Management Guidelines

Invitae Breast and Gyn Cancers Guidelines-Based Cancer Panel

GENE	BREAST CANCER RISK	GYNECOLOGIC CANCER RISK	OTHER ASSOCIATED CANCERS	MANAGEMENT GUIDELINES*
ATM	♀ 17–52% (PMID: 15928302, 16998505, 1961222) ♂ No known risk	Ovarian—unknown risk (PMID: 25622547)	Pancreatic, colorectal	**FEMALES:** Screening: Annual mammography with consideration of tomosynthesis starting at age 40 years and consider annual breast MRI with contrast starting at age 40, with modification as appropriate based on family history or specific gene mutation. Prophylactic risk-reducing mastectomy: evidence insufficient; manage based on family history. Insufficient evidence to recommend against radiation therapy. Counsel for risk of autosomal recessive condition in offspring.
BRCA1	♀ Up to 87% (PMID: 7907678; 12677558) ♂ 1–2% (PMID: 18042939, 20587410)	Ovarian—up to 54% (PMID: 7907678, 12677558)	Pancreatic, prostate	**FEMALES:** Breast awareness starting at age 18. Clinical breast exams every 6–12 months beginning at 25 years of age. Annual breast MRIs with contrast beginning between the ages of 25 and 29 (or annual mammograms with consideration of tomosynthesis if MRI is unavailable), although the age to initiate screening may be individualized based on family history. Annual breast MRI with contrast and annual mammography with consideration of tomosynthesis between the ages of 30 and 75. After age 75, management should be considered on an individual basis. For women treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue. Discuss the option of risk-reducing mastectomy and counsel regarding degree of protection, degree of cancer risk, and reconstruction options. Address the psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy. Recommend risk-reducing salpingo-oophorectomy, typically between age 35 and 40 years and upon the completion of childbearing. See specific Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol in NCCN Guidelines for Ovarian Cancer – Principles of Surgery. Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short-term hormonal replacement, and medical issues. Salpingectomy alone is not the standard of care for risk reduction, although clinical trials of interval salpingectomy and delayed oophorectomy are ongoing. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in pre-menopausal women, oophorectomy likely reduces the risk of developing breast cancer, but the magnitude is uncertain and may be gene-specific. For those patients who have not elected RRSO, transvaginal ultrasound combined with serum CA-125 for ovarian cancer screening, but, although of uncertain benefit, it may be considered at the clinician's discretion starting at age 30–35 years. Consider risk-reducing agents as options for breast and ovarian cancer and discuss their risks and benefits. **MALES:** Breast self-exam training and education starting at age 35 years. Clinical breast exam every 12 months, beginning at age 35 years. Consider prostate-cancer screening beginning at age 45 years. **MALES AND FEMALES:** Advise affected individuals of reproductive age regarding prenatal diagnosis and assisted reproduction options. Encourage affected individuals to inform relatives about possible inherited cancer risks, options for risk assessment and management. Genetic counseling and testing are recommended for at-risk relatives.
