Ashkenazi Jewish individuals.^{1,2}

¹ Prevalence and penetrance of *BRCA1* and *BRCA2* mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. *Br J Cancer*. 2000;83(10):1301-8.

² Moyer VA on behalf of the US Preventive Services Task Force. Risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer in women: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. February 2014;160(4):271-81.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *BRCA2* gene, her chances of developing breast, ovarian, melanoma, and pancreatic cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 80 | Average US woman ³ | With <i>BRCA2</i> mutation ^{4,5,6,7,8,9} |
|------------------|-------------------------------|---|
| Breast | 7.2% | Up to 85% |
| Ovarian | <1% | Up to 23% |
| Melanoma | <1% | Elevated |
| Pancreatic | <1% | Elevated (2-3%) |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

³Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

⁴King MC, Marks JH, Mandell JB, New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in *BRCA1* and *BRCA2*. *Science*. October 2003;302(5645):643-6.

⁵Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers. *JAMA*. 2017;317(23):2402-2416.

⁶Mavaddat N, Peock S, Frost D, et al. Cancer risks for *BRCA1* and *BRCA2* mutation carriers: results from prospective analysis of EMBRACE. *J Natl Cancer Inst*. 2013;105(11):812-22.

⁷Cancer risks in *BRCA2* mutation carriers. Journal of the National Cancer Institute, 1999. *Journal of the National Cancer Institute*. August 1999; 91(15):1310-6.

⁸Mocci E, Milne RL, Mendez-Villamil EY, et al. Risk of pancreatic cancer in breast cancer families from the breast cancer family registry. *Cancer Epidemiology Biomarkers Prev*. May 2013;22(5):803-11.

⁹Gumaste PV, Penn LA, Cymerman RM, Kirchhoff T, Polsky D, Mclellan B. Skin cancer risk in *BRCA1/2* mutation carriers. *Br J Dermatol*. 2015;172(6):1498-506.

Men

If a man has a mutation in the *BRCA2* gene, his chances of developing male breast, prostate, pancreatic cancer and melanoma are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 80 | Average US man ³ | With <i>BRCA2</i> mutation ^{7,8,9,10,11,12,13,} |
|------------------|-----------------------------|--|
| Male breast | <1% | Elevated (6-9%) |
| Prostate | 9.7% | Elevated (7-34%) |
| Pancreatic | <1% | Elevated (3-5%) |
| Melanoma | 1.2% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Screening guidelines

These screening guidelines are for individuals who have a mutation in the *BRCA2* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.¹⁴

¹⁰ Thompson D, Easton D: Variation in cancer risks, by mutation position, in *BRCA2* mutation carriers. *Am J Hum Genet.* 2001;68:410-419.

¹¹ Tai YC, Domchek S, Parmigiani G, Chen S. Breast cancer risk among male *BRCA1* and *BRCA2* mutation carriers. *J Natl Cancer Inst.* December 2007; 99(23):1811-4.

¹² Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in *BRCA1* or *BRCA2*: a review of the literature. *J Clin Oncol.* February 2004; 22(4):735-42.

¹³ van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al. Cancer risks in *BRCA2* families: estimates for sites other than breast and ovary. *J Med Genet.* September 2005; 42(9):711-9.

¹⁴ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V.1.2018. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed April 2, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Women

Breast and ovarian:¹⁵

- **Starting at age 18:** Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider. Performing regular breast self exams may help increase breast awareness, especially when checked at the end of the menstrual cycle.
- **Starting at age 25:** Breast exam by your provider every 6-12 months.
- **Between ages 25-29 or individualized based on family history:** Breast MRI screening with contrast every year. Your provider may discuss screening with tomosynthesis (3D mammogram) if MRI is unavailable.
- **Between ages 30-75:** Breast MRI screening with contrast and mammogram every year. Your provider may discuss screening with tomosynthesis and may wish to alternate between these two screenings every 6 months.
- **Between ages 40-45, or after you are finished having children:** NCCN recommends a risk-reducing salpingo-oophorectomy (the surgical removal of the ovaries and fallopian tubes) to lower the risk of developing breast and ovarian cancers.
- **After age 75:** Your provider may discuss an individualized management plan with you.
- Your provider may discuss the option of having a risk-reducing bilateral mastectomy (the surgical removal of both breasts).
- Your provider may discuss the use of medications that might reduce the risk of developing breast or ovarian cancer.
- **Starting at age 30-35:** Your provider may discuss circumstances where ovarian cancer screening with transvaginal ultrasound and a blood test for a protein called CA-125 are helpful, but these techniques have not been shown to be effective in detecting early ovarian cancer.

Melanoma:^{15,16}

- Your healthcare provider may discuss skin exams and eye exams for melanoma screening.
- To reduce the chance of developing melanoma, the American Cancer Society recommends limiting exposure to UV light by avoiding excess sun exposure, wearing a hat, sunglasses and long protective clothing, applying sunscreen with SPF of 30 or higher and avoiding tanning beds and sun lamps.
- Any new, unusual, or changing moles should be reported to your provider or dermatologist.

¹⁵ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. *NCCN Guidelines Version 1.2018*. Available at www.nccn.org. Published October 2017.

¹⁶ Skin Cancer Prevention and Early Detection. The American Cancer Society website.

<https://www.cancer.org/cancer/skin-cancer/prevention-and-early-detection.html>. Updated March 19, 2017. Accessed April 2, 2018.

Pancreatic:^{15,17}

- Currently, there are no pancreatic cancer screening guidelines specific to *BRCA2* mutation carriers. Your provider may discuss screening or referral to a specialist.

MenMale breast:¹⁵

- **Starting at age 35:** Breast self-exam training and education. Breast exam by your provider every year.

Prostate:¹⁵

- **Starting at age 45:** NCCN recommends prostate cancer screening.

Melanoma:^{15,16,}

- Your healthcare provider may discuss skin exams and eye exams for melanoma screening.
- To reduce the chance of developing melanoma, the American Cancer Society recommends limiting exposure to UV light by avoiding excess sun exposure, wearing a hat, sunglasses and long protective clothing, applying sunscreen with SPF of 30 or higher and avoiding tanning beds and sun lamps.
- Any new, unusual, or changing moles should be reported to your provider or dermatologist.

Pancreatic:^{15,17}

- Currently, there are no pancreatic cancer screening guidelines specific to *BRCA2* mutation carriers. Your provider may discuss screening or referral to a specialist.

¹⁷ Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*. 2013;62(3):339-47.

Useful resources

FORCE

Providing support, education, research, and resources for survivors and people at increased risk of cancer due to an inherited mutation or family history of cancer.

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His Breast Cancer

Information about male breast cancer. Here to inform, educate, bring awareness, and teach prevention regarding breast cancer in men.

www.hisbreastcancer.org

Version 1.1, last updated June 8, 2018

BRIP1

The *BRIP1* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *BRIP1* is the unwinding of damaged DNA so that it can be repaired.

Like most genes, each person has two copies of the *BRIP1* gene: one inherited from each parent. A mutation in a single copy of the *BRIP1* gene inherited from either parent is known to increase risk of specific cancers (breast and ovarian) over a lifetime.

In very rare cases, a person can inherit two *BRIP1* mutations, one from each parent. This causes a blood condition called Fanconi anemia, which is associated with bone marrow failure, physical disabilities, and childhood cancers.

How common are mutations in the *BRIP1* gene?

Mutations in the *BRIP1* gene are rare—the exact frequency is not yet known. Studies to establish the frequency of *BRIP1* mutations are ongoing.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *BRIP1* gene, her chances of developing breast and ovarian cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 80 | Average US woman ¹ | With <i>BRIP1</i> mutation ^{2,3,4,5,6,7} |
|------------------|-------------------------------|---|
| Breast | 10% | Elevated |
| Ovarian | <1% | Elevated (up to 6%) |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Men

If a man has a mutation in the *BRIP1* gene, his chance of developing cancer is not known to be increased.

¹ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov1./devcan>) V 6.7.5. Accessed April 2018.

² Seal S, Thompson D, Renwick A, et al. Truncating mutations in the Fanconi anemia J gene BRIP1 are low-penetrance breast cancer susceptibility alleles. *Nat Genet.* 2006 Nov;38(11):1239-4

³ Easton DF, Pharoah PD, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. *N Engl J Med.* 2015;372(23):2243-57.

⁴ Ramus SJ, Song H, Dicks E, et al. Germline Mutations in the BRIP1, BARD1, PALB2, and NBN Genes in Women With Ovarian Cancer. *J Natl Cancer Inst.* 2015;107(11).

⁵ Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol.* 2016;13(9):581-8.

⁶ Walsh T, Casadei S, Lee MK, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc Natl Acad Sci U S A.* 2011 Nov 1;108(44):18032-7.

⁷ Rafnar T, Gudbjartsson DF, Sulem P, et al. Mutations in BRIP1 confer high risk of ovarian cancer. *Nat Genet.* 2011 Oct 2;43(11):1104-7. doi: 10.1038/ng.955.

Screening guidelines

These screening guidelines are for women who have a mutation in the *BRIP1* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.⁸

Women

Breast:⁹

- There are currently no breast cancer screening guidelines specific to women with *BRIP1* mutations. Therefore, these guidelines are for women who have the same breast cancer risk as the average US woman. However, your healthcare provider may recommend additional breast cancer screening and risk reduction options, such as earlier and more frequent screening, screening using breast MRI, and medications to reduce the risk of breast cancer.
- **Starting at age 25:** Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider.
- **Between ages 25-39:** Breast exam, risk assessment, and risk reduction counseling by your provider every 1-3 years.
- **Starting at age 40:** Breast exam, risk assessment, and risk reduction counseling by your provider and mammogram every year. Your provider may discuss screening with tomosynthesis (3D mammogram).

Ovarian:¹⁰

- **Starting at age 45-50, or earlier based on family history of ovarian cancer:** Your healthcare provider may discuss a risk-reducing salpingo-oophorectomy (the surgical removal of the ovaries and fallopian tubes) with you to lower the risk of developing ovarian cancer.

⁸ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V.1.2018 and Breast Cancer Screening and Diagnosis V.2.2018. © National Comprehensive Cancer Network, Inc 2018. Accessed May 23, 2018. To view the most recent and complete version of the guideline, go online to [NCCN.org](http://www.nccn.org). NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

⁹ National Comprehensive Cancer Network. Breast Cancer Screening and Diagnosis. *NCCN Guidelines Version 2.2018*. Available at www.nccn.org. Published May 2018.

¹⁰ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. *NCCN Guidelines Version 1.2018*. Available at www.nccn.org. Published October 2017.

Useful resources

FORCE

Providing support, education, research, and resources for survivors and people at increased risk of cancer due to an inherited mutation or family history of cancer.

www.facingourrisk.org

Bright Pink

Focused on the prevention and early detection of breast and ovarian cancer in young women, while providing support for high-risk individuals.

www.brightpink.org

Susan G. Komen

Dedicated to reducing deaths from breast cancer by funding breast cancer research, ensuring access to care through community programs worldwide and supporting public health policies that help people facing breast cancer.

www.komen.org/

Version 1.1, last updated June 8, 2018

CDH1

The *CDH1* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *CDH1* is to send signals between epithelial cells, or the cells that cover the surfaces and cavities of the body. This signaling allows epithelial cells to interact and stick together to prevent cancer cells from spreading and invading tissues.

Like most genes, each person has two copies of the *CDH1* gene: one inherited from each parent. A mutation in a single copy of the *CDH1* gene inherited from either parent is known to cause hereditary diffuse gastric cancer (HDGC). *CDH1* mutations are associated with increased risk of specific cancers (breast, particularly a type called lobular breast cancer and gastric, particularly a rare type called diffuse gastric cancer) over a lifetime.

How common are mutations in the *CDH1* gene?

Mutations in the *CDH1* gene are rare—but they are estimated to account for about 1% of all stomach cancers.¹

How mutations in this gene impact risk

Women

If a woman has a mutation in the *CDH1* gene, her chances of developing breast cancer (particularly a type called lobular breast cancer) and gastric (also called stomach) cancer, particularly a rare type called diffuse gastric cancer, are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 80 | Average US woman ² | With <i>CDH1</i> mutation ^{3,4} |
|------------------|-------------------------------|--|
| Breast | 10% | 39-42% |
| Stomach | <1% | 56-83% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

¹Brooks-Wilson AR, Kaurah P, Suriano G, et al. Germline E-cadherin mutations in hereditary diffuse gastric cancer: assessment of 42 new families and review of genetic screening criteria. *J Med Genet.* 2004;41(7):508-17.

²Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

³Hansford S, Kaurah P, Li-chang H, et al. Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. *JAMA Oncol.* 2015;1(1):23-32.

⁴Pharoah PD, Guilford P, Caldas C. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. *Gastroenterology.* 2001;121(6):1348-53.

Men

If a man has a mutation in the *CDH1* gene, his chance of developing gastric (also called stomach) cancer, particularly a rare type called diffuse gastric cancer, is greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 80 | Average US man ² | With <i>CDH1</i> mutation ^{3,4} |
|------------------|-----------------------------|--|
| Stomach | <1% | 67-70% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Screening guidelines

These screening guidelines are for individuals with a mutation in the *CDH1* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.⁵

Women

Breast:^{6,7}

- **Starting at age 25:** Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider.
- **Between ages 25-29:** Breast exam, risk assessment, and risk reduction counseling by your provider every 1-3 years.
- **Starting at age 30 or 5-10 years prior to the earliest diagnosis of breast cancer in your family (whichever is earlier):** Breast exam, risk assessment, and risk reduction counseling by your provider and mammogram every year. Your provider may discuss screening with tomosynthesis (3D mammogram) and breast MRI with contrast every year.
- Your provider may discuss the option of having a risk-reducing bilateral mastectomy (the surgical removal of both breasts) based on family history.

⁵ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V.1.2018, Breast Cancer Screening and Diagnosis V.2.2018, and Gastric Cancer V.1.2018. © National Comprehensive Cancer Network, Inc 2018. All rights reserved. Accessed May 23, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

⁶ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. *NCCN Guidelines Version 1.2018*. Available at www.nccn.org. Published October 2017.

⁷ National Comprehensive Cancer Network. Breast Cancer Screening and Diagnosis. *NCCN Guidelines Version 2.2018*. Available at www.nccn.org. Published May 2018.

Gastric:⁸

- **Between ages 18-40, or earlier based on family history of gastric cancer:** NCCN recommends a risk-reducing gastrectomy (the surgical removal of the stomach). Prior to gastrectomy, NCCN recommends an initial endoscopy (examination of digestive tract).
- **For those who choose not to undergo risk-reducing gastrectomy:** upper endoscopy with multiple biopsies every 6-12 months.

Men

Gastric⁸

- **Between ages 18-40, or earlier based on family history of gastric cancer:** NCCN recommends a risk-reducing gastrectomy (the surgical removal of the stomach). Prior to gastrectomy, NCCN recommends an initial endoscopy (examination of digestive tract) with multiple biopsies.
- For those who choose not to undergo risk-reducing gastrectomy: upper endoscopy with multiple biopsies every 6-12 months.

Useful resources

FORCE

Providing support, education, research, and resources for survivors and people at increased risk of cancer due to an inherited mutation or family history of cancer.

www.facingourrisk.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions

www.kintalk.org

No Stomach For Cancer

Supporting research and uniting the caring power of people worldwide affected by stomach cancer and Hereditary Diffuse Gastric Cancer.

www.nostomachforcancer.org

Susan G. Komen

Dedicated to reducing deaths from breast cancer by funding breast cancer research, ensuring access to care through community programs worldwide and supporting public health policies that help people facing breast cancer.

www.komen.org/

Version 1.1, last updated June 8, 2018

⁸ National Comprehensive Cancer Network. Gastric Cancer. *NCCN Guidelines Version 1.2018*. Available at www.nccn.org. Published March 2018.

CDK4

The *CDK4* gene is an oncogene. Oncogenes are involved in cell growth. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *CDK4* is to guide the cell through the process of the copying its genetic material in order to divide.

Like most genes, each person has two copies of the *CDK4* gene: one inherited from each parent. A mutation in a single copy of the *CDK4* gene inherited from either parent is known to increase risk of melanoma over a lifetime.

Individuals with a *CDK4* mutation have an increased risk of developing dysplastic nevi (atypical moles) which must be monitored because they can change into melanoma. Certain factors can greatly increase risk of melanoma, including a person's geographical region, ethnicity and sun exposure. For example, melanoma is 20 times more common in Caucasians than it is in African Americans.¹

How common are mutations in the *CDK4* gene?

Mutations in the *CDK4* gene are rare—the exact frequency is not yet known. Studies to establish the frequency of *CDK4* mutations are ongoing.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *CDK4* gene, her chance of developing melanoma is greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 95 | Average US woman ² | With <i>CDK4</i> mutation ^{3,4} |
|------------------|-------------------------------|--|
| Melanoma | 1.7% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

¹ What are the risk factors for melanoma skin cancer? American Cancer Society website. <http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-risk-factors> Updated May 20, 2016. Accessed April 2, 2018

² Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

³ Goldstein AM, Chan M, Harland M, et al. High-risk melanoma susceptibility genes and pancreatic cancer, neural system tumors, and uveal melanoma across GenoMEL. *Cancer Res.* 2006;66(20):9818-28.

