

# CancerCHECK

**C** O M P L E T E  
**H** E R E D I T A R Y  
**E** V A L U A T I O N  
**C** L I N I C  
**K** I T



# CancerCHECK

Cancer Complete Hereditary Evaluation Clinic Kit



Welcome to Invitae CancerCHECK, your Complete Hereditary Evaluation Clinic Kit! This kit is designed to help you manage your patients' hereditary cancer genetic testing needs as easily and smoothly as possible. This step-by-step kit includes all of the basics to help you identify a candidate for genetic testing, choose the right test, and interpret a report.

## STEP 1 CHECKlist for patient family history

Determine if your patient could benefit from genetic testing using the considerations for breast, gynecologic, and colorectal cancer testing checklist.

## STEP 2 CHECK the proper test to order

Depending on the checklist results, select the appropriate guidelines-based panel.

## STEP 3 CHECK that you have everything you need to place an order

- How-to-order guide, included in this kit and also available at [www.invitae.com/ordering](http://www.invitae.com/ordering)
- Blood or saliva sample collection kit

## STEP 4 CHECK the management guidelines tables

After receiving your results, use the management guidelines tables as a reference to develop a management plan for your patient.

## STEP 5 CHECK that you have the appropriate billing information for your patient

## STEP 6 CHECK out the additional resources that Invitae has to offer

Invitae's certified genetic counselors and client services staff are here to support you.

## QUICK RESOURCES

### INVITAE CLIENT SERVICES

800-436-3037

[clientservices@invitae.com](mailto:clientservices@invitae.com)

### LABORATORY & SHIPPING

1400 16th Street

San Francisco, CA 94103

### INVITAE CLINICAL CONSULT SERVICES

[clinconsult@invitae.com](mailto:clinconsult@invitae.com)

## Considerations for genetic testing



INVITAE

Does your patient or a close blood relative (sibling, half-sibling, parent, child, aunt/uncle, niece/nephew, grandparent, or grandchild) have any of the following?

### HEREDITARY BREAST AND OVARIAN CANCER

- ovarian cancer
- early-onset breast cancer (age 45 or younger)
- triple-negative (ER-, PR-, HER2-) breast cancer at or before age 60
- male breast cancer
- multiple BRCA-associated cancers in the same person
- a family history of ovarian, breast, pancreatic, melanoma, or prostate cancer
- breast or ovarian cancer and Ashkenazi Jewish ancestry

If you checked any boxes above, you should consider genetic testing. Invitae test options include the [Invitae Breast and Gyn Cancer Guidelines-based Panel](#).

#### CLINICIAN NOTES

- Order genetic testing for this patient. Panels and tests available at [www.invitae.com](http://www.invitae.com).

**PATIENT NAME:** \_\_\_\_\_

*A patient's risk may change over time. We recommend updating family history records at annual appointments.*



Does your patient or a close blood relative (sibling, half-sibling, parent, child, aunt/uncle, niece/nephew, grandparent, or grandchild) have any of the following?

## COLORECTAL CANCER

- colorectal or endometrial cancer diagnosed before age 50
- multiple primary colorectal tumors
- tumors of the colorectum, uterus, stomach, ovary, pancreas, ureter, renal pelvis, biliary tract, brain, small bowel, sebaceous glands, or keratoacanthomas in three or more relatives
- more than 10 colorectal adenomas
- desmoid tumors, cribriform-morular variant of papillary thyroid cancer, multiple extraintestinal gastrointestinal adenomas, or hepatoblastoma
- gastrointestinal ganglioneuromas or polyps of the hamartomatous, juvenile, ganglio, or serrated type
- abnormal tumor pathology suggestive of a mismatch repair defect (MSI, IHC, Crohn-like lymphocytic reaction, mucinous/signet cell differentiation, or medullary growth pattern)

If you checked any boxes above, you should consider genetic testing. Invitae test options include the [Invitae Colorectal Cancer Guidelines-based Panel](#).

### CLINICIAN NOTES

- Order genetic testing for this patient. Panels and tests available at [www.invitae.com](http://www.invitae.com).