BRCA2	♀ Up to 84% (PMID: 9497246) ♂ Up to 8.9% (PMID: 18042939, 20587410)	Ovarian—up to 27% (PMID: 9497246)	Pancreatic, prostate, melanoma	**FEMALES:** Breast awareness starting at age 18. Clinical breast exams every 6–12 months beginning at 25 years of age. Annual breast MRIs with contrast beginning between the ages of 25 and 29 (or annual mammograms with consideration of tomosynthesis if MRI is unavailable), although the age to initiate screening may be individualized based on family history. Annual breast MRI with contrast and annual mammography with consideration of tomosynthesis between the ages of 30 and 75. After age 75, management should be considered on an individual basis. For women treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue. Discuss the option of risk-reducing mastectomy and counsel regarding degree of protection, degree of cancer risk, and reconstruction options. Address the psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy. Recommend risk-reducing salpingo-oophorectomy, typically between age 35 and 40 years and upon the completion of childbearing; however, risk-reducing salpingo-oophorectomy may be delayed in BRCA2 mutation carriers. See specific Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol in NCCN Guidelines for Ovarian Cancer – Principles of Surgery. Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short-term hormonal replacement, and medical issues. Salpingectomy alone is not the standard of care for risk reduction, although clinical trials of interval salpingectomy and delayed oophorectomy are ongoing. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in pre-menopausal women, oophorectomy likely reduces the risk of developing breast cancer, but the magnitude is uncertain and may be gene-specific. For those patients who have not elected RRSO, transvaginal ultrasound combined with serum CA-125 for ovarian cancer screening, but, although of uncertain benefit, it may be considered at the clinician's discretion starting at age 30-35 years. Consider risk-reducing agents as options for breast and ovarian cancer and discuss their risks and benefits. **MALES:** Breast self-exam training and education starting at age 35 years. Clinical breast exam every 12 months, beginning at age 35 years. Recommend prostate-cancer screening beginning at age 45 years. **MALES AND FEMALES:** Advise affected individuals of reproductive age regarding prenatal diagnosis and assisted reproduction options. Encourage affected individuals to inform relatives about possible inherited cancer risks, options for risk assessment and management. Genetic counseling and testing are recommended for at-risk relatives.
BRIP1	Possibly elevated (PMID: 17033622, 21964575, 26921362)	Ovarian—8% (PMID: 21964575)		**FEMALES:** Consider risk-reducing salpingo-oophorectomy at age 45–50. Counsel for risk of autosomal recessive disease in offspring. Discussion regarding risk-reducing salpingo-oophorectomy may need to be held earlier with patients with a family history of earlier-onset ovarian cancer.

All information based on published literature as of March 2018.

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GENE	BREAST CANCER RISK	GYNECOLOGIC CANCER RISK	OTHER ASSOCIATED CANCERS	MANAGEMENT GUIDELINES*
CDH1	♀ 39–52% (lobular) (PMID: 11729114, 17545690, 25979631) ♂ No known risk		Gastric, colorectal	**FEMALES:** Annual mammography with consideration of tomosynthesis beginning at age 30. Consider annual breast MRI with contrast beginning at age 30, with modification as appropriate based on family history or specific gene mutation. Prophylactic risk-reducing mastectomy: evidence insufficient; manage based on family history. **MALES AND FEMALES:** Prophylactic total gastrectomy between the ages of 18 and 40. Prophylactic gastrectomy is not recommended prior to 18 years of age but may be considered for those with family members diagnosed with gastric cancer prior to age 25. Baseline endoscopy is recommended prior to prophylactic total gastrectomy. Intraoperative frozen sections should be performed to verify that the proximal margin contains esophageal squamous mucosa and the distal margin contains duodenal mucosa, to ensure the complete removal of gastric tissue. A D2 lymph node dissection is not necessary for prophylactic total gastrectomy. Upper endoscopy is proposed for those with HDGC, who do not opt for prophylactic gastrectomy or for whom gastrectomy has been deferred. Endoscopic screening with multiple random biopsies and biopsies of subtle lesions is recommended at six- to twelve-month intervals.
CHEK2	♀ 25–39% (PMID: 18172190, 21876083 ♂ Possibly elevated (PMID: 21956126)	Ovarian—unknown risk (PMID: 24240112; 24879340)	Colorectal, prostate	**FEMALES:** Annual mammogram with consideration of tomosynthesis; also consider breast MRI with contrast beginning at age 40, with modification as appropriate based on family history or specific gene mutation. Evidence of risk-reducing mastectomy is insufficient, manage based on family history. **MALES AND FEMALES:** Colonoscopy screening every 5 years beginning at age 40; if individual has first-degree relative with colorectal cancer, screening should begin 10 years prior to relative's diagnosis age if before 40; if individual has a personal history of colorectal cancer, screening recommendations should be based on recommendations for post-colorectal cancer resection.
