Management Guidelines

Invitae Colorectal Cancers Guidelines-Based Cancer Panel

GENE	LIFETIME RISK	OTHER ASSOCIATED CANCERS	MANAGEMENT GUIDELINES*
APC	70–100% (PMID: 1673441, 18063416, 19822006)	Sarcoma, duodenal, brain, thyroid, hepatoblastoma, upper stomach	**Classic FAP: Colon:** Annual colonoscopy (preferred) or flexible sigmoidoscopy beginning at 10–15 years of age. A colectomy or proctocolectomy is recommended after numerous polyps are detected. Total proctocolectomy with ileal pouch-anal anastomosis (IPAA) is generally the recommended surgical approach for individuals with FAP. If colectomy with ileorectal anastomosis (IRA) is performed, endoscopic evaluation of the remaining rectum is recommended every 6–12 months depending on polyp burden. If total proctocolectomy with IPAA or ileostomy is performed, endoscopic evaluation of the ileal pouch or ileostomy is recommended every 1–3 years depending on polyp burden. If large, flat polyps with villous histology and/or polyps with high-grade dysplasia are identified, then surveillance frequency should be every 6 months. Chemoprevention can aid in management of the remaining rectum; however, there are no medications currently approved by the FDA for this indication. There are data to suggest that sulindac showed the most significant polyp regression, but it is unclear if the decrease in polyp burden equates to reduction in colorectal cancer risk. **Extracolonic:** Upper endoscopy with complete visualization of the ampulla of Vater beginning at age 20–25 years. Consider upper endoscopy at an earlier age if colectomy is performed prior to age 20 years. It is important to note that fundic gland polyps are common in individuals with FAP and while focal low-grade dysplasia can be identified, it is typically non-progressive. Non-fundic gland polyps should be managed endoscopically if possible. Polyps with high-grade dysplasia or invasive cancer detected on biopsy should be referred for gastrectomy. Annual thyroid examination beginning in the late teenage years. Annual thyroid ultrasound may be considered, but data are lacking to support this recommendation. Annual physical examination for CNS cancers. Annual abdominal palpation for desmoids. If family history of symptomatic desmoids: consider abdominal MRI with or without contrast or CT with contrast within 1–3 years post-colectomy, then every 5–10 years. Suggestive abdominal symptoms should prompt immediate abdominal imaging; however, data to support screening and treatment are limited. For small bowel polyps and cancer, consider adding small bowel visualization to MRI or CT for desmoids especially, if duodenal polyposis is advanced. Preferably in the context of a clinical trial, screening for hepatoblastoma should include liver palpitation, abdominal ultrasound, and measurement of AFP every 3–6 months during the first 5 years of life. **AFAP: Colon:** Colonoscopy beginning in the late teens, then every 2–3 years. If less than 21 years and if a small polyp burden is found, repeat colonoscopy with polypectomy every 1–2 years. If at least 21 years of age, colectomy and IRA may be considered. Consider colectomy with ileorectal anastomosis (IRA) or proctocolectomy with ileal pouch-anal anastomosis (IPAA). Following colectomy with IRA, endoscopic evaluation of the remaining rectum is recommended every 6–12 months depending on polyp burden. Chemoprevention can aid in management of the remaining rectum; however, there are no medications currently approved by the FDA for this indication. There are data to suggest that sulindac showed the most significant polyp regression, but it is unclear if the decrease in polyp burden equates to reduction in colorectal cancer risk. **Extracolonic:** Annual physical examination. Annual thyroid examination. Upper endoscopy with complete visualization of the ampulla of Vater beginning at around age 20–25 years. Consider upper endoscopy at an earlier age if colectomy is performed prior to age 20 years.
APC (I1307K mutation)	Elevated (PMID: 23896379)	None known	**UNAFFECTED INDIVIDUALS:** If there is no personal history of colorectal cancer but there is a diagnosis of colorectal cancer in a first-degree relative, colonoscopy is recommended every 5 years beginning at age 40, or 10 years prior to the first-degree relative's age at diagnosis. If there is no personal history of colorectal cancer and no diagnosis of colorectal cancer in a first-degree relative, colonoscopy is recommended every 5 years beginning at age 40. **AFFECTED INDIVIDUALS:** Patients with colon cancer and this variant should follow guidelines post cancer resection.
AXIN2	Elevated (PMID: 15042511, 21416598, 26025668)		Begin colonoscopy at age 25–30 and every 2–3 years if negative. If polyps are found, colonoscopy every 1–2 years with consideration of surgery if polyp burden becomes unmanageable by colonoscopy. Surgical evaluation if appropriate.
BMPR1A	38–68% (PMID: 16246179, 17303595, 25645574)	Gastric, pancreatic	Colonoscopy, and upper endoscopy beginning at age 15 years and repeated every 2–3 yearsif no polyps are detected or annually if there are polyps. In individuals with *SMAD4* mutations, screen for vascular lesions associated with hereditary hemorrhagic telangiectasia (HHT); refer to a specialized team as guidelines for HHT are published elsewhere.

All information based on published literature as of March 2018.

INVITAE

Management Guidelines

Invitae Colorectal Cancers Guidelines-Based Cancer Panel

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CHEK2	Elevated (PMID: 17164383, 21807500, 23713947, 23946381)	Breast, 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	75–82% (PMID: 20301390, 21145788)	Uterine, ovarian, gastric, pancreatic, duodenal, urinary tract, brain, prostate	**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.
GREM1	Elevated (PMID: 22561515, 25419707, 26169059)	None known	Begin colonoscopy at age 25–30 and every 2–3 years if negative. If polyps are found, colonsocopy every 1–2 years with consideration of surgery if polyp burden becomes unmanageable by colonoscopy. Surgical evaluation if appropriate

All information based on published literature as of March 2018.