⁴ Puntervoll HE, Yang XR, Vetti HH, et al. Melanoma prone families with *CDK4* germline mutation: phenotypic profile and associations with MC1R variants. *J Med Genet.* 2013;50(4):264-70.

Men

If a man has a mutation in the *CDK4* gene, his chance of developing melanoma is greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 95 | Average US man ² | With <i>CDK4</i> mutation ^{3,4} |
|------------------|-----------------------------|--|
| Melanoma | 2.7% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Additional information

Not all *CDK4* mutations are linked to increased cancer risk.

For *CDK4*, only chr12:g.58145429-58145431 (codon 24) is analyzed, because other positions are not known to impact cancer risk.

Screening guidelines

There are no published screening guidelines specific to individuals with *CDK4* mutations. Below are guidelines for individuals who have the same risk of melanoma as the average US man and woman. Speak with your healthcare provider about additional recommendations to reduce the risk of melanoma. Your healthcare provider may use these guidelines to help create a customized screening plan for you.

Women and Men

Melanoma:⁵

- Your healthcare provider may discuss skin exams and eye exams for melanoma screening.
- To reduce the chance of developing melanoma, the American Cancer Society recommends limiting exposure to UV light by avoiding excess sun exposure, wearing a hat, sunglasses and long protective clothing, applying sunscreen with SPF of 30 or higher and avoiding tanning beds and sun lamps.
- Any new, unusual, or changing moles should be reported to your provider or dermatologist.

⁵Skin Cancer Prevention and Early Detection. The American Cancer Society website. <https://www.cancer.org/cancer/skin-cancer/prevention-and-early-detection.html>. Updated March 19, 2017. Accessed April 2, 2018.

Useful resources

American Melanoma Foundation

An organization supporting melanoma research, and providing advocacy and public awareness of melanoma.

www.melanomafoundation.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions.

www.kintalk.org

Version 1.1, last updated June 8, 2018

CDKN2A

The *CDKN2A* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *CDKN2A* is to code for two different proteins called p16(INK4a) and p14(ARF). The p16(INK4a) protein interacts with other proteins to help regulate how the cell copies itself. The p14(ARF) protein interacts with other proteins to help regulate cell division and death. Mutations in *CDKN2A* can affect one or both of the proteins.

Like most genes, each person has two copies of the *CDKN2A* gene: one inherited from each parent. A mutation in a single copy of the *CDKN2A* gene inherited from either parent is known to increase risks of specific cancers (melanoma, including multiple melanomas diagnosed at younger ages, and pancreatic) over a lifetime.

Mutations in the *CDKN2A* gene are thought to account for 20-40% of hereditary melanoma.¹ Individuals with a *CDKN2A* mutation have an increased risk of developing dysplastic nevi (atypical moles) which must be monitored because they can change into melanoma.

Certain factors can greatly increase risk of melanoma, including person's geographical region, ethnicity and sun exposure. For example, melanoma is 20 times more common in Caucasians than it is in African Americans.² The risk of pancreatic cancer also varies depending on whether a person has a history of smoking cigarettes.³

In general, the risks of melanoma and pancreatic cancer are lower for mutations in the *CDKN2A* gene that affect the p14(ARF) protein compared to mutations that affect the p16(INK4a) protein, but the age of onset of pancreatic cancer may be younger.^{1,3,4}

How common are mutations in the *CDKN2A* gene?

Mutations in the *CDKN2A* gene are rare—the exact frequency is not yet known. Studies to establish the frequency of *CDKN2A* mutations are ongoing.

¹ Goldstein AM, Chan M, Harland M, et al. High-risk melanoma susceptibility genes and pancreatic cancer, neural system tumors, and uveal melanoma across GenoMEL. *Cancer Res.* 2006;66(20):9818-28.

² What are the risk factors for melanoma skin cancer? American Cancer Society website. <http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-risk-factors> Updated May 20, 2016. Accessed April 2, 2018

³ McWilliams RR, Wieben ED, Rabe KG, et al. Prevalence of *CDKN2A* mutations in pancreatic cancer patients: implications for genetic counseling. *Eur J Hum Genet.* 2011;19(4):472-8.

⁴ Bishop DT, Demenais F, Goldstein AM, et al. Geographical variation in the penetrance of *CDKN2A* mutations for melanoma. *J Natl Cancer Inst.* 2002;94(12):894-903.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *CDKN2A* gene, her chances of developing melanoma and pancreatic cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 80 | Average US woman ⁵ | With <i>CDKN2A</i> mutation ^{1,3,4,6,7,8,9} |
|------------------|-------------------------------|--|
| Melanoma | 1.4% | 28-67% |
| Pancreatic | <1% | 14-58% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Men

If a man has a mutation in the *CDKN2A* gene, his chances of developing melanoma and pancreatic cancer are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 80 | Average US man ⁵ | With <i>CDKN2A</i> mutation ^{1,3,4,6,7,8,9} |
|------------------|-----------------------------|--|
| Melanoma | 2% | 28-67% |
| Pancreatic | 1.1% | 14-58% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

⁵ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

⁶ Begg CB, Orlow I, Hummer AJ, et al. Lifetime risk of melanoma in CDKN2A mutation carriers in a population-based sample. *J Natl Cancer Inst.* 2005;97(20):1507-15.

⁷ Vasen H, Ibrahim I, Ponce CG, et al. Benefit of Surveillance for Pancreatic Cancer in High-Risk Individuals: Outcome of Long-Term Prospective Follow-Up Studies From Three European Expert Centers. *J Clin Oncol.* 2016;34(17):2010-9.

⁸ Vasen HF, et al. Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). *Int J Cancer.* 2000 87:809-11.

⁹ Helgadottir H, Höiom V, Jönsson G, et al. High-Risk of tobacco-related cancers in CDKN2A mutation-positive melanoma families. *J Med Genet.* 2014;51(8):545-52.

Screening guidelines

There are no published screening guidelines specific to individuals with *CDKN2A* mutations. Below are guidelines for individuals who have the same risk of melanoma as the average US man or woman. Speak with your healthcare provider about additional recommendations to reduce the risk of melanoma. Your healthcare provider may use these guidelines to help create a customized screening plan for you.

Women and Men

Melanoma:¹⁰

- Your healthcare provider may discuss skin exams and eye exams for melanoma screening.
- To reduce the chance of developing melanoma, the American Cancer Society recommends limiting exposure to UV light by avoiding excess sun exposure, wearing a hat, sunglasses and long protective clothing, applying sunscreen with SPF of 30 or higher and avoiding tanning beds and sun lamps.
- Any new, unusual, or changing moles should be reported to your provider or dermatologist.

Pancreatic:¹¹

- Currently, there are no pancreatic cancer screening guidelines specific to *CDKN2A* mutation carriers. Your provider may discuss screening or referral to a specialist.

Useful resources

American Melanoma Foundation

An organization supporting melanoma research, and providing advocacy and public awareness of melanoma.

www.melanomafoundation.org

National Pancreas Foundation

An organization committed to funding pancreatic cancer research, and providing support and education about pancreatic cancer.

www.pancreasfoundation.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions.

www.kintalk.org

Version 1.1, last updated June 8, 2018

¹⁰ Skin Cancer Prevention and Early Detection. The American Cancer Society website. <https://www.cancer.org/cancer/skin-cancer/prevention-and-early-detection.html>. Updated March 19, 2017. Accessed April 2, 2018.

¹¹ Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*. 2013;62(3):339-47.

CHEK2

The *CHEK2* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *CHEK2* is to pause cell division in order to make the critical decision of whether to repair damaged DNA or instruct the cell to die by a process known as apoptosis. The death of cells with significant DNA damage helps to prevent these cells from replicating out of control and forming a tumor.

Like most genes, each person has two copies of the *CHEK2* gene: one inherited from each parent. A mutation in a single copy of the *CHEK2* gene inherited from either parent is known to increase risk of specific cancers (including breast, colorectal, prostate, and possibly others) over a lifetime.

Lifetime breast cancer risk estimates for women with *CHEK2* mutations range from 20% for those with no relatives with breast cancer to 44% for those with strong family history (defined as more than one close relative affected with breast cancer).^{1,2} Further research is needed to understand the interactions of *CHEK2* and family history on lifetime breast cancer risk.

Mutations in the *CHEK2* gene are not common in the general population. But if an individual inherits two *CHEK2* mutations (one from each parent), they may have a significantly increased risk for cancer, particularly female breast cancer as an adult.³

How common are mutations in the *CHEK2* gene?

Mutations in the *CHEK2* gene are rare—one mutation is found in approximately 3-7 out of 1,000 (0.3-0.7%) people of Dutch descent.^{4,5} Studies to establish how common *CHEK2* mutations are in other populations are ongoing.

¹ Cybulski C, Wokołarczyk D, Jakubowska A, et al. Risk of breast cancer in women with a *CHEK2* mutation with and without a family history of breast cancer. *J Clin Oncol*. 2011 Oct 1;29(28):3747-52.

² Weischer M, Bojesen SE, Ellervik C, Tybjaerg-Hansen A, Nordestgaard BG. *CHEK2**1100delC genotyping for clinical assessment of breast cancer risk: meta-analyses of 26,000 patient cases and 27,000 controls. *J Clin Oncol*. 2008 Feb 1;26(4):542-8.

³ Adank MA, Jonker MA, Kluijdt I, et al. *CHEK2**1100delC Homozygosity is Associated With a High Breast Cancer Risk in Women. *J Med Genet*. 2011;48(12):860-863.

⁴ Offit K, Pierce H, Kirchhoff T, et al. Frequency of *CHEK2**1100delC in New York breast cancer cases and controls. *BMC Med Genet*. 2003;4:1.

⁵ Neuhausen S, Dunning A, Steele L, et al. Role of *CHEK2**1100delC in unselected series of non-BRCA1/2 male breast cancers. *Int J Cancer*. 2004;108(3):477-8.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *CHEK2* gene, her chances of developing breast and colorectal cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 70 | Average US woman ⁶ | With <i>CHEK2</i> mutation ^{1,2,7,8} |
|------------------|-------------------------------|---|
| Breast | 7.2% | 20-44% |
| Colorectal | 1.6% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Men

If a man has a mutation in the *CHEK2* gene, his chance of developing colorectal and prostate cancers is greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 70 | Average US man ⁶ | With <i>CHEK2</i> mutation ^{7,8,9} |
|------------------|-----------------------------|---|
| Colorectal | 2% | Elevated |
| Prostate | 5.9% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Additional information

CHEK2 studies have focused on one specific mutation.

The majority of studies related to *CHEK2* are for individuals with one specific mutation called 1100delC. This mutation is more commonly reported in those of Dutch ancestry.

⁶ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

⁷ Han FF, Guo CL, Liu LH. The effect of CHEK2 variant I157T on cancer susceptibility: evidence from a meta-analysis. *DNA Cell Biol.* 2013;32(6):329-35.

⁸ Ma X, Zhang B, Zheng W. Genetic variants associated with colorectal cancer risk: comprehensive research synopsis, meta-analysis, and epidemiological evidence. *Gut.* 2014;63(2):326-36.

⁹ Cybulski C, Wokołorczyk D, Huzarski T, Byrski T, Gronwald J, Górski B, et al. A large germline deletion in the Chek2 kinase gene is associated with an increased risk of prostate cancer. *J Med Genet.* 2006 Nov;43(11):863-6.

Screening guidelines

These screening guidelines are for women with a mutation in the *CHEK2* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.¹⁰

Women

Breast:^{11,12}

- **Starting at age 25:** Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider.
- **Between ages 25-39:** Breast exam, risk assessment, and risk reduction counseling by your provider every 1-3 years.
- **Starting at age 40 or 5-10 years prior to the earliest diagnosis of breast cancer in your family (whichever is earlier):** Breast exam, risk assessment, and risk reduction counseling by your provider and mammogram every year. Your provider may discuss screening with tomosynthesis (3D mammogram) and breast MRI with contrast every year.

Colorectal:¹³

- **Beginning at age 40 or 10 years younger than the earliest diagnosis of colorectal cancer in a parent, sibling, or child (whichever is earlier):** Colonoscopy every 5 years.
- These recommendations may change if you have polyps, colorectal cancer, inflammatory bowel disease (IBD), or family history of colorectal cancer.

Men

Colorectal:¹³

- **Beginning at age 40 or 10 years younger than the earliest diagnosis of colorectal cancer in a parent, sibling, or child (whichever is earlier):** Colonoscopy every 5 years.
- These recommendations may change if you have polyps, colorectal cancer, inflammatory bowel disease (IBD), or family history of colorectal cancer.

¹⁰ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V.1.2018, Breast Cancer Screening and Diagnosis V.2.2018, and Genetic/Familial High-Risk Assessment: Colorectal V.3.2017. © National Comprehensive Cancer Network, Inc 2018. All rights reserved. Accessed May 23, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

¹¹ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. *NCCN Guidelines Version 1.2018*. Available at www.nccn.org. Published October 2017.

¹² National Comprehensive Cancer Network. Breast Cancer Screening and Diagnosis. *NCCN Guidelines Version 2.2018*. Available at www.nccn.org. Published May 2018.

¹³ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal Cancer. *NCCN Guidelines Version 3.2017*. Available at www.nccn.org. Published October 2017.

Prostate:

- Currently, there are no prostate cancer screening guidelines specific to *CHEK2* mutation carriers. Your provider may discuss earlier or more frequent screening or referral to a specialist.

Useful resources**FORCE**

Providing support, education, research, and resources for survivors and people at increased risk of cancer due to an inherited mutation or family history of cancer.

www.facingourrisk.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions.

www.kintalk.org

Susan G. Komen

Dedicated to reducing deaths from breast cancer by funding breast cancer research, ensuring access to care through community programs worldwide and supporting public health policies that help people facing breast cancer.

www.komen.org/

Version 1.1, last updated June 8, 2018

EPCAM

The *EPCAM* gene is associated with an increased risk of cancer because it is located next to the *MSH2* gene. *MSH2* works together with other genes, including *MSH6* and *MSH3*, to scan the DNA for mistakes and signal for other genes, including *MLH1* and *PMS2*, to make repairs. Certain large deletions at the far end of the *EPCAM* gene can inactivate *MSH2*.

Like most genes, each person has two copies of the *EPCAM* gene: one inherited from each parent. A mutation in a single copy of the *EPCAM* gene inherited from either parent that impairs the function of the *MSH2* gene causes Lynch syndrome, which is known to increase risks of specific cancers (colorectal, uterine, ovarian, and other cancers) over a lifetime.

In very rare cases, a person can inherit two *EPCAM* mutations, one from each parent. This causes a condition called constitutional mismatch repair deficiency (CMMR-D), which is associated with cancers in childhood such as colorectal, small intestine, brain, leukemia/lymphoma, and others.

How common are mutations in the *EPCAM* gene?

Mutations that cause Lynch syndrome are rare—found in approximately 1 in 370 individuals.¹ Lynch syndrome accounts for approximately 3% of all colorectal cancers.²

¹ Hampel H, De la chapelle A. The search for unaffected individuals with Lynch syndrome: do the ends justify the means?. *Cancer Prev Res (Phila)*. 2011;4(1):1-5.

² Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. *Am J Gastroenterol*. 2014;109(8):1159-79.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *EPCAM* gene, her chances of developing brain, colorectal, hepatobiliary tract, ovarian, pancreatic, sebaceous neoplasms, small bowel, stomach, urinary tract, and uterine cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 70 | Average US woman ^{3,4} | With <i>EPCAM</i> mutation ^{5,6,7,8,9,10,11} |
|---------------------|---------------------------------|---|
| Colorectal | 1.6% | 37-48% |
| Uterine | 1.8% | 21-53% |
| Ovarian | <1% | 8-10% |
| Brain | <1% | 2-6% |
| Hepatobiliary tract | <1% | Elevated |
| Pancreatic | <1% | 4% |
| Sebaceous neoplasms | <0.1% | Elevated |
| Small bowel | <1% | 1-3% |
| Stomach | <1% | 5-8% |
| Urinary tract | 1.1% | 4-10% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

³ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

⁴ Tripathi R, Chen Z, Li L, Bordeaux JS. Incidence and survival of sebaceous carcinoma in the United States. *J Am Acad Dermatol*. 2016;75(6):1210-1215.

⁵ Dowty JG, Win AK, Buchanan DD, et al. Cancer risks for MLH1 and MSH2 mutation carriers. *Hum Mutat*. March 2013; 34(3):490-7.

⁶ Barrow E, Robinson L, Alduaij W, et al. Cumulative lifetime incidence of extracolonic cancers in Lynch syndrome: a report of 121 families with proven mutations. *Clin Genet*. February 2009; 75(2):141-9.