EPCAM	Unknown (PMID: 18398828, 23091106)	Uterine—12–55% (PMID: 21145788) Ovarian—elevated (PMID: 19177550)	Colorectal, gastric, pancreatic, small bowel, prostate, brain, sebaceous adenoma/carcinoma, urinary tract	**Colon cancer:** Colonoscopy at age 20–25 or 2–5 years prior to the earliest colon cancer if it is diagnosed before age 25; repeat every 1–2 years. There are data to suggest that aspirin may decrease the risk of colon cancer in Lynch syndrome (LS), but optimal dose and duration of aspirin therapy are unclear. **Other extracolonic cancers (gastric and small bowel cancer):** There are no clear data to support surveillance for gastric, duodenal, and small bowel cancers in LS. Select individuals with family history of these cancers or those of Asian descent have an increased risk and may benefit from surveillance. If surveillance is performed, may consider upper endoscopy with visualization of the duodenum at the time of colonoscopy every 3–5 years beginning at 30–35. Consider testing and treating H. pylori. **Urothelial cancer:** Selected individuals such as those with family history of urothelial cancer or *MSH2* mutations (especially males) may want to consider screening. Surveillance options may include annual urinalysis starting at 30–35; however, there is insufficient evidence to recommend a particular surveillance strategy. **Central nervous system cancer:** Consider annual physical/neurological examination starting at 25–30 years. **Pancreatic cancer:** Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore there are no screening recommendations. **Breast cancer:** There have been suggestions that there is an increased risk for breast cancer in LS patients; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations. **Endometrial cancers:** Women should be educated regarding prompt reporting and evaluation of abnormal uterine bleeding and post-menopausal bleeding. The evaluation of these symptoms should include endometrial biopsy. Hysterectomy is a risk-reducing option that should be considered. Timing should be individualized based on when childbearing is complete, family history, comorbidities, and LS gene mutations. Screening via endometrial biopsy every 1–2 years can be considered. Transvaginal ultrasound may be considered at the physician's discretion, but is not recommended as a screening tool in premenopausal women due to the wide range of endometrial stripe thickness throughout normal menstrual cycle. **Ovarian cancer:** Bilateral salpingo-oophrectomy may reduce incidence of ovarian cancer, but decision to consider as a risk-reducing option by women who have completed childbearing should be individualized. Timing should be individualized based on when childbearing is complete, family history, comorbidities, menopause status, and LS gene mutations. Since there is no effective screening of ovarian cancer, women should be educated on the signs and symptoms that might be associated with the development of ovarian cancer (such as pelvic or abdominal pain, bloating, early satiety, increased abdominal girth, difficulty eating, or urinary frequency or urgency). Transvaginal ultrasound and serum CA-125 screening test can be considered at clinicians discretion. **Reproductive options:** For patients of reproductive age, advise about the risk of risk of rare recessive syndrome (CMMRD) (Constitutional MMR Deficiency); if both partners are carriers of a mutation(s) in the same MMR gene or *EPCAM* (e.g., *PMS2* mutation), their future offspring have a risk for CMMRD; advise about options for prenatal diagnosis.