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INVITAE

Management Guidelines

Invitae Colorectal Cancers Guidelines-Based Cancer Panel

GENE	LIFETIME RISK	OTHER ASSOCIATED CANCERS	MANAGEMENT GUIDELINES*
MLH1	Up to 82% (PMID: 20301390, 25070057)	Uterine, ovarian, gastric, pancreatic, duodenal, urinary tract, brain, prostate	**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.

All information based on published literature as of March 2018.

INVITAE

Management Guidelines

Invitae Colorectal Cancers Guidelines-Based Cancer Panel

GENE	LIFETIME RISK	OTHER ASSOCIATED CANCERS	MANAGEMENT GUIDELINES*
MSH2	Up to 82% (PMID: 20301390, 25070057)	Uterine, ovarian, gastric, pancreatic, duodenal, urinary tract, brain, prostate	**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.
MSH3	Elevated (PMID: 27476653)	None known	Begin colonoscopy at age 25–30 and every 2–3 years if negative. If polyps are found, colonoscopy every 1–2 years with consideration of surgery if polyp burden becomes unmanageable by colonoscopy. Surgical evaluation if appropriate.

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INVITAE

Management Guidelines

Invitae Colorectal Cancers Guidelines-Based Cancer Panel

GENE	LIFETIME RISK	OTHER ASSOCIATED CANCERS	MANAGEMENT GUIDELINES*
MSH6	♀ Up to 44% ♂ Up to 20% (PMID: 20028993)	Uterine, ovarian, gastric, pancreatic, duodenal, urinary tract, brain, prostate	**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.
MUTYH	43–100% (PMID: 19620482, 23035301)	Duodenal	Colonoscopy beginning 25–30 years and repeated every 2–3 years if no polyps are detected. If less than 21 years and a small polyp burden is found, repeat colonoscopy with polypectomy every 1–2 years. If at least 21 years of age, colectomy and IRA may be considered. Consider colectomy with ileorectal anastomosis (IRA) or proctocolectomy with ileal pouch-anal anastomosis (IPAA). If a colectomy with IRA has been performed, then endoscopic evaluation of the rectum every 6–12 months; baseline upper endoscopy (including complete visualization of the ampulla of Vater) beginning between age 30–35 years, scheduled depending on the duodenal polyp burden; advise relatives on hereditary risk and recommend genetic counseling.
MUTYH (heterozygotes)	Elevated (PMID: 24444654)	None known	**UNAFFECTED INDIVIDUALS:** 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 age at diagnosis if before 40. If unaffected by colon cancer and no family history of colon cancer, data are uncertain if specialized screening is warranted. **AFFECTED INDIVIDUALS:** Individuals with colon/rectal cancer should follow surveillance recommendations post resection.
NTHL1	Elevated (PMID: 17029639, 25938944, 26431160, 26559593, 27713038, 27720914)	None known	Begin colonoscopy at age 25–30 and every 2–3 years if negative. If polyps are found, colonoscopy every 1–2 years with consideration of surgery if polyp burden becomes unmanageable by colonoscopy. Surgical evaluation if appropriate.

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INVITAE

Management Guidelines

Invitae Colorectal Cancers Guidelines-Based Cancer Panel

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PMS2	Up to 20% (PMID: 18602922)	Uterine, ovarian, gastric, pancreatic, duodenal, urinary tract, brain, prostate	**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.
POLD1	Elevated (PMID: 23263490, 25529843, 26133394)	None known	Begin colonoscopy at age 25–30 and every 2–3 years if negative. If polyps are found, colonoscopy every 1–2 years with consideration of surgery if polyp burden becomes unmanageable by colonoscopy. Surgical evaluation if appropriate
POLE	Elevated (PMID: 23263490, 25529843, 26133394)	None known	Begin colonoscopy at age 25–30 and every 2–3 years if negative. If polyps are found, colonoscopy every 1–2 years with consideration of surgery if polyp burden becomes unmanageable by colonoscopy. Surgical evaluation if appropriate

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INVITAE

Management Guidelines

Invitae Colorectal Cancers Guidelines-Based Cancer Panel

GENE	LIFETIME RISK	OTHER ASSOCIATED CANCERS	MANAGEMENT GUIDELINES*
PTEN	9% (PMID: 22252256)	Breast, uterine, renal, thyroid, brain, skin	**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.
SMAD4	38–68% (PMID: 16246179, 17303595, 25645574)	Gastric, pancreatic	Colonoscopy, and upper endoscopy beginning at age 15 years and repeated every 2–3 years if no polyps are detected or annually if there are polyps. In individuals with *SMAD4* mutations, screen for vascular lesions associated with hereditary hemorrhagic telangiectasia (HHT). Refer to a specialized team as guidelines for HHT are published elsewhere.
STK11	39% (PMID: 20051941)	Breast, ovarian, uterine, gastric, pancreatic, duodenal, 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 to 20 years of age. Consider transvaginal ultrasound beginning at 18 to 20 years of age. **MALES:** Annual testicular exam and observation for feminizing changes beginning at 10 years of age. **MALES and FEMALES:** Colonoscopy every 2–3 years beginning during late teens. Upper endoscopy every 2–3 years beginning at approximately age 18. 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.

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Management Guidelines

Invitae Colorectal Cancers Guidelines-Based Cancer Panel

GENE	LIFETIME RISK	OTHER ASSOCIATED CANCERS	MANAGEMENT GUIDELINES*
TP53	Elevated (PMID: 16401470)	Breast, ovarian, uterine, gastric, pancreatic, sarcoma, brain, lung, adrenal, leukemia	**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). 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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