⁷ Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA*. June 2011; 305(22):2304-10.

⁸ Watson P, Vasen HF, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. *Int J Cancer*. July 2008; 123(2):444-9.

⁹ Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. *JAMA*. October 2009; 302(16):1790-5.

¹⁰ South CD, Hampel H, Comeras I, et al. The frequency of Muir-Torre syndrome among Lynch syndrome families. *JNCI*. February 2008; 100(4):277-81.

¹¹ Møller P, Seppälä TT, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut*. 2017.

Men

If a man has a mutation in the *EPCAM* gene, his chances of developing brain, colorectal, hepatobiliary tract, pancreatic, prostate, sebaceous neoplasms, small bowel, stomach, and urinary tract cancer are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 70 | Average US man ^{3,4} | With <i>EPCAM</i> mutation ^{5,6,7,8,9,10,11,12} |
|---------------------|-------------------------------|--|
| Colorectal | 2% | 48% |
| Brain | <1% | 2-6% |
| Hepatobiliary tract | <1% | Elevated |
| Pancreatic | <1% | 4% |
| Prostate | 5.9% | Elevated |
| Sebaceous neoplasms | <0.01% | Elevated |
| Small bowel | <1% | 1-6% |
| Stomach | <1% | 5-8% |
| Urinary tract | 2.1% | 3-8% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Additional information

Mutations in five different genes can lead to Lynch syndrome.

Having a mutation in *EPCAM*, *MLH1*, *MSH2*, *MSH6*, or *PMS2* can cause Lynch syndrome. Lynch syndrome used to be referred to as hereditary non-polyposis colorectal cancer, or HNPCC. It is an inherited condition that increases the risk of colorectal and other cancers. The associated cancer types and risk levels vary, depending on the gene in which the mutation is found.

¹² Ryan S, Jenkins MA, Win AK. Risk of prostate cancer in Lynch syndrome: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2014;23(3):437-49.

The relationship between *EPCAM* and *MSH2*.

Cancer risks for individuals with mutation in the *EPCAM* gene are estimated to be the same as for those with a mutation in the *MSH2* gene. This is because the type of mutations in *EPCAM* that cause Lynch syndrome (called large deletions and duplications including the 3' end of the gene) silence or inactivate the *MSH2* gene.

Not all *EPCAM* mutations are linked to increased cancer risk.

For *EPCAM*, only large deletions and duplications including 3' end of the gene are analyzed, because other positions are not known to impact cancer risk.

Screening guidelines

These screening guidelines are for individuals who have a mutation in the *EPCAM* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.¹³

Women

Uterine and ovarian:¹⁴

- **When you are finished having children, and depending on other factors such as menopause and family history:** Your healthcare provider may discuss a risk-reducing hysterectomy (the surgical removal of the uterus) and salpingo-oophorectomy (the surgical removal of the ovaries and fallopian tubes) with you to lower the risk of developing uterine and ovarian cancers.
- Your healthcare provider may discuss the symptoms of uterine and ovarian cancer, and the benefits and limitations of uterine biopsies (sampling) every 1-2 years along with a transvaginal ultrasound after menopause.
- While there may be circumstances where ovarian cancer screening with transvaginal ultrasound and a blood test for a protein called CA-125 are helpful, these techniques have not been shown to be effective in detecting early ovarian cancer.
- Your provider may discuss the use of medications that might reduce the risk of developing uterine or ovarian cancers.

¹³ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal. V.3.2017. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed April 2, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

¹⁴ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. *NCCN Guidelines Version 3.2017*. Available at www.nccn.org. Published October 2017.

Colorectal:¹⁴

- **Starting at age 20-25 or 2-5 years prior to the earliest colorectal cancer diagnosis in your family if the first diagnosis was before age 25, and depending on other factors such as menopause and family history:** Colonoscopy every 1-2 years.
- Your provider may discuss the use of medications such as aspirin that might reduce the risk of developing colorectal cancer.

Brain:¹⁴

- **Starting at age 25-30:** Physical and neurological examination by your provider every year.

Hepatobiliary tract:¹⁴

- Currently, there are no hepatobiliary tract cancer screening guidelines specific to *EPCAM* mutation carriers. Your provider may discuss screening or referral to a specialist.

Pancreatic:^{14,15}

- Currently, there are no pancreatic cancer screening guidelines specific to *EPCAM* mutation carriers. Your provider may discuss screening or referral to a specialist.

Sebaceous neoplasms:¹⁴

- Currently, there are no sebaceous neoplasm screening guidelines specific to *EPCAM* mutation carriers. Your provider may discuss screening or referral to a specialist.

Stomach and small bowel:¹⁴

- **Starting at age 30-35:** Your healthcare provider may discuss an upper endoscopy with visualization of the duodenum every 3-5 years at the time of colonoscopy, depending on your risk factors such as family history or ancestry.
- Your provider may discuss testing and treatment for a bacteria called *H. pylori*.

Urinary tract:¹⁴

- **Starting at age 30-35:** Your healthcare provider may discuss a urinalysis every year, especially for those with family history of urinary tract cancer.

Men

Colorectal:¹⁴

- **Starting at age 20-25 or 2-5 years prior to the earliest colorectal cancer diagnosis in your family if the first diagnosis was before age 25:** Colonoscopy every 1-2 years.
- Your provider may discuss the use of medications such as aspirin that might reduce the risk of developing colorectal cancer.

¹⁵ Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*. 2013;62(3):339-47.

Brain:¹⁴

- **Starting at age 25-30:** Physical and neurological examination by your provider every year.

Hepatobiliary tract:¹⁴

- Currently, there are no hepatobiliary tract cancer screening guidelines specific to *EPCAM* mutation carriers. Your provider may discuss screening or referral to a specialist.

Pancreatic:^{14,15}

- Currently, there are no pancreatic cancer screening guidelines specific to *EPCAM* mutation carriers. Your provider may discuss screening or referral to a specialist.

Prostate:

- Currently, there are no prostate cancer screening guidelines specific to *EPCAM* mutation carriers. Your provider may discuss screening or referral to a specialist.

Sebaceous neoplasms:¹⁴

- Currently, there are no sebaceous neoplasm screening guidelines specific to *EPCAM* mutation carriers. Your provider may discuss screening or referral to a specialist.

Stomach and small bowel:¹⁴

- **Starting at age 30-35:** Your healthcare provider may discuss an upper endoscopy with visualization of the duodenum every 3-5 years at the time of colonoscopy, depending on your risk factors such as family history or ancestry.
- Your provider may discuss testing and treatment for a bacteria called *H. pylori*.

Urinary tract:¹⁴

- **Starting at age 30-35:** Your healthcare provider may discuss a urinalysis every year, especially for those with family history of urinary tract cancer.

Useful resources

Hereditary Colon Cancer Foundation

A nonprofit organization serving the hereditary colorectal cancer community.

www.hcctakesguts.org

Lynch Syndrome International

Primary mission is to provide support for individuals afflicted with Lynch syndrome.

www.lynchcancers.com

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions

www.kintalk.org

Version 1.1, last updated June 8, 2018

GREM1

The *GREM1* gene is a cancer predisposition gene. The primary role of *GREM1* is to interact with other proteins that help regulate the growth of cells in the gastrointestinal tract.

Like most genes, each person has two copies of the *GREM1* gene: one inherited from each parent. A mutation in a single copy of the *GREM1* gene inherited from either parent causes hereditary mixed polyposis syndrome (HMPS), which is known to increase risks for specific cancers (colorectal, and multiple types of colorectal polyps) over a lifetime.

Research on the *GREM1* gene is ongoing, especially related to the exact cancers and cancer risks associated with mutations in this gene. To date, studies on this gene have been focused only on duplications in the upstream regulatory region in people of Ashkenazi Jewish descent.

How common are mutations in the *GREM1* gene?

Mutations in the *GREM1* gene are rare—the exact frequency is not yet known. Studies to establish the frequency of *GREM1* mutations are ongoing.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *GREM1* gene, her chance of developing colorectal cancer is greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 95 | Average US woman ¹ | With <i>GREM1</i> mutation ² |
|------------------|-------------------------------|---|
| Colorectal | 4% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

¹ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

² Jaeger E, Leedham S, Lewis A, et al. Hereditary mixed polyposis syndrome is caused by a 40-kb upstream duplication that leads to increased and ectopic expression of the BMP antagonist GREM1. *Nat Genet.* 2012;44(6):699-703.

Men

If a man has a mutation in the *GREM1* gene, his chance of developing colorectal cancer is greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 95 | Average US man ¹ | With <i>GREM1</i> mutation |
|------------------|-----------------------------|----------------------------|
| Colorectal | 4.4% | Elevated ² |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Additional information

Not all *GREM1* mutations are linked to increased cancer risk.

For *GREM1*, only duplications in the upstream regulatory region are analyzed, because other positions are not known to impact cancer risk.

Screening guidelines

These screening guidelines are for individuals who have a mutation in the *GREM1* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.³

Women and Men

Colorectal cancer⁴

- **Starting at age 25-30:** Colonoscopy every 2-3 years.
- **Depending on age and number of polyps:** Colonoscopy every 1-2 years and evaluation for colectomy (surgical removal of the colon and/or rectum).
- These recommendations may change if you have colorectal cancer, inflammatory bowel disease (IBD), or family history of colorectal cancer.

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⁴ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. *NCCN Guidelines Version 3.2017*. Available at www.nccn.org. Published October 2017.

Useful resources

Colon Cancer Alliance

An organization dedicated to colon cancer prevention, funding colon cancer research and providing support to patients.

www.ccalliance.org

Hereditary Colon Cancer Foundation

A nonprofit organization serving the hereditary colorectal cancer community.

www.hcctakesguts.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions

www.kintalk.org

Version 1.1, last updated June 8, 2018

MITF

The *MITF* gene is an oncogene. Oncogenes are involved in cell growth. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *MITF* is to control melanocytes, the cells that make skin pigment.

Like most genes, each person has two copies of the *MITF* gene: one inherited from each parent. A mutation in a single copy of the *MITF* gene inherited from either parent is known to increase risk of specific cancers (melanoma and kidney cancer) over a lifetime.

Certain factors can greatly increase risk of melanoma, including person's geographical region, ethnicity and sun exposure. For example, melanoma is 20 times more common in Caucasians than it is in African Americans.¹ The risk of kidney cancer also varies depending on whether a person has a history of smoking cigarettes or exposure to certain substances and chemicals.²

How common are mutations in the *MITF* gene?

Mutations in the *MITF* gene are rare—the exact frequency is not yet known. Studies to establish the frequency of *MITF* mutations are ongoing.

¹ What are the Risk Factors for Melanoma Skin Cancer? American Cancer Society website. <http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-risk-factors> Updated May 20, 2016. Accessed April 2, 2018.

² Risk Factors for Kidney Cancer. American Cancer Society website. <https://www.cancer.org/cancer/kidney-cancer/causes-risks-prevention/risk-factors.html>. Updated August 1, 2017. Accessed April 2, 2018.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *MITF* gene, her chances of developing melanoma and kidney cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 95 | Average US woman ³ | With <i>MITF</i> mutation ⁴ |
|------------------|-------------------------------|--|
| Melanoma | 1.7% | Elevated |
| Kidney | 1.2% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Men

If a man has a mutation in the *MITF* gene, his chances of developing melanoma and kidney cancer are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 95 | Average US man ³ | With <i>MITF</i> mutation ⁴ |
|------------------|-----------------------------|--|
| Melanoma | 2.7% | Elevated |
| Kidney | 2.1% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Additional information

Not all *MITF* mutations are linked to increased cancer risk.

For *MITF*, only chr3:g.70014091 (including c.952G>A) is analyzed, because other positions are not known to impact cancer risk.

³ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

⁴ Bertolotto C, Lesueur F, Giuliano S, et al. A SUMOylation-defective MITF germline mutation predisposes to melanoma and renal carcinoma. *Nature*. 2011;480(7375):94-98.

Screening guidelines

There are no published screening guidelines specific to individuals with *MITF* mutations. Below are guidelines for individuals who have the same risk of melanoma as the average US woman and man. Speak with your healthcare provider about additional recommendations to reduce the risk of melanoma. Your healthcare provider may use these guidelines to help create a customized screening plan for you.

Women and Men

Melanoma:⁵

- Your healthcare provider may discuss skin exams and eye exams for melanoma screening.
- To reduce the chance of developing melanoma, the American Cancer Society recommends limiting exposure to UV light by avoiding excess sun exposure, wearing a hat, sunglasses and long protective clothing, applying sunscreen with SPF of 30 or higher and avoiding tanning beds and sun lamps.
- Any new, unusual, or changing moles should be reported to your provider or dermatologist.

Kidney cancer

- Currently, there are no kidney cancer screening guidelines specific to *MITF* mutation carriers. Your provider may discuss screening or referral to a specialist.

Useful resources

American Melanoma Foundation

An organization supporting melanoma research, and providing advocacy and public awareness of melanoma.

www.melanomafoundation.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions.

www.kintalk.org

Version 1.1, last updated June 8, 2018

⁵ Skin Cancer Prevention and Early Detection. The American Cancer Society website. <https://www.cancer.org/cancer/skin-cancer/prevention-and-early-detection.html>. Updated March 19, 2017. Accessed April 2, 2018.

MLH1

The *MLH1* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. *MLH1* works together with the *PMS2* gene to remove and repair DNA errors when signaled by the *MSH2* and *MSH6* genes.

Like most genes, each person has two copies of the *MLH1* gene: one inherited from each parent. A mutation in a single copy of the *MLH1* gene inherited from either parent causes Lynch syndrome, which is known to increase risks of specific cancers (colorectal, uterine, ovarian, and other cancers) over a lifetime.

In very rare cases, a person can inherit two *MLH1* mutations, one from each parent. This causes a condition called constitutional mismatch repair deficiency (CMMR-D), which is associated with cancers in childhood such as colorectal, small intestine, brain, leukemia/lymphoma, and others.

How common are mutations in the *MLH1* gene?

Mutations that cause Lynch syndrome are rare—found in approximately 1 in 370 individuals.¹ Lynch syndrome accounts for approximately 3% of all colorectal cancers.²

¹ Hampel H, De la chapelle A. The search for unaffected individuals with Lynch syndrome: do the ends justify the means?. *Cancer Prev Res (Phila)*. 2011;4(1):1-5.

² Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. *Am J Gastroenterol*. 2014;109(8):1159-79.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *MLH1* gene, her chances of developing brain, colorectal, hepatobiliary tract, ovarian, pancreatic, sebaceous neoplasms, small bowel, stomach, urinary tract, and uterine cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 70 | Average US woman ^{3,4} | With <i>MLH1</i> mutation ^{5,6,7,8,9,10,11} |
|---------------------|---------------------------------|--|
| Colorectal | 1.6% | 36-50% |
| Uterine | 1.8% | 18-54% |
| Ovarian | <1% | 6-13% |
| Brain | <1% | 2% |
| Hepatobiliary tract | <1% | 3% |
| Pancreatic | <1% | 4% |
| Sebaceous neoplasms | <0.1% | Elevated |
| Small bowel | <1% | 3-5% |
| Stomach | <1% | 6-11% |
| Urinary tract | 1.1% | 1-3% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

³ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2010-2012. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.0, Accessed June 2015.

⁴ Tripathi R, Chen Z, Li L, Bordeaux JS. Incidence and survival of sebaceous carcinoma in the United States. *J Am Acad Dermatol*. 2016;75(6):1210-1215.

⁵ Dowty JG, Win AK, Buchanan DD, et al. Cancer risks for MLH1 and MSH2 mutation carriers. *Hum Mutat*. March 2013; 34(3):490-7.

⁶ Barrow E, Robinson L, Alduaij W, et al. Cumulative lifetime incidence of extracolonic cancers in Lynch syndrome: a report of 121 families with proven mutations. *Clin Genet*. February 2009; 75(2):141-9.

⁷ Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA*. June 2011; 305(22):2304-10.

⁸ Watson P, Vasen HF, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. *Int J Cancer*. July 2008; 123(2):444-9.

⁹ Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. *JAMA*. October 2009; 302(16):1790-5.

¹⁰ South CD, Hampel H, Comeras I, et al. The frequency of Muir-Torre syndrome among Lynch syndrome families. *JNCI*. February 2008; 100(4):277-81.

¹¹ Møller P, Seppälä TT, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut*. 2017.

Men

If a man has a mutation in the *MLH1* gene, his chances of developing brain, colorectal, hepatobiliary tract, pancreatic, prostate, sebaceous neoplasms, small bowel, stomach, and urinary tract cancer are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 70 | Average US man ^{3,4} | With <i>MLH1</i> mutation ^{5,6,7,8,9,10,11,12} |
|---------------------|-------------------------------|---|
| Colorectal | 2% | 34-41% |
| Brain | <1% | 2% |
| Hepatobiliary tract | <1% | 3% |
| Pancreatic | <1% | 4% |
| Prostate | 5.9% | Elevated |
| Sebaceous neoplasms | <0.01% | Elevated |
| Small bowel | <1% | 5-6% |
| Stomach | <1% | 6-20% |
| Urinary tract | 2.1% | 3-4% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Additional information

Mutations in five different genes can lead to Lynch syndrome.