**PATIENT NAME:** \_\_\_\_\_

*A patient's risk may change over time. We recommend updating family history records at annual appointments.*



# Comprehensive cancer genetic testing, simplified

## The answers you need, the support you expect

### INVITAE OFFERS ONE OF THE BROADEST ONCOLOGY MENUS

- Select carefully curated tests designed by medical and genetic experts or design your own test for each patient
- Guidelines-based panels for breast, gynecologic, and colorectal cancers
- Breast cancer STAT panels to inform surgery and medical management
- Other testing options—including cross-cancer panels—that test for hereditary risk of brain, breast and gynecologic, endocrine, gastrointestinal, genitourinary, hematologic, pediatric, and skin cancers

### HIGH-QUALITY GENETIC TESTING, WITH THOROUGHLY VALIDATED CLINICAL EVIDENCE

- >1,000-patient study showed equivalence to established standards
- 100% analytic sensitivity and specificity compared to traditional genetic test results

### THE TOOLS YOU NEED TO GIVE YOUR PATIENTS ANSWERS, RELIABLY AND QUICKLY

- Clinical Consult Services to help identify the right test for each patient and clarify results, for no additional charge
- Genetics Provider Network to connect patients and genetics providers

### TRANSPARENT PRICING ON THE PANELS YOU NEED

- Affordable pricing, including \$250 patient-pay option
- Re-requisition additional oncology genes for no additional charge
- Results available in 10–21 calendar days (14 days on average) for standard tests and 5–12 calendar days (7 days on average) for STAT panels
- Saliva and blood samples accepted (including complimentary blood draw service within the US and Canada)
- In-network for more than 200 million patients in the United States, including Medicare
- Out-of-pocket cost estimate tool for tests related to HBOC and Lynch syndrome



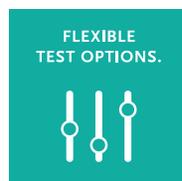
CONFIDENCE  
AND QUALITY.



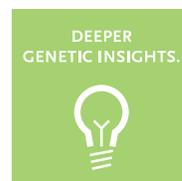
FASTER TIME  
TO ANSWERS.



AFFORDABLE,  
TRANSPARENT  
PRICING.



FLEXIBLE  
TEST OPTIONS.



DEEPER  
GENETIC INSIGHTS.



SUPPORT EVERY  
STEP OF THE WAY.

Join us in our mission to improve healthcare for everyone. Please visit [www.invitae.com](http://www.invitae.com) to see our full test catalog and pricing.



Invitae offers several panels based entirely on oncology management guidelines. Testing of these genes may help guide medical decisions that prevent cancer, lead to earlier diagnosis, or increase the chances of successful treatment and survival.

Additionally, Invitae offers breast cancer STAT panels to inform surgical and medical management decisions, with results in 5–12 calendar days (7 days on average) from sample receipt. These panels include the option to re-requisition additional genes if needed within 90 days of receiving the STAT report. Due to the expedited processing time, the STAT panels cannot be customized.

## BREAST CANCER

Invitae BRCA1 and BRCA2 STAT Panel	Invitae Breast Cancer STAT Panel	Invitae Breast Cancer Guidelines-Based Panel	Invitae Breast Cancer Panel
BRCA1	BRCA1	BRCA1	BRCA1
BRCA2	BRCA2	BRCA2	BRCA2
	CDH1	CDH1	CDH1
	PALB2	PALB2	PALB2
	PTEN	PTEN	PTEN
	STK11	STK11	STK11
	TP53	TP53	TP53
	ATM	ATM	ATM
	CHEK2	CHEK2	CHEK2
		NBN	NBN
		NF1	NF1
			BRIP1
			BARD1
			RAD50

## GYNECOLOGIC CANCER

Invitae Breast and Gyn Cancers Guidelines-Based Panel	Invitae Breast and Gyn Cancers Panel
BRCA1	BRCA1
BRCA2	BRCA2
CDH1	CDH1
PALB2	PALB2
PTEN	PTEN
STK11	STK11
TP53	TP53
ATM	ATM
CHEK2	CHEK2
NBN	NBN
NF1	NF1
EPCAM	EPCAM
MLH1	MLH1
MSH2	MSH2
MSH6	MSH6
PMS2	PMS2
BRIP1	BRIP1
	BARD1
	RAD50
RAD51C	RAD51C
RAD51D	RAD51D
	DICER1
	SMARCA4

## COLORECTAL CANCER

Invitae Lynch Syndrome Panel	Invitae Colorectal Cancer Guidelines-Based Panel	Invitae Colorectal Cancer Panel
EPCAM	EPCAM	EPCAM
MLH1	MLH1	MLH1
MSH2	MSH2	MSH2
MSH6	MSH6	MSH6
PMS2	PMS2	PMS2
	APC	APC
	AXIN2	AXIN2
	BMPR1A	BMPR1A
	CHEK2	CHEK2
	GREM1	GREM1
	MSH3	MSH3
	MUTYH	MUTYH
	NTHL1	NTHL1
	POLD1	POLD1
	POLE	POLE
	PTEN	PTEN
	SMAD4	SMAD4
	STK11	STK11
	TP53	TP53
		CDH1

## PLACE YOUR ORDER

Place your order online for the most efficient processing.