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MLH1	Unknown (PMID: 18398828, 23091106, 26101330)	Uterine—14–54% (PMID: 25070057) Ovarian—up to 20% (PMID: 25070057)	Colorectal, gastric, pancreatic, small bowel, prostate, brain, sebaceous adenoma, sebaceous carcinoma, urinary tract	**Colon cancer:** Colonoscopy at age 20–25 or 2–5 years prior to the earliest colon cancer if it is diagnosed before age 25; repeat every 1–2 years. There are data to suggest that aspirin may decrease the risk of colon cancer in Lynch syndrome (LS), but optimal dose and duration of aspirin therapy are unclear. **Other extracolonic cancers (gastric and small bowel cancer):** There are no clear data to support surveillance for gastric, duodenal, and small bowel cancers in LS. Select individuals with family history of these cancers or those of Asian descent have an increased risk and may benefit from surveillance. If surveillance is performed, may consider upper endoscopy with visualization of the duodenum at the time of colonoscopy every 3–5 years beginning at 30–35. Consider testing and treating H. pylori. **Urothelial cancer:** Selected individuals such as those with family history of urothelial cancer or *MSH2* mutations (especially males) may want to consider screening. Surveillance options may include annual urinalysis starting at 30–35; however, there is insufficient evidence to recommend a particular surveillance strategy. **Central nervous system cancer:** Consider annual physical/neurological examination starting at 25–30 years. **Pancreatic cancer:** Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore there are no screening recommendations. **Breast cancer:** There have been suggestions that there is an increased risk for breast cancer in LS patients; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations. **Endometrial cancers:** Women should be educated regarding prompt reporting and evaluation of abnormal uterine bleeding and post-menopausal bleeding. The evaluation of these symptoms should include endometrial biopsy. Hysterectomy is a risk-reducing option that should be considered. Timing should be individualized based on when childbearing is complete, family history, comorbidities, and LS gene mutations. Screening via endometrial biopsy every 1–2 years can be considered. Transvaginal ultrasound may be considered at the physician's discretion, but is not recommended as a screening tool in premenopausal women due to the wide range of endometrial stripe thickness throughout normal menstrual cycle. **Ovarian cancer:** Bilateral salpingo-oophrectomy may reduce incidence of ovarian cancer, but decision to consider as a risk-reducing option by women who have completed childbearing should be individualized. Timing should be individualized based on when childbearing is complete, family history, comorbidities, menopause status, and LS gene mutations. Since there is no effective screening of ovarian cancer, women should be educated on the signs and symptoms that might be associated with the development of ovarian cancer (such as pelvic or abdominal pain, bloating, early satiety, increased abdominal girth, difficulty eating, or urinary frequency or urgency). Transvaginal ultrasound and serum CA-125 screening test can be considered at clinicians discretion. **Reproductive options:** For patients of reproductive age, advise about the risk of risk of rare recessive syndrome (CMMRD) (Constitutional MMR Deficiency); if both partners are carriers of a mutation(s) in the same MMR gene or *EPCAM* (e.g., *PMS2* mutation), their future offspring have a risk for CMMRD; advise about options for prenatal diagnosis.
MSH2	Unknown (PMID: 18398828, 23091106)	Uterine—20–54% (PMID: 15236168, 21642682, 23255516) Ovarian—up to 24% (PMID: 21642682)	Colorectal, gastric, pancreatic, small bowel, prostate, brain, sebaceous adenoma, sebaceous carcinoma, urinary tract	**Colon cancer:** Colonoscopy at age 20–25 or 2–5 years prior to the earliest colon cancer if it is diagnosed before age 25; repeat every 1–2 years. There are data to suggest that aspirin may decrease the risk of colon cancer in Lynch syndrome (LS), but optimal dose and duration of aspirin therapy are unclear. **Other extracolonic cancers (gastric and small bowel cancer):** There are no clear data to support surveillance for gastric, duodenal, and small bowel cancers in LS. Select individuals with family history of these cancers or those of Asian descent have an increased risk and may benefit from surveillance. If surveillance is performed, may consider upper endoscopy with visualization of the duodenum at the time of colonoscopy every 3–5 years beginning at 30–35. Consider testing and treating H. pylori. **Urothelial cancer:** Selected individuals such as those with family history of urothelial cancer or *MSH2* mutations (especially males) may want to consider screening. Surveillance options may include annual urinalysis starting at 30–35; however, there is insufficient evidence to recommend a particular surveillance strategy. **Central nervous system cancer:** Consider annual physical/neurological examination starting at 25–30 years. **Pancreatic cancer:** Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore there are no screening recommendations. **Breast cancer:** There have been suggestions that there is an increased risk for breast cancer in LS patients; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations. **Endometrial