Having a mutation in *EPCAM*, *MLH1*, *MSH2*, *MSH6*, or *PMS2* can cause Lynch syndrome. Lynch syndrome used to be referred to as hereditary non-polyposis colorectal cancer, or HNPCC. It is an inherited condition that increases the risk of colorectal and other cancers. The associated cancer types and risk levels vary, depending on the gene in which the mutation is found.

Lynch syndrome is sometimes uncovered by testing a cancer or tumor.

Lynch syndrome can sometimes be evaluated by performing certain tests on cancers or tumors. These tests are called immunohistochemistry (IHC) and microsatellite instability (MSI) and are often the first line of screening tests when someone is suspected to have Lynch syndrome.

¹² Ryan S, Jenkins MA, Win AK. Risk of prostate cancer in Lynch syndrome: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2014;23(3):437-49.

If a cancer or tumor is missing the protein made by the *MLH1* gene on the IHC test, other tests may be performed on the tumor or cancer. These tests are called *MLH1* promoter methylation testing and *BRAF* V600E mutation testing. The results may help clarify whether the cancer was caused by Lynch syndrome.

Screening guidelines

These screening guidelines are for individuals who have a mutation in the *MLH1* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.¹³

Women

Uterine and ovarian:¹⁴

- **When you are finished having children, and depending on other factors such as menopause and family history:** Your healthcare provider may discuss a risk-reducing hysterectomy (the surgical removal of the uterus) and salpingo-oophorectomy (the surgical removal of the ovaries and fallopian tubes) with you to lower the risk of developing uterine and ovarian cancers.
- Your healthcare provider may discuss the symptoms of uterine and ovarian cancer, and the benefits and limitations of uterine biopsies (sampling) every 1-2 years along with a transvaginal ultrasound after menopause.
- While there may be circumstances where ovarian cancer screening with transvaginal ultrasound and a blood test for a protein called CA-125 are helpful, these techniques have not been shown to be effective in detecting early ovarian cancer.
- Your provider may discuss the use of medications that might reduce the risk of developing uterine or ovarian cancers..

Colorectal:¹⁴

- **Starting at age 20-25 or 2-5 years prior to the earliest colorectal cancer diagnosis in your family if the first diagnosis was before age 25:** Colonoscopy every 1-2 years.
- Your provider may discuss the use of medications such as aspirin that might reduce the risk of developing colorectal cancer.

Brain:¹⁴

- **Starting at age 25-30:** Physical and neurological examination by your provider every year.

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¹⁴ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. *NCCN Guidelines Version 3.2017*. Available at www.nccn.org. Published October 2017.

Hepatobiliary tract:¹⁴

- Currently, there are no hepatobiliary tract cancer screening guidelines specific to *MLH1* mutation carriers. Your provider may discuss screening or referral to a specialist.

Pancreatic:^{14,15}

- Currently, there are no pancreatic cancer screening guidelines specific to *MLH1* mutation carriers. Your provider may discuss screening or referral to a specialist.

Sebaceous neoplasms:¹⁴

- Currently, there are no sebaceous neoplasm screening guidelines specific to *MLH1* mutation carriers. Your provider may discuss screening or referral to a specialist.

Stomach and small bowel:¹⁴

- **Starting at age 30-35:** Your healthcare provider may discuss an upper endoscopy with visualization of the duodenum every 3-5 years at the time of colonoscopy, depending on your risk factors such as family history or ancestry.
- Your provider may discuss testing and treatment for a bacteria called *H. pylori*.

Urinary tract:¹⁴

- **Starting at age 30-35:** Your healthcare provider may discuss a urinalysis every year, especially for those with family history of urinary tract cancer.

Men

Colorectal:¹⁴

- **Starting at age 20-25 or 2-5 years prior to the earliest colorectal cancer diagnosis in your family if the first diagnosis was before age 25:** Colonoscopy every 1-2 years.
- Your provider may discuss the use of medications such as aspirin that might reduce the risk of developing colorectal cancer.

Brain:¹⁴

- **Starting at age 25-30:** Physical and neurological examination by your provider every year.

Hepatobiliary tract:¹⁴

- Currently, there are no hepatobiliary tract cancer screening guidelines specific to *MLH1* mutation carriers. Your provider may discuss screening or referral to a specialist.

¹⁵International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*. March 2013; 62(3):339-47.

Pancreatic:^{14,15}

- Currently, there are no pancreatic cancer screening guidelines specific to *MLH1* mutation carriers. Your provider may discuss screening or referral to a specialist.

Prostate

- Currently, there are no prostate cancer screening guidelines specific to *MLH1* mutation carriers. Your provider may discuss screening or referral to a specialist.

Sebaceous neoplasms:¹⁴

- Currently, there are no sebaceous neoplasm screening guidelines specific to *MLH1* mutation carriers. Your provider may discuss screening or referral to a specialist.

Stomach and small bowel:¹⁴

- **Starting at age 30-35:** Your healthcare provider may discuss an upper endoscopy every 3-5 years, depending on your risk factors such as family history or ancestry.
- Your provider may discuss testing and treatment for a bacteria called *H. pylori*.

Urinary tract:¹⁴

- **Starting at age 30-35:** Your healthcare provider may discuss a urinalysis every year, especially for those with family history of urinary tract cancer.

Useful resources

Hereditary Colon Cancer Foundation

A nonprofit organization serving the hereditary colorectal cancer community.

www.hcctakesguts.org

Lynch Syndrome International

Primary mission is to provide support for individuals afflicted with Lynch syndrome.

www.lynchcancers.com

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions

www.kintalk.org

Version 1.1, last updated June 8, 2018

MSH2

The *MSH2* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. *MSH2* works together with other genes, including *MSH6* and *MSH3*, to scan the DNA for mistakes and signal for other genes, including *MLH1* and *PMS2*, to make repairs.

Like most genes, each person has two copies of the *MSH2* gene: one inherited from each parent. A mutation in a single copy of the *MSH2* gene inherited from either parent causes Lynch syndrome, which is known to increase risks of specific cancers (colorectal, uterine, ovarian, and other cancers) over a lifetime.

In very rare cases, a person can inherit two *MSH2* mutations, one from each parent. This causes a condition called constitutional mismatch repair deficiency (CMMR-D), which is associated with cancers in childhood such as colorectal, small intestine, brain, leukemia/lymphoma, and others.

How common are mutations in the *MSH2* gene?

Mutations that cause Lynch syndrome are rare—found in approximately 1 in 370 individuals.¹ Lynch syndrome accounts for approximately 3% of all colorectal cancers.²

¹ Hampel H, De la chapelle A. The search for unaffected individuals with Lynch syndrome: do the ends justify the means?. *Cancer Prev Res (Phila)*. 2011;4(1):1-5.

² Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. *Am J Gastroenterol*. 2014;109(8):1159-79.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *MSH2* gene, her chances of developing brain, colorectal, hepatobiliary tract, ovarian, pancreatic, sebaceous neoplasms, small bowel, stomach, urinary tract, and uterine cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 70 | Average US woman ^{3,4} | With <i>MSH2</i> mutation ^{5,6,7,8,9,10,11} |
|---------------------|---------------------------------|--|
| Colorectal | 1.6% | 37-48% |
| Uterine | 1.8% | 21-53% |
| Ovarian | <1% | 8-10% |
| Brain | <1% | 2-6% |
| Hepatobiliary tract | <1% | Elevated |
| Pancreatic | <1% | 4% |
| Sebaceous neoplasms | <0.1% | Elevated |
| Small bowel | <1% | 1-3% |
| Stomach | <1% | 5-8% |
| Urinary tract | 1.1% | 4-10% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

³ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2010-2012. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.0, Accessed June 2015.

⁴ Tripathi R, Chen Z, Li L, Bordeaux JS. Incidence and survival of sebaceous carcinoma in the United States. *J Am Acad Dermatol*. 2016;75(6):1210-1215.

⁵ Dowty JG, Win AK, Buchanan DD, et al. Cancer risks for MLH1 and MSH2 mutation carriers. *Hum Mutat*. March 2013; 34(3):490-7.

⁶ Barrow E, Robinson L, Alduaij W, et al. Cumulative lifetime incidence of extracolonic cancers in Lynch syndrome: a report of 121 families with proven mutations. *Clin Genet*. February 2009; 75(2):141-9.

⁷ Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA*. June 2011; 305(22):2304-10.

⁸ Watson P, Vasen HF, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. *Int J Cancer*. July 2008; 123(2):444-9.

⁹ Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. *JAMA*. October 2009; 302(16):1790-5.

¹⁰ South CD, Hampel H, Comeras I, et al. The frequency of Muir-Torre syndrome among Lynch syndrome families. *JNCI*. February 2008; 100(4):277-81.

¹¹ Møller P, Seppälä TT, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut*. 2017.

Men

If a man has a mutation in the *MSH2* gene, his chances of developing brain, colorectal, hepatobiliary tract, pancreatic, prostate, sebaceous neoplasms, small bowel, stomach, and urinary tract cancer are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 70 | Average US man ^{3,4} | With <i>MSH2</i> mutation ^{5,6,7,8,9,10,11,12} |
|---------------------|-------------------------------|---|
| Colorectal | 2% | 48% |
| Brain | <1% | 2-6% |
| Hepatobiliary tract | <1% | Elevated |
| Pancreatic | <1% | 4% |
| Prostate | 5.9% | Elevated |
| Sebaceous neoplasms | <0.01% | Elevated |
| Small bowel | <1% | 1-6% |
| Stomach | <1% | 5-8% |
| Urinary tract | 2.1% | 3-8% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Additional information

Mutations in five different genes can lead to Lynch syndrome.

Having a mutation in *EPCAM*, *MLH1*, *MSH2*, *MSH6*, or *PMS2* can cause Lynch syndrome. Lynch syndrome used to be referred to as hereditary non-polyposis colorectal cancer, or HNPCC. It is an inherited condition that increases the risk of colorectal and other cancers. The associated cancer types and risk levels vary, depending on the gene in which the mutation is found.

Lynch syndrome is sometimes uncovered by testing a cancer or tumor.

Lynch syndrome can sometimes be evaluated by performing certain tests on cancers or tumors. These tests are called immunohistochemistry (IHC) and microsatellite instability (MSI) and are often the first line of screening tests when someone is suspected to have Lynch syndrome.

¹² Ryan S, Jenkins MA, Win AK. Risk of prostate cancer in Lynch syndrome: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2014;23(3):437-49.

Screening guidelines

These screening guidelines are for individuals who have a mutation in the *MSH2* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.¹³

Women

Uterine and ovarian:¹⁴

- **When you are finished having children, and depending on other factors such as menopause and family history:** Your healthcare provider may discuss a risk-reducing hysterectomy (the surgical removal of the uterus) and salpingo-oophorectomy (the surgical removal of the ovaries and fallopian tubes) with you to lower the risk of developing uterine and ovarian cancers.
- Your healthcare provider may discuss the symptoms of uterine and ovarian cancer, and the benefits and limitations of uterine biopsies (sampling) every 1-2 years along with a transvaginal ultrasound after menopause.
- While there may be circumstances where ovarian cancer screening with transvaginal ultrasound and a blood test for a protein called CA-125 are helpful, these techniques have not been shown to be effective in detecting early ovarian cancer.
- Your provider may discuss the use of medications that might reduce the risk of developing uterine or ovarian cancers.

Colorectal:¹⁴

- **Starting at age 20-25 or 2-5 years prior to the earliest colorectal cancer diagnosis in your family if the first diagnosis was before age 25:** Colonoscopy every 1-2 years.
- Your provider may discuss the use of medications such as aspirin that might reduce the risk of developing colorectal cancer.

Brain:¹⁴

- **Starting at age 25-30:** Physical and neurological examination by your provider every year.

Hepatobiliary tract:¹⁴

- Currently, there are no hepatobiliary tract cancer screening guidelines specific to *MSH2* mutation carriers. Your provider may discuss screening or referral to a specialist.

¹³ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal. V.3.2017. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed April 2, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

¹⁴ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. *NCCN Guidelines Version 3.2017*. Available at www.nccn.org. Published October 2017.

Pancreatic:^{14,15}

- Currently, there are no pancreatic cancer screening guidelines specific to *MSH2* mutation carriers. Your provider may discuss screening or referral to a specialist.

Sebaceous neoplasms:¹⁴

- Currently, there are no sebaceous neoplasm screening guidelines from the NCCN specific to *MSH2* mutation carriers. Your provider may discuss screening or referral to a specialist.

Stomach and small bowel:¹⁴

- **Starting at age 30-35:** Your healthcare provider may discuss an upper endoscopy with visualization of the duodenum every 3-5 years at the time of colonoscopy, depending on your risk factors such as family history or ancestry.
- Your provider may discuss testing and treatment for a bacteria called *H. pylori*.

Urinary tract:¹⁴

- **Starting at age 30-35:** Your healthcare provider may discuss a urinalysis every year, especially for those with family history of urinary tract cancer.

Men

Colorectal:¹⁴

- **Starting at age 20-25 or 2-5 years prior to the earliest colorectal cancer diagnosis in your family if the first diagnosis was before age 25:** Colonoscopy every 1-2 years.
- Your provider may discuss the use of medications such as aspirin that might reduce the risk of developing colorectal cancer.

Brain:¹⁴

- **Starting at age 25-30:** Physical and neurological examination by your provider every year.

Hepatobiliary tract:¹⁴

- Currently, there are no hepatobiliary tract cancer screening guidelines specific to *MSH2* mutation carriers. Your provider may discuss screening or referral to a specialist.

Pancreatic:^{14,15}

- Currently, there are no pancreatic cancer screening guidelines specific to *MSH2* mutation carriers. Your provider may discuss screening or referral to a specialist.

¹⁵ Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*. 2013;62(3):339-47.

Prostate

- Currently, there are no prostate cancer screening guidelines specific to *MSH2* mutation carriers. Your provider may discuss screening or referral to a specialist.

Sebaceous neoplasms:¹⁴

- Currently, there are no sebaceous neoplasm screening guidelines specific to *MSH2* mutation carriers. Your provider may discuss screening or referral to a specialist.

Stomach and small bowel:¹⁴

- **Starting at age 30-35:** Your healthcare provider may discuss an upper endoscopy with visualization of the duodenum every 3-5 years at the time of colonoscopy, depending on your risk factors such as family history or ancestry.
- Your provider may discuss testing and treatment for a bacteria called *H. pylori*.

Urinary tract:¹⁴

- **Starting at age 30-35:** Your healthcare provider may discuss a urinalysis every year, especially for those with family history of urinary tract cancer or men with *MSH2* mutations.

Useful resources

Hereditary Colon Cancer Foundation

A nonprofit organization serving the hereditary colorectal cancer community.

www.hcctakesguts.org

Lynch Syndrome International

Primary mission is to provide support for individuals afflicted with Lynch syndrome.

www.lynchcancers.com

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions

www.kintalk.org

Version 1.1, last updated June 8, 2018

MSH6

The *MSH6* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. *MSH6* works together with the *MSH2* gene to scan the DNA for mistakes and signal for other genes, including *MLH1* and *PMS2*, to make repairs.

Like most genes, each person has two copies of the *MSH6* gene: one inherited from each parent. A mutation in a single copy of the *MSH6* gene inherited from either parent causes Lynch syndrome, which is known to increase risks of specific cancers (colorectal, uterine, ovarian, and other cancers) over a lifetime.

In very rare cases, a person can inherit two *MSH6* mutations, one from each parent. This causes a condition called constitutional mismatch repair deficiency (CMMR-D), which is associated with cancers in childhood such as colorectal, small intestine, brain, leukemia/lymphoma, and others.

How common are mutations in the *MSH6* gene?

Mutations that cause Lynch syndrome are rare—found in approximately 1 in 370 individuals.¹ Lynch syndrome accounts for approximately 3% of all colorectal cancers.²

¹ Hampel H, De la chapelle A. The search for unaffected individuals with Lynch syndrome: do the ends justify the means?. *Cancer Prev Res (Phila)*. 2011;4(1):1-5.

² Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. *Am J Gastroenterol*. 2014;109(8):1159-79.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *MSH6* gene, her chances of developing brain, colorectal, hepatobiliary tract, ovarian, pancreatic, sebaceous neoplasms, small bowel, stomach, urinary tract, and uterine cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 70 | Average US woman ^{3,4} | With <i>MSH6</i> mutation ^{5,6,7,8,9} |
|---------------------|---------------------------------|--|
| Colorectal | 1.6% | 10-18% |
| Uterine | 1.8% | 16-46% |
| Ovarian | <1% | Elevated |
| Other Lynch cancers | 3% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

³ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

⁴ Tripathi R, Chen Z, Li L, Bordeaux JS. Incidence and survival of sebaceous carcinoma in the United States. *J Am Acad Dermatol*. 2016;75(6):1210-1215.