1. Create an account by visiting [www.invitae.com/signup](http://www.invitae.com/signup).
2. Sign in and then click **Start an order**.
3. Under **Test selection**, browse Invitae's panels to select a pre-curated panel or create a custom test and add it to your order. You can also select a test from your recent or custom orders; order family follow-up testing; or order through a sponsored testing program or clinical trial by choosing the **Partnership programs** tab.
4. Fill out the requested information, including patient information in any order; save your entries at any time to come back to them later.
5. Enter billing information.
6. Submit your order.

If you prefer to open an account by speaking with an Invitae representative, please contact us at 800-436-3037.

## COLLECT A SPECIMEN

1. Order Invitae blood or saliva collection kits, which you need for collecting and returning your specimen, at [www.invitae.com/request-a-kit](http://www.invitae.com/request-a-kit).
2. Label the specimen tube with the patient's full name, date of birth, and specimen collection date.
3. If you need additional details on our specimen requirements, please visit [www.invitae.com/specimen-requirements](http://www.invitae.com/specimen-requirements).

# Ordering from Invitae *(continued)*

## PRINT THE REQUISITION FORM

1. Print the requisition form that was created during the online ordering process.
2. If you prefer to place a paper-based order for panel testing, you can also download our paper test requisition from [www.invitae.com/order-forms](http://www.invitae.com/order-forms). Please note that exome testing is ordered exclusively online.

## SEND THE SPECIMEN AND FORMS TO INVITAE

1. Package the requisition form with your patient's specimen in the provided collection box.
2. You're now ready to call your shipping carrier to schedule a pick-up. Within the US, return shipping is offered at no additional charge and a label is included in the collection kit.
3. We recommend shipping the specimen overnight, on the same day the specimen is collected. We also recommend shipping at the beginning of the week to avoid any transport delays over a weekend.

## RESULTS

1. Once Invitae receives the shipment, you will receive the results in:
  - Panel testing: 10–21 calendar days (14 days on average)
  - STAT panel testing: 5–12 calendar days (7 days on average)
  - Exome testing: 20 weeks on average
2. If you ordered online, you can view the status of your order by logging in to your account. Alternatively, if you provided your email address on your paper-based order form, you can create an online account following the steps above to view the status of your order.
3. You will receive a notification email once the test results are ready.

If you have any questions about the ordering process, please contact Client Services at [clientservices@invitae.com](mailto:clientservices@invitae.com) or 800-436-3037. Local contact information outside the US can be found at [www.invitae.com/contact](http://www.invitae.com/contact).

# 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	<b>FEMALES:</b> 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	<b>FEMALES:</b> 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. <b>MALES:</b> 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. <b>MALES AND FEMALES:</b> 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	<b>FEMALES:</b> 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. <b>MALES:</b> 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. <b>MALES AND FEMALES:</b> 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)		<b>FEMALES:</b> 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.

# Management Guidelines

## Invitae Breast and Gyn Cancers Guidelines-Based Cancer Panel

GENE	BREAST CANCER RISK	GYNECOLOGIC CANCER RISK	OTHER ASSOCIATED CANCERS	MANAGEMENT GUIDELINES*
CDH1	<p>♀ 39–52% (lobular) (PMID: 11729114, 17545690, 25979631)</p> <p>♂ No known risk</p>		Gastric, colorectal	<p><b>FEMALES:</b> 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.</p> <p><b>MALES AND FEMALES:</b> 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.</p>
CHEK2	<p>♀ 25–39% (PMID: 18172190, 21876083)</p> <p>♂ Possibly elevated (PMID: 21956126)</p>	Ovarian—unknown risk (PMID: 24240112; 24879340)	Colorectal, prostate	<p><b>FEMALES:</b> 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.</p> <p><b>MALES AND FEMALES:</b> 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.</p>
EPCAM	Unknown (PMID: 18398828, 23091106)	<p>Uterine—12–55% (PMID: 21145788)</p> <p>Ovarian—elevated (PMID: 19177550)</p>	Colorectal, gastric, pancreatic, small bowel, prostate, brain, sebaceous adenoma/ carcinoma, urinary tract	<p><b>Colon cancer:</b> 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. <b>Other extracolonic cancers (gastric and small bowel cancer):</b> 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 <i>H. pylori</i>. <b>Urothelial cancer:</b> Selected individuals such as those with family history of urothelial cancer or <i>MSH2</i> 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. <b>Central nervous system cancer:</b> Consider annual physical/neurological examination starting at 25–30 years. <b>Pancreatic cancer:</b> Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore there are no screening recommendations. <b>Breast cancer:</b> 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. <b>Endometrial cancers:</b> 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. <b>Ovarian cancer:</b> Bilateral salpingo-oophorectomy 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. <b>Reproductive options:</b> 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 <i>EPCAM</i> (e.g., <i>PMS2</i> mutation), their future offspring have a risk for CMMRD; advise about options for prenatal diagnosis.</p>