cancers:** Women should be educated regarding prompt reporting and evaluation of abnormal uterine bleeding and post-menopausal bleeding. The evaluation of these symptoms should include endometrial biopsy. Hysterectomy is a risk-reducing option that should be considered. Timing should be individualized based on when childbearing is complete, family history, comorbidities, and LS gene mutations. Screening via endometrial biopsy every 1–2 years can be considered. Transvaginal ultrasound may be considered at the physician's discretion, but is not recommended as a screening tool in premenopausal women due to the wide range of endometrial stripe thickness throughout normal menstrual cycle. **Ovarian cancer:** Bilateral salpingo-oophrectomy may reduce incidence of ovarian cancer, but decision to consider as a risk-reducing option by women who have completed childbearing should be individualized. Timing should be individualized based on when childbearing is complete, family history, comorbidities, menopause status, and LS gene mutations. Since there is no effective screening of ovarian cancer, women should be educated on the signs and symptoms that might be associated with the development of ovarian cancer (such as pelvic or abdominal pain, bloating, early satiety, increased abdominal girth, difficulty eating, or urinary frequency or urgency). Transvaginal ultrasound and serum CA-125 screening test can be considered at clinicians discretion. **Reproductive options:** For patients of reproductive age, advise about the risk of risk of rare recessive syndrome (CMMRD) (Constitutional MMR Deficiency); if both partners are carriers of a mutation(s) in the same MMR gene or *EPCAM* (e.g., *PMS2* mutation), their future offspring have a risk for CMMRD; advise about options for prenatal diagnosis.

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MSH6	Unknown (PMID: 18398828, 23091106)	Uterine—up to 71% (PMID: 15236168; 22619739) Ovarian—6–8% (PMID: 23091106)	Colorectal, gastric, pancreatic, small bowel, prostate, brain, urinary tract	**Colon cancer:** Colonoscopy at age 20–25 or 2–5 years prior to the earliest colon cancer if it is diagnosed before age 25; repeat every 1–2 years. There are data to suggest that aspirin may decrease the risk of colon cancer in Lynch syndrome (LS), but optimal dose and duration of aspirin therapy are unclear. **Other extracolonic cancers (gastric and small bowel cancer):** There are no clear data to support surveillance for gastric, duodenal, and small bowel cancers in LS. Select individuals with family history of these cancers or those of Asian descent have an increased risk and may benefit from surveillance. If surveillance is performed, may consider upper endoscopy with visualization of the duodenum at the time of colonoscopy every 3–5 years beginning at 30–35. Consider testing and treating H. pylori. **Urothelial cancer:** Selected individuals such as those with family history of urothelial cancer or *MSH2* mutations (especially males) may want to consider screening. Surveillance options may include annual urinalysis starting at 30–35; however, there is insufficient evidence to recommend a particular surveillance strategy. **Central nervous system cancer:** Consider annual physical/neurological examination starting at 25–30 years. **Pancreatic cancer:** Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore there are no screening recommendations. **Breast cancer:** There have been suggestions that there is an increased risk for breast cancer in LS patients; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations. **Endometrial cancers:** Women should be educated regarding prompt reporting and evaluation of abnormal uterine bleeding and post-menopausal bleeding. The evaluation of these symptoms should include endometrial biopsy. Hysterectomy is a risk-reducing option that should be considered. Timing should be individualized based on when childbearing is complete, family history, comorbidities, and LS gene mutations. Screening via endometrial biopsy every 1–2 years can be considered. Transvaginal ultrasound may be considered at the physician's discretion, but is not recommended as a screening tool in premenopausal women due to the wide range of endometrial stripe thickness throughout normal menstrual cycle. **Ovarian cancer:** Bilateral salpingo-oophrectomy may reduce incidence of ovarian cancer, but decision to consider as a risk-reducing option by women who have completed childbearing should be individualized. Timing should be individualized based on when childbearing is complete, family history, comorbidities, menopause status, and LS gene mutations. Since there is no effective screening of ovarian cancer, women should be educated on the signs and symptoms that might be associated with the development of ovarian cancer (such as pelvic or abdominal pain, bloating, early satiety, increased abdominal girth, difficulty eating, or urinary frequency or urgency). Transvaginal ultrasound and serum CA-125 screening test can be considered at clinicians discretion. **Reproductive options:** For patients of reproductive age, advise about the risk of risk of rare recessive syndrome (CMMRD) (Constitutional MMR Deficiency); if both partners are carriers of a mutation(s) in the same MMR gene or *EPCAM* (e.g., *PMS2* mutation), their future offspring have a risk for CMMRD; advise about options for prenatal diagnosis.