⁵ Bonadona V, Bonaïti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA*. 2011;305(22):2304-2310.

⁶ Baglietto L, Lindor NM, Dowty JG, et al. Risks of Lynch syndrome cancers for MSH6 mutation carriers. *J Natl Cancer Inst*. 2010 Feb 3;102(3):193-201.

⁷ Barrow E, Robinson L, Alduaij W, et al. Cumulative lifetime incidence of extracolonic cancers in Lynch syndrome: a report of 121 families with proven mutations. *Clin Genet*. 2009 Feb;75(2):141-9.

⁸ Møller P, Seppälä TT, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut*. 2017.

⁹ Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. *JAMA*. October 2009; 302(16):1790-5.

Men

If a man has a mutation in the *MSH6* gene, his chances of developing brain, colorectal, hepatobiliary tract, pancreatic, prostate, sebaceous neoplasms, small bowel, stomach, and urinary tract cancer are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 70 | Average US man ^{3,4} | With <i>MSH6</i> mutation ^{5,6,7,8,9,10} |
|---------------------|-------------------------------|---|
| Colorectal | 2% | 12-22% |
| Other Lynch cancers | 12.1% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Additional information

Mutations in five different genes can lead to Lynch syndrome.

Having a mutation in *EPCAM*, *MLH1*, *MSH2*, *MSH6*, or *PMS2* can cause Lynch syndrome. Lynch syndrome used to be referred to as hereditary non-polyposis colorectal cancer, or HNPCC. It is an inherited condition that increases the risk of colorectal and other cancers. The associated cancer types and risk levels vary, depending on the gene in which the mutation is found.

Lynch syndrome is sometimes uncovered by testing a cancer or tumor.

Lynch syndrome can sometimes be evaluated by performing certain tests on cancers or tumors. These tests are called immunohistochemistry (IHC) and microsatellite instability (MSI) and are often the first line of screening tests when someone is suspected to have Lynch syndrome.

Screening guidelines

These screening guidelines are for individuals with Lynch syndrome, but are not specific to the *MSH6* gene. Your provider may make different recommendations based on studies showing lower cancer risks associated with mutations in *MSH6* compared to other Lynch syndrome genes. Your healthcare provider may use these guidelines to help create a customized screening plan for you.¹¹

¹⁰ Ryan S, Jenkins MA, Win AK. Risk of prostate cancer in Lynch syndrome: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2014;23(3):437-49.

¹¹ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal. V.3.2017. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed April 2, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Women

Uterine and ovarian:¹²

- **When you are finished having children, and depending on other factors such as menopause and family history:** Your healthcare provider may discuss a risk-reducing hysterectomy (the surgical removal of the uterus) and salpingo-oophorectomy (the surgical removal of the ovaries and fallopian tubes) with you to lower the risk of developing uterine and ovarian cancers.
- Your healthcare provider may discuss the symptoms of uterine and ovarian cancer, and the benefits and limitations of uterine biopsies (sampling) every 1-2 years and transvaginal ultrasound after menopause.
- While there may be circumstances where ovarian cancer screening with transvaginal ultrasound and a blood test for a protein called CA-125 are helpful, these techniques have not been shown to be effective in detecting early ovarian cancer.
- Your provider may discuss the use of medications that might reduce the risk of developing uterine or ovarian cancers.

Colorectal:¹²

- **Starting at age 20-25 or 2-5 years prior to the earliest colorectal cancer diagnosis in your family if the first diagnosis was before age 25:** Colonoscopy every 1-2 years.
- Your provider may discuss the use of medications such as aspirin that might reduce the risk of developing colorectal cancer.

Brain:¹²

- **Starting at age 25-30:** Physical and neurological examination by your provider every year.

Hepatobiliary tract:¹²

- Currently, there are no hepatobiliary tract cancer screening guidelines specific to *MSH6* mutation carriers. Your provider may discuss screening or referral to a specialist.

Pancreatic:^{12,13}

- Currently, there are no pancreatic cancer screening guidelines specific to *MSH6* mutation carriers. Your provider may discuss screening or referral to a specialist.

Sebaceous neoplasms:¹²

- Currently, there are no sebaceous neoplasm screening guidelines specific to *MSH6* mutation carriers. Your provider may discuss screening or referral to a specialist.

Stomach and small bowel:¹²

¹² National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: *Colorectal*. NCCN Guidelines Version 3.2017. Available at www.nccn.org. Published October 2017.

¹³ Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*. 2013;62(3):339-47.

- **Starting at age 30-35:** Your healthcare provider may discuss an upper endoscopy with visualization of the duodenum every 3-5 years at the time of colonoscopy, depending on your risk factors such as family history or ancestry.
- Your provider may discuss testing and treatment for a bacteria called *H. pylori*.

Urinary tract:¹²

- **Starting at age 30-35:** Your healthcare provider may discuss a urinalysis every year, especially for those with family history of urinary tract cancer.

Men

Colorectal:¹²

- **Starting at age 20-25 or 2-5 years prior to the earliest colorectal cancer diagnosis in your family if the first diagnosis was before age 25:** Colonoscopy every 1-2 years.
- Your provider may discuss the use of medications such as aspirin that might reduce the risk of developing colorectal cancer.

Brain:¹²

- **Starting at age 25-30:** Physical and neurological examination by your provider every year.

Hepatobiliary tract:¹²

- Currently, there are no hepatobiliary tract cancer screening guidelines specific to *MSH6* mutation carriers. Your provider may discuss screening or referral to a specialist.

Pancreatic:^{12,13}

- Currently, there are no pancreatic cancer screening guidelines specific to *MSH6* mutation carriers. Your provider may discuss screening or referral to a specialist.

Prostate

- Currently, there are no prostate cancer screening guidelines specific to *MSH6* mutation carriers. Your provider may discuss screening or referral to a specialist.

Sebaceous neoplasms:¹²

- Currently, there are no sebaceous neoplasm screening guidelines specific to *MSH6* mutation carriers. Your provider may discuss screening or referral to a specialist.

Stomach and small bowel:¹²

- **Starting at age 30-35:** Your healthcare provider may discuss an upper endoscopy with visualization of the duodenum every 3-5 years at the time of colonoscopy, depending on your risk factors such as family history or ancestry.
- Your provider may discuss testing and treatment for a bacteria called *H. pylori*.

Urinary tract:¹²

- **Starting at age 30-35:** Your healthcare provider may discuss a urinalysis every year, especially for those with family history of urinary tract cancer.

Useful resources

Hereditary Colon Cancer Foundation

A nonprofit organization serving the hereditary colorectal cancer community.

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www.lynchcancers.com

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions

www.kintalk.org

Version 1.1, last updated June 8, 2018

MUTYH

The *MUTYH* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *MUTYH* is to work together with other genes, including *MSH2* and *MSH6*, to recognize DNA mistakes and signal other genes to make repairs.

Like most genes, each person has two copies of the *MUTYH* gene: one inherited from each parent. Having two *MUTYH* mutations, one from each parent, causes a condition called *MUTYH*-associated polyposis (MAP). MAP is associated with a significantly increased risk for colorectal polyps and specific cancers (colorectal and others) over a lifetime.

A mutation in a single copy of the *MUTYH* gene inherited from either parent slightly increases the risk for colorectal cancer.

How common are mutations in the *MUTYH* gene?

A single mutation in the *MUTYH* gene is found in 1-2% of people with Caucasian ancestry.¹ Further research is needed to clarify the frequency of mutations in the *MUTYH* gene in other populations.

How mutations in this gene impact risk

How a single *MUTYH* mutation affects women

If a woman has a mutations in the *MUTYH* gene, her chance of developing colorectal cancer is greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 80 | Average US woman ² | With single <i>MUTYH</i> mutation ^{3,4} |
|------------------|-------------------------------|--|
| Colorectal | 2.7% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

¹ Cleary SP, Cotterchio M, Jenkins MA, et al. Germline MutY human homologue mutations and colorectal cancer: a multisite case-control study. *Gastroenterology*. 2009;136:1251–60.

² Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

³ Win AK, Dowty JG, Cleary SP, et al. Risk of colorectal cancer for carriers of mutations in *MUTYH*, with and without a family history of cancer. *Gastroenterology*. 2014;146(5):1208-11.e1-5.

⁴ Theodoratou E, Campbell H, Tenesa A, et al. A large-scale meta-analysis to refine colorectal cancer risk estimates associated with *MUTYH* variants. *Br J Cancer*. 2010;103(12):1875-84.

How a mutation in each copy of the *MUTYH* gene affects women

If a woman has a mutation in each copy of the *MUTYH* gene, her chances of developing colorectal and small bowel cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 80 | Average US woman ² | With mutation in each copy of <i>MUTYH</i> ^{3,5,6} |
|------------------------|-------------------------------|---|
| Colorectal | 2.7% | 86% |
| Small Bowel (Duodenal) | <1% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

How a single *MUTYH* mutation affects men

If a man has a mutation in the *MUTYH* gene, his chance of developing colorectal cancer is greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 80 | Average US man ² | With single <i>MUTYH</i> mutation ^{3,4} |
|------------------|-----------------------------|--|
| Colorectal | 3.3% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

How a mutation in each copy of the *MUTYH* gene affects men

If a man has a mutation in each copy in the *MUTYH* gene, his chance of developing colorectal and small bowel cancers are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 80 | Average US man ² | With mutation in each copy of <i>MUTYH</i> ^{3,5,6} |
|------------------------|-----------------------------|---|
| Colorectal | 3.3% | 88% |
| Small Bowel (Duodenal) | <1% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

⁵ Nieuwenhuis MH, Vogt S, Jones N, et al. Evidence for accelerated colorectal adenoma–carcinoma progression in *MUTYH*-associated polyposis?. *Gut*. 2012;61(5):734-8.

⁶ Vogt S, Jones N, Christian D, et al. Expanded extracolonic tumor spectrum in *MUTYH*-associated polyposis. *Gastroenterology*. 2009;137(6):1976-85.e1-10.

Additional information

Like most genes, our understanding of *MUTYH* has evolved with time.

The *MUTYH* gene was initially thought to be important only if a person had a mutation in each copy, causing MAP. Only in the last several years have researchers discovered having a single mutation is also associated with an increased colorectal cancer risk, though to a much milder extent.

Screening guidelines for individuals with a single *MUTYH* mutation

These screening guidelines are for individuals with a mutation in the *MUTYH* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.⁷

Women and Men

Colorectal:⁸

- **Beginning at age 40 or 10 years younger than the earliest diagnosis of colorectal cancer in a parent, sibling, or child (whichever is earlier):** Your provider may discuss colonoscopy every 5 years. Research on the benefit of screening in individuals with no family history of colorectal cancer is ongoing.
- These recommendations may change if you have polyps, colorectal cancer, or inflammatory bowel disease (IBD).

Screening guidelines for individuals with a mutation in each copy of *MUTYH*

These screening guidelines are for individuals with a mutation in in each copy of the *MUTYH* gene.⁷ Your healthcare provider may use these guidelines to help create a customized screening plan for you.

Women and Men

Colorectal:⁸

- **Starting at age 25-30:** Colonoscopy every 2-3 years if no polyps are found.
- **Depending on age and number of polyps:** Colonoscopy every 1-2 years and evaluation for colectomy (surgical removal of the colon and/or rectum).
- **If colectomy is necessary:** Speak to your provider about recommended follow up, which may include surveillance with endoscopy, and medications to reduce the risk of polyps and cancer.

⁷ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal V.3.2017. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed April 2, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

⁸ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. *NCCN Guidelines Version 3.2017*. Available at www.nccn.org. Published October 2017.

Small bowel (duodenal and other sections):⁸

- **Starting at age 30-35 years:** Baseline upper endoscopy (including complete visualization of the ampulla of Vater). Frequency of the endoscopy depends on the number and size of polyps identified.

Other *MUTYH*-associated polyposis (MAP)-related conditions:⁸

- **Ongoing:** Physical exam annually.

Useful resources

Colon Cancer Alliance

An organization dedicated to colon cancer prevention, funding colon cancer research and providing support to patients.

www.ccalliance.org

Hereditary Colon Cancer Foundation

A nonprofit organization serving the hereditary colorectal cancer community.

www.hcctakesguts.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions

www.kintalk.org

Version 1.1, last updated June 8, 2018

NBN

The *NBN* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *NBN* is coordinating a response to damaged DNA so it can be repaired. *NBN* works together with other genes, specifically *MRE11A*, *RAD50*, and *ATM*.

Like most genes, each person has two copies of the *NBN* gene: one inherited from each parent. A mutation in a single copy of the *NBN* gene inherited from either parent is known to increase risks of specific cancers (breast and prostate) over a lifetime.

In very rare cases, a person can inherit two *NBN* mutations, one from each parent. This causes a condition called Nijmegen breakage syndrome (NBS), which is associated with increased risks for childhood cancers, as well as physical and intellectual disabilities.

How common are mutations in the *NBN* gene?

Mutations in the *NBN* gene are rare—the exact frequency is not yet known. Studies to establish the frequency of *NBN* mutations are ongoing.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *NBN* gene, her chance of developing breast cancer is greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 70 | Average US woman ¹ | With <i>NBN</i> mutation ^{2,3,4} |
|------------------|-------------------------------|---|
| Breast | 12% | Elevated (21%) |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

¹ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

² Zhang G, Zeng Y, Liu Z, Wei W. Significant association between Nijmegen breakage syndrome 1 657del5 polymorphism and breast cancer risk. *Tumour Biol*. 2013 Oct;34(5):2753-7.

³ Zhang B, Beeghly-Fadiel A, Long J, Zheng W. Genetic variants associated with breast-cancer risk: comprehensive research synopsis, meta-analysis, and epidemiological evidence. *Lancet Oncol*. 2011 May;12(5):477-88.

⁴ Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol*. 2016;13(9):581-8.

Men

If a man has a mutation in the *NBN* gene, his chance of developing prostate cancer is greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.⁶

| Cancer by age 70 | Average US man ¹ | With <i>NBN</i> mutation ⁵ |
|------------------|-----------------------------|---------------------------------------|
| Prostate | 5.9% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Screening guidelines

These screening guidelines are for women with a mutation in the *NBN* gene. There are no published screening guidelines specific to men with *NBN* mutations. Speak with your healthcare provider about cancer screening. Your healthcare provider may use these guidelines to help create a customized screening plan for you.⁶

Women

Breast:^{7,8}

- **Starting at age 25:** Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider.
- **Between ages 25-39:** Breast exam, risk assessment, and risk reduction counseling by your provider every 1-3 years.
- **Starting at age 40 or 5-10 years prior to the earliest diagnosis of breast cancer in your family (whichever is earlier):** Breast exam, risk assessment, and risk reduction counseling by your provider and mammogram every year. Your provider may discuss screening with tomosynthesis (3D mammogram) and breast MRI with contrast every year.

⁵ Cybulski C, Górski B, Debniak T, et al. NBS1 is a prostate cancer susceptibility gene. *Cancer Res.* 2004 Feb 15;64(4):1215-9.

⁶ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V.1.2018 and Breast Cancer Screening and Diagnosis V.2.2018. © National Comprehensive Cancer Network, Inc 2018. All rights reserved. Accessed May 23, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

⁷ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. *NCCN Guidelines Version 1.2018*. Available at www.nccn.org. Published October 2017.

⁸ National Comprehensive Cancer Network. Breast Cancer Screening and Diagnosis. *NCCN Guidelines Version 2.2018*. Available at www.nccn.org. Published May 2018.

Men**Prostate:**

- Currently, there are no prostate cancer screening guidelines specific to *NBN* mutation carriers. Your provider may discuss earlier or more frequent screening or referral to a specialist.

Useful resources**FORCE**

Providing support, education, research, and resources for survivors and people at increased risk of cancer due to an inherited mutation or family history of cancer.

www.facingourrisk.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions.

www.kintalk.org

Susan G. Komen

Dedicated to reducing deaths from breast cancer by funding breast cancer research, ensuring access to care through community programs worldwide and supporting public health policies that help people facing breast cancer.

www.komen.org/

PALB2

The *PALB2* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *PALB2* is to stabilize and assist other genes, specifically *BRCA1* and *BRCA2*, in repairing damaged DNA before a cell divides to make more copies of itself.

Like most genes, each person has two copies of the *PALB2* gene: one inherited from each parent. A mutation in a single copy of the *PALB2* gene inherited from either parent is known to increase risks of specific cancers (breast, ovarian and pancreatic) over a lifetime.

In very rare cases, a person can inherit two *PALB2* mutations, one from each parent. This causes a blood condition called Fanconi anemia, which is associated with bone marrow failure, physical disabilities, and childhood cancers.

How common are mutations in the *PALB2* gene?