All information based on published literature as of March 2018.

# Management Guidelines

## Invitae Breast and Gyn Cancers Guidelines-Based Cancer Panel

GENE	BREAST CANCER RISK	GYNECOLOGIC CANCER RISK	OTHER ASSOCIATED CANCERS	MANAGEMENT GUIDELINES*
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	<b>Colon cancer:</b> 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. <b>Other extracolonic cancers (gastric and small bowel cancer):</b> 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 <i>H. pylori</i> . <b>Urothelial cancer:</b> Selected individuals such as those with family history of urothelial cancer or <i>MSH2</i> 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. <b>Central nervous system cancer:</b> Consider annual physical/neurological examination starting at 25–30 years. <b>Pancreatic cancer:</b> Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore there are no screening recommendations. <b>Breast cancer:</b> 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. <b>Endometrial cancers:</b> 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. <b>Ovarian cancer:</b> Bilateral salpingo-oophorectomy 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. <b>Reproductive options:</b> 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 <i>EPCAM</i> (e.g., <i>PMS2</i> 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	<b>Colon cancer:</b> 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. <b>Other extracolonic cancers (gastric and small bowel cancer):</b> 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 <i>H. pylori</i> . <b>Urothelial cancer:</b> Selected individuals such as those with family history of urothelial cancer or <i>MSH2</i> 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. <b>Central nervous system cancer:</b> Consider annual physical/neurological examination starting at 25–30 years. <b>Pancreatic cancer:</b> Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore there are no screening recommendations. <b>Breast cancer:</b> 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. <b>Endometrial cancers:</b> 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. <b>Ovarian cancer:</b> Bilateral salpingo-oophorectomy 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. <b>Reproductive options:</b> 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 <i>EPCAM</i> (e.g., <i>PMS2</i> 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.

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# Management Guidelines

## Invitae Breast and Gyn Cancers Guidelines-Based Cancer Panel

GENE	BREAST CANCER RISK	GYNECOLOGIC CANCER RISK	OTHER ASSOCIATED CANCERS	MANAGEMENT GUIDELINES*
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	<b>Colon cancer:</b> 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. <b>Other extracolonic cancers (gastric and small bowel cancer):</b> 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 <i>H. pylori</i> . <b>Urothelial cancer:</b> Selected individuals such as those with family history of urothelial cancer or <i>MSH2</i> 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. <b>Central nervous system cancer:</b> Consider annual physical/neurological examination starting at 25–30 years. <b>Pancreatic cancer:</b> Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore there are no screening recommendations. <b>Breast cancer:</b> 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. <b>Endometrial cancers:</b> 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. <b>Ovarian cancer:</b> Bilateral salpingo-oophorectomy 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 clinician's discretion. <b>Reproductive options:</b> For patients of reproductive age, advise about the risk of rare recessive syndrome (CMMRD) (Constitutional MMR Deficiency); if both partners are carriers of a mutation(s) in the same MMR gene or <i>EPCAM</i> (e.g., <i>PMS2</i> 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)	<b>FEMALES:</b> 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)	<b>FEMALES:</b> 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. <b>MALES AND FEMALES:</b> 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	<b>FEMALES:</b> 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.

All information based on published literature as of March 2018.