NBN	Up to 30% (PMID: 16770759, 21514219)	Ovarian—unknown (PMID: 22006311, 26315354)	Colorectal and gastric—unknown (PMID: 15185344, 21171015)	**FEMALES:** Screening: Annual mammography with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40, with modification as appropriate based on family history or specific gene mutation. Prophylactic risk-reducing mastectomy: evidence insufficient; manage based on family history. Counsel for risk of autosomal recessive condition in offspring.
NF1	Elevated (PMID: 23165953, 23257896)	Unknown (PMID: 23257896)	Peripheral nerve sheath tumors, optic gliomas, brain tumors, and gastrointestinal stromal tumors (GIST)	**FEMALES:** Screening: Annual mammography with consideration of tomosynthesis starting at age 30 years and consider annual breast MRI with contrast from ages 30–50, with modification as appropriate based on family history or specific gene mutation. Prophylactic risk-reducing mastectomy: evidence insufficient; manage based on family history. **MALES AND FEMALES:** Referral to a neurofibromatosis specialist for evaluation and management.
PALB2	♀ Up to 58% (PMID: 25099575) ♂ Possibly elevated (PMID: 21285249)	Ovarian—unknown (PMID: 22505525, 26075229)	Pancreatic	**FEMALES:** Screening: Annual mammography with consideration of tomosynthesis and annual breast MRI with contrast starting at age 30, with modification as appropriate based on family history or specific gene mutation. Prophylactic risk-reducing mastectomy: evidence insufficient; manage based on family history. Counsel for risk of autosomal recessive condition in offspring.

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PMS2	Unknown (PMID: 18398828, 23091106)	Uterine—up to 15% (PMID: 25856668) Ovarian—elevated (PMID: 25856668)	Colorectal, gastric, pancreatic, small bowel, prostate, brain, urinary tract	**Colon cancer:** Colonoscopy at age 20–25 or 2–5 years prior to the earliest colon cancer if it is diagnosed before age 25; repeat every 1–2 years. There are data to suggest that aspirin may decrease the risk of colon cancer in Lynch syndrome (LS), but optimal dose and duration of aspirin therapy are unclear. **Other extracolonic cancers (gastric and small bowel cancer):** There are no clear data to support surveillance for gastric, duodenal, and small bowel cancers in LS. Select individuals with family history of these cancers or those of Asian descent have an increased risk and may benefit from surveillance. If surveillance is performed, may consider upper endoscopy with visualization of the duodenum at the time of colonoscopy every 3–5 years beginning at 30–35. Consider testing and treating H. pylori. **Urothelial cancer:** Selected individuals such as those with family history of urothelial cancer or *MSH2* mutations (especially males) may want to consider screening. Surveillance options may include annual urinalysis starting at 30–35; however, there is insufficient evidence to recommend a particular surveillance strategy. **Central nervous system cancer:** Consider annual physical/neurological examination starting at 25–30 years. **Pancreatic cancer:** Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore there are no screening recommendations. **Breast cancer:** There have been suggestions that there is an increased risk for breast cancer in LS patients; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations. **Endometrial cancers:** Women should be educated regarding prompt reporting and evaluation of abnormal uterine bleeding and post-menopausal bleeding. The evaluation of these symptoms should include endometrial biopsy. Hysterectomy is a risk-reducing option that should be considered. Timing should be individualized based on when childbearing is complete, family history, comorbidities, and LS gene mutations. Screening via endometrial biopsy every 1–2 years can be considered. Transvaginal ultrasound may be considered at the physician's discretion, but is not recommended as a screening tool in premenopausal women due to the wide range of endometrial stripe thickness throughout normal menstrual cycle. **Ovarian cancer:** Bilateral salpingo-oophrectomy may reduce incidence of ovarian cancer, but decision to consider as a risk-reducing option by women who have completed childbearing should be individualized. Timing should be individualized based on when childbearing is complete, family history, comorbidities, menopause status, and LS gene mutations. Since there is no effective screening of ovarian cancer, women should be educated on the signs and symptoms that might be associated with the development of ovarian cancer (such as pelvic or abdominal pain, bloating, early satiety, increased abdominal girth, difficulty eating, or urinary frequency or urgency). Transvaginal ultrasound and serum CA-125 screening test can be considered at clinicians discretion. **Reproductive options:** For patients of reproductive age, advise about the risk of risk of rare recessive syndrome (CMMRD) (Constitutional MMR Deficiency); if both partners are carriers of a mutation(s) in the same MMR gene or *EPCAM* (e.g., *PMS2* mutation), their future offspring have a risk for CMMRD; advise about options for prenatal diagnosis.