Mutations in the *PALB2* gene are rare—the exact frequency is not yet known. Studies to establish the frequency of *PALB2* mutations are ongoing.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *PALB2* gene, her chances of developing breast, ovarian, and pancreatic cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 70 | Average US woman ¹ | With <i>PALB2</i> mutation ^{2,3,4,5,6} |
|------------------|-------------------------------|---|
| Breast | 7.1% | Elevated (35-58%) |
| Ovarian | <1% | Elevated |
| Pancreatic | <1% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Men

If a man has a mutation in the *PALB2* gene, his chances of developing male breast and pancreatic cancer are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 70 | Average US man ¹ | With <i>PALB2</i> mutation ^{2,3,6} |
|------------------|-----------------------------|---|
| Male breast | <0.1% | Elevated (<1%) |
| Pancreatic | <1% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

¹ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

² Casadei S, Norquist BM, Walsh T, et al. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. *Cancer Res.* 2011 Mar 15;71(6):2222-9.

³ Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med.* 2014 Aug 7;371(6):497-506.

⁴ Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol.* 2016;13(9):581-8.

⁵ Walsh T, Casadei S, Lee MK, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc Natl Acad Sci U S A.* 2011 Nov 1;108(44):18032-7.

⁶ Becker AE, Hernandez YG, Frucht H, Lucas AL. Pancreatic ductal adenocarcinoma: risk factors, screening, and early detection. *World J Gastroenterol.* 2014 Aug 28;20(32):11182-98.

Additional information

The relationship between *PALB2* and *BRCA2*.

The name of the *PALB2* gene stands for “Partner and Localizer of *BRCA2*.” *PALB2* works closely with *BRCA2* and other genes inside the cells of the body to repair damaged DNA.

Screening guidelines

These screening guidelines are for individuals who have a mutation in the *PALB2* gene.⁷ Your healthcare provider may use these guidelines to help create a customized screening plan for you.

Women

Breast:^{8,9}

- **Starting at age 25:** Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider.
- **Between ages 25-29:** Breast exam, risk assessment, and risk reduction counseling by your provider every 1-3 years.
- **Starting at age 30 or 5-10 years prior to the earliest diagnosis of breast cancer in your family (whichever is earlier):** Breast exam, risk assessment, and risk reduction counseling by your provider and mammogram every year. Your provider may discuss screening with tomosynthesis (3D mammogram) and breast MRI with contrast every year.
- Your provider may discuss the option of having a risk-reducing bilateral mastectomy (the surgical removal of both breasts) based on family history.

Ovarian:⁷

- Currently, there are no ovarian cancer screening guidelines specific to *PALB2* mutation carriers. Your provider may discuss screening or referral to a specialist.

Men

Male breast:

- Currently, there are no male breast cancer screening guidelines specific to *PALB2* mutation carriers. Your provider may discuss screening or referral to a specialist.

⁷ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V.1.2018 and Breast Cancer Screening and Diagnosis V.2.2018. © National Comprehensive Cancer Network, Inc 2018. All rights reserved. Accessed May 23, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

⁸ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. *NCCN Guidelines Version 1.2018*. Available at www.nccn.org. Published October 2017.

⁹ National Comprehensive Cancer Network. Breast Cancer Screening and Diagnosis. *NCCN Guidelines Version 2.2018*. Available at www.nccn.org. Published May 2018.

Women and Men

Pancreatic:¹⁰

- Currently, there are no pancreatic cancer screening guidelines specific to *PALB2* mutation carriers. Your provider may discuss screening or referral to a specialist.

Useful resources**FORCE**

Providing support, education, research, and resources for survivors and people at increased risk of cancer due to an inherited mutation or family history of cancer.

www.facingourrisk.org

Bright Pink

Focused on the prevention and early detection of breast and ovarian cancer in young women, while providing support for high-risk individuals.

www.brightpink.org

Susan G. Komen

Dedicated to reducing deaths from breast cancer by funding breast cancer research, ensuring access to care through community programs worldwide and supporting public health policies that help people facing breast cancer.

www.komen.org

Version 1.1, last updated June 8, 2018

¹⁰ Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*. 2013;62(3):339-47.

PMS2

The *PMS2* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. *PMS2* works together with the *MLH1* gene to remove and repair DNA errors when signaled by the *MSH2* and *MSH6* genes.

Like most genes, each person has two copies of the *PMS2* gene: one inherited from each parent. A mutation in a single copy of the *PMS2* gene inherited from either parent causes Lynch syndrome, which is known to increase risks of specific cancers (colorectal, uterine, ovarian, and other cancers) over a lifetime.

In very rare cases, a person can inherit two *PMS2* mutations, one from each parent. This causes a condition called constitutional mismatch repair deficiency (CMMR-D), which is associated with childhood cancers such as colon, small intestine, brain, leukemia, lymphoma, and others.

How common are mutations in the *PMS2* gene?

Mutations that cause Lynch syndrome are rare—found in approximately 1 in 370 individuals.¹ Lynch syndrome accounts for approximately 3% of all colorectal cancers.²

¹ Hampel H, De la chapelle A. The search for unaffected individuals with Lynch syndrome: do the ends justify the means?. *Cancer Prev Res (Phila)*. 2011;4(1):1-5.

² Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. *Am J Gastroenterol*. 2014;109(8):1159-79.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *PMS2* gene, her chances of developing colorectal, ovarian, renal pelvis, small bowel and uterine cancers are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 70 | Average US woman ³ | With <i>PMS2</i> mutation ^{4,5,6} |
|------------------|-------------------------------|--|
| Colorectal | 1.6% | 11-15% |
| Uterine | 1.8% | 12-15% |
| Ovarian | <1% | Elevated |
| Renal pelvis | <1% | Elevated |
| Small bowel | <1% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

³ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

⁴ ten Broeke SW, Brohet RM, Tops CM, et al. Lynch syndrome caused by germline *PMS2* mutations: delineating the cancer risk. *J Clin Oncol*. February 2015 1;33(4):319-25.

⁵ Senter L, Clendenning M, Sotamaa K, et al. The clinical phenotype of Lynch syndrome due to germ-line *PMS2* mutations. *Gastroenterology*. 2008 Aug;135(2):419-28.

⁶ Møller P, Seppälä TT, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut*. 2017

Men

If a man has a mutation in the *PMS2* gene, his chances of developing colorectal, prostate, renal pelvis and small bowel cancers are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 70 | Average US man ³ | With <i>PMS2</i> mutation ^{4,5,6,7} |
|------------------|-----------------------------|--|
| Colorectal | 2% | 20% |
| Prostate | 5.9% | Elevated |
| Renal pelvis | 1.1% | Elevated |
| Small bowel | <1% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Additional information

Mutations in five different genes can lead to Lynch syndrome.

Having a mutation in *EPCAM*, *MLH1*, *MSH2*, *MSH6*, or *PMS2* can cause Lynch syndrome. Lynch syndrome used to be referred to as hereditary non-polyposis colorectal cancer, or HNPCC. It is an inherited condition that increases the risk of colorectal and other cancers. The associated cancer types and risk levels vary, depending on the gene in which the mutation is found.

Lynch syndrome is sometimes uncovered by testing a cancer or tumor.

Lynch syndrome can sometimes be evaluated by performing certain tests on cancers or tumors. These tests are called immunohistochemistry (IHC) and microsatellite instability (MSI) and are often the first line of screening tests when someone is suspected to have Lynch syndrome.

Screening guidelines

These screening guidelines are for individuals with Lynch syndrome, but are not specific to the *PMS2* gene. Your provider may make different recommendations based on studies showing lower cancer risks associated with mutations in *PMS2* compared to other Lynch syndrome genes. Your healthcare provider may use these guidelines to help create a customized screening plan for you.⁸

⁷ Ryan S, Jenkins MA, Win AK. Risk of prostate cancer in Lynch syndrome: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2014;23(3):437-49.

⁸ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal. V.3.2017. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed April 2, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Women

Uterine and ovarian:⁹

- **When you are finished having children, and depending on other factors such as menopause and family history:** Your healthcare provider may discuss a risk-reducing hysterectomy (the surgical removal of the uterus) and salpingo-oophorectomy (the surgical removal of the ovaries and fallopian tubes) with you to lower the risk of developing uterine and ovarian cancers.
- Your healthcare provider may discuss the symptoms of uterine and ovarian cancer, and the benefits and limitations of uterine biopsies (sampling) every 1-2 years and transvaginal ultrasound after menopause.
- While there may be circumstances where ovarian cancer screening with transvaginal ultrasound and a blood test for a protein called CA-125 are helpful, these techniques have not been shown to be effective in detecting early ovarian cancer.
- Your provider may discuss the use of medications that might reduce the risk of developing uterine or ovarian cancers.

Colorectal:⁹

- **Starting at age 20-25 or 2-5 years prior to the earliest colorectal cancer diagnosis in your family if the first diagnosis was before age 25:** Colonoscopy every 1-2 years.
- Your provider may discuss the use of medications such as aspirin that might reduce the risk of developing colorectal cancer.

Brain:⁹

- **Starting at age 25-30:** Physical and neurological examination by your provider every year.

Hepatobiliary tract:⁹

- Currently, there are no hepatobiliary tract cancer screening guidelines specific to *PMS2* mutation carriers. Your provider may discuss screening or referral to a specialist.

Pancreatic cancer^{9,10}

- Currently, there are no pancreatic cancer screening guidelines from the NCCN specific to *PMS2* mutation carriers. Your provider may discuss screening or referral to a specialist.

Sebaceous neoplasms:⁹

- Currently, there are no sebaceous neoplasm screening guidelines specific to *PMS2* mutation carriers. Your provider may discuss screening or referral to a specialist.

⁹ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. *NCCN Guidelines Version 3.2017*. Available at www.nccn.org. Published October 2017.

¹⁰ International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*. March 2013; 62(3):339-47.

Stomach and small bowel:⁹

- **Starting at age 30-35:** Your healthcare provider may discuss an upper endoscopy with visualization of the duodenum every 3-5 years at the time of colonoscopy, depending on your risk factors such as family history or ancestry.
- Your provider may discuss testing and treatment for a bacteria called *H. pylori*.

Urinary tract:⁹

- **Starting at age 30-35:** Your healthcare provider may discuss a urinalysis every year, especially for those with family history of urinary tract cancer.

Men

Colorectal:⁹

- **Starting at age 20-25 or 2-5 years prior to the earliest colorectal cancer diagnosis in your family if the first diagnosis was before age 25:** Colonoscopy every 1-2 years.
- Your provider may discuss the use of medications such as aspirin that might reduce the risk of developing colorectal cancer.

Brain:⁹

- **Starting at age 25-30:** Physical and neurological examination by your provider every year.

Hepatobiliary tract:⁹

- Currently, there are no hepatobiliary tract cancer screening guidelines specific to *PMS2* mutation carriers. Your provider may discuss screening or referral to a specialist.

Pancreatic:^{9,10}

- Currently, there are no pancreatic cancer screening guidelines from the NCCN specific to *PMS2* mutation carriers. Your provider may discuss screening or referral to a specialist.

Sebaceous neoplasms⁹

- Currently, there are no pancreatic cancer screening guidelines specific to *PMS2* mutation carriers. Your provider may discuss screening or referral to a specialist.

Prostate

- Currently, there are no prostate cancer screening guidelines specific to *PMS2* mutation carriers. Your provider may discuss screening or referral to a specialist.

Stomach and small bowel:⁹

- **Starting at age 30-35:** Your healthcare provider may discuss an upper endoscopy with visualization of the duodenum every 3-5 years at the time of colonoscopy, depending on your risk factors such as family history or ancestry.

- Your provider may discuss testing and treatment for a bacteria called H. pylori.

Urinary tract (including renal pelvis):⁹

- **Starting at age 30-35:** Your healthcare provider may discuss a urinalysis every year, especially for those with family history of urinary tract cancer.

Useful resources

Hereditary Colon Cancer Foundation

A nonprofit organization serving the hereditary colorectal cancer community.

www.hcctakesguts.org

Lynch Syndrome International

Primary mission is to provide support for individuals afflicted with Lynch syndrome.

www.lynchcancers.com

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions

www.kintalk.org

POLD1

The *POLD1* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *POLD1* is to fix mutations that occur as the DNA in the cell copies itself.

Like most genes, each person has two copies of the *POLD1* gene: one inherited from each parent. A mutation in a single copy of the *POLD1* gene inherited from either parent causes polymerase proofreading-associated polyposis (PPAP), which is known to increase risks for colorectal polyps and specific cancers (colorectal) over a lifetime.

To date, studies on the *POLD1* gene have been focused primarily on one specific mutation. Research on the *POLD1* gene is ongoing, especially related to the exact cancers and cancer risks associated with other mutations in this gene.

How common are mutations in the *POLD1* gene?

Mutations in the *POLD1* gene are rare—the exact frequency is not yet known. Studies to establish the frequency of *POLD1* mutations are ongoing.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *POLD1* gene, her chance of developing colorectal cancer is greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 95 | Average US woman ¹ | With <i>POLD1</i> mutation ^{2,3,4,5} |
|------------------|-------------------------------|---|
| Colorectal | 4% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

¹ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

² Bellido F, Pineda M, Aiza G, et al. POLE and POLD1 mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance. *Genet Med*. 2016;18(4):325-32.

³ Palles C, Cazier JB, Howarth KM, et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. *Nat Genet*. 2013;45(2):136-44.

⁴ Church JM. Polymerase proofreading-associated polyposis: a new, dominantly inherited syndrome of hereditary colorectal cancer predisposition. *Dis Colon Rectum*. 2014;57(3):396-7.

⁵ Valle L, Hernández-illán E, Bellido F, et al. New insights into POLE and POLD1 germline mutations in familial colorectal cancer and polyposis. *Hum Mol Genet*. 2014;23(13):3506-12.

Men

If a man has a mutation in the *POLD1* gene, his chance of developing colorectal cancer is greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 95 | Average US man ¹ | With <i>POLD1</i> mutation ^{2,3,4,5} |
|------------------|-----------------------------|---|
| Colorectal | 4.4% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Additional information

Not all *POLD1* mutations are linked to increased cancer risk.

For *POLD1*, only chr19:g.50909713 (including c.1433G>A) is analyzed, because other positions are not known to impact cancer risk.

Screening guidelines

These screening guidelines are for individuals who have a mutation in the *POLD1* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.⁶

Women and Men

Colorectal:⁷

- **Starting at age 25-30:** Colonoscopy every 2–3 years.
- **Depending on age and number of polyps:** Colonoscopy every 1-2 years and evaluation for colectomy (surgical removal of the colon and/or rectum).
- These recommendations may change if you have colorectal cancer, inflammatory bowel disease (IBD), or family history of colorectal cancer.

⁶ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal. V.3.2017. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed April 2, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

⁷ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. *NCCN Guidelines Version 3.2017*. Available at www.nccn.org. Published October 2017.

Useful resources

Colon Cancer Alliance

An organization dedicated to colon cancer prevention, funding colon cancer research and providing support to patients.

www.ccalliance.org

Hereditary Colon Cancer Foundation

A nonprofit organization serving the hereditary colorectal cancer community.

www.hcctakesguts.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions

www.kintalk.org

Version 1.1, last updated June 18, 2018

POLE

The *POLE* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *POLE* is to fix mutations that occur as the DNA in the cell copies itself.

Like most genes, each person has two copies of the *POLE* gene: one inherited from each parent. A mutation in a single copy of the *POLE* gene inherited from either parent causes polymerase proofreading-associated polyposis (PPAP), which is known to increase risks for colorectal polyps and specific cancers (colorectal) over a lifetime.

To date, studies on the *POLE* gene have been focused primarily on one specific mutation. Research on the *POLE* gene is ongoing, especially related to the exact cancers and cancer risks associated with other mutations in this gene.

How common are mutations in the *POLE* gene?

Mutations in the *POLE* gene are rare—the exact frequency is not yet known. Studies to establish the frequency of *POLE* mutations are ongoing.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *POLE* gene, her chance of developing colorectal cancer is greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 95 | Average US woman ¹ | With <i>POLE</i> mutation ^{2,3,4,5,6} |
|------------------|-------------------------------|--|
| Colorectal | 4% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

¹ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

² Bellido F, Pineda M, Aiza G, et al. *POLE* and *POLD1* mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance. *Genet Med*. 2016;18(4):325-32.

³ Palles C, Cazier JB, Howarth KM, et al. Germline mutations affecting the proofreading domains of *POLE* and *POLD1* predispose to colorectal adenomas and carcinomas. *Nat Genet*. 2013;45(2):136-44.

⁴ Church JM. Polymerase proofreading-associated polyposis: a new, dominantly inherited syndrome of hereditary colorectal cancer predisposition. *Dis Colon Rectum*. 2014;57(3):396-7.

⁵ Valle L, Hernández-illán E, Bellido F, et al. New insights into *POLE* and *POLD1* germline mutations in familial colorectal cancer and polyposis. *Hum Mol Genet*. 2014;23(13):3506-12.