# Management Guidelines

## Invitae Breast and Gyn Cancers Guidelines-Based Cancer Panel

GENE	BREAST CANCER RISK	GYNECOLOGIC CANCER RISK	OTHER ASSOCIATED CANCERS	MANAGEMENT GUIDELINES*
PMS2	Unknown (PMID: 18398828, 23091106)	Uterine—up to 15% (PMID: 25856668) Ovarian—elevated (PMID: 25856668)	Colorectal, gastric, pancreatic, small bowel, prostate, brain, urinary tract	<b>Colon cancer:</b> 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. <b>Other extracolonic cancers (gastric and small bowel cancer):</b> 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 <i>H. pylori</i> . <b>Urothelial cancer:</b> Selected individuals such as those with family history of urothelial cancer or <i>MSH2</i> 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. <b>Central nervous system cancer:</b> Consider annual physical/neurological examination starting at 25–30 years. <b>Pancreatic cancer:</b> Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore there are no screening recommendations. <b>Breast cancer:</b> 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. <b>Endometrial cancers:</b> 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. <b>Ovarian cancer:</b> Bilateral salpingo-oophorectomy 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. <b>Reproductive options:</b> 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 <i>EPCAM</i> (e.g., <i>PMS2</i> 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	<b>FEMALES:</b> 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. <b>MALES AND FEMALES:</b> 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)		<b>FEMALES:</b> 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)		<b>FEMALES:</b> 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.

All information based on published literature as of March 2018.

# Management Guidelines

## Invitae Breast and Gyn Cancers Guidelines-Based Cancer Panel

GENE	BREAST CANCER RISK	GYNECOLOGIC CANCER RISK	OTHER ASSOCIATED CANCERS	MANAGEMENT GUIDELINES*
STK11	<p>♀ 40–50% (PMID: 20051941)</p> <p>♂ No known risk</p>	<p>Ovarian—18–20% (PMID: 20051941)</p> <p>Uterine—9% (PMID: 20051941)</p> <p>Cervical (adenoma malignum)—10% (PMID: 10499464, 21503748, 2678968)</p>	Colorectal, pancreatic, gastric, small bowel, lung	<p><b>FEMALES:</b> 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.</p> <p><b>MALES:</b> Annual testicular exam and observation for feminizing changes beginning at 10 years of age.</p> <p><b>MALES AND FEMALES:</b> 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.</p>
TP53	<p>♀ Up to 79% (PMID: 10864200; 26014290)</p> <p>♂ No known risk</p>	<p>Ovarian—elevated (PMID: 14583457)</p> <p>Uterine—elevated (PMID: 20301488)</p>	Sarcoma, brain, lung, colorectal, gastric, pancreatic	<p><b>FEMALES:</b> 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 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 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.</p> <p><b>MALES AND FEMALES:</b> 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.</p>

All information based on published literature as of March 2018.

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# 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	<p><b>Classic FAP: Colon:</b> 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. <b>Extracolonic:</b> 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 palpation, abdominal ultrasound, and measurement of AFP every 3–6 months during the first 5 years of life.</p> <p><b>AFAP: Colon:</b> 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. <b>Extracolonic:</b> 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.</p>
APC (I1307K mutation)	Elevated (PMID: 23896379)	None known	<p><b>UNAFFECTED INDIVIDUALS:</b> 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.</p> <p><b>AFFECTED INDIVIDUALS:</b> Patients with colon cancer and this variant should follow guidelines post cancer resection.</p>
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 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.

All information based on published literature as of March 2018.

# Management Guidelines

## Invitae Colorectal Cancers Guidelines-Based Cancer Panel

GENE	LIFETIME RISK	OTHER ASSOCIATED CANCERS	MANAGEMENT GUIDELINES*
CHEK2	Elevated (PMID: 17164383, 21807500, 23713947, 23946381)	Breast, prostate	<p><b>FEMALES:</b> 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.</p> <p><b>MALES AND FEMALES:</b> 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.</p>
EPCAM	75–82% (PMID: 20301390, 21145788)	Uterine, ovarian, gastric, pancreatic, duodenal, urinary tract, brain, prostate	<p><b>Colon cancer:</b> 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. <b>Other extracolonic cancers (gastric and small bowel cancer):</b> 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 <i>H. pylori</i>. <b>Urothelial cancer:</b> Selected individuals such as those with family history of urothelial cancer or <i>MSH2</i> 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. <b>Central nervous system cancer:</b> Consider annual physical/neurological examination starting at 25–30 years. <b>Pancreatic cancer:</b> Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore there are no screening recommendations. <b>Breast cancer:</b> 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. <b>Endometrial cancers:</b> 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. <b>Ovarian cancer:</b> Bilateral salpingo-oophorectomy 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. <b>Reproductive options:</b> 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 <i>EPCAM</i> (e.g. <i>PMS2</i> mutation), their future offspring have a risk for CMMRD; advise about options for prenatal diagnosis.</p>
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, colonoscopy 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.