PTEN	♀ Up to 85% (PMID: 22252256) ♂ Unknown (PMID: 11238682)	Uterine—up to 28% (PMID: 22252256)	Thyroid, kidney, colorectal, melanoma, brain	**FEMALES:** Breast awareness starting at age 18. Clinical breast exam every 6–12 months starting at age 25 or 5–10 years before the earliest breast cancer in the family (whichever comes first). Annual mammography with consideration of tomosynthesis and breast MRI screening with contrast starting at age 30–35 or 5–10 years before the earliest breast cancer diagnosis in the family (whichever comes first). After age 75, screening should be considered on an individualized basis. For women treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue. For endometrial cancer screening, encourage education and prompt response to symptoms such as abnormal bleeding and consider annual endometrial biopsy and/or ultrasound beginning at age 30–35 years of age. Discuss option of hysterectomy after childbearing is complete and counsel regarding the degree of protection such a procedure provides, extent of endometrial cancer risk, reproductive desires, and the psychosocial and quality-of-life aspects of such a procedure. Note that oophorectomy for CS/PHTS is not indicated; however, it may be indicated for other reasons. Counsel regarding the option of risk-reducing mastectomy with consideration of the degree of protection such a procedure provides, extent of breast cancer risk, reconstruction options, and the psychosocial and quality-of-life aspects of such a procedure. **MALES AND FEMALES:** Annual comprehensive physical exams beginning at age 18, or 5 years prior to the earliest known age of cancer diagnosis in the family, with particular attention to the thyroid. Annual thyroid ultrasound examination beginning at the time of CS/PHTS diagnosis. Colonoscopies every 5 years, starting at age 35, unless symptomatic. If there is a close relative with colon cancer diagnosed before age 40, begin colonoscopies 5–10 years before the earliest known colon cancer diagnosis in the family. Intervals for screening should be reduced if symptoms or polyps are identified. Consider renal ultrasound starting at age 40, and every 1–2 years thereafter. Dermatological management may be indicated in some affected individuals. Consider a baseline psychomotor assessment in childhood at the time of diagnosis. If symptomatic, consider brain MRI. Educate regarding the signs and symptoms of cancer. Advise affected individuals of reproductive age regarding prenatal diagnosis and assisted reproduction options. Encourage affected individuals to inform relatives about possible inherited cancer risks, options for risk assessment and management. Genetic counseling and testing are recommended for at-risk relatives.
RAD51C	Unknown (PMID: 22725699, 23300655)	Ovarian—6.5% (PMID: 20400964, 21616938, 22538716)		**FEMALES:** Consider risk-reducing salpingo-oophorectomy at age 45–50. Counsel for risk of autosomal recessive disease in offspring.
RAD51D	Unknown (PMID: 21822267)	Ovarian—7–10% (PMID: 21822267, 23372765)		**FEMALES:** Consider risk-reducing salpingo-oophorectomy at age 45–50. For women treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue.