⁶ Spier I, Holzapfel S, Altmüller J, et al. Frequency and phenotypic spectrum of germline mutations in *POLE* and seven other polymerase genes in 266 patients with colorectal adenomas and carcinomas. *Int J Cancer*. 2015;137(2):320-31.

Men

If a man has a mutation in the *POLE* gene, his chance of developing colorectal cancer is greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 95 | Average US man ¹ | With <i>POLE</i> mutation ^{2,3,4,5,6} |
|------------------|-----------------------------|--|
| Colorectal | 4.4% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Additional information

Not all *POLE* mutations are linked to increased cancer risk.

For *POLE*, only chr12:g.133250250 (including c.1270C>G) is analyzed, because other positions are not known to impact cancer risk.

Screening guidelines

These screening guidelines are for individuals who have a mutation in the *POLE* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.⁷

Women and Men

Colorectal:⁸

- **Starting at age 25-30:** Colonoscopy every 2–3 years.
- **Depending on age and number of polyps:** Colonoscopy every 1-2 years and evaluation for colectomy (surgical removal of the colon and/or rectum).
- These recommendations may change if you have, colorectal cancer, inflammatory bowel disease (IBD), or family history of colorectal cancer.

⁷ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal. V.3.2017. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed April 2, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

⁸ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. *NCCN Guidelines Version 3.2017*. Available at www.nccn.org. Published October 2017.

Useful resources

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An organization dedicated to colon cancer prevention, funding colon cancer research and providing support to patients.

www.ccalliance.org

Hereditary Colon Cancer Foundation

A nonprofit organization serving the hereditary colorectal cancer community.

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Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions

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Version 1.1, last updated June 8, 2018

PTEN

The *PTEN* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. *PTEN* has many important roles, including regulating cell movement and interaction, sending signals that prevent cell growth and survival, and instructing abnormal cells to die by a process known as apoptosis. The death of cells with significant DNA damage helps to prevent these cells from growing out of control and becoming a tumor.

Like most genes, each person has two copies of the *PTEN* gene: one inherited from each parent. A mutation in a single copy of the *PTEN* gene inherited from either parent is known to increase risks of specific cancers (breast, kidney, thyroid, uterine, and others) over a lifetime. Individuals with Cowden syndrome often have many non-cancerous findings, including non-cancerous skin bumps (called trichilemmomas and papillomatous papules), very large head circumference (macrocephaly), uterine fibroids, multinodular goiter of the thyroid, learning disabilities, and autism spectrum disorders.

Mutations in the *PTEN* gene can also cause other hereditary syndromes, such as Bannayan-Riley-Ruvalcaba syndrome (BRRS) and Proteus syndrome (PS). BRRS and PS are associated with increased tumor and cancer risks as well as specific physical and intellectual disabilities that occur in childhood. The entire spectrum of genetic syndromes related to mutations in the *PTEN* gene are collectively referred to as *PTEN* hamartoma tumor syndrome (PHTS). Rarely, individuals have been reported who have deletions of the *PTEN* gene as well as the *BMPR1A* gene. This causes a condition called juvenile polyposis of infancy (JPI), which is typically diagnosed prior to age six.

How common are mutations in the *PTEN* gene?

Mutations in the *PTEN* gene are rare—the exact frequency is not yet known. Studies to establish the frequency of *PTEN* mutations are ongoing.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *PTEN* gene, her chances of developing breast, colorectal, kidney, melanoma, thyroid, and uterine cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 70 | Average US woman ¹ | With <i>PTEN</i> mutation ^{2,3} |
|------------------|-------------------------------|--|
| Breast | 7.2% | 77-80% |
| Kidney | <1% | 34% |
| Thyroid | 1.5% | 35-38% |
| Uterine | 1.8% | 28% |
| Colorectal | 1.6% | 9% |
| Melanoma | <1% | 6% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Men

If a man has a mutation in the *PTEN* gene, his chances of developing colorectal, kidney, melanoma, and thyroid cancer are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 70 | Average US man ¹ | With <i>PTEN</i> mutation ^{2,3} |
|------------------|-----------------------------|--|
| Kidney | 1.1% | 34% |
| Thyroid | <1% | 35-38% |
| Colorectal | 2% | 9% |
| Melanoma | 1.2% | 6% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

¹ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

² Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. *Clin Cancer Res.* 2012;18(2):400-7.

³ Bubien V, Bonnet F, Brouste V, et al. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. *J Med Genet.* 2013;50(4):255-63.

Additional information

Cowden syndrome is often diagnosed based on a physical exam, checking for specific clinical features, both cancerous and non-cancerous. Approximately 25% of individuals who meet the clinical criteria for Cowden syndrome will have a mutation in the *PTEN* gene.⁴

Screening guidelines

These screening guidelines are for individuals who have a mutation in the *PTEN* gene that causes Cowden syndrome. Your healthcare provider may use these guidelines to help create a customized screening plan for you.⁵

Women

Breast:⁶

- **Starting at age 18:** Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider. Performing regular breast self exams may help increase breast awareness, especially when checked at the end of the menstrual cycle.
- **Starting at age 25 or 5-10 years before the earliest known breast cancer in the family:** Breast exam by your provider every 6-12 months.
- **Starting at age 30-35 or 5-10 years before the earliest known breast cancer in the family:** Breast MRI screening with contrast and mammogram every year. Your provider may discuss screening with tomosynthesis (3D mammogram) and may wish to alternate between these two screenings every 6 months.
- **After age 75:** Your provider may discuss an individualized management plan with you.
- Your provider may discuss the option of having a risk-reducing bilateral mastectomy (the surgical removal of both breasts).

Uterine:⁶

- **Starting at age 30-35:** Your healthcare provider may discuss the benefits and limitations of a transvaginal ultrasound along with endometrial biopsies (sampling) every year.
- Report any vaginal bleeding that is not typical to your provider.
- Your provider may discuss the option of having a risk-reducing hysterectomy (the surgical removal of the uterus).

⁴ Tan MH, Mester J, Peterson C, et al. A clinical scoring system for selection of patients for PTEN mutation testing is proposed on the basis of a prospective study of 3042 probands. *Am J Hum Genet.* 2011;88(1):42-56.

⁵ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V.1.2018. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed April 2, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

⁶ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. *NCCN Guidelines Version 1.2018.* Available at www.nccn.org. Published October 2017.

Thyroid:⁶

- **Starting at age 18 or 5 years before the earliest age of diagnosis of cancer in the family:** Comprehensive physical exam by your provider every year, with particular attention to examining the thyroid.
- Thyroid ultrasound every year.

Kidney:⁶

- **Starting at age 40:** Your healthcare provider may discuss a renal (kidney) ultrasound every 1-2 years.

Colorectal:⁶

- **Starting at age 35, or 5-10 years younger than the earliest diagnosed colorectal cancer in the family, if under age 40:** Colonoscopy every five years, or more frequently if polyps are found or symptoms of colorectal cancer arise.

Melanoma^{6,7}

- Your provider may discuss a skin exam every year.
- To reduce the chance of developing melanoma, the American Cancer Society recommends limiting exposure to UV light by avoiding excess sun exposure, wearing a hat, sunglasses and long protective clothing, applying sunscreen with SPF of 30 or higher and avoiding tanning beds and sun lamps.
- Any new, unusual, or changing moles should be reported to your provider or dermatologist.

Men

Thyroid:⁶

- **Starting at age 18 or 5 years before the earliest age of diagnosis of cancer in the family:** Comprehensive physical exam by your provider every year, with particular attention to examining the thyroid.
- Thyroid ultrasound every year.

Kidney:⁶

- **Starting at age 40:** Your healthcare provider may discuss a renal (kidney) ultrasound every 1-2 years.

Colorectal:⁶

- **Starting at age 35, or 5-10 years younger than the earliest diagnosed colorectal cancer in the family, if under age 40:** Colonoscopy every five years, or more frequently if polyps are found or symptoms of colorectal cancer arise.

⁷ Skin Cancer Prevention and Early Detection. The American Cancer Society website.

<https://www.cancer.org/cancer/skin-cancer/prevention-and-early-detection.html>. Updated March 19, 2017. Accessed April 2, 2018.

Melanoma:^{6,7}

- Your provider may discuss a skin exam every year.
- To reduce the chance of developing melanoma, the American Cancer Society recommends limiting exposure to UV light by avoiding excess sun exposure, wearing a hat, sunglasses and long protective clothing, applying sunscreen with SPF of 30 or higher and avoiding tanning beds and sun lamps.
- Any new, unusual, or changing moles should be reported to your provider or dermatologist.

Useful resources**FORCE**

Providing support, education, research, and resources for survivors and people at increased risk of cancer due to an inherited mutation or family history of cancer.

www.facingourrisk.org

PTEN Foundation

Founded with a mission to educate about PTEN syndromes, provide financial support to patients, support research, and to promote awareness.

www.ptenfoundation.org

Hereditary Colon Cancer Foundation

A nonprofit organization serving the hereditary colorectal cancer community.

www.hcctakesguts.org

RAD51C

The *RAD51C* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *RAD51C* is to work together with the *RAD51* family of genes to repair damaged DNA.

Like most genes, each person has two copies of the *RAD51C* gene: one inherited from each parent. A mutation in a single copy of the *RAD51C* gene inherited from either parent is known to increase risks of specific cancers (ovarian) over a lifetime. Some studies have suggested that women with *RAD51C* mutations have an increased risk for breast cancer, while other studies have shown no increase in breast cancer risk.¹ More studies are needed to clarify the possible association between breast cancer and *RAD51C* mutations.

In very rare cases, a person can inherit two *RAD51C* mutations, one from each parent. This causes a blood condition called Fanconi anemia, which is associated with bone marrow failure, physical disabilities, and childhood cancers.

How common are mutations in the *RAD51C* gene?

Mutations in the *RAD51C* gene are rare—the exact frequency is not yet known. Studies to establish the frequency of *RAD51C* mutations are ongoing.

¹ Blanco A, et al. *RAD51C* germline mutations found in Spanish site-specific breast cancer and breast-ovarian cancer families. *Breast Cancer Res Treat.* 2014 Aug;147(1):133-43.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *RAD51C* gene, her chance of developing ovarian cancer is greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 80 | Average US woman ² | With <i>RAD51C</i> mutation ^{3,4,5} |
|------------------|-------------------------------|--|
| Ovarian | <1% | Elevated (9%) |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Men

If a man has a mutation in the *RAD51C* gene, his chance of developing cancer is not known to be increased.

Screening guidelines

These screening guidelines are for women who have a mutation in the *RAD51C* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.⁶

Women

Ovarian:⁷

- **Starting at age 45-50, or earlier based on family history of ovarian cancer:** Your healthcare provider may discuss a risk-reducing salpingo-oophorectomy (the surgical removal of the ovaries and fallopian tubes) with you to lower the risk of developing ovarian cancer.

² Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

³ Loveday C, Turnbull C, Ruark E, et al. Germline *RAD51C* mutations confer susceptibility to ovarian cancer. *Nat Genet.* 2012;44(5):475-6.

⁴ Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol.* 2016;13(9):581-8.

⁵ Song H, Dicks E, Ramus SJ, et al. Contribution of Germline Mutations in the *RAD51B*, *RAD51C*, and *RAD51D* Genes to Ovarian Cancer in the Population. *J Clin Oncol.* 2015;33(26):2901-7.

⁶ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V.1.2018. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed April 2, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

⁷ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. *NCCN Guidelines Version 1.2018*. Available at www.nccn.org. Published October 2017.

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www.ovarian.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions.

www.kintalk.org

Version 1.1, last updated June 8, 2018

RAD51D

The *RAD51D* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *RAD51D* is to work together with the *RAD51* family of genes to repair damaged DNA.

Like most genes, each person has two copies of the *RAD51D* gene: one inherited from each parent. A mutation in a single copy of the *RAD51D* gene inherited from either parent is known to increase risks of specific cancers (ovarian) over a lifetime. Some studies have suggested that women with *RAD51D* mutations have an increased risk for breast cancer, while other studies have shown no increase in breast cancer risk.^{1,2,3} More studies are needed to clarify the possible association between breast cancer and *RAD51D* mutations.

How common are mutations in the *RAD51D* gene?

Mutations in the *RAD51D* gene are rare—the exact frequency is not yet known. Studies to establish the frequency of *RAD51D* mutations are ongoing.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *RAD51D* gene, her chance of developing ovarian cancer is greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 80 | Average US woman ⁴ | With <i>RAD51D</i> mutation ^{1,5,6} |
|------------------|-------------------------------|--|
| Ovarian | <1% | Elevated (10%) |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

¹ Loveday C, Turnbull C, Ramsay E, et al. Germline mutations in *RAD51D* confer susceptibility to ovarian cancer. *Nat Genet.* 2011;43(9):879-82.

² Osher DJ, De leeneer K, Michils G, et al. Mutation analysis of *RAD51D* in non-BRCA1/2 ovarian and breast cancer families. *Br J Cancer.* 2012;106(8):1460-3.

³ Wickramanayake A, Bernier G, Pennil C et al. Loss of function germline mutations in *RAD51D* in women with ovarian carcinoma. *Gynecol Oncol.* 2012;127(3):552-5.

⁴ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

⁵ Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol.* 2016;13(9):581-8.

⁶ Song H, Dicks E, Ramus SJ, et al. Contribution of Germline Mutations in the *RAD51B*, *RAD51C*, and *RAD51D* Genes to Ovarian Cancer in the Population. *J Clin Oncol.* 2015;33(26):2901-7

Men

If a man has a mutation in the *RAD51D* gene, his chance of developing cancer is not known to be increased.

Screening guidelines

These screening guidelines are for women who have a mutation in the *RAD51D* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.⁷

Women

Ovarian:⁸

- **Starting at age 45-50, or earlier based on family history of ovarian cancer:** Your healthcare provider may discuss a risk-reducing salpingo-oophorectomy (the surgical removal of the ovaries and fallopian tubes) with you to lower the risk of developing ovarian cancer.

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⁸ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. *NCCN Guidelines Version 1.2018*. Available at www.nccn.org. Published October 2017.

SMAD4

The *SMAD4* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *SMAD4* is helping to regulate the stability and growth of cells in the gastrointestinal tract.

Like most genes, each person has two copies of the *SMAD4* gene, one inherited from each parent. A mutation in a single copy of the *SMAD4* gene inherited from either parent causes juvenile polyposis syndrome (JPS), which is associated with gastrointestinal polyps, especially a type of polyp called juvenile polyps, and is also known to increase risk of specific cancers (colorectal, stomach, pancreatic and small bowel) over a lifetime.

Approximately 25% of individuals with juvenile polyposis syndrome are the first in their family to carry the mutation.¹ This is referred to as a “*de novo*” mutation. Individuals with *de novo* mutations have the same cancer risks as those with an inherited mutation from a parent, and have a 50% chance of passing the mutation on to their children.

Individuals with mutations in the *SMAD4* gene may also have a condition called hereditary hemorrhagic telangiectasia (HHT).² HHT is associated with abnormal connections between blood vessels called arteries and veins (arteriovenous malformation, or AVM), which can occur in the lungs, brain, liver, and other parts of the body. One of the first symptoms of HHT is regular and frequent nosebleeds in childhood or later in life.

How common are mutations in the *SMAD4* gene?

Mutations in the *SMAD4* gene are rare—but approximately 20-25% of individuals with JPS have a pathogenic mutation in *SMAD4*.³

¹ Larsen Haidle J, Howe JR. 2015 December 3. Juvenile Polyposis Syndrome. In: GeneReviews® (database online). Copyright, University of Washington, Seattle. 1993-2016. Available at <http://www.ncbi.nlm.nih.gov/books/NBK1469/>. April 21, 2016.

² Aretz S, Stienen D, Uhlhaas S, et al. High proportion of large genomic deletions and a genotype phenotype update in 80 unrelated families with juvenile polyposis syndrome. *J Med Genet*. 2007;44(11):702-9.

³ Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. *Ann Surg Oncol*. 1998;5(8):751-6.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *SMAD4* gene, her chances of developing colorectal, stomach, pancreatic, and small bowel (especially in the duodenum) cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 80 | Average US woman ⁴ | With <i>SMAD4</i> mutation ^{3,5} |
|------------------------|-------------------------------|---|
| Colorectal | 2.7% | 39% |
| Stomach | <1% | Elevated (21%) |
| Pancreatic | <1% | Elevated |
| Small Bowel (Duodenal) | <1% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Men

If a man has a mutation in the *SMAD4* gene, his chances of developing colorectal, stomach, pancreatic, and small bowel (especially in the duodenum) cancer are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 80 | Average US man ⁴ | With <i>SMAD4</i> mutation ^{3,5} |
|------------------------|-----------------------------|---|
| Colorectal | 3.4% | 39% |
| Stomach | <1% | Elevated (21%) |
| Pancreatic | 1.1% | Elevated |
| Small Bowel (Duodenal) | <1% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

⁴ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

⁵ Brosens LA, Van hattem A, Hyland LM, et al. Risk of colorectal cancer in juvenile polyposis. *Gut*. 2007;56(7):965-7.