# 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	<p><b>Colorectal cancer:</b> 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. <b>Other extracolonic cancers (gastric and small bowel cancer):</b> 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 <i>H. pylori</i>. <b>Urothelial cancer:</b> Selected individuals such as those with family history of urothelial cancer or <i>MSH2</i> 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. <b>Central nervous system cancer:</b> Consider annual physical/neurological examination starting at 25–30 years. <b>Pancreatic cancer:</b> Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore there are no screening recommendations. <b>Breast cancer:</b> 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. <b>Endometrial cancers:</b> 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. <b>Ovarian cancer:</b> Bilateral salpingo-oophorectomy 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. <b>Reproductive options:</b> For patients of reproductive age, advise about the risk of rare recessive syndrome (CMMRD) (Constitutional MMR Deficiency); if both partners are carriers of a mutation(s) in the same MMR gene or <i>EPCAM</i> (e.g. <i>PMS2</i> mutation), their future offspring have a risk for CMMRD; advise about options for prenatal diagnosis.</p>

All information based on published literature as of March 2018.

# 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	<p><b>Colorectal cancer:</b> 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. <b>Other extracolonic cancers (gastric and small bowel cancer):</b> 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 <i>H. pylori</i>. <b>Urothelial cancer:</b> Selected individuals such as those with family history of urothelial cancer or <i>MSH2</i> 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. <b>Central nervous system cancer:</b> Consider annual physical/neurological examination starting at 25–30 years. <b>Pancreatic cancer:</b> Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore there are no screening recommendations. <b>Breast cancer:</b> 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. <b>Endometrial cancers:</b> 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. <b>Ovarian cancer:</b> Bilateral salpingo-oophorectomy 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. <b>Reproductive options:</b> For patients of reproductive age, advise about the risk of rare recessive syndrome (CMMRD) (Constitutional MMR Deficiency); if both partners are carriers of a mutation(s) in the same MMR gene or <i>EPCAM</i> (e.g. <i>PMS2</i> mutation), their future offspring have a risk for CMMRD; advise about options for prenatal diagnosis.</p>
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.

All information based on published literature as of March 2018.

# 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	<b>Colorectal cancer:</b> 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. <b>Other extracolonic cancers (gastric and small bowel cancer):</b> 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 <i>H. pylori</i> . <b>Urothelial cancer:</b> Selected individuals such as those with family history of urothelial cancer or <i>MSH2</i> 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. <b>Central nervous system cancer:</b> Consider annual physical/neurological examination starting at 25–30 years. <b>Pancreatic cancer:</b> Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore there are no screening recommendations. <b>Breast cancer:</b> 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. <b>Endometrial cancers:</b> 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. <b>Ovarian cancer:</b> Bilateral salpingo-oophorectomy 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 clinician's discretion. <b>Reproductive options:</b> For patients of reproductive age, advise about the risk of rare recessive syndrome (CMMRD) (Constitutional MMR Deficiency); if both partners are carriers of a mutation(s) in the same MMR gene or <i>EPCAM</i> (e.g. <i>PMS2</i> 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	<b>UNAFFECTED INDIVIDUALS:</b> 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. <b>AFFECTED INDIVIDUALS:</b> Individuals with colon/rectal cancer should follow surveillance recommendations post resection.
NHTL1	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.

All information based on published literature as of March 2018.

# Management Guidelines

## Invitae Colorectal Cancers Guidelines-Based Cancer Panel

GENE	LIFETIME RISK	OTHER ASSOCIATED CANCERS	MANAGEMENT GUIDELINES*
PMS2	Up to 20% (PMID: 18602922)	Uterine, ovarian, gastric, pancreatic, duodenal, urinary tract, brain, prostate	<p><b>Colorectal cancer:</b> 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. <b>Other extracolonic cancers (gastric and small bowel cancer):</b> 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 <i>H. pylori</i>. <b>Urothelial cancer:</b> Selected individuals such as those with family history of urothelial cancer or <i>MSH2</i> 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. <b>Central nervous system cancer:</b> Consider annual physical/neurological examination starting at 25–30 years. <b>Pancreatic cancer:</b> Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore there are no screening recommendations. <b>Breast cancer:</b> 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. <b>Endometrial cancers:</b> 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. <b>Ovarian cancer:</b> Bilateral salpingo-oophorectomy 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. <b>Reproductive options:</b> For patients of reproductive age, advise about the risk of rare recessive syndrome (CMMRD) (Constitutional MMR Deficiency); if both partners are carriers of a mutation(s) in the same MMR gene or <i>EPCAM</i> (e.g. <i>PMS2</i> mutation), their future offspring have a risk for CMMRD; advise about options for prenatal diagnosis.</p>
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

All information based on published literature as of March 2018.