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GENE	BREAST CANCER RISK	GYNECOLOGIC CANCER RISK	OTHER ASSOCIATED CANCERS	MANAGEMENT GUIDELINES*
STK11	♀ 40–50% (PMID: 20051941) ♂ No known risk	Ovarian—18–20% (PMID: 20051941) Uterine—9% (PMID: 20051941) Cervical (adenoma malignum)—10% (PMID: 10499464, 21503748, 2678968)	Colorectal, pancreatic, gastric, small bowel, lung	**FEMALES:** Clinical breast exams every 6 months beginning at age 25. Annual mammograms and breast MRIs with contrast beginning at age 25. Pelvic exams and pap smears annually beginning at 18–20 years of age; consider transvaginal ultrasound beginning at 18–20 years of age. **MALES:** Annual testicular exam and observation for feminizing changes beginning at 10 years of age. **MALES AND FEMALES:** Colonoscopy and Upper endoscopy every 2–3 years beginning during late teens. Baseline small bowel visualization via CT or MRI enterography at approximately 8–10 years of age with follow-up intervals based on findings. Beginning at approximately age 18, screening should be performed every 2–3 years; however, this may be individualized or with symptoms. MRI cholangiopancreatography or endoscopic ultrasound every 1–2 years beginning at approximately 30 to 35 years of age. Education regarding the signs and symptoms of lung cancer and discuss smoking cessation, if applicable.
TP53	♀ Up to 79% (PMID: 10864200; 26014290) ♂ No known risk	Ovarian—elevated (PMID: 14583457) Uterine—elevated (PMID: 20301488)	Sarcoma, brain, lung, colorectal, gastric, pancreatic	**FEMALES:** Breast awareness starting at age 18. Clinical breast exams every 6–12 months beginning at age 20 or at the age of the earliest diagnosed breast cancer in the family, if younger than age 20. Annual breast MRI with contrast beginning between the ages of 20 and 29 (or annual mammograms if MRI is unavailable), although the age to initiate screening may be individualized based on family history. Annual breast MRI with contrast and annual mammography with consideration of tomosynthsis between the ages of 30 and 75. After age 75, management should be considered on an individual basis. For women treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue. Discuss option of risk-reducing mastectomy and counsel regarding degree of protection, degree of cancer risk, and reconstruction options. Address the psychosocial, social, and quality of life aspects of undergoing risk-reducing mastectomy. **MALES AND FEMALES:** Annual comprehensive physical exam including neurologic examination with high index of suspicion for rare cancers and second malignancies in cancer survivors every 6–12 months. Colonoscopy and upper endoscopy every 2–5 years starting at 25 years of age or 5 years before the earliest known colon cancer in the family (whichever comes first). Perform annual dermatologic examination starting at 18 years old. Perform annual whole-body MRI (category 2B). Whole-body MRI is not uniformly available. If whole-body MRI is not available, then individuals with Li-Fraumeni syndrome (LFS) are encouraged to participate in clinical trials or consider alternate comprehensive imaging methods. Whole-body MRI is being evaluated in multiple international trials. Other components of screening are being evaluated in protocols, including biochemical screening and regular blood screening for hematologic malignancies. Annual brain MRI (category 2B) may be performed as part of the whole-body MRI or as a separate exam. Provide additional, individualized surveillance based on family history of cancer. Provide education regarding the signs and symptoms of cancer. Pediatricians should be apprised of the risk of childhood cancers in affected families. Therapeutic radiation for cancer should be avoided when possible. Address the limitations of screening for many cancers associated with LFS. Because of the high risk of additional primary neoplasms, screening may be considered for cancer survivors with a good prognosis from their primary tumor(s). It is preferred that individuals with LFS be followed at centers with expertise in management. The psychosocial, social, and quality-of-life aspects of managing LFS should be discussed. Advise affected individuals of reproductive age regarding prenatal diagnosis and assisted reproduction options. Encourage affected individuals to inform relatives about possible inherited cancer risks, options for risk assessment and management. Genetic counseling and testing are recommended for at-risk relatives.

All information based on published literature as of March 2018.

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