Screening guidelines

These screening guidelines are for individuals with JPS who have a mutation in the *SMAD4* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.⁶

Women and Men

Colorectal:⁷

- **Starting around age 15:** Colonoscopy every 2-3 years, or every year if polyps are found.

Stomach:⁷

- **Starting around age 15:** Upper endoscopy every 2-3 years, or every year if polyps are found.

Pancreatic:⁷

- Currently, there are no pancreatic cancer screening guidelines specific to *SMAD4* mutation carriers. Your provider may discuss screening or referral to a specialist.

Small bowel cancer (duodenal and other sections):⁷

- Currently, there are no small bowel cancer screening guidelines specific to *SMAD4* mutation carriers. Your provider may discuss screening or referral to a specialist.

Other *SMAD4*-related recommendations:

- Speak with your provider about screening recommended for individuals who may have HHT.

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⁷ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. *NCCN Guidelines Version 3.2017*. Available at www.nccn.org. Published October 2017.

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Version 1.1, last updated June 8, 2018

STK11

The *STK11* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *STK11* is to slow down cell growth and production when the cell does not have enough energy and nutrients to grow and divide. *STK11* also helps the cell maintain its shape and aids in its ability to move.

Like most genes, each person has two copies of the *STK11* gene: one inherited from each parent. A mutation in a single copy of the *STK11* gene inherited from either parent causes Peutz-Jeghers syndrome (PJS), which is known to increase risk of specific cancers (breast, ovarian, colorectal, stomach, and others) over a lifetime.

Mutations in *STK11* can be a risk factor for many non-cancerous findings. These include a high number of colon polyps that may lead to bowel obstruction; dark blue to dark brown pigmented spots on the fingers, inside of the cheeks, and around the mouth, eyes, nostrils, and anus that may fade in puberty and adulthood; non-cancerous ovarian tumors called sex cord tumors with annular tubules (SCTAT) and mucinous ovarian tumors; and non-cancerous testicular tumors called large calcifying Sertoli cell tumors (LCST). Some of these non-cancerous findings can have symptoms, while others will have no effect on health.

How common are mutations in the *STK11* gene?

Mutations in the *STK11* gene are rare—but approximately 80-94% of individuals with PJS have a pathogenic mutation in *STK11*.¹

¹ Aretz S, Stienen D, Uhlhaas S, et al. High proportion of large genomic *STK11* deletions in Peutz-Jeghers syndrome. *Hum Mut.* 2005; 26(6):513–519.

How mutations in this gene impact risk

Women

If a woman has a mutation in the *STK11* gene, her chances of developing breast, ovarian, colorectal, stomach, cervical, lung, pancreatic, small bowel, and uterine cancer are greater than that of the average US woman. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

| Cancer by age 65 or 70 | Average US woman ² | With <i>STK11</i> mutation ^{3,4,5,6} |
|------------------------|-------------------------------|---|
| Breast | 7.2% | 32-54% |
| Ovarian | <1% | 21% |
| Colorectal | 1.6% | 39% |
| Stomach | <1% | 29% |
| Cervical | <1% | Elevated |
| Lung | 2.0% | 7-17% |
| Pancreatic | <1% | 11% |
| Small bowel | <1% | 13% |
| Uterine | 1.7% | 9% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

² Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

³ Lim W, Olschwang S, Keller JJ, et al. Relative frequency and morphology of cancers in STK11 mutation carriers. *Gastroenterology*. 2004;126(7):1788-94.

⁴ Hearle N, Schumacher V, Menko FH, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. *Clin Cancer Res*. 2006;12(10):3209-15.

⁵ Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. *Gastroenterology*. 2000;119(6):1447-53.

⁶ van Lier MG, Wagner A, Mathus-vliegen EM, Kuipers EJ, Steyerberg EW, Van leerdam ME. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. *Am J Gastroenterol*. 2010;105(6):1258-64.

Men

If a man has a mutation in the *STK11* gene, his chances of colorectal, lung, pancreatic, small bowel, stomach, and testicular cancer are greater than that of the average US man. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

| Cancer by age 65 or 70 | Average US man ² | With <i>STK11</i> mutation ^{3,4,5,6} |
|------------------------|-----------------------------|---|
| Colorectal | 2% | 39% |
| Lung | 2.4% | 7-17% |
| Pancreatic | <1% | 11% |
| Small bowel | <1% | 13% |
| Stomach | <1% | 29% |
| Testicular | <1% | Elevated |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Screening guidelines

These screening guidelines are for individuals who have a mutation in the *STK11* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.⁷

Women

Breast:^{8,9}

- **Starting at age 18:** Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider. Performing regular breast self exams may help increase breast awareness, especially when checked at the end of the menstrual cycle.
- **Starting at age 25:** Breast exam by your provider every 6-12 months.

⁷ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal V.3.2017 and Genetic/Familial High-Risk Assessment: Breast and Ovarian V.1.2018. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed April 2, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

⁸ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. NCCN Guidelines Version 1.2017. Available at www.nccn.org. Published September 2016.

⁹ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Colorectal. NCCN Guidelines Version 3.2017. Available at www.nccn.org. Published October 2017.

- **Between ages 25-29 or individualized based on family history:** Breast MRI screening with contrast every year. Your provider may discuss screening with tomosynthesis (3D mammogram) if MRI is unavailable.
- **Between ages 30-75:** Breast MRI screening with contrast and mammogram every year. Your provider may discuss screening with tomosynthesis and may wish to alternate between these two screenings every 6 months.
- **After age 75:** Your provider may discuss an individualized management plan with you.

Cervical, ovarian, and uterine:⁹

- **Starting at age 18-20:** Pelvic examination by your provider and Pap smear every year. Your provider may also discuss the benefits and limitations of a transvaginal ultrasound.

Colorectal:⁹

- **Starting in the late teens:** Colonoscopy every 2-3 years.

Stomach:⁹

- **Starting in the late teens:** Upper endoscopy every 2-3 years.

Lung:

- Currently, there are no lung cancer screening guidelines specific to *STK11* mutation carriers. Your provider may discuss smoking cessation and symptoms of lung cancer.

Pancreatic:^{9,10}

- **Starting at age 30-35:** Magnetic resonance cholangiopancreatography (MRCP) with contrast or endoscopic ultrasound (EUS) every 1-2 years.

Small bowel:⁹

- **Starting at age 8-10:** Baseline small bowel visualization (CT, MRI enterography, or video capsule endoscopy) with follow-up visualizations based on findings.
- **Starting at age 18:** Small bowel visualization (CT, MRI enterography, or video capsule endoscopy) every 2-3 years, though this may be individualized.

Men

Testicular:⁹

- **Starting at age 10:** Annual testicular exam and observation for breast tissue development due to hormonal changes.

Colorectal:⁹

- **Starting in the late teens:** Colonoscopy every 2-3 years.

¹⁰ Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*. 2013;62(3):339-47.

Stomach:⁹

- **Starting in the late teens:** Upper endoscopy every 2-3 years.

Lung:⁹

- Currently, there are no lung cancer screening guidelines specific to *STK11* mutation carriers. Your provider may discuss smoking cessation and symptoms of lung cancer.

Pancreatic:^{9,10}

- **Starting at age 30-35:** Magnetic resonance cholangiopancreatography (MRCP) with contrast or endoscopic ultrasound (EUS) every 1-2 years.

Small bowel:⁹

- **Starting at age 8-10:** Baseline small bowel visualization (CT, MRI enterography, or video capsule endoscopy) with follow-up visualizations based on findings.
- **Starting at age 18:** Small bowel visualization (CT, MRI enterography, or video capsule endoscopy) every 2-3 years, though this may be individualized.

Useful resources

Hereditary Colon Cancer Foundation

A nonprofit organization serving the hereditary colorectal cancer community.

www.hcctakesguts.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions

www.kintalk.org

Bright Pink

Focused on the prevention and early detection of breast and ovarian cancer in young women, while providing support for high-risk individuals.

www.brightpink.org

Version 1.1, last updated June 8, 2018

TP53

The *TP53* gene is a tumor suppressor gene. Tumor suppressor genes slow down cell division, repair DNA mistakes, or tell cells when to die. When they don't work properly, cells can grow out of control, which can lead to cancer. The primary role of *TP53* is to make the critical decision of whether to repair damaged DNA or instruct the cell to die by a process known as apoptosis. The death of cells with significant DNA damage helps to prevent these cells from growing out of control and becoming a tumor.

Like most genes, each person has two copies of the *TP53* gene: one inherited from each parent. A mutation in a single copy of the *TP53* gene inherited from either parent is known to cause Li-Fraumeni syndrome, which is known to increase risk of specific cancers (breast, brain, sarcoma, and others) over a lifetime at unusually young ages.

Approximately 7% to 20% of individuals with *TP53* mutations are the first in their family to carry the mutation.¹ This is referred to as a “*de novo*” mutation. Individuals with *de novo* mutations have the same cancer risks as those with an inherited mutation from a parent, and have a 50% chance of passing the mutation on to their children.

How common are mutations in the *TP53* gene?

Mutations in the *TP53* gene are extremely rare—found in approximately 1 in 20,000 individuals in the general population.²

How mutations in this gene impact risk

Women

If a woman has a mutation in the *TP53* gene, her chance of developing certain cancers, especially breast, brain, and sarcoma (cancer of the bone and soft tissue), is greater than that of the average US woman. Other Li-Fraumeni related cancers include adrenocortical carcinoma, colorectal, leukemia, liver, lung, lymphoma, melanoma, ovarian, pancreas, and stomach. This does not mean that she has a diagnosis of cancer or that she will definitely develop cancer in her lifetime.

Because having a *TP53* mutation is rare, specific risk estimates for each cancer are not available.

¹ Gonzalez KD, Buzin CH, Noltner KA, et al. High frequency of *de novo* mutations in Li-Fraumeni syndrome. *J Med Genet*. 2009;46(10):689-93.

² Gonzalez KD, Noltner KA, Buzin CH, et al. Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations. *J Clin Oncol*. 2009;27(8):1250-6.

| Any cancer by age | Average US woman ³ | With <i>TP53</i> mutation ^{4,5} |
|-------------------|-------------------------------|--|
| 20 | <1% | 18% |
| 30 | <1% | 49% |
| 40 | 2.3% | 77% |
| 50 | 5.5% | 93% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

Men

If a man has a mutation in the *TP53* gene, his chances of developing certain cancers, especially brain cancer and sarcoma (cancer of the bone and soft tissue), are greater than that of the average US man. Other Li-Fraumeni related cancers include adrenocortical carcinoma, colorectal, leukemia, liver, lung, lymphoma, melanoma, pancreas, and stomach. This does not mean that he has a diagnosis of cancer or that he will definitely develop cancer in his lifetime.

Because having a *TP53* mutation is rare, specific risk estimates for each cancer are not available.

| Any cancer by age | Average US man ³ | With <i>TP53</i> mutation ^{4,5} |
|-------------------|-----------------------------|--|
| 20 | <1% | 10% |
| 30 | <1% | 21% |
| 40 | 1.5% | 33% |
| 50 | 3.4% | 68% |

Elevated: The specific chance of developing cancer has not been fully established and is based on data from one or more sources.

³ Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. 2012-2014. DevCan software (<http://surveillance.cancer.gov/devcan>) V 6.7.5. Accessed April 2018.

⁴ Hwang SJ, Lozano G, Amos CI, Strong LC. Germline p53 mutations in a cohort with childhood sarcoma: sex differences in cancer risk. *Am J Hum Genet.* 2003;72(4):975-83.

⁵ Mai PL, Best AF, Peters JA, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. *Cancer.* 2016;122(23):3673-3681.

Additional information

Many cancers and tumors have a mutation in the *TP53* gene.

Genetic testing on tumor tissue is sometimes performed to provide information about prognosis and potential targeted treatments. These tests look for DNA changes that occurred while the cancer was forming, and often a mutation is found in the *TP53* gene. These changes are only in the cancer cells, not in any other cells of the body, and were not inherited from parents, nor can they be passed down to children. On the other hand, tests like the Color tests analyze the genetic makeup that was inherited from parents, which can be found in all cells of the body. The primary purpose of the Color tests is to find any potential inherited risk factors for cancer in order to provide detailed information about the risk of developing other cancers in the future, as well as to give important information to family members.

Screening guidelines

These screening guidelines are for individuals who have a mutation in the *TP53* gene. Your healthcare provider may use these guidelines to help create a customized screening plan for you.⁶

Women

Breast:⁷

- **Starting at age 18:** Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider. Performing regular breast self exams may help increase breast awareness, especially when checked at the end of the menstrual cycle.
- **Starting at age 20, or at the age of the earliest diagnosed breast cancer in the family, if below age 20 years:** Breast exam by your provider every six months.
- **Between ages 20-29:** Breast MRI screening with contrast (preferred) every year or mammogram with consideration of tomosynthesis (3D mammogram) if MRI is unavailable.
- **Between ages 30-75:** Breast MRI screening with contrast and mammogram with consideration of tomosynthesis every year. Your provider may wish to alternate between these two screenings every 6 months.
- **After age 75:** Your provider may discuss an individualized management plan with you.
- Your provider may discuss the option of having a risk-reducing bilateral mastectomy (the surgical removal of both breasts).

⁶ Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian V.1.2018. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed April 2, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

⁷ National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. *NCCN Guidelines Version 1.2018*. Available at www.nccn.org. Published October 2017.

Brain cancer and tumors^{7,8}

- Brain MRI every year, which may be part of a whole body MRI (as recommended for sarcoma)

Sarcoma:^{7,8}

- Whole body MRI or equivalent every year. Your provider may discuss participation in clinical trials or alternatives to whole body MRI if it is not available.
- Ultrasound of abdomen and pelvis every 3-4 months.

Adrenocortical carcinoma:⁸

- **Until age 40:** Ultrasound of abdomen and pelvis and blood tests (17-OH-progesterone, total testosterone, dehydroepiandrosterone sulfate, and androstenedione) every 3-4 months, and urine tests (24 hour urine cortisol)

Colorectal:⁷

- **Starting at age 25, or 5 years before the earliest known colorectal cancer in the family:** Colonoscopy and upper endoscopy every 2-5 years

Leukemia and lymphoma:⁸

- Blood tests (complete blood count, erythrocyte sedimentation rate, and lactate dehydrogenase) every 3 months

Melanoma:^{7,8}

- **Starting at age 18:** Skin examination by a dermatologist every year

Other cancers related to Li-Fraumeni syndrome:⁷

- Comprehensive physical exam by your provider, including a neurologic exam every 6-12 months
- Avoid radiation therapy for treatment of cancer when possible.
- Other screening may be recommended by your provider based on your family history of cancer

Men

Brain cancer and tumors:^{7,8}

- Brain MRI every year, which may be part of a whole body MRI (recommended for sarcoma)

⁸ Villani A, Shore A, Wasserman JD, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. *Lancet Oncol*. 2016;17(9):1295-305.

Sarcoma:^{7,8}

- Whole body MRI or equivalent every year. Your provider may discuss participation in clinical trials or alternatives to whole body MRI if it is not available.
- Ultrasound of abdomen and pelvis every 3-4 months.

Adrenocortical carcinoma:⁸

- **Until age 40:** Ultrasound of abdomen and pelvis and blood tests (17-OH-progesterone, total testosterone, dehydroepiandrosterone sulfate, and androstenedione) every 3-4 months, and urine tests (24 hour urine cortisol).

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- **Starting at age 18:** Skin examination by a dermatologist every year.

Other cancers related to Li-Fraumeni syndrome:⁷

- Comprehensive physical exam by your provider, including a neurologic exam every 6-12 months
- Avoid radiation therapy for treatment of cancer when possible.
- Other screening may be recommended by your provider based on your family history of cancer

Useful resources

Li-Fraumeni Syndrome (LFS) Association

Provides a wide range of information, advocacy, and support services for individuals and families with Li-Fraumeni Syndrome.

www.lfsassociation.org

FORCE

Providing support, education, research, and resources for survivors and people at increased risk of cancer due to an inherited mutation or family history of cancer.

www.facingourrisk.org

Bright Pink

Focused on the prevention and early detection of breast and ovarian cancer in young women, while providing support for high-risk individuals.

www.brightpink.org

Kintalk

An educational and family communication site for individuals and their families with hereditary cancer conditions.

www.kintalk.org

About Color

Color is a health service that helps people better understand their risk of hereditary conditions, such as cancer and heart disease. By partnering with Color, healthcare providers can offer their patients improved access to genetic health information that can drive personalized patient care and lead to improved health outcomes.

Your patients' privacy is our priority

Color takes privacy very seriously and only collects the information that is needed to provide a high-quality experience. We comply with HIPAA requirements regarding protected health information. To learn more, you can review our privacy policy at color.com/privacy or contact us to request a copy.

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