# 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	<p><b>FEMALES:</b> 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.</p> <p><b>MALES AND FEMALES:</b> 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.</p>
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 <i>SMAD4</i> 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	<p><b>FEMALES:</b> 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.</p> <p><b>MALES:</b> Annual testicular exam and observation for feminizing changes beginning at 10 years of age.</p> <p><b>MALES and FEMALES:</b> 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.</p>

All information based on published literature as of March 2018.

# 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	<p><b>FEMALES:</b> 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 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 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.</p> <p><b>MALES AND FEMALES:</b> 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.</p>

All information based on published literature as of March 2018.

\*Referenced with permission from the NCCN:

Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 1.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed February, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org.

Genetic/Familial High-Risk Assessment: Colorectal. Version 3.2017. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed February, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org.

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# Transparent pricing. Ethical billing.

MAKING GENETIC TESTING MORE ACCESSIBLE THAN EVER

Genetic testing should be affordable and accessible. At Invitae, we believe in ethical and transparent billing. We offer multiple billing options and have an exceptional Client Services team ready to work with you.

For a flat price, your healthcare provider can order testing on any number of genes within a single clinical area. (For example, hereditary cancer is a clinical area, as are cardiology and pediatric genetics.)

**\$100**  
OUT OF POCKET



Typically patients pay no more than \$100 out of pocket for one of our tests

**\$1500**  
LIST PRICE



The most Invitae will ever bill an insurance company or institution is \$1500 per clinical area

**\$250**  
PATIENT PAY



If preferred, patients have the option to pay \$250 per clinical area

## INSURANCE BILLING

Invitae can bill insurance directly for panel tests; please visit [www.invitae.com/in-network-partners](http://www.invitae.com/in-network-partners) for a list of insurance companies that have brought Invitae in-network. We also accept Medicare and Medicaid. You won't need to contact your insurance company; Invitae will work directly with them to coordinate coverage and payment.

### Out-of-pocket expenses

Regardless of whether our laboratory is in-network or out-of-network with your insurance provider, Invitae is committed to making genetic testing affordable. For testing related to a personal or family history of breast, ovarian, colorectal, or uterine cancer (also referred to as HBOC and Lynch syndrome), Invitae offers an out-of-pocket cost estimator, accessible at [www.invitae.com/patient-billing](http://www.invitae.com/patient-billing). Typically patients pay no more than \$100 out of pocket for one of our tests. If you receive a bill for more than \$100, please call our billing experts at 800-436-3037 for access to patient programs.

## PATIENT PAY

If preferred, you have the option to pay \$250 per clinical area for panel testing. To take advantage of this pricing, you must submit payment upfront and in full before testing begins. In addition, your clinician must place the order online and provide your e-mail address. The patient-pay option is available as a prepaid option only and does not allow Invitae to submit claims to your insurance company. It also does not allow Invitae to apply financial assistance programs.

## PATIENT ASSISTANCE PROGRAM

Invitae is committed to making genetic testing affordable and accessible by removing financial and logistical barriers. Our Patient Assistance Program (PAP) is available to patients in the US who undergo testing with Invitae and meet income criteria. Please contact Client Services to learn more about our interest-free payment plans and financial assistance program.

*continued on next page*

**Insurance Company**  
P.O. Box 1234  
Anytown, US 12345-6789

**Insurance Company**

Forwarding Service Required

If you have questions regarding this claim,  
please call  
(123) 456-7890 or (800) 123-4567

1234 1.1234 12 0.1234  
ALL FOR AADC 940  
[Barcode]

Claim No.: 123456789-123  
Paid date: 10/23/2016  
Insured: Jane Doe  
Patient: 1234567  
Group: 1234  
Network: N/A

JANE DOE  
123 MAIN STREET  
ANYTOWN, US 12345-6789

**PAYMENT SUMMARY**  
Amount Billed: 1,500.00  
Excluded Amount: 0.00  
Allowed Amount: 1,500.00  
Patient Responsibility: 0.00

**EXPLANATION OF BENEFITS — THIS IS NOT A BILL**

Line No.	Provider	Date(s) of Service From Thru	Amount Billed	Excluded Amount	Remark Code	Co-pay	Deductible	Amount Allowed	Paid At %	Benefits Payable
01	Invitae Corporation	06/02-06/02/2016	1,500.00	0.00	AD	0.00	0.00	1,500.00	100	1,500.00
<b>TOTALS</b>			1,500.00	0.00		0.00	0.00	1,500.00		1,500.00

Network Discount 0.00

Amount Payable 1,500.00

Copy To: INVITAE CORPORATION      Check No. 00123456      Amount 1,500.00

Remark Code	Explanation
AD	THIS IS AN ADJUSTMENT TO A PREVIOUSLY PROCESSED CLAIM

**EXPLANATION OF BENEFITS**

The most Invitae will ever bill an insurance company or institution is \$1500 per clinical area—considerably lower than most other genetic testing providers. In many cases the amount will be lower due to contracts between Invitae and the insurance company. If you pay coinsurance (a percentage of costs of a covered healthcare service), that means your payment will also be less than another laboratory—whether they are in-network or out-of-network.

The amount Invitae bills your insurance company will be reflected on your “explanation of benefits” letter. If you receive such a letter from your insurance company, please know that it is not a bill. Invitae will also receive this letter and will handle any appeals processes.

**MORE INFORMATION**

If you have questions about Invitae’s payment options, our Client Services team is available to help. You can reach them at [clientservices@invitae.com](mailto:clientservices@invitae.com) or 800-436-3037. Additional information can also be found at [www.invitae.com/patients](http://www.invitae.com/patients).

This flyer describes billing options for Invitae’s single-gene and panel tests. To see billing options for Invitae’s exome tests, please visit [www.invitae.com/exome](http://www.invitae.com/exome).

# The support you expect

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Invitae's goal is to ensure you have the tools you need to give your patients answers, reliably and quickly.

## CLINICAL CONSULT

Invitae's team of board-certified and experienced genetic counselors trained in medical genetics is available to assist clinicians. Our genetic counselors are available throughout the testing process to help:

- review patient cases that may benefit from genetic testing
- differentiate between genetic tests to select the one that is most suitable for your patient
- interpret results

## CLIENT SERVICES

Our dedicated team is here to support you every step of the way. If you have questions about genetic testing with Invitae, please contact our Client Services team at 415-374-7782 or [clientservices@invitae.com](mailto:clientservices@invitae.com). We look forward to hearing from you.

## GENETIC COUNSELING SERVICES

Invitae's genetic counselors are available to help your patients understand the genetic testing process and their specific genetic test results. For more information on Invitae's genetic counseling services, please visit [www.invitae.com/clinical-support-services](http://www.invitae.com/clinical-support-services).

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## INVITAE FAMILY HISTORY TOOL

Capturing a complete and accurate family history is a key part of evaluating your patient's genetic health and determining if genetic testing is right for them. The Invitae Family History Tool allows you to digitally record your patient's pedigree, assess their risks, and decide on the appropriate genetic test.

The Invitae Family History Tool is available for use through the web or as an iPad app. For more information, please visit [www.invitae.com/familyhistory](http://www.invitae.com/familyhistory).

## GENETICS PROVIDER NETWORK

Invitae believes in the importance of genetic counseling. For healthcare professionals who would like to refer a patient for genetics services, Invitae offers the Genetics Provider Network (GPN). The GPN is a network of genetics professionals, including genetic counselors, geneticists, and genetic nurses, who are available throughout the US and Canada. Through our network, we can help your patients identify a genetics provider in their local area who can provide genetic counseling. Genetics providers included in the GPN cover a broad range of genetics specialties and offer both face-to-face and remote consultations.

If you have a patient interested in locating a genetics provider, they can search our GPN by signing in to their Invitae patient account at [www.invitae.com/patients/signin](http://www.invitae.com/patients/signin) or by creating a patient account at [www.invitae.com/patients/signup](http://www.invitae.com/patients/signup).

## ABOUT INVITAE

Invitae's mission is to bring comprehensive genetic information into mainstream medical practice to improve the quality of healthcare for everyone. Our goal is to aggregate most of the world's genetic tests into a single service with higher quality, faster turnaround time, and lower price than many single-gene tests today.

For more information about Invitae's genetic tests, please visit [www.invitae.com](http://www.invitae